eighth edition

Goldfrank's TOXICOLOGIC EMERGENCIES

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Chapter 70, â€œSerotonin Reuptake Inhibitors and Atypical Antidepressantsâ€•

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Chapter 101, â€œHydrofluoric Acid and Fluoridesâ€•

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Chapter 126, â€œChemical Weaponsâ€•

Chapter 127, â€œBiological Weaponsâ€•

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Antidotes in Depth A20, â€œDantrolene Sodiumâ€•

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Chapter 87, â€œCadmiumâ€•

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Chapter 44, â€œAthletic Performance Enhancersâ€•

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Chapter 1, â€œHistorical Principles and Perspectivesâ€•

Chapter 2, â€œToxicologic Plagues and Disasters in Historyâ€•

Chapter 98, â€œAntiseptics, Disinfectants and Sterilantsâ€•

Antidotes in Depth A1, â€œAntiquated Antidotesâ€•

Antidotes in Depth A6, â€œSodium Bicarbonateâ€•

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Notice

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The editors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the editors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

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Dedicated to â€¦

The staffs of our hospital emergency departments who have worked with remarkable courage, concern, compassion, and understanding in treating the patients discussed in this text and many thousands more like them

The staff of the New York City Poison Control Center who have quietly and conscientiously integrated their skills with ours to serve these patients; and to the many others who never needed a hospital visit because of their efforts

To the memories of my parents Mollie and Lieutenant H. Stanley Flomenbaum whose constant encouragement to help others nonjudgmentally led me to consider toxicologic emergencies many years ago. To my wife Meredith Altman Flomenbaum, RNP, and to my children Adam, David, and Sari who have competed with this text for my attention but who have underscored the importance of these efforts

N. F.

To my children Rebecca, Jennifer, Andrew and Joan, Michelle and James; to my grandchildren Benjamin, Adam, Sarah, Kay, and Samantha who have kept me acutely aware of the ready availability of possible poisons; and to my wife, partner, and best friend Susan whose support was and is essential and whose

contributions will be found throughout the text

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To my wife Ali, my children Casey Jesse, my parents, my friends, family, and colleagues for their never-ending patience and forgiveness for the time spent away from them

R. H.

To my husband Bob; to my children Robert and Marcy; to my mother and to the loving memory of my father; and to family, friends, colleagues, and students for all their help and continuing inspiration

M. A. H.

To my wife Gail; to my children Justin and Jesse; for their support and patience; and to my parents, who made it possible

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L. N.

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Preface

In this eighth edition of *Goldfrank's Toxicologic Emergencies*, we continue to proudly offer readers an approach to medical toxicology based on case studies. The addition of almost 30 new chapters and five Antidotes in Depth and the elimination of seven other chapters are a reflection of major advances, changes in understanding new intellectual approaches, and of the ever expanding role of toxicologists at the beginning of the twenty-first century.

We have expanded the number of authors in this edition and have reassigned more than 15 percent of the chapters in an attempt to capture new and unique perspectives on toxicology. Critical events and concerns at the turn of the new century led us to add a chapter on chemical and biological weapons to the seventh edition, which we now have expanded into two independent chapters. We have also tried to prepare an appropriate context for discussing these issues more effectively by adding a chapter on risk assessment and risk communication.

The increasing emphasis on improving our use of medications is reflected by new chapters on patient safety and poison prevention that focus on public health, the potential of medical informatics, and the critical roles that providers play in improving clinical care.

We have added a new chapter on international toxicology that

describes the worldwide epidemiology of toxicology and further added to our international focus by enlisting international authors to broaden the scope of many chapters.

Goldfrank's Toxicologic Emergencies, originally a collection of medical toxicology case discussions by two authors, is now a multi-authored text of more than 2000 pages prepared by utilizing the principles we apply at the New York City Poison Center. As the text has expanded in size and scope over the past two decades, we have sought to address issues in medical toxicology in unique and creative ways that would continue to make the book a valuable resource to the growing number of clinicians and researchers working in the field. In the second edition of our text (1982), we expanded the case study material to make the work a more comprehensive clinical resource. In the third edition (1986), we added an organ-system approach to medical toxicology and also began a series of Antidotes in Depth to provide specific detailed information about newer and, in some cases, experimental antidotes. In the fourth edition (1990), we expanded both of these newer sections and began to address such subjects as nursing care, medical-legal issues, and the toxicology of AIDS treatments. For the fifth edition (1994), we added a section addressing the needs of special populations, including reproductive, perinatal, pediatric and geriatric principles, and intensive care unit patients; we also began to extensively expand basic science issues such as neurotransmitters and biochemical and metabolic pathways.

In the last two editions we have continued our analytic approach to medical toxicology by adding, fusing, and splitting chapters based on the evolving educational principles and in response to reviews by and suggestions of our many readers and colleagues. For example, a single chapter on metals in prior editions has been divided into separate chapters on antimony, bismuth, cadmium, chromium, cobalt, copper, selenium, silver, and zinc in order to describe these important elements and other related xenobiotics in greater detail. Similarly, the single chapter on rodenticides has

been divided into an introductory discussion of rodenticides among other pesticides followed by detailed discussions of barium, monofluoroacetate and fluoroacetamide, phosphorus, and strychnine.

The appearance of the eighth edition marks our first extensive use of the â€œelectronic deliveryâ€• of the text. The complete â€œtextâ€• now consists of a hard copy component that faithful readers can read and consult as they have previously and also an electronic component available by pass code and user registration to *Goldfrank's Toxicologic Emergencies* Web site (http://www.goldfrankstoxicology.com). The electronic version includes six core chapters with a large number of faithfully reproduced visual images that are critical to the understanding of these chapters. The six chapters are Dermatology, Plants, Mushrooms, Marine Envenomations, Snakes, and Arthropods. Electronic delivery allows us to offer you a large selection of pertinent images for these highly visual chapters as well as several other valuable images.

Similarly, the workbook including case studies and annotated multiple choice questions will now be available on this Web site. Some of the cases are still relevant classic examples of toxicologic emergencies from previous editions, and the remainder are new, extensively discussed cases from our regional monthly meetings at the New York City Poison Center. The collective wisdom of many of the current and former text authors continues to guide these sessions as it has for more than 20 years. Lewis Nelson and Robert Hoffman have analyzed these problems, distilled the discussions, and recreated the spirit of these meetings in the printed versions of the cases. As previously, 10 annotated multiple choice questions based on each chapter were developed by the respective chapter authors in an attempt to enhance self-learning and meet the intellectual needs of our readers.

All our principles developed in detail in the textbook and workbook

will be adapted into a concise handbook of medical toxicology. We expect this lighter and less expensive version of our text to be more portable and affordable yet equally rigorous. We hope this new approach to the description of medical toxicology will be useful for students and many others who may not as yet be fully committed to an in-depth study of our field.

After long and serious discussions in preparation of the seventh edition we came to the conclusion that the format of utilizing cases to begin each chapter in: *Part C. The Clinical Basis of Medical Toxicology* is an important and useful feature that distinguishes our text from others and therefore should be retained. At the same time, we decided that the ease with which readers can find needed information in a traditionally organized comprehensive medical textbook is also valuable. We have therefore formatted each chapter into standard sections to allow readers to find essential information easily when reviewing a topic or preparing for and treating a toxicologic emergency. Most chapters in this section now begin with a case followed by a brief Introduction, the History and Epidemiology, Pharmacology, Pharmacokinetics and Toxicokinetics, Pathophysiology, Clinical Manifestations, Diagnostic Testing, and Management, concluding with a brief summary.

The usefulness of this chapter organization is improved by our further development of the indexing features of the text. The index has now been restructured in such a way that each chapter component is listed under the aforementioned subheads and includes almost all cross-references from other chapters within their subheads. Additional alphabetical listings of unique and important terms are also retained.

Even more than previously, the rewriting and reorganization of this edition of the text has required an enormous personal effort by each author which we hope will facilitate your learning, reading and patient care. Work on the next edition of this text literally begins the day that the current edition is published. Although

many of the chapters in this eighth edition may appear familiar to readers of previous editions, every chapter has been discussed, analyzed, criticized, dissected, updated, and rewritten accordingly by its old or new authors.

Although â€œtearing downâ€• and reconstructing the text between each edition may seem like an extreme exercise to some, only in this manner can we hope to prevent ourselves from accepting and promulgating unfounded treatments and outdated concepts. We hope that you agree that this exercise is worthwhile and that each â€œnew textâ€• continues to serve you well. As always, we encourage your comments and thoughtful criticism, and we will do our best once again to incorporate your suggestions into future editions.

If this text helps to provide better patient care and stimulates interest in medical toxicology by students of medicine, nursing, and pharmacy; by residents in emergency medicine, internal medicine, pediatrics, preventive health, critical care, family practice, and others; by fellows in medical and clinical toxicology; and by attending physicians and faculty, as well as diverse toxicologists, then our efforts; will have indeed been worthwhile.

Neal E. Flomenbaum

Lewis R. Goldfrank

Robert S. Hoffman

Mary Ann Howland

Neal A. Lewin

Lewis S. Nelson

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Table of Antidotes in Depth

Readers of previous editions of Goldfrank's Toxicologic Emergencies *are undoubtedly aware that the editors have always felt that an emphasis on general management of poisoning or overdoses coupled with sound medical management is more important or as important as the selection and use of a specific antidote in the vast majority of cases. Nevertheless, there are some instances where nothing other than the timely use of a specific antidote or antagonist will save a patient. For this reason, and also because the use of such antidotes may be problematic, controversial, or unfamiliar to the practitioner (as new antidotes continue to emerge), we have included a section (or sections) at the end of each chapter where an in-depth discussion of such antidotes is relevant. The following Antidotes in Depth are included in this edition.*

Anthony F. Pizon, Bradley D. Riley, Anne-Michelle Ruha, James R. Roberts, Edward J. Otten

- Antivenom (Scorpion and Spider)
  Jeffrey N. Bernstein
- Atropine
  Mary Ann Howland
- Botulinum Antitoxin
  Lewis R. Goldfrank
- Calcium
  Mary Ann Howland
- L-Carnitine
  Mary Ann Howland
- Dantrolene Sodium
  Kenneth M. Sutin, Brian Kaufman, and Sanford M. Miller
- Deferoxamine
  Mary Ann Howland
- Dextrose
  Larissa I. Velez and Kathleen A. Delaney
- Digoxin-Specific Antibody Fragments (Fab)
  Mary Ann Howland
- Dimercaprol (British Anti-Lewisite or BAL)
  Mary Ann Howland
- Edetate Calcium Disodium ($CaNa_2EDTA$)
  Mary Ann Howland
- Ethanol
  Mary Ann Howland
- Flumazenil
  Mary Ann Howland
- Fomepizole

- Sodium Thiosulfate
  Mary Ann Howland
- Succimer (2,3-Dimercaptosuccinic Acid)
  Mary Ann Howland
- Syrup of Ipecac
  Mary Ann Howland
- Thiamine Hydrochloride
  Robert S. Hoffman
- Vitamin K_1
  Mary Ann Howland
- Whole-Bowel Irrigation and Other Intestinal Evacuants
  Mary Ann Howland

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Chapter 1

Historical Principles and Perspectives

Paul M. Wax

The term *poison* first appeared in the English literature around the year 1230 A.D. to describe a potion or draught that was prepared with deadly ingredients.[42 , 141] The history of poisons and poisoning, however, dates back thousands of years. Throughout the millennia, poisons have played an important role in human historyâ€”from political assassination in Roman times, to weapons of war, to contemporary environmental concerns, and to weapons of terrorism.

This chapter offers a perspective on the impact of poisons and poisoning on history. It also provides a historic overview of human understanding of poisons and the development of toxicology from antiquity to the present. The development of the modern poison control center, the genesis of the field of medical toxicology, and the recent increasing focus on medication errors and biologic and chemical weapons are examined. An Antidote in Depth at the end of the chapter scrutinizes changes in poison management over the years, analyzing obsolete antidotes and other discarded

therapeutic modalities. Chapter 2 describes poison plagues and unintentional disasters throughout history and examines the societal consequences of these unfortunate events. An appreciation of past failures and mistakes in dealing with poisons and poisoning promotes a keener insight and a more critical evaluation of present-day toxicologic issues, and helps in the assessment and management of future toxicologic problems.

Poisons, Poisoners, and Antidotes of Antiquity

The earliest poisons consisted of plant extracts, animal venoms, and minerals. They were used for hunting, waging war, and sanctioned and unsanctioned executions. The *Ebers Papyrus* , an ancient Egyptian text written about 1500 B.C. that is considered to be among the earliest medical texts, describes many ancient poisons, including aconite, antimony, arsenic, cyanogenic glycosides, hemlock, lead, mandrake, opium, and wormwood.[94 , 141] These poisons were thought to have mystical properties, and their use was surrounded by superstition and intrigue. Some agents, such as the Calabar bean (*Physostigma venenosum*) containing physostigmine, were referred to as â€œordeal poisons.â€• Ingestion of these substances was believed to be lethal to the guilty and harmless to the innocent.[94] The â€œpenalty of the peachâ€• involved the administration of peach pits, which we now know contain the cyanide precursor amygdalin, as an ordeal poison. Magicians, sorcerers, and religious figures were the toxicologists of antiquity. The Sumerians, in about 4500 B.C., were said to worship the deity Gula, who was known as the â€œmistress of charms and spellsâ€• and the â€œcontroller of noxious poisonsâ€• (Table 1-1).[141]

Arrow and Dart Poisons

The prehistoric Masai hunters of Kenya, who lived 18,000 years ago, used arrow and dart poisons to increase the lethality of their weapons.[20] One of these poisons appears to have consisted of extracts of *Strophanthus* species, an indigenous plant that contains strophanthin, a digitalis-like substance.[94] Cave paintings of arrowheads and spearheads reveal that these weapons were crafted with small depressions at the end to hold the poison.[142] In fact, the term *toxicology* is derived from the Greek terms *toxikos* (â€œbowâ€•) and *toxikon* (â€œpoison into which arrowheads are dippedâ€•).[8 , 142]

References to arrow poisons are cited in a number of other important literary works. The ancient Indian text *Rig Veda* , written in the 12th century B.C., refers to the use of *Aconitum* species for arrow poisons.[20] In the *Odyssey* , Homer (ca. 850 B.C.) wrote that Ulysses anointed his arrows with a variety of poisons, including extracts of *Helleborus orientalis* (thought to act as a heart poison) and snake venoms.[109] Aristotle (384â€“322 B.C.) described how the Scythians prepared and used arrow poisons.[143] Finally, reference to weapons poisoned with the blood of serpents can be found in the writings of Ovid (43 B.C.â€“ 18 A.D.).[148]

Classification of Poisons

The first attempts at poison identification and classification, and the introduction of the first antidotes, took place during Greek and Roman times. An early categorization of poisons divided them into fast poisons, such as strychnine, and slow poisons, such as arsenic. In his treatise, *Materia Medica* , the Greek physician Dioscorides (40â€“80 A.D.), categorized poisons by their origin: animal, vegetable, or mineral.[142] This categorization remained the standard classification for the next 1500 years.[142]

Animal Poisons

Animal poisons usually referred to the venom from poisonous animals. Although the venom from poisonous snakes has always been among the most commonly feared poisons, poisons from toads, salamanders, jellyfish, stingrays, and sea hares are also of concern. Nicander of Colophon (204â€“135 B.C.), a Greek poet and physician who is considered to be one of the earliest toxicologists, experimented with animal poisons on condemned criminals.[128] Nicander's poems *Theriaca* and *Alexipharmaca* are considered to be the earliest extant Greek toxicologic texts, describing the presentations and treatment of poisonings from animal

toxins.[141] A notable fatality from the effects of an animal toxin was Cleopatra (69â€“30 B.C.), who reportedly committed suicide by deliberately falling on an asp.[72]

Gula
ca. 4500 B.C.
First deity associated with poisons
Shen Nung
ca. 2000 B.C.
Chinese emperor who experimented with poisons and antidotes and wrote treatise on herbal medicine
Homer
ca. 850 B.C.
Wrote how Ulysses anointed arrows with the venom of serpents
Aristotle
384â€“322 B.C.
Described the preparation and use of arrow poisons
Theophrastus
ca. 370â€“286 B.C.
Referred to poisonous plants in *De Historia Plantarum*
Socrates
ca. 470â€“399 B.C.
Executed by poison hemlock

Nicander

204â€“135 B.C.

Wrote two poems that are among the earliest works on poisons: *Theriaca* and *Alexipharmaca*

King Mithridates VI

ca. 132â€“63 B.C.

Fanatical fear of poisons; developed mithradatum, one of first universal antidotes

Sulla

81 B.C.

Issued *Lex Cornelia*, the first antipoisoning law

Cleopatra

69â€“30 B.C.

Committed suicide from deliberate cobra envenomation

Andromachus

37â€“68 A.D.

Refined mithradatum; known as the Theriac of Andromachus

Dioscorides

40â€“80 A.D.

Wrote *Materia Medica*, which classified poison by animal, vegetable, and mineral

Galen

ca. 129â€“200 A.D.

Prepared â€œNut Theriacâ€• for Roman emperors, a remedy against bites, stings, and poisons; wrote *De Antidotis I* and *II*, which provided recipes for different antidotes, including mithradatum and panacea

Ibn Wahshiya

9th Century

Famed Arab toxicologist; wrote toxicology treatise *Book on Poisons*, combining contemporary science, magic, and astrology

Moses Maimonides

1135â€“1204

Wrote *Treatise on Poisons and Their Antidotes*

Petrus Abbonus
1250â€“1315
Wrote *De Venenis* , major work on poisoning

Person Date Importance

TABLE 1-1. Important Early Figures in the History of Toxicology

Vegetable Poisons

Theophrastus (ca. 370â€“286 B.C.) described vegetable poisons in his treatise *De Historia Plantarum* .[74] Notorious poisonous plants included *Aconitum* species (aconite, monkshood), *Conium maculatum* (poison hemlock), *Hyoscyamus niger* (henbane), *Mandragora officinarum* (mandrake), *Papaver somniferum* (opium poppy), and *Veratrum album* (hellebore). Aconite was among the most frequently encountered poisonous plants and was described as the â€œqueen mother of poisons.â€•[141] Hemlock was the official poison used by the Greeks and was employed in the execution of Socrates (ca. 470â€“399 B.C.) and many others.[130] Poisonous plants used in India at this time included *Cannabis indica* (marijuana), *Croton tiglium* (croton oil), and *Strychnos nux vomica* (poison nut, strychnine).[74]

Mineral Poisons

The mineral poisons of antiquity consisted of the metals antimony, arsenic, lead, and mercury. Undoubtedly the most famous of these was lead. Lead was discovered as early as 3500 B.C. Although controversy continues about whether an epidemic of lead poisoning among the Roman aristocracy contributed to the fall of the Roman Empire, lead was certainly used extensively during this period.[54 , 108] In addition to its considerable use in plumbing, lead was also used in the production of food and drink containers.[61] It

was common practice to add lead directly to wine, or to intentionally prepare the wine in a lead kettle to improve its taste. Not surprisingly, chronic lead poisoning became widespread. Nicander described the first case of lead poisoning in the 2nd century B.C.[145] Dioscorides, writing in the 1st century A.D., noted that fortified wine was â€œmost hurtful to the nerves.â€•[145] Lead-induced gout (â€œsaturnine goutâ€•) may have also been widespread among the Roman elite.[108]

Gases

Although not animal, vegetable, or mineral in origin, the toxic effects of gases were also appreciated during antiquity. In the 3rd century B.C., Aristotle commented that â€œcoal fumes (carbon monoxide) lead to a heavy head and deathâ€•[71] and Cicero (106â€“43 B.C.) referred to the use of coal fumes in suicide and execution.

Poisoners of Antiquity

Given the increasing awareness of the toxic properties of some naturally occurring substances and the lack of analytical detection techniques, homicidal poisoning was common during Roman times. In an attempt to curtail this practice, in 81 B.C. the Roman dictator Sulla issued the first law against poisoning, the *Lex Cornelia* . According to its provisions, if convicted of poisoning, the perpetrator was sentenced to either loss of property and exile (if the perpetrator was of high social rank) or exposure to wild beasts (if the perpetrator was of low social rank). During this period, members of the aristocracy commonly employed â€œtastersâ€• to shield themselves from potential poisoners, a practice that was also in vogue during the reign of Louis XIV in 16th century France.[148]

One of the most infamous poisoners of Ancient Rome was Locusta, who was known to experiment on slaves with poisons, including

aconite, arsenic, belladonna, henbane, and poisonous fungi. In 54 A.D., Nero's mother, Agrippina, hired Locusta to poison Emperor Claudius (Agrippina's husband and Nero's stepfather) as part of a scheme to make Nero emperor. As a result of these activities, Claudius, who was a great lover of mushrooms, died from *Amanita phalloides* poisoning,[18] and in the next year, Britannicus (Nero's stepbrother) also became one of Locusta's victims. In this case, Locusta managed to fool the taster by preparing unusually hot soup that required additional cooling after the soup had been officially tasted. At the time of cooling, the poison was surreptitiously slipped into the soup. Almost immediately after drinking the soup Britannicus collapsed and died. The exact poison remains debatable, but some authorities suggest that it was a cyanogenic glycoside.[134]

Early Quests for the Universal Antidote

The recognition, classification, and use of poisons in Ancient Greece and Rome were accompanied by an intensive search for a universal antidote. In fact, many of the physicians of this period

devoted significant parts of their careers to this endeavor.[141] Mystery and superstition surrounded the origin and source of these proposed antidotes. One of the earliest specific references to a protective agent can be found in Homer's *Odyssey* , when Ulysses is advised to protect himself by taking the antidote â€œmoli.â€• Recent speculation suggests that moli referred to *Galanthus nivalis* , which contains a cholinesterase inhibitor. This agent could have been used as an antidote against poisonous plants such as *Datura stramonium* (jimsonweed) that contain the anticholinergic alkaloids scopolamine, atropine, and hyoscyamine.[115]

Theriacs and the Mithradatum

The Greeks referred to the universal antidote as the *alexipharmaca*

or *theriac* .[141] The term *alexipharmaca* was derived from the words *alexipharmakos* (â€œwhich keeps off poisonâ€•) and *antipharmakon* (â€œantidoteâ€•). Over the years, *alexipharmaca* increasingly was used to refer to a method of treatment, such as the induction of emesis by using a feather. *Theriac* , which originally had referred to poisonous reptiles or wild beasts, was later used to refer to the antidotes. Consumption of the early theriacs (ca. 200 B.C.) was reputed to make people â€œpoison-proofâ€• against bites of all venomous animals except the asp. Their ingredients included aniseed, anmi, apoponax, fennel, meru, parsley, and wild thyme.[141]

The quest for the universal antidote was epitomized by the work of King Mithradates VI of Pontus (132â€“63 B.C.).[73] After repeatedly being subjected to poisoning attempts by his enemies during his youth, Mithradates sought protection by the development of universal antidotes. To find the best antidote, he performed acute toxicity experiments on criminals and slaves. The theriac he concocted, known as the â€œmithradatum,â€• contained a minimum of 36 ingredients and was thought to be protective against aconite, scorpions, sea slugs, spiders, vipers, and all other poisonous substances.[71] Mithradates took his concoction every day. Ironically, when an old man, Mithradates attempted suicide by poison but supposedly was unsuccessful because he had become poison-proof. Having failed at self-poisoning, Mithradates was compelled to have a soldier kill him with a sword. Galen described Mithradates' experiences in a series of three books: *De Antidotis I, De Antidotis II* , and *De Theriaca ad Pisonem* .[73 , 146]

The Theriac of Andromachus, also known as the â€œVenice treacleâ€• or â€œgalene,â€• is probably the most famous theriac. According to Galen, this preparation, formulated during the 1st century A.D., was considered an improvement over the mithradatum.[146] It was prepared by Andromachus (37â€“68 A.D.), physician to Emperor Nero. Andromachus added to the mithradatum ingredients such as the flesh of vipers, squills, and

generous amounts of opium.[151] Other ingredients were removed. Altogether, 73 ingredients were required. It was advocated to â€œcounteract all poisons and bites of venomous animals,â€• as well as a host of other medical problems, such as colic, dropsy, and jaundice, and it was used both therapeutically and prophylactically.[141 , 146] As evidence of its efficacy, Galen demonstrated that fowl receiving poison followed by theriac had a higher survival rate than fowl receiving poison alone.[141] It is likely, however, that the scientific rigor and methodology employed differed from current scientific practice.

By the Middle Ages, the Theriac of Andromachus contained more than 100 ingredients. Its synthesis was quite elaborate; the initial phase of production lasted months, followed by an aging process that lasted years, somewhat like vintage wine.[90] The final product was often more solid than liquid in consistency.

Other theriac preparations were named after famous physicians (Damocrates, Nicolaus, Amando, Arnauld, and Abano) who contributed additional ingredients to the original formulation. Over the centuries certain localities were celebrated for their own peculiar brand of theriac. Notable centers of theriac production included Bologna, Cairo, Florence, Genoa, Istanbul, and Venice. At times, theriac production was accompanied by great fanfare. For example, in Bologna, the mixing of the theriac could take place only under the direction of the medical professors at the university.[141]

Whether these preparations were of actual benefit is uncertain. Some suggest that the theriac may have had an antiseptic effect on the gastrointestinal tract, whereas others state that theriac's sole benefit derived from its formulation with opium.[90] Theriacs remained in vogue throughout the Middle Ages and Renaissance, and it was not until 1745 that their efficacy was finally questioned by William Heberden in *Antitheriaka: An Essay on Mithradatum and Theriaca* .[73] Nonetheless, pharmacopeias in France, Spain, and

Germany continued to list these agents until the last quarter of the 19th century and theriac was still available in Italy and Turkey in the early 20th century.[19 , 90]

Sacred Earth

Beginning in the 5th century B.C., an adsorbent agent called *terra sigillata* was promoted as a universal antidote. This agent, also known as the â€œsacred sealed earth,â€• consisted of red clay that could be found on only one particular hill on the Greek island of Lemnos. Perhaps somewhat akin to the 20th-century â€œuniversal antidote,â€• it was advocated as effective in counteracting all poisons.[141] With great ceremony, once per year, the terra sigillata was retrieved from this hill and prepared for subsequent use. According to Dioscorides, this clay was formulated with goat's blood to make it into a paste. At one time, it was included as part of the Theriac of Andromachus. Demand for terra sigillata continued into the 15th century. Similar antidotal clays were found in Italy, Malta, Silesia, and England.[141]

Charms

Charms, such as toadstones, snakestones, unicorn horns, and bezoar stones, were also promoted as universal antidotes. Toadstones, found in the heads of old toads, were reputed to have the capability to extract poison from the site of a venomous bite or sting. In addition, the toadstone was supposedly able to detect the mere presence of poison by producing a sensation of heat upon contact with a poisonous substance.[141]

Similarly, snakestones extracted from the heads of cobras (known as *piedras della cobra de Capelos*) were also reported to have similar magical qualities.[15] The 17th-century Italian philosopher Athanasius Kircher (1602â€“1680) became an enthusiastic supporter of snakestone therapy for the treatment of snakebite after conducting experiments, demonstrating the antidotal

attributes of these charms â€œin front of amazed spectators.â€• Kircher attributed the snakestone's efficacy to the theory of â€œattraction of like substances.â€• Francesco Redi (1626â€“1698), a court physician and contemporary of Kircher, debunked this quixotic approach. A harbinger of future experimental toxicologists, Redi was unwilling to accept isolated case reports and field demonstrations as proof of the snakestone's utility. Using a considerably more rigorous approach, *provando et riprovando* (by testing and retesting), Redi assessed the antidotal efficacy of snakestone on different animal species and different toxins and failed to confirm any benefit.[15]

Much lore has surrounded the antidotal effects of the mythical unicorn horn. Ctesias, writing in 390 B.C., was the first to chronicle the wonders of the unicorn horn, claiming that drinking water or

wine from the â€œhorn of the unicornâ€• would protect against poison.[141] The horns were usually narwhal tusks or rhinoceros horns and during the Middle Ages, the unicorn horn may have been worth as much as 10 times the price of gold. Similar to the toadstone, the unicorn horn was used both to detect poisons and to neutralize them. Supposedly a cup made of unicorn horn would sweat if a poisonous substance was placed in it.[88] To give further credence to its use, a 1593 study on arsenic-poisoned dogs reportedly showed that the horn was protective.[88]

Bezoar stones, also touted as universal antidotes, consisted of stomach or intestinal calculi formed by the deposition of calcium phosphate around a hair, fruit pit, or gallstone. They were removed from wild goats, cows, and apes and administered orally to humans. The Persian name for the bezoar stone was *pad zahr* (â€œexpeller of poisonsâ€•); the ancient Hebrews referred to the bezoar stone as *bel Zaard* (â€œevery cure for poisonsâ€•). Over the years, regional variations of bezoar stones were popularized, including an Asian variety from wild goat of Persia, an Occidental

variety from llamas of Peru, and a European variety from chamois of the Swiss mountains.[49 , 141]

Opium, Coca, and Hallucinogens in Antiquity

Although it was not until the mid-19th century that the peril of opiate addiction was first recognized, juice from the *Papaver somniferum* was known for its medicinal value in Egypt at least as early as the writing of the *Ebers Papyrus* in 1500 B.C. Egyptian pharmacologists of that time reportedly recommended opium poppy extract as a pacifier for children who exhibited incessant crying.[127] In Ancient Greece, Dioscorides and Galen were early advocates of opium as a therapeutic agent. During this time, it was also used as a means of suicide. Mithradates' lack of success in his own attempted suicide by poisoning may have been the result of an opium tolerance that had developed from previous repetitive use.[127] One of the earliest descriptions of the abuse potential of opium is attributed to Epistratos (304â€“257 B.C.), who criticized the use of opium for earache because it â€œdulled the sight and is a narcotic.â€•[127]

Cocaine use dates back to at least 300 B.C., when South American Indians reportedly chewed coca leaves during religious ceremonies.[102] Chewing coca to increase work efficacy and to elevate mood has remained commonplace in some South American societies for thousands of years. An Egyptian mummy from about 950 B.C. revealed significant amounts of cocaine in the stomach and liver, suggesting oral use of cocaine during this time period.[106] Large amounts of tetrahydrocannabinol (THC) were found in the lung and muscle of the same mummy. Another investigation of 11 Egyptian (1079 B.C.â€“ 395 A.D.) and 72 Peruvian (200â€“1500 A.D.) mummies, found cocaine, thought to be indigenous only to South America, and hashish, thought to be indigenous only to Asia, in both groups.[114]

Other currently abused agents that were known to the ancients include cannabis, hallucinogenic mushrooms, nutmeg, and peyote. As early as 1300 B.C., Peruvian indian tribal ceremonies included the use of mescaline-containing San Pedro cacti.[102] The hallucinogenic mushroom, *Amanita muscaria* , known as â€œfly agaric,â€• was used as a ritual drug and may have been known in India as â€œsomaâ€• around 2000 B.C. Cannabis use in China dates back even further, to around 2700 B.C., when it was known as the â€œliberator of sin.â€•[102] In India and Iran, cannabis was used as early as 1000 B.C. as an intoxicant known as *bhang* .[105]

Early Attempts at Gastrointestinal Decontamination

Nicander's *Alexipharmaca* (â€œAntidotes for Poisonsâ€•) recommended induction of emesis by one of several methods: (a) ingesting warm linseed oil; (b) tickling the hypopharynx with a feather; or (c) â€œemptying the gullet with a small twisted and curved paper.â€•[90] Nicander also advocated the use of suction to limit envenomation.[142] The Romans referred to the feather as the â€œvomiting featherâ€• or â€œpinna.â€• Most commonly, the feather was used after a hearty feast to avoid the gastrointestinal discomfort associated with overeating. At times, the pinna was dipped into a nauseating mixture to increase its efficacy.[93]

Toxicology During the Medieval and Renaissance Periods

After Galen (ca. A.D. 129â€“200), there is relatively little documented attention to the subject of poisons until the works of Ibn Wahshiya in the 9th century. Citing Greek, Persian, and Indian texts, Wahshiya's work, entitled *Book of Poisons* , combines contemporary science, magic, and astrology during his discussion of poison mechanisms (as they were understood at that time),

symptomatology, antidotes, including his own recommendation for a universal antidote, and prophylaxis. He categorized poisons as lethal by sight, smell, touch, and sound, as well as by drinking and eating. For victims of an aconite-containing dart arrow, Ibn Wahshiya recommended excision, followed by cauterization and topical treatment with onion and salt.[85]

Another significant medieval contribution to toxicology can be found in Moses Maimonides' (1135â€“1204) *Treatise on Poisons and Their Antidotes* (1198). In part one of this treatise, Maimonides discussed the bites of snakes and mad dogs, and the stings of bees, wasps, spiders, and scorpions.[125] He also discussed the use of cupping glasses for bites (a progenitor of the modern suctioning device), and was one of the first to differentiate the hematotoxic (hot) from the neurotoxic (cold) effects of poison. In part two, he discussed mineral and vegetable poisons and their antidotes. He described belladonna poisoning as causing a â€œredness and a sort of excitation.â€• [125] He suggested that emesis should be induced by hot water, *Anethum graveolens* (dill), and oil, followed by fresh milk, butter, and honey. Although he rejected some of the popular treatments of the day, he advocated the use of the great theriac and the mithradatum as first- and second-line agents in the management of snakebite.[125]

On the subject of oleander poisoning, Petrus Abbonus (1250â€“1315) wrote that those who drink the juice, spines, or bark of oleander will develop anxiety, palpitations, and syncope.[22] He described the clinical presentation of opium overdose as someone who â€œwill be dull, lazy, and sleepy, without feeling, and he will neither understand nor feel anything, and if he does not receive succor, he will die.â€• Although this â€œsuccorâ€• is not defined, he recommended that treatment of opium intoxication include drinking the strongest wine, rubbing the extremities with alkali and soap, and olfactory stimulation with pepper. To treat snakebite, Abbonus suggested the immediate application of a tourniquet, as well as oral suctioning of the bite

woundâ€”preferably performed by a servant. Interestingly, from a 21st-century perspective, Abbonus also suggested that St. John's wort had the magical power to free anything from poisons and attributed this virtue to the influence of the stars.[22]

Paracelsus
1493â€“1541
Introduced dose-response concept to toxicology
Ambroise Pare
1510â€“1590
Spoke out against unicorn horns and bezoars as antidotes
William Piso
1611â€“1678
First to study emetic qualities of ipecacuanha
Bernardino Ramazzini
1633â€“1714
Father of occupational medicine; wrote *De Morbis Artificum Diatriba*
Richard Mead
1673â€“1754
Wrote English-language book dedicated to poisoning
Percivall Pott
1714â€“1788
First description of occupational cancer, relating the chimney sweep occupation to scrotal cancer
Felice Fontana
1730â€“1805
First scientific study of venomous snakes
Philip Physick
1767â€“1837
Early advocate of orogastric lavage to remove poisons
Baron Guillaume Dupuytren
1777â€“1835
Early advocate of orogastric lavage to remove poisons
Edward Jukes

1820

Self-experimented with orogastric lavage apparatus known as Jukes' syringe

Grand Marshall Bertrand

1813

Demonstrated the efficacy of charcoal in arsenic ingestion

Pierre Touery

1831

Demonstrated the efficacy of charcoal in strychnine ingestion

Alfred Garrod

1846

First systematic study of charcoal in an animal model

Benjamin Howard Rand

1848

First study of the efficacy of charcoal in humans

Bonaventure Orfila

1787â€“1853

Father of modern toxicology; wrote *Traite des Poisons* ; first to isolate arsenic from humans organs

Robert Christison

1797â€“1882

Wrote *Treatise on Poisons* , one of the most influential texts in early 19th century

Francois Magendie

1783â€“1855

Discovered emetine and studied mechanism of cyanide and strychnine

Claude Bernard

1813â€“1878

Studied mechanism of toxicity of carbon monoxide and curare

O.H. Costill

1848

Wrote first book on symptoms and treatment of poisoning

Theodore Wormley

Person	Date	Importance
Wrote *Micro-Chemistry of Poisons* , the first American book devoted exclusively to toxicology	1826â€“1897	James Marsh
Developed reduction test for arsenic	1794â€“1846	Hugo Reinsch
Developed qualitative tests for arsenic and mercury	1842â€“1884	Max Gutzeit
Developed method to quantitate small amounts of arsenic	1847â€“1915	Albert Niemann
Isolated cocaine alkaloid	1860	Rudolf Kobert
Studied digitalis and ergot alkaloids	1854â€“1918	Louis Lewin
Studied many toxins, including methanol, chloroform, snake venom, carbon monoxide, lead, opiates, and hallucinogenic plants	1850â€“1929	Alice Hamilton
Conducted landmark investigations associating worksite chemical hazards with disease; led reform movement to improve worker safety	1869â€“1970	

TABLE 1-2. Important Figures in the Field of Toxicology from Paracelsus to the 1900s

The Scientists

Paracelsus' (1493â€“1541) study on the doseâ€“response relationship is usually considered the beginning of the scientific approach to toxicology (Table 1-2). He was the first to emphasize the chemical nature of toxic agents.[112] Paracelsus stressed the need for proper observation and experimentation regarding the true response to chemicals. He underscored the need to differentiate between the therapeutic and toxic properties of chemicals when he stated in his *Third Defense* , â€œWhat is there that is not poison? All things are poison and nothing [is] without poison. Solely, the dose determines that a thing is not a poison.â€• [41]

Although Paracelsus is the best known Renaissance toxicologist, Ambroise Pare (1510â€“1590) and William Piso (1611â€“1678) also contributed to the field. Pare argued against the use of the unicorn horn and bezoar stone.[92] He also wrote an early treatise on carbon monoxide poisoning. Piso is credited as one of the first to recognize the emetic properties of ipecacuanha.[122]

Medieval and Renaissance Poisoners

Along with these advances in toxicologic knowledge, the Renaissance is mainly remembered as the age of the poisoner, a time when the art of poisoning reached new heights (Table 1-3). In fact, poisoning was so rampant during this time that in 1531 King Henry VIII decreed that convicted poisoners should be boiled alive.[51] From the 15th to 17th centuries, schools of poisoning existed in Venice and Rome. In Venice, poisoning services were provided by a group called the Council of Ten, whose members were hired to perform murder by poison.[148]

Members of the infamous Borgia family were credited with many poisonings during this period. They preferred to use a poison called â€œLa Cantarella,â€• a mixture of arsenic and

phosphorus.[143] Rodrigo Borgia (1431â€“1503), who became Pope Alexander VI, and his son, Cesare Borgia, were reportedly responsible for the poisoning of cardinals and kings.

In the late 16th century, Catherine de Medici, wife of Henry II of France, introduced Italian poisoning techniques to France. She experimented on the poor, the sick, and the criminal. By analyzing the subsequent complaints of her victims, she is said to have learned the site of action and time of onset, the clinical signs and symptoms, and the efficacy of poisons.[55]

Murder by poison remained quite popular during the latter half of the 17th and the early part of the 18th centuries in Italy and France.

The Marchioness de Brinvilliers (1630â€“1676) tested her poison concoctions on hospitalized patients and on her servants, and allegedly murdered her husband, father, and two siblings.[53 , 134] Among the favorite poisons of the Marchioness were arsenic, copper sulfate, corrosive sublimate (mercury bichloride), lead, and tartar emetic (antimony potassium tartrate).[143] Catherine Deshayes (1640â€“1680), a fortuneteller and sorcerer, was one of the last â€œpoisoners for hire,â€• and was implicated in countless poisonings, including the killing of more than 2000 infants.[55] Better known as â€œLa Voisine,â€• she reportedly sold poisons to women wishing to rid themselves of their husbands. Her particular brand of poison was a

concoction of aconite, arsenic, belladonna, and opium known as â€œla poudre de succession.â€•[143] Ultimately, de Brinvilliers was beheaded and Deshayes was burned alive for their crimes. In an attempt to curtail these rampant poisonings, Louis XIV issued a decree in 1662 banning the sale of arsenic, mercury, and other poisons to customers not known to the apothecaries and requiring poison buyers to sign a register declaring the purpose for their purchase.[134]

Locusta
54â€“55 A.D.
Claudius and Britannicus
Amanita phalloides , cyanide
Cesare Borgia
1400s
Cardinals and kings
La Cantarella (arsenic and phosphorus)
Catherine de Medici
1519â€“1589
Poor, sick, criminals
Unknown agents
Hieronyma Spara
Died 1659
Taught women how to poison their husbands
Mana of St. Nicholas of Bari (arsenic trioxide)
Marchioness de Brinvilliers
Died 1676
Hospitalized patients, husband, father
Antimony, arsenic, copper, lead, mercury
Catherine Deshayes
Died 1680
>2000 infants, many husbands
La poudre de succession (arsenic mixed with aconite, belladonna, and opium)
Madame Giulia Toffana
Died 1719
>600 people
Aqua toffana (arsenic trioxide)
Mary Blandy
1752
Father
Arsenic
Anna Maria Zwanizer

1807
Random people
Antimony, arsenic
Marie Lefarge
1839
Husband
Arsenic (first use of Marsh test)
John Tawell
1845
Mistress
Cyanide
William Palmer, MD
1855
Fellow gambler
Strychnine
Madeline Smith (acquitted)
1857
Lover
Arsenic
Edmond de la Pommerais, MD
1863
Patient and mistress
Digitalis
Edward William Pritchard, MD
1865
Wife and mother-in-law
Antimony
George Henry Lamson, MD
1881
Brother-in-law
Aconite
Adelaide Bartlett (acquitted)
1886
Husband

Chloroform
Florence Maybrick
1889
Husband
Arsenic
Thomas Neville Cream, MD
1891
Prostitutes
Strychnine
Johann Hoch
1892â€“1905
Serial wives
Arsenic
Cordelia Botkin
1898
Feminine rival
Arsenic (in chocolate candy)
Roland Molineux
1898
Acquaintance
Cyanide of mercury
Hawley Harvey Crippen, MD
1910
Wife
Hyoscine
Frederick Henry Seddon
1911
Boarder
Arsenic (fly paper)
Henri Girard Landru
1912
Acquaintances
Amanita phalloides
Robert Armstrong

1921
Wife
Arsenic (weed killer)
Landru
1922
Many women
Cyanide
Suzanne Fazekas
1929
Supplied poison to 100 wives to kill husbands
Arsenic
Sadamichi Hirasawa
1948
Bank employees
Potassium cyanide
Christa Ambros Lehmann
1954
Friend, husband, father-in-law
E-605 (parathion)
Nannie Doss
1954
11 relatives, including 5 husbands
Arsenic
Carl Coppolino, MD
1965
Wife
Succinylcholine
Graham Frederick Young
1971
Stepmother, coworkers
Antimony, thallium
Judias V. Buenoano
1971
Husband, son

Arsenic
Ronald Clark O'Bryan
1974
Son and neighborhood children
Cyanide (in Halloween candy)
???
1978
Georgi Markov, Bulgarian diplomat
Ricin
Jim Jones
1978
911 people in mass suicide
Cyanide
Harold Shipman, MD
1974â€“1998
Patients (up to 297)
Heroin
â€œTylenolâ€• tamperer
1982
7 people
Extra Strength Tylenol mixed with cyanide
Donald Harvey
1983â€“1987
Patients
Arsenic
George Trepal
1988
Neighbors
Thallium
Michael Swango, MD
1980sâ€“1990s
Hospitalized patients
Arsenic, potassium chloride, succinylcholine
Charles Cullen, RN

1990sâ€“2003
Hospitalized patients
Digoxin
???
2004
Viktor Yushchenko, Ukrainian presidential candidate
Dioxin

Poisoner	Date	Victim(s)	Poison(s)

TABLE 1-3. Notable Poisoners from Antiquity to the Present[134, 141, 143]

A major center for poison practitioners was Naples, the home of the notorious Madame Giulia Toffana. She reportedly poisoned more than 600 people, preferring a particular solution of white arsenic (arsenic trioxide), better known as â€œaqua toffana,â€• and dispensed under the guise of a cosmetic. Eventually convicted of poisoning, Madame Toffana was executed in 1719.[21]

Eighteenth- and Nineteenth-Century Developments in Toxicology

The development of toxicology as a distinct specialty began during the 18th and 19th centuries (see Table 1-2).[113] The poison mystiqueâ€”mythologic and magicalâ€”was gradually replaced by an increasingly rational, scientific, and experimental approach to the study of these agents. Much of the poison lore that had survived for almost 2000 years was finally debunked and discarded. The 18th-century Italian Felice Fontana was one of the first to usher in the modern age. He was an early experimental toxicologist who studied the venom of the

European viper and wrote the classic text *Traite sur le Venin de la*

Vipere in 1781.[77] Through his exacting experimental study on the effects of venom, Fontana brought a scientific insight to toxicology that had previously been lacking, demonstrating that clinical symptoms are a result of the poison (venom) acting on specific target organs. During the 18th and 19th centuries, attention focused on the detection of poisons and the study of toxic effects of drugs and chemicals in animals.[107] Issues relating to adverse effects of industrialization and unintentional poisoning in the workplace and home environment were raised. Also during this time, early experience and experimentation with methods of gastrointestinal decontamination took place.

Development of Analytical Toxicology and the Study of Poisons

The French physician Bonaventure Orfila (1787â€“1853) is often called the father of modern toxicology.[107] He emphasized toxicology as a distinct, scientific discipline, separate from clinical medicine and pharmacology.[12] He also was an early medical-legal expert who championed the use of chemical analysis and autopsy material as evidence to prove that a poisoning had occurred. His treatise *Traite des Poisons* (1814)[111] had five editions and was regarded as the foundation of experimental and forensic toxicology.[149] This text classified poisons into six groups: acrids, astringents, corrosives, narcoticoacrids, septics or putrefiants, and stupefacients and narcotics.

A number of other landmark works on poisoning also first appeared during this period. In 1829, Robert Christison (1797â€“1882), a professor of medical jurisprudence and Orfila's student, wrote *A Treatise on Poisons* .[31] This work simplified Orfila's poison classification schema by categorizing poisons into three groups: irritants, narcotics, and narcoticoacrids. Less concerned with jurisprudence than with clinical toxicology, O.H. Costill's *A Practical Treatise on Poisons* , published in 1848, was

the first modern clinically oriented text to emphasize the symptoms and treatment of poisoning.[35] In 1867, Theodore Wormley (1826â€“1897) published the first American book written exclusively on poisons entitled the *Micro-Chemistry of Poisons* .[47, 150]

During this time, important breakthroughs in the chemical analysis of poisons resulted from the search for a more reliable assay for arsenic. Arsenic was widely available and was the suspected etiology of a large number of deaths. In one study, arsenic was employed in 31% of 679 homicidal poisonings.[143] A reliable means of detecting arsenic was much needed by the courts.

Until the 19th century, poisoning was mainly diagnosed by symptoms rather than by analytic tests. The first use of a chemical test as evidence in a poisoning trial occurred in the 1752 trial of Mary Blandy, who was accused of poisoning her father with arsenic.[96] Although Blandy was convicted and hanged publicly, the test employed in this case was not very sensitive and depended in part on eliciting a garlic odor upon heating the gruel that the accused had fed to her father.

During the 19th century, James Marsh (1794â€“1846), Hugo Reinsch, and Max Gutzeit (1847â€“1915) each worked on this problem. Assays bearing their names are important contributions to the early history of analytic toxicology.[97, 107] The â€œMarsh testâ€• to detect arsenic was first used in a criminal case in 1839 during the trial of Marie Lefarge, who was accused of using arsenic to murder her husband.[134] Orfila's trial testimony that the victim's viscera contained minute amounts of arsenic helped to convict the defendant although subsequent debate suggested that contamination of the forensic specimen may have also played a role.

In a further attempt to curtail criminal poisoning by arsenic, the British Parliament passed the Arsenic Act in 1851. This bill, which was one of the first modern laws to regulate the sale of poisons,

required that the retail sale of arsenic be restricted to chemists, druggists, and apothecaries, and that a poison book be maintained to record all arsenic sales.[16]

Homicidal poisonings remained common during the 19th and early 20th century. Infamous poisoners of the late 19th century and early 20th century included William Palmer, Edward Pritchard, Harvey Crippen, and Frederick Seddon.[143] Many of these poisoners were physicians who used their knowledge of medicine and toxicology in an attempt to solve their domestic and financial difficulties by committing the â€œperfectâ€• murder. Some of the poisons employed were aconitine (Lamson, who was a classmate of Christison), *Amanita phalloides* (Girard), arsenic (Maybrick, Seddon, others), antimony (Pritchard), cyanide (Molineux, Tawell), digitalis (Pommerais), hyoscine (Crippen), and strychnine (Palmer, Cream) (see Table 1-3).[24 , 141 , 143]

In the early 20th century, forensic investigation into suspicious deaths, including poisonings, was significantly advanced with the development of the medical examiner system that replaced the much-flawed coroner system that was subject to widespread corruption. In 1918, the first centrally controlled medical examiner system was established in New York City. Alexander Gettler, considered the father of forensic toxicology in the United States, established a toxicology laboratory within the newly created New York City Medical Examiner's Office. Gettler pioneered new techniques for the detection of a variety of substances in biologic fluids including carbon monoxide, chloroform, cyanide, and heavy metals.[48 , 107]

Systematic investigation into the underlying mechanisms of toxic substances also commenced during the 19th century. To cite just a few important accomplishments, Francois Magendie (1783â€“1855) studied the mechanisms of toxicity and sites of action of cyanide, emetine, and strychnine.[46] Claude Bernard (1813â€“1878), the pioneering physiologist and a student of Magendie, made

important contributions to the understanding the toxicity of carbon monoxide and curare.[84] Rudolf Kobert (1854â€“1918) studied digitalis and ergot alkaloids, and also authored a textbook on toxicology for physicians and students.[79 , 109] Louis Lewin (1850â€“1929) was the first person to intensively study the differences between the pharmacologic and toxicologic actions of drugs. Lewin studied chronic opium intoxication, as well as the toxicity of carbon monoxide, chloroform, lead, methanol, and snake venom. He also developed a classification system for psychoactive drugs, dividing them into euphorics, phantastics, inebriants, hypnotics, and excitants.[91]

The Origin of Occupational Toxicology

The origins of occupational toxicology can be traced to the early 18th century and to the contributions of Bernardino Ramazzini (1633â€“1714). Considered the father of occupational medicine, Ramazzini wrote *De Morbis Artificum Diatriba* (*Diseases of Workers*) in 1700, which was the first comprehensive text discussing the relationship between disease and workplace hazards.[52] Ramazzini's essential contribution to the care of the patient is epitomized by the addition of a question to the medical history, â€œWhat occupation does the patient follow?â€•[50] Altogether Ramazzini described diseases associated with 54 occupations, including hydrocarbon poisoning in painters, mercury poisoning in mirror makers, and pulmonary diseases in miners.

In 1775, Sir Percivall Pott proposed the first association between workplace exposure and cancer when he noticed a high incidence of scrotal cancer in English chimney sweeps. Pott's belief that the scrotal cancer was caused by prolonged exposure to tar and soot was confirmed by other investigation in the 1920s, indicating that the polycyclic aromatic hydrocarbons contained in coal tar (including benzo[*a*]pyrene) are carcinogenic.[69]

Dr. Alice Hamilton (1869â€“1970) was another pioneer in occupational toxicology, whose rigorous scientific inquiry had a profound impact on linking chemical toxins with human disease. A physician, scientist, humanitarian, and social reformer, Hamilton, who would become the first female professor at Harvard University, conducted groundbreaking studies of many different occupational exposures and problems, including carbon monoxide poisoning in steelworkers, mercury poisoning in hatters, and wrist drop in lead workers. Her overriding concerns about these â€œdangerous tradesâ€• and her commitment to improve the health of workers would lead to extensive voluntary and regulatory reforms in the workplace.[59,63]

Advances in Gastrointestinal Decontamination

Using gastric lavage and charcoal to treat the poisoned patient was introduced in the late 18th and early 19th century. A stomach pump was first designed by Munro Secundus in 1769 to administer neutralizing substances to sheep and cattle for the treatment of bloat.[25] The American surgeon Philip Physick (1768â€“1837) and the French surgeon Baron Guillaume Dupuytren (1777â€“1835) were two of the first physicians to advocate gastric lavage for the removal of poisons.[25] As early as 1805, Physick demonstrated the use of a â€œstomach tubeâ€• for this purpose. Using brandy and water as the irrigation fluid, he performed stomach washings in twins to wash out excessive doses of tincture of opium.[25] Dupuytren performed gastric emptying by first introducing warm water into the stomach via a large syringe attached to a long flexible sound and then withdrawing the â€œsame water charged with poison.â€•[25] Edward Jukes, a British surgeon, was another early advocate of poison removal by gastric lavage. Jukes first experimented on animals, performing gastric lavage after the oral administration of tincture of opium. Attempting to gain human

experience, he experimented on himself, by first ingesting 10 drams (600 g) of tincture of opium and then performing gastric lavage using a 25-inch-long, 0.5-inch-diameter tube, which became known as Jukes' syringe.[101] Other than some nausea and a 3-hour sleep he suffered no ill effects, and the experiment was deemed a success.

The principle of using charcoal to adsorb poisons was first described by Scheele (1773) and Lowitz (1785), but the medicinal use of charcoal dates to ancient times.[34] The earliest reference to the medicinal uses of charcoal is found in the Egyptian Papyrus of about 1500 B.C.[34] The charcoal employed during Greek and Roman times, referred to as wood charcoal, was used to treat anthrax, chlorosis, epilepsy, and vertigo. By the late 18th century, topical application of charcoal was recommended for gangrenous skin ulcers, and internal use of a charcoal-water suspension was recommended for use as a mouthwash and in the treatment of bilious conditions.[34]

The first hint that charcoal might have a role in the treatment of poisoning came from a series of courageous self-experiments in France during the early 19th century. In 1813, the French chemist M. Bertrand publicly demonstrated the antidotal properties of charcoal by surviving a 5-g ingestion of arsenic trioxide that had been mixed with charcoal.[66] Eighteen years later, before the French Academy of Medicine, the pharmacist P.F. Touery survived an ingestion consisting of 10 times the lethal dose of strychnine mixed with 15 g of charcoal.[66] One of the first reports of charcoal used in a poisoned patient was in 1834 by the American Hort, who successfully treated a mercury bichloride-poisoned patient with large amounts of powdered charcoal.[4]

In the 1840s, A. Garrod performed the first controlled study of charcoal when he examined its utility on a variety of poisons in animal models.[66] Garrod used dogs, cats, guinea pigs, and rabbits to demonstrate the potential benefits of charcoal in the

management of strychnine poisoning. He also emphasized the importance of early use of charcoal and the proper ratio of charcoal to poison. Other toxic substances, such as aconite, hemlock, mercury bichloride, and morphine were also studied during this period. The first charcoal efficacy studies in humans were performed by the American physician B. Rand in 1848.[66]

It was not until the early 20th century that an activation process was added to the manufacture of charcoal. In 1900, the Russian Ostrejko demonstrated that treating charcoal with superheated steam significantly enhanced its adsorbing power.[34] Despite this improvement and the favorable reports mentioned, charcoal was only occasionally used in gastrointestinal decontamination until the early 1960s, when Holt and Holz repopularized its use.[62]

The Increasing Recognition of the Perils of Drug Abuse

Opioids

Although the medical use of opium was promoted by Paracelsus in the 16th century, the popularity of this agent was given a significant boost when the distinguished British physician Thomas Sydenham (1624â€“1689) formulated laudanum, which was a tincture of opium containing cinnamon, cloves, saffron, and sherry. Sydenham also formulated a different opium concoction known as â€œsyrup of poppies.â€•[82] A third opium preparation called Dover's powder was designed by Sydenham's protÃ©gÃ©, Thomas Dover; this preparation contained ipecac, licorice, opium, saltpeter, and tartaric acid.

John Jones, the author of the 18th century text *The Mysteries of Opium Reveal'd* , was another enthusiastic advocate of the medicinal uses of opium.[82] A well-known opium user himself, Jones provided one of the earliest descriptions of opiate addiction.

He insisted that opium offered many benefits if the dose was moderate, but that discontinuation or a decrease in dose, particularly after â€œleaving off after long and lavish use,â€• would result in such symptoms as sweating, itching, diarrhea, and melancholy. His recommendation for the treatment of these withdrawal symptoms included decreasing the dose of opium by 1% each day until the drug was totally withdrawn. During this period, a number of English writers became well-known opium addicts, including Elizabeth Barrett Browning, Samuel Taylor Coleridge, and Thomas De Quincey. De Quincey, author of *Confessions of an English Opium Eater* , was an early advocate of the recreational use of opiates. The famed Coleridge poem *Kubla Khan* referred to opium as the â€œmilk of paradise,â€• and De Quincey's *Confessions* suggested that opium held the â€œkey to paradise.â€• In many of these cases, the initiation of opium use for medical reasons led to recreational use, tolerance, and dependence.[82]

Although opium was first introduced to Asian societies by Arab physicians some time after the fall of the Roman Empire, the use of opium in Asian countries grew considerably during the 18th and

19th centuries. In one of the more deplorable chapters in world history, China's growing dependence on opium was spurred on by the English desire to establish and profit from a flourishing drug trade.[127] Opium was grown in India and exported east. Despite Chinese protests and edicts against this practice, the importation of opium persisted throughout the 19th century, with the British going to war twice in order to maintain their right to sell opium. Not surprisingly, by the beginning of the 20th century, opium abuse in China was endemic.

In England, opium use continued to increase during the first half of the 19th century. During this period, opium was legal and freely available from the neighborhood grocer. To many, its use was considered no more problematic than alcohol.[57] The Chinese

usually self-administered opium by smoking, a custom that was brought to the United States in the mid-19th century by Chinese immigrants, whereas the English use of opium was more often by ingestion, that is, â€œopium eating.â€•

The liberal use of opiates as infant-soothing agents was one of the most unfortunate aspects of this period of unregulated opiate use.[81] Godfrey's Cordial, Mother's Friend, Mrs. Winslow's Soothing Syrup, and Quietness were among the most popular of children's opiates.[86] They were advertised as producing a natural sleep and recommended for teething and bowel regulation, as well as for crying. Because of the wide availability of opiates during this period, the number of acute opiate overdoses in children was consequential and would remain problematic until these unsavory remedies were condemned and removed from the market.

With the discovery of morphine in 1805 and Alexander Wood's invention of the hypodermic syringe in 1853, parenteral administration of morphine became the preferred route of opiate administration for therapeutic use and abuse.[68] A legacy of the generous use of opium and morphine during the United States Civil War was â€œsoldiers' disease,â€• referring to a rather large veteran population that returned from the war with a lingering opiate habit.[119] One hundred years later, opiate abuse and addiction would again become common among US military serving during the Vietnam War. Surveys indicated that as many as 20% of American soldiers in Vietnam were addicted to opiates during the warâ€”in part because of its widespread availability and high purity in Vietnam.[124]

Growing concerns about opiate abuse in England led to the passing of the Pharmacy Act of 1868, which restricted the sale of opium to registered chemists. But in 1898, the Bayer Pharmaceutical Company of Germany synthesized heroin from opium (Bayer also introduced aspirin that same year).[135] Although initially touted as a nonaddictive morphine substitute, problems with heroin use soon

became evident in the United States.

Cocaine

Ironically, during the later part of the 19th century, Sigmund Freud and Robert Christison, among others, were enthusiastically recommending cocaine as a treatment for opiate addiction. After Albert Niemann's isolation of cocaine alkaloid from coca leaf in 1860, growing enthusiasm for cocaine as a panacea ensued.[76] Some of the most important medical figures of the time, including William Halsted, the famed Johns Hopkins surgeon, enthusiastically promoted the use of cocaine. Halsted championed the anesthetic properties of this drug, although his own use of cocaine and subsequent morphine use in an attempt to overcome his cocaine dependency would later take a considerable toll.[110] In 1884, Freud wrote *Uber Cocaine* ,[27] advocating cocaine as a cure for opium and morphine addiction and as a treatment for fatigue and hysteria.

During the last third of the 19th century, cocaine was added to many popular over-the-counter tonics of the day. In 1863, Angelo Mariani, a Frenchman, introduced a new wine, â€œVin Mariani,â€• that consisted of a mixture of cocaine and wine (6 mg of cocaine alkaloid per ounce) and was sold as a digestive aid and restorative.[102] In direct competition with the French tonic was the American-made Coca-Cola, developed by J.S. Pemberton. Coca-Cola was originally formulated with coca and caffeine and was marketed as a headache remedy and invigorator. With the public demand for cocaine increasing, patent medication manufacturers were adding cocaine to thousands of products. One such asthma remedy was â€œDr. Tucker's Asthma Specific,â€• which contained 420 mg of cocaine per ounce and was applied directly to the nasal mucosa.[76] By the end of the 19th century, the first American cocaine epidemic was underway.[104]

Similar to the medical and societal adversities associated with opiate use, the increasing use of cocaine led to a growing concern

about comparable adverse effects. In 1886, the first reports of cocaine-related cardiac arrest and stroke were published.[120] Reports of cocaine habituation occurring in patients using cocaine to treat their underlying opiate addiction also began to appear. In 1902, a popular book, *Eight Years in Cocaine Hell* , described some of these problems. *Century Magazine* called cocaine â€œthe most harmful of all habit-forming drugs,â€• and a report in the *New York Times* stated that cocaine was destroying â€œits victims more swiftly and surely than opium.â€•[40] In 1910, President William Taft proclaimed cocaine to be Public Enemy Number 1.

In an attempt to curb the increasing problems associated with drug abuse and addiction, the 1914 Harrison Narcotics Act mandated stringent control over the sale and distribution of narcotics (defined as opium, opium derivatives, and cocaine).[40] It was the first federal law in the United States to criminalize the nonmedical use of drugs. The bill required doctors, pharmacists, and others who prescribed narcotics to register and to pay a tax. A similar law, the Dangerous Drugs Act, was passed in the United Kingdom in 1920.[57] To help enforce these drug laws in the United States, the Narcotics Division of the Prohibition Unit of the Internal Revenue Service (a progenitor of the Drug Enforcement Agency) was established in 1920. In 1924, the Harrison Act was further strengthened with the passage of new legislation that banned the importation of opium for the purpose of manufacturing heroin, essentially outlawing the medicinal uses of heroin. With the legal venues to purchase these drugs now eliminated, users were forced to buy from illegal street dealers, creating a burgeoning black market that still exists today.

Sedative-Hypnotics

The introduction to medical practice of the anesthetic agents nitrous oxide, ether, and chloroform during the 19th century was accompanied by the recreational use of these agents and the first

reports of volatile substance abuse. Chloroform â€œjags,â€• ether â€œfrolics,â€• and nitrous parties became a new type of entertainment. Humphrey Davies was an early self-experimenter with the exhilarating effects associated with nitrous oxide inhalation. In certain Irish towns, especially where the temperance movement was strong, ether drinking became quite popular.[99] Horace Wells, the American dentist who introduced chloroform as an anesthetic, became dependent on this volatile solvent and later committed suicide.

Until the last half of the 19th century aconite, alcohol, hemlock, opium, and prussic acid (cyanide) were the primary agents used for sedation.[32] During the 1860s, new, more specific

sedative-hypnotics, such as chloral hydrate and potassium bromide, were introduced into medical practice. In particular, chloral hydrate was hailed as a wonder drug that was relatively safe, as compared to opium, and recommended for insomnia, anxiety, and delirium tremens, as well as for scarlet fever, asthma, and cancer. But within a few years, problems with acute toxicity of chloral hydrate, as well as its potential to produce tolerance and physical dependence, became apparent.[32] Mixing chloral hydrate with ethanol was noted to produce a rather powerful â€œknockoutâ€• combination that would become known as a â€œMickey Finn.â€• Abuse of chloral hydrate, as well as other new sedatives such as potassium bromide, would prove to be a harbinger of 20th-century sedative-hypnotic abuse.

Hallucinogens

American Indians used peyote in religious ceremonies since at least the 17th century. Hallucinogenic mushrooms, particularly *Psilocybe* mushrooms, were also used in the religious life of Native Americans. These were called â€œteonanacatl,â€• which means â€œGod's sacred mushroomsâ€• or â€œGod's flesh.â€•[116]

Interest in the recreational use of cannabis also accelerated during the 19th century after Napoleon's troops brought the drug back from Egypt, where its use among the lower classes was widespread. In 1843, several French Romantics, including Balzac, Baudelaire, Gautier, and Hugo, formed a hashish club called â€œLe Club des Hachichinsâ€• in the Parisian apartment of a young French painter. Fitz Hugh Ludlow's *The Hasheesh Eater* , published in 1857, was an early American text espousing the virtues of marijuana.[89]

Absinthe, an ethanol-containing beverage that was manufactured with an extract from wormwood (*Artemisia absinthium*), was very popular during the last half of the 19th century.[83] This emerald-colored, very bitter drink was memorialized in the paintings of Degas, Toulouse-Lautrec, and Van Gogh and was a staple of French society during this period.[13] Î±-Thujone, a psychoactive component of wormwood, and a noncompetitive Î³-aminobutyric acid type A ($GABA_A$) blocker is thought to be responsible for the pleasant feelings, as well as for the hallucinogenic effects, hyperexcitability, and significant neurotoxicity associated with this drink.[65] Van Gogh's debilitating episodes of psychosis were likely exacerbated by absinthe drinking.[138] Given the medical problems associated with its use, absinthe was banned throughout most of Europe by the early 20th century.

A more recent event that would have significant impact on modern-day hallucinogen use was the synthesis of lysergic acid diethylamide (LSD) by Albert Hofmann in 1938.[64] Working for Sandoz Pharmaceutical Company, Hofmann synthesized LSD while investigating the pharmacologic properties of ergot alkaloids. Subsequent self-experimentation by Hofmann led to the first description of its hallucinogenic effects and stimulated research into the use of LSD as a therapeutic agent. Hofmann is also credited with isolating psilocybin as the active ingredient in *Psilocybe mexicana* mushrooms in 1958.[102]

Twentieth-Century Events

Early Regulatory Initiatives

The development of the specialty of medical toxicology and the role of poison control centers began shortly after World War II. Prior to this time, serious attention to the problem of household poisonings in the United States had been limited to a few federal legislative antipoisoning initiatives (Table 1-4). The 1906 Pure Food and Drug Act was the first federal legislation that sought to protect the public from problematic and potentially unsafe drugs and food. The driving force behind this reform was Dr. Harvey W. Wiley, the chief chemist at the Department of Agriculture. Beginning in the 1880s, Wiley investigated the problems of contaminated food. In 1902, he organized the â€œpoison squad,â€• which consisted of a group of volunteers who did self-experiments with food preservatives.[5] Revelations from the â€œpoison squad,â€• as well as the publication of Upton Sinclair's muckraking novel *The Jungle* [133] in 1906, exposing unhygienic practices of the meatpacking industry, led to growing support for legislative intervention. Samuel Hopkins Adams' reports about the patent medicine industry revealed that some drug manufacturers added opiates to soothing syrups for infants, and added to the call for reform.[121] Although the 1906 regulations were mostly concerned with protecting the public from adulterated food, regulations protecting against misbranded patent medications were also included.

The Federal Caustic Poison Act of 1927 was the first federal legislation to specifically address household poisoning. As early as 1859, bottles clearly demarcated â€œpoisonâ€• were manufactured in response to a rash of unfortunate dispensing errors that occurred when oxalic acid was unintentionally substituted for a similarly appearing Epsom salts solution.[28] Prior to 1927, however, â€œpoisonâ€• warning labels were not

required on chemical containers, regardless of toxicity or availability. The 1927 Caustic Act was spearheaded by the efforts of Dr. Chevalier Jackson, an otolaryngologist, who showed that unintentional exposures to household caustic agents were an increasingly frequent cause of severe oropharyngeal and gastrointestinal burns. Under this statute, for the first time, alkali and acid-containing products had to clearly display a â€œpoisonâ€• warning label.[140]

The most pivotal regulatory initiative in the United States prior to World War II, and perhaps the most significant American toxicologic regulation of the 20th century, was the Federal Food, Drug, and Cosmetic Act of 1938. Although the Food and Drug Administration (FDA) had been established in 1930, and legislation to strengthen the 1906 Pure Food and Drug Act was considered by Congress beginning with President Franklin Roosevelt's first inauguration in 1933, by 1938 proposed revisions still had not been passed. The Elixir of Sulfanilamide tragedy in 1938 (Chap. 2) claimed the lives of 105 people who ingested a prescribed liquid preparation of the antibiotic sulfanilamide inappropriately dissolved in diethylene glycol. This event finally provided the catalyst for legislative intervention.[100 , 147] Prior to the elixir disaster, proposed legislation called only for the banning of false and misleading drug labeling and for the outlawing of dangerous drugs without mandatory drug safety testing. After the tragedy, the 1938 proposal was strengthened, requiring assessment of drug safety prior to marketing, and ultimately passed.

The Development of Poison Control Centers

World War II led to the rapid proliferation of new drugs and chemicals in the marketplace and in the household.[38] At the same time, suicide as a leading cause of death from these agents was recognized.[10] Both of these factors led the medical community to

develop a response to the serious problems of both unintentional and intentional poisonings. In Europe during the late 1940s, special toxicology wards were organized in Copenhagen and Budapest,[58] and a poison information service was begun in the Netherlands

(Table 1-5).[144] A 1952 American Academy of Pediatrics study revealed that more than 50% of childhood â€œaccidentsâ€• in the United States were the result of unintentional poisonings.[60] This study led to the opening of the first US poison control center in Chicago in 1953, under the leadership of Dr. Edward Press.[117] Press believed that it had become extremely difficult for the individual physician to keep abreast of product information, toxicity, and treatment for the rapidly increasing number of potentially poisonous household products. This initial center was organized as a cooperative effort among the departments of pediatrics at several Chicago medical schools, with the goal of collecting and disseminating product information to inquiring physicians, mainly pediatricians.[117]

1906
Pure Food and Drug Act
Early regulatory initiative. Prohibits interstate commerce of misbranded and adulterated foods and drugs.
1914
Harrison Narcotics Act
First federal law to criminalize the nonmedical use of drugs. Taxed and regulated distribution and sale of narcotics (opium, opium derivatives, and cocaine). It required doctors, pharmacists, and others who prescribed narcotics to register and pay a tax.
1927
Federal Caustic Poison Act
Mandated labeling of concentrated caustics.
1930
Food and Drug Administration (FDA) established

Successor to the Bureau of Chemistry; promulgation of food and drug regulations.

1937

Marijuana Tax Act

Applied controls to marijuana similar to those applied to narcotics.

1938

Federal Food, Drug, and Cosmetic Act

Required toxicity testing of pharmaceuticals prior to marketing.

1948

Federal Insecticide, Fungicide, and Rodenticide Act

Provided federal control for pesticide sale, distribution, and use.

1951

Durham-Humphrey Amendment

Restricted many therapeutic drugs to sale by prescription only

1960

Federal Hazardous Substances Labeling Act

Mandated prominent labeling warnings on hazardous household chemical products.

1962

Kefauver-Harris Drug Amendments

Required drug manufacturer to demonstrate efficacy before marketing

1963

Clean Air Act

Regulated air emissions by setting maximum pollutant standards.

1966

Child Protection Act

Banned hazardous toys when adequate label warnings could not be written.

1970

Comprehensive Drug Abuse and Control Act

Replaced and updated all previous laws concerning narcotics and other dangerous drugs.

1970

Environmental Protection Agency (EPA) established
Established and enforced environmental protection standards.
1970
Occupational Safety and Health Act (OSHA)
Enacted to improve worker and workplace safety. Created National Institute for Occupational Safety and Health (NIOSH) as research institution for OSHA.
1970
Poison Prevention Packaging Act
Mandated child-resistant safety caps on certain pharmaceutical preparations to decrease unintentional childhood poisoning.
1972
Clean Water Act
Regulated discharge of pollutants into US waters.
1972
Consumer Product Safety Act
Established Consumer Product Safety Commission to reduce injuries and deaths from consumer products.
1972
Hazardous Material Transportation Act
Authorized the Department of Transportation to develop, promulgate, and enforce regulations for the safe transportation of hazardous materials.
1973
Drug Enforcement Administration (DEA) created
Successor to the Bureau of Narcotics and Dangerous Drugs; charged with enforcing federal drug laws.
1973
Lead-based Paint Poison Prevention Act
Regulated the use of lead in residential paint. Lead in some paints later banned by Congress in 1978.
1974
Safe Drinking Water Act
Set safe standards for water purity.

1976

Resource Conservation and Recovery Act (RCRA)

Authorized EPA to control hazardous waste from the â€œcradle-to-grave,â€• including the generation, transportation, treatment, storage, and disposal of hazardous waste.

1976

Toxic Substance Control Act

Emphasis on law enforcement. Authorized EPA to track 75,000 industrial chemicals produced or imported into the United States. Required testing of chemicals that pose environmental or human health risk.

1980

Comprehensive Environmental Response Compensation and Liability act (CERCLA)

Set controls for hazardous waste sites. Established trust fund (Superfund) to provide cleanup for these sites. Agency for Toxic Substances and Disease Registry (ATSDR) created.

1983

Federal Anti-Tampering Act

Response to cyanide-Tylenol deaths. Outlawed tampering with packaged consumer products.

1986

Controlled Substance Analogue Enforcement Act

Instituted legal controls on analog (designer) drugs with chemical structures similar to controlled substances.

1986

Drug-Free Federal Workplace Program

Executive order mandating drug testing of federal employees in sensitive positions.

1986

Superfund Amendments and Reauthorization Act (SARA)

Amendment to CERCLA. Increased funding for the research and cleanup of hazardous waste (SARA) sites.

1988

Labeling of Hazardous Art Materials Act	Required review of all art materials to determine hazard potential and mandated warning labels for hazardous materials.
1994	
Dietary Supplement Health and Education Act	Permitted dietary supplements including many herbal preparations to bypass FDA scrutiny.
1997	
FDA Modernization Act	Accelerated FDA reviews, regulated advertising of unapproved uses of approved drugs
2002	
The Public Health Security and Bioterrorism Preparedness and Response Act	Tightened control on biologic agents and toxins; increased safety of the US food and drug supply, and drinking water; and strengthened the Strategic National Stockpile.

Date Federal Legislation Intent

TABLE 1-4. Protecting Our Health: Important US Regulatory Initiatives Pertaining to Xenobiotics Since 1900

By 1957, 17 poison control centers were operating in the United States.[38] With the Chicago center serving as a model,

these early centers responded to physician callers by providing ingredient and toxicity information about drug and household products, and making treatment recommendations. Records were kept of the calls, and preventive strategies were introduced into the community. As more poison control centers opened, a second important function, providing information to callers from the general public, became increasingly commonplace. The physician

pioneers in poison prevention and poison treatment were predominantly pediatricians who focused on unintentional childhood ingestions.[1][2][3]

1949
First toxicology wards open in Budapest and Copenhagen
1949
First poison information service begins in the Netherlands
1952
American Academy of Pediatrics study shows that 51% of children's â€œaccidentsâ€• are the result of the ingestion of potential poisons
1953
First US poison control center opens in Chicago
1957
National Clearinghouse for Poison Control Centers established
1958
American Association of Poison Control Centers (AAPCC) founded
1961
First Poison Prevention Week
1963
Initial call for development of regional Poison Control Centers (PCCs)
1964
Creation of European Association for PCCs
1968
American Academy of Clinical Toxicology (AACT) established
1972
Introduction of microfiche technology to poison information
1974
American Board of Medical Toxicology (ABMT) established
1978
AAPCC introduces standards of regional designation
1983
First examination given for Specialist in Poison Information (SPI)

Year	Milestone
1985	American Board of Applied Toxicology (ABAT) established
1992	Medical Toxicology recognized by American Board of Medical Specialties (ABMS)
1994	First ABMS examination in Medical Toxicology
2000	Accreditation Council for Graduate Medical Education (ACGME) approval of residency training programs in Medical Toxicology
2000	Poison Control Center Enhancement and Awareness Act
2004	Institute of Medicine (IOM) Report on the future of poison centers is released calling on a greater integration between public health sector and poison control services

TABLE 1-5. Milestones in the Development of Medical Toxicology

During these early years in the development of poison control centers, each center had to collect its own product information, which was a laborious, and often redundant, task.[37] In an effort to coordinate poison control center operations and to avoid unnecessary duplication, Surgeon General Dr. James Goddard responded to the recommendation of the American Public Health Service and established the National Clearinghouse for Poison Control Centers in 1957.[98] This organization, placed under the Bureau of Product Safety of the Food and Drug Administration, disseminated 5-inch by 8-inch index cards containing poison information to each center to help standardize poison center information resources. The Clearinghouse also collected and

tabulated poison data from each of the centers.

Between 1953 and 1972, a rapid, uncoordinated proliferation of poison control centers occurred in the United States.[95] In 1962, there were 462 poison control centers.[1] By 1970, this number had risen to 590,[87] and by 1978, there were 661 poison control centers in the United States, including 100 centers in the state of Illinois.[129] The nature of calls to centers changed as lay public-generated calls began to outnumber physician-generated calls. Recognizing the publicity value and strong popular support associated with poison centers, some hospitals started poison control centers for public relations reasons without adequately recognizing or providing for the associated responsibilities. Unfortunately, many of these centers offered no more than a part-time telephone service located in the back of the emergency department or pharmacy, staffed by poorly trained personnel.[129]

Despite the growing pains of the poison control services during this period, there were many significant achievements. A dedicated group of physicians and other healthcare professionals began devoting an increasing proportion of their time to matters pertaining to poisoning. In 1958, the American Association of Poison Control Centers (AAPCC) was founded to promote closer cooperation between poison centers, to establish uniform standards, and to develop educational programs for the general public and other healthcare professionals.[60] Annual research meetings were held, and important legislative initiatives were stimulated by the organization's efforts.[98] Examples of such legislation include the Federal Hazardous Substances Labeling Act of 1960, which improved product labeling; the Child Protection Act of 1966, which extended labeling statutes to pesticides and other hazardous substances; and the Poison Prevention Packaging Act of 1970, which mandated safety packaging. In 1961, in an attempt to heighten public awareness of the dangers of unintentional poisoning, the third week of March was designated as the Annual National Poison Prevention Week.

Another organization that would become important, the American Academy of Clinical Toxicology (AACT), was founded in 1968 by a diverse group of toxicologists.[33] This group was â€œinterested in applying principles of rational toxicology to patient treatmentâ€• and in improving the standards of care on a national basis.[126] The journal *Clinical Toxicology* , sponsored by AACT, also began publication in 1968. The first modern textbooks of clinical toxicology began to appear in the mid-1950s with the publication of Dreisbach's *Handbook of Poisoning* (1955),[44] Gleason, Gosselin, and Hodge's *Clinical Toxicology of Commercial Products* (1957),[56] and Arena's *Poisoning* (1963).[11] Major advancements in the storage and retrieval of poison information were instituted during these years. Information regarding consumer products initially appeared on index cards distributed regularly to poison centers by the National Clearinghouse. By 1978, more than 16,000 individual product cards had been assembled.[129] The introduction of microfiche technology in 1972 enabled the storage of much larger amounts of data in much smaller spaces at the individual poison centers. Toxifile and POISINDEX, two large drug and poison databases employing microfiche technology, were introduced and gradually replaced the much more limited index card system.[129] During the 1980s, POISINDEX, which had become the standard database, was made more accessible by using CD-ROM technology. Sophisticated information about the most obscure toxins was now instantaneously available by computer at every poison center.

In 1978, the poison control center movement entered an important new stage in its development when the AAPCC introduced standards for regional poison center designation.[95] By defining strict criteria, the AAPCC sought to upgrade poison center operations significantly and to offer a national standard of service. These criteria included employing poison specialists dedicated

exclusively to operating the poison control center 24 hours per day and serving a catchment area of between 1 and 10 million people.

Not surprisingly, this professionalization of the poison center movement led to a rapid consolidation of services, and the number of centers decreased to 62 by 2005. Fifty-one of the 62 centers (82%) are regionally certified. An AAPCC credentialing examination for poison information specialists was inaugurated in 1983 to help ensure the quality and standards of poison center staff.[9]

In 2000, the Poison Control Center Enhancement and Awareness Act was passed by Congress and signed into law by President William Clinton. For the first time, federal funding became available to provide assistance for poison prevention and to stabilize the funding of regional poison control centers. This federal assistance has permitted the establishment of a single nationwide toll-free phone number (800-222-1222) to access poison centers.

A poison control center movement has also evolved in Europe over the last 35 years, but unlike the movement in the United States, from the beginning its growth focused on the development of strong centralized toxicology treatment centers. In the late 1950s, Dr. M. Gaultier in Paris developed an inpatient unit that was dedicated to the care of poisoned patients.[58] In Great Britain, the National Poison Information Service was developed at Guys Hospital in 1963 under Dr. Roy Goulding.[58] Dr. Henry Matthew initiated a regional poisoning treatment center in Edinburgh about the same time,[118] and in 1964, the European Association for Poison Control Centers was formed at Tours, France.[58]

The Rise of Environmental Toxicology and Further Regulatory Protection from Toxic Substances

The rise of the environmental movement during the 1960s can be traced, in part, to the publication of Rachel Carson's *Silent Spring*

in 1962, which revealed the perils of an increasingly toxic environment,[29] and to the increasing awareness among those involved with the poison control movement of the growing menace of toxins in the home environment.[26] Battery casing fume poisoning, which resulted from the burning of discarded lead battery cases, and acrodynia, which resulted from exposure to a variety of mercury-containing products,[39] demonstrated that young children seemed particularly vulnerable to low-dose exposures from certain toxins. Worries about the persistence of pesticides in the ecosystem and the increasing number of chemicals introduced into the environment added to the concern that the environment was a potential source of illness, heralding a drive for additional regulatory protection.

Starting with the Clean Air Act in 1963, laws were passed to help reduce the toxic burden on our environment (see Table 1-4). The establishment of the Environmental Protection Agency in 1970 spearheaded this attempt at protecting our environment, and during the next 10 years, numerous protective regulations were introduced. Among the most important initiatives were the Occupational Safety and Health Act of 1970 that established the Occupational Safety and Health Administration (OSHA). This act mandated that employers provide safe work conditions for their employees. Specific exposure limits to toxic chemicals in the workplace were promulgated. The Consumer Product Safety Commission was created in 1972 to protect the public from consumer products that posed an unreasonable risk of illness or injury. Cancer-producing substances, such as asbestos, benzene, and vinyl chloride, were banned from consumer products as a result of these new regulations. Toxic waste disasters at Love Canal, New York, and Times Beach, Missouri, led to the passing of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA, also known as the Superfund) in 1980. This fund would help to pay for cleanup of hazardous substance releases that posed a potential threat to public health. The

Superfund legislation also led to the creation of the Agency for Toxic Substances and Disease Registry (ATSDR) a federal public health agency that is charged with determining the nature and extent of health problems at Superfund sites and advising the US Environmental Protection Agency and state health and environmental agencies on the need for clean-up and other actions to protect the public's health. In 2003, ATSDR became part of the National Center for Environmental Health of the Centers for Disease Control.

Medical Toxicology Comes of Age

Over the last 25 years, the primary specialties of medical toxicologists have changed. The development of emergency medicine and preventive medicine as medical specialties led to the training of more physicians with a dedicated interest in toxicology. By the early 1990s, emergency physicians accounted for more than half the number of medical toxicologists.[43] The increased diversity of medical toxicologists with primary training in emergency medicine, pediatrics, preventive medicine, or internal medicine has helped to broaden the goals of poison control centers and medical toxicologists beyond the treatment of acute unintentional childhood ingestions. The broad scope of medical toxicology now includes a much wider array of toxic exposures including acute and chronic, adult and pediatric, unintentional and intentional, occupational and environmental.

The development of medical toxicology as a medical subspecialty began in 1974, when the AACT established the American Board of Medical Toxicology (ABMT) to recognize physician practitioners of medical toxicology.[7] From 1974 to 1992, 209 physicians obtained board certification from the ABMT. Formal subspecialty recognition of medical toxicology by the American Board of Medical Specialties (ABMS) was granted in 1992, and a conjoint subboard with representatives from the American Board of Emergency Medicine,

American Board of Pediatrics, and American Board of Preventive Medicine was created. The first ABMS-sponsored examination in medical toxicology was offered in 1994. By 2004, more than 300 physicians were board-certified in medical toxicology by the ABMT and/or ABMS. The American College of Medical Toxicology was founded in 1994 as a physician-based organization designed to advance clinical, educational, and research goals in medical toxicology. In 1999, the Accreditation Council of Graduate Medical Education (ACGME) in the United States formally recognized postgraduate education in medical toxicology, and by 2004, 24 training programs had been approved.

During the 1990s in the United States, some medical toxicologists began to work on establishing regional toxicology treatment centers. Adapting the European model, toxicology treatment centers would serve as referral centers for patients requiring advanced toxicologic evaluation and treatment. Goals of such inpatient regional centers included enhancing care of the poisoned patient, strengthening toxicology training, and facilitating research. The evaluation of the clinical efficacy and fiscal viability of such programs is ongoing.

The professional maturation of advanced practice pharmacists and nurses with a primary interest in clinical toxicology has also

taken place over the past two decades. In 1985, the AACT established the American Board of Applied Toxicology (ABAT), to administer a certifying examination for nonphysician practitioners of medical toxicology who meet their rigorous standards.[6] By 2004, more than 70 toxicologists were certified by this board, most of whom held either a PharmD or a PhD in pharmacology or toxicology.

Recent Poisonings and Poisoners

Although accounting for just a tiny fraction of all homicidal deaths

(0.16% in the United States), notorious lethal poisonings continued throughout the 20th century (Table 1-3).[2]

In England, Graham Frederick Young developed a macabre fascination with poisons.[75] In 1971, at age 14 he killed his stepmother and other family members with arsenic and antimony. Sent away to a psychiatric hospital, he was released at age 24 years, when he was no longer considered to be a threat to society. Within months of his release he again engaged in lethal poisonings, killing several of his coworkers with thallium. Ultimately, he died in prison in 1990.

In 1978, Georgi Markov, a Bulgarian defector living in London, developed multisystem failure and died 4 days after having been stabbed by an umbrella carried by an unknown assailant. The postmortem examination revealed a pinhead-sized metal sphere embedded in his thigh where he had been stabbed. Investigators hypothesized that this sphere had most likely carried a lethal dose of ricin into the victim.[36] This theory was greatly supported when ricin was isolated from the pellet of a second victim who was stabbed under similar circumstances.

In 1982, deliberate tampering with nonprescription acetaminophen preparations with potassium cyanide caused 7 deaths in Chicago.[45] Because of this tragedy, packaging of nonprescription medications was changed to decrease the possibility of future product tampering.[103] The perpetrator(s) were never apprehended, and other deaths from nonprescription product tampering were reported in 1991.[30]

In 1998, Judias Buenoano, known as the â€œblack widow,â€• was executed for murdering her husband with arsenic in 1971 in order to collect insurance money. She was the first female executed in Florida in 150 years. The fatal poisoning had remained undetected until 1983, when Buenoano was accused of trying to murder her fiancÃ© with arsenic and by car bombing. Exhumation of the husband's body, 12 years after he died, revealed substantial

amounts of arsenic in the remains.[3]

Healthcare providers have been implicated in several poisoning homicides. An epidemic of mysterious cardiopulmonary arrests at the Ann Arbor Veterans Administration Hospital in Michigan, in July and August 1975, was attributed to the homicidal use of pancuronium by two nurses.[139] Intentional digoxin poisoning by hospital personnel may have explained some of the increased number of deaths on a cardiology ward of a Toronto pediatric hospital in 1981, but the cause of the high mortality rate remained unclear.[23] In 2000, an English general practitioner Harold Shipman was convicted of murdering 15 female patients with heroin and may have murdered as many as 297 patients during his 24-year career. These recent revelations prompted calls for strengthening the death certification process, for improving preservation of case records, and for better procedures for monitoring controlled drugs.[67]

Also in 2000, an American physician Michael Swango pleaded guilty to the charge of poisoning a number of patients under his care during his residency training. Succinylcholine, potassium chloride, and arsenic were some of the agents he used to kill his patients.[137] Attention to more careful physician credentialing and to maintenance of a national physician database arose from this case because the poisonings occurred at several different hospitals across the country. Continuing concerns about health care providers acting as serial killers is highlighted by a recent case in New Jersey where a nurse Charles Cullen was found responsible for killing patients with digoxin.[17]

By the end of the 20th century, 24 centuries after Socrates was executed by poison hemlock, the means of implementing capital punishment had come full circle. Government-sanctioned execution in the United States again favored the use of a â€œstateâ€• poison: this time, the combination of sodium thiopental, pancuronium, and potassium chloride.

The use of a poison to achieve a political end resurfaced in December 2004 when it was announced that the Ukrainian presidential candidate Viktor Yushchenko was poisoned with the potent dioxin, 2,3,7,8-tetrachlorodibenzo-*p* -dioxin (TCDD).[131] The dramatic development of chloracne over the face of this public person during the previous several months suggested dioxin as a possibly culprit. Given the paucity of reports of acute dioxin poisoning, however, it wasn't until laboratory tests confirmed that Yushenko's dioxin levels were more than 6000 times normal that this diagnosis was confirmed.

Medical Errors

In late 1999, the problem of medical errors became a highly visible issue in the United States with the publication and subsequent reaction to an Institute of Medicine (IOM) report suggesting that 44,000 to 98,000 fatalities each year were the result of medical errors.[80] Many of these errors were attributed to preventable medication errors. The IOM report focused on the fact that errors usually resulted from system faults and not solely from the carelessness of individuals.

Several recent, highly publicized, medication errors received considerable public attention and provided a stimulus for the initiation of change in policies and systems. Ironically, all of the cases occurred at nationally preeminent university teaching hospitals. In 1984, 18-year-old Libby Zion died from severe hyperthermia soon after hospital admission. Although the cause of her death was likely multifactorial, drugâ€“drug interactions and the failure to recognize and appropriately treat her agitated delirium also contributed to her death.[14] State and national guidelines for closer house staff supervision, improved working conditions, and a heightened awareness of consequential drugâ€“drug interactions resulted from the medical, legislative, and legal issues of this case. In 1994, a prominent health

journalist for the *Boston Globe* , Betsy Lehman, was the unfortunate victim of another preventable dosing error when she inadvertently received four times the dose of the chemotherapeutic agent cyclophosphamide as part of an experimental protocol.[78] Despite treatment at a world-renowned cancer center, multiple physicians, nurses, and pharmacists failed to notice this erroneous medication order. An overhaul of the medication-ordering system was implemented at that institution after this tragic event.

Another highly publicized death occurred in 1999, when 18-year-old Jesse Gelsinger died after enrolling in an experimental gene-therapy study. Mr. Gelsinger, who had ornithine transcarbamylase deficiency, died from multiorgan failure 4 days after receiving, by hepatic infusion, the first dose of an engineered

adenovirus containing the normal gene. While this unexpected death was not the direct result of a dosing or drugâ€“drug interaction error, the FDA review concluded that major research violations had occurred, including failure to report adverse effects with this therapy in animals and earlier clinical trials and to properly obtain informed consent.[132] In 2001, Ellen Roche, a 24-year-old healthy volunteer in an asthma study at John Hopkins University, developed a progressive pulmonary illness and died 1 month after receiving 1 g of hexamethonium by inhalation as part of the study protocol.[136] Hexamethonium, a ganglionic blocker, was once used to treat hypertension but was removed from the market in 1972. The investigators were cited for failing to indicate on the consent form that hexamethonium was experimental and not FDA approved. Calls for additional safeguards to protect patients in research studies resulted from these cases.

Chemical Terrorism and Preparedness

The terrorist attacks on the World Trade Center and the Pentagon

on September 11, 2001, and the mailing of letters containing lethal amounts of anthrax in October 2001, resulted in profound changes in preparedness strategies against future terrorist strikes. Defending against biologic and chemical terrorism suddenly took on a much heightened sense of urgency. The asymmetric nature of the terrorism menace has led to increasing concerns that traditional industrial chemicalsâ€”so-called chemical agents of opportunityâ€”may pose a more likely threat than a military chemical warfare agent attack. Responding to these events, medical toxicologists and poison control centers are playing an increasingly visible role in terrorism preparedness. Medical toxicologists from both emergency response and public health backgrounds provide leadership in preparedness planning and training.

These events have led to a new realization that poison control centers serve an essential public health function that extends significantly beyond the traditional prevention of childhood poisonings. Responding to these new challenges an IOM report released in 2004 calls for a more formal integration of poison center services into local, state, and federal public health preparedness and response.[70]

Summary

Since the dawn of recorded history, toxicology has had a great impact on human events. And although over the millennia the important poisons of the day have changed to some degree, toxic substances continue to challenge our safety. The era of poisoners for hire may have long ago reached its pinnacle, but problems with drug abuse, intentional self-poisoning, exposure to environmental chemicals, and the potential for biological and chemical terrorism continues to challenge us. Unfortunately, knowledge acquired by one generation is often forgotten or discarded inappropriately by the next generation, leading to a cyclical historic course. This

historic review is meant to describe the past and to better prepare toxicologists and society for the future.

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Antidotes in Depth

Antiquated Antidotes

Paul M. Wax

While the judicious use of certain antidotes (eg, *N* -acetylcysteine, naloxone, pyridoxine) is critically important in the management of select poisoned patients, other antidotes do not necessarily offer a distinct clinical advantage and may create additional problems (eg, flumazenil, physostigmine). A perpetual search for better and improved antidotes features prominently in the history of toxicology. Unfortunately, many of the â€œantidotal breakthroughsâ€• over the years have not lived up to their promise (Table A1-1). A number of these antidotes, such as caffeine, are ineffective. Others, such as propylene glycol, were insufficiently tested or were replaced by â€œsafer,â€• more effective treatment such as paraldehyde.[13] Most troubling, the use of some of these agents, such as analeptics and copper sulfate, actually worsened the clinical situation. Unfortunately, just as the various classic theriac preparations remained popular into the 20th century, the use of many of these â€œmodern antidotesâ€• had persisted long after scientific investigation demonstrated their ineffectiveness. An emphasis on physiologic antagonism with antidotes, such as analeptics, has often taken precedence over good supportive care. Not surprisingly, the use of modern-day

theriacs, such as the â€œuniversal antidote,â€• persisted until quite recently, despite a lack of serious scientific support. This section highlights some of the critical changes in poison management during the last century.

Analeptics

One of the most interesting changes in poison management took place during the 1940s and 1950s with regard to the use of analeptics in the treatment of barbiturate overdose.[58] Analeptics are nonspecific arousal agents and include such stimulants as strychnine, camphor, caffeine, picrotoxin, pentylenetetrazol, nikethamide, amphetamine, and methylphenidate. Barbiturates, the first widely available sedative-hypnotics, were introduced in the early 20th century. Within a few years they became the most common cause of serious overdose.[6] In the 1920s, barbiturate overdose management recommendations still included blood-letting techniques.[41] By the next decade, as interest in principles of antagonism between stimulants and depressants became widespread, much attention was focused on the use of analeptic agents to combat the sedative effects of barbiturates. Proponents of analeptics argued that because the effects of cocaine intoxication appeared to be neutralized by barbiturates, a reciprocal approachâ€”treating depressant overdoses with stimulantsâ€”should also be effective.[41] The principal goal of analeptic therapy was to awaken the patient as soon as possible.

Numerous analeptic agents were recommended over the years. Prior to the development of the first synthetic analeptics in the late 1920s, naturally occurring stimulants, such as caffeine, lobeline, strychnine, cocaine, and camphor, were utilized for this purpose. According to Leschke's *Clinical Toxicology* , a standard textbook published in 1934, the most effective remedy for the treatment of a sedative-hypnotic overdose was the intrathecal injection of 10% camphorated oil.[37]

Picrotoxin, obtained from the berries of the *Cocculus indicus* plant, was first suggested as an antagonist to morphine in 1847.[35] After a series of animal studies in the early 1930s, picrotoxin was enthusiastically endorsed as the analeptic of choice.[40] Picrotoxin acts as a Î³-aminobutyric acid type A ($GABA_A$) and type C ($GABA_C$) receptor antagonist and as a glycine-receptor antagonist facilitating excitatory neurotransmission.[21] Although picrotoxin remains one of the most powerful CNS and respiratory stimulants in our pharmacopeia, it is a proconvulsant.

The subsequent introduction of synthetic analeptics, such as pentylenetetrazol (Metrazol, Cardiazol) and nikethamide (Coramine), increased the growing dependence on analeptics as the major treatment modality for barbiturate overdose.[31, 34, 42] During his search for an effective camphor substitute, Schmidt synthesized pentylenetetrazol, the first synthetic analeptic, in 1924, and it was initially introduced as a cardiac stimulant.[57] Mechanistically, it reduces GABAergic inhibition and interacts with picrotoxin-binding sites. It may also work by changing extraneuronal potassium permeability, thereby partially depolarizing neuronal membranes and increasing excitability. Pentylenetetrazol was employed as a CNS stimulant in the treatment of depressant overdoses from the 1930s through the 1960s,[19, 31] but was considered less effective than picrotoxin or strychnine.

Nikethamide was also used as a cardiac and respiratory stimulant and was reputed to be helpful in overcoming the respiratory depression of morphine, sedative-hypnotics, and volatile anesthetics.[42] Further experience showed that it was a less efficacious analeptic than either picrotoxin or pentylenetetrazol.[23] Its exact mechanisms of enhancing excitation are unknown.

Analeptic treatment strategies were often referred to as â€œvery energetic,â€• because large doses of multiple analeptics were frequently used.[45] As recently as the 1950s, newer analeptics,

such as bemegride, were being introduced as the â€œreal antidoteâ€• to barbiturate overdoses.[53] During this time, methylphenidate was also used in the treatment of barbiturate overdoses. In 1967, one enthusiastic methylphenidate proponent emphasized, â€œDon't let comatose patients remain comatose after barbiturate overdose. Methylphenidate will waken them safely.â€•[42] Toxicology textbooks published in the 1950s and 1960s continued to recommend caffeine, picrotoxin, and nikethamide as useful analeptic agents.[15,22,38] Subconvulsive electric shock therapy was also advocated as an alternative or adjunct to these chemical convulsants during this period.[48]

Unfortunately, many adverse effects occurred with the use of these analeptics, including hyperthermia, dysrhythmias, seizures, and psychoses.[33,42,47] It gradually became evident that analeptic therapy, despite its theoretic benefits, offered no real advantage, did not reduce mortality, and, placed the patient at risk for significant iatrogenic complications.[9] A different strategy was required.

Beginning in the mid-1940s, a distinctive approach to barbiturate overdose was pioneered by Eric Nilsson and Carl Clemmesen at the Bispebjerg Hospital in Copenhagen, Denmark.[9,44] This treatment regimen, known as the *Scandinavian method*, abandoned the use of analeptics in the treatment of barbiturate overdoses. Instead

of primarily emphasizing the termination of coma, attention was directed at intensive supportive therapy with respiratory ventilation, oxygenation, and cardiovascular support. This strategy was analogous to the postanesthetic recovery room care provided to surgical patients. Using this â€œrevolutionaryâ€• approach, barbiturate overdose mortality significantly dropped from approximately 20% with stimulation therapy to 1â€“2% with the Scandinavian method.[9]

Analeptic

Amphetamine
Sedative overdose
Seizures, hyperthermia, aspiration
Bemegride
Sedative overdose
Seizures, hyperthermia, aspiration
Caffeine
Sedative overdose
Seizures, hyperthermia, aspiration
Camphorated oil
Sedative overdose
Seizures, hyperthermia, aspiration
Lobeline
Sedative overdose
Seizures, hyperthermia, aspiration
Nikethamide (Coramine)
Sedative overdose
Seizures, hyperthermia, aspiration
Pentylenetetrazol (Metrazol)
Sedative overdose
Seizures, hyperthermia, aspiration
Picrotoxin
Sedative overdose
Seizures, hyperthermia, aspiration
Strychnine
Sedative overdose
Seizures, hyperthermia, aspiration
Adsorbent
Universal antidote
Gastrointestinal decontamination
Ineffective; tannic acid hepatotoxicity
Burnt toast
Gastrointestinal decontamination
Ineffective

Complexing agent
Sodium phosphate (Phospho-Soda)
Iron
Hyperphosphatemia
Emetic
Apomorphine
Gastric emptying
CNS depression, aspiration
Copper sulfate
Gastric emptying
Caustic; increased copper load
Mechanical stimulation
Gastric emptying
Oropharyngeal trauma; ineffective
Mustard powder
Gastric emptying
Ineffective
Salt water
Gastric emptying
Hypernatremia
Tartar emetic
Gastric emptying
GI toxicity
Zinc sulfate
Gastric emptying
GI toxicity
Metal antidote
Ascorbic acid
Lead, arsenic
Ineffective
Calcium bromide
Lead
Ineffective
Ferric hydroxide/magnesium hydroxide

Arsenic
Ineffective
Potassium ferrocyanide
Copper
Ineffective
Potassium iodide
Lead
Ineffective
Sodium formaldehyde sulfoxylate
Mercury bichloride
Ineffective
Miscellaneous
Acetazolamide
Salicylate
Acidemia; increased CNS salicylates
Hypochlorites
Snakebites
Ineffective
Potassium permanganate
Alkaloids (morphine, strychnine, aconite)
Caustic
Propylene glycol
Phenolphthalein

Raw rabbit brain
Amanita phalloides
Ineffective
Neutralizing agent
Calcium carbonate
Acid
Exothermic reaction; gas formation; ineffective
Hydrochloric acid
Alkali
Exothermic reaction; gas formation; ineffective

Lemon juice
Alkali
Exothermic reaction; gas formation; ineffective
Lime water
Acid
Exothermic reaction; gas formation; ineffective
Magnesium hydroxide
Acid
Exothermic reaction; gas formation; ineffective
Sodium bicarbonate
Acid
Exothermic reaction; gas formation; ineffective
Vinegar
Alkali
Exothermic reaction; gas formation; ineffective
Sedative
Chloroform
Delirium tremens, strychnine
Hepatotoxin, dysrhythmias
Digitalis
Delirium tremens
Ineffective
Ethanol
Delirium tremens
Difficult to titrate; metabolic abnormalities
Ether
Delirium tremens; agitation/seizures
Difficult to administer; irritating
Paraldehyde
Delirium tremens
Acidosis; difficult to administer
Sodium bromide
Delirium tremens
Difficult to use; bromism

Tribromoethanol (Avertin)
Agitation/seizures
Sedation

Type of Antidote	Therapeutic Agent	Uses	Adverse Effects

TABLE A1-1. Antiquated Antidotes

Early Treatments of Opioid Overdoses

Prior to the 1950s, opioid overdose was treated with many of the same analeptic agents. In the early 1950s, an important development in the history of poison management occurred when two

specific opioid antidotes were introduced: nalorphine (Nalline) and levallorphan (Lorfan).[16] These drugs were capable of reversing the respiratory effects of an opioid overdose by blocking opioid receptors. Nalorphine was also routinely administered to determine the presence or absence of opioids in suspected opioid abusers. This test, known as the *Nalline test* , was used as a monitoring tool in drug abuse programs.[25] The test was considered positive if it precipitated signs of opioid withdrawal such as pupillary dilation.

Unfortunately, neither nalorphine nor levallorphan was a pure opioid antagonist. Instead, the mixed agonistâ€“antagonist properties of these drugs significantly limited their usefulness. Respiratory depression could be potentiated, especially in opioid-free patients. This was most likely to occur when these drugs were administered to comatose patients with mild hypoventilation who had overdosed on sedative-hypnotics or ethanol.

Naloxone, which was introduced in the 1970s, is a much safer drug

because of its pure opioid antagonistic properties. It has completely replaced nalorphine and levallorphan in the treatment of opioid overdoses.[18] Naloxone has no agonist properties, does not cause any additional respiratory depression, regardless of the ingestion, is short-acting and safe to use for patients with coma following an undefined overdose. In addition, it is useful in treating patients with an overdose of other mixed agonistâ€“antagonist opioids, such as pentazocine, who do not typically respond to nalorphine.

Outmoded Treatments for Ethanol Withdrawal

The treatment modalities employed in the treatment of ethanol withdrawal have changed considerably over the last 200 years.[17] Until the development of the first inhalational anesthetics in the mid 19th century, opium and, later, morphine were the primary pharmacologic treatments of severe ethanol withdrawal. Unfortunately, this approach was associated with problems related to opioid toxicity in these unmonitored patients. Adjuncts used with the opioids included digitalis that was thought to provide benefit to counteract the adverse cardiac effects associated with ethanol withdrawal. Once the first general anesthetics were introduced, a new treatment approach for delirium tremens was advocated in which ether or chloroform was inhalationally administered to induce sleep for up to 24 hours. Case reports from this time suggested that such an approach was effective and that patients would awaken without further signs of ethanol withdrawal.[30] Other drugs that were employed included the bromide salts but they proved difficult to use and in some cases were associated with the development of bromism.

By the early 20th century, chloral hydrate was routinely administered in the treatment of ethanol withdrawal and opioid use in this setting decreased.[55] Soon thereafter, barbiturates and

paraldehyde also became a mainstay of ethanol withdrawal therapy. While some patients responded well to paraldehyde, it proved very difficult to administer at times and was also associated with the development of metabolic acidosis. It is considerably more toxic than benzodiazepines and is very difficult to titrate because of variable rates of absorption. Other disadvantages include hepatotoxicity, gastritis when given orally, sterile abscesses when given intramuscularly, and proctitis following rectal administration. It also has a notoriously unpleasant odor.[28]

Ethanol administered intravenously or orally also has been used to suppress withdrawal for many years. Recent advocacy for prophylactic use of ethanol in hospitalized patients can be found in the surgical literature.[50] However, there are several problems with the use of ethanol in the treatment of ethanol withdrawal.[27] It has a very short duration of action and is difficult to titrate, and its CNS and hepatotoxicity are well known. Continued intravenous use of ethanol intensifies the biochemical abnormalities associated with ethanol metabolism, shifting energy production toward lactate and ketogenesis. Finally, extravasation of ethanol may cause local tissue necrosis, which in a recent report required excision and grafting.

Other discredited approaches popularized in the 1940s include insulin therapy[49] as a means to replenish glycogen and improve hepatic function, and nonconvulsive electroshock therapy.[7] Gradually, increased attention to adequate hydration, nutrition, vitamin replacement, and proper monitoring, as well as the need for appropriate sedation with cross-tolerant drugs such as the benzodiazepines, became the modern standard for the care of the ethanol-withdrawal patient.

Outdated and Dangerous Emetics

The role of emetics in poison management, both in the home and

at the hospital, has undergone significant transformation over the years. The antimony salt commonly known as tartar emetic had a long history of use as an emetic, as well as a sedative, expectorant, cathartic, and diaphoretic. During the 19th century, tartar emetic was one of the three most widely prescribed drugs, the other drugs being opium and calomel (mercurous chloride).[26] Tartar emetic is no longer recommended for any purpose because of its inherent toxicity.[8]

Standard gastrointestinal decontamination recommendations during the 1960s included mechanical stimulation of the throat and the ingestion of saltwater emetics, or mustard water in the home, and copper sulfate, zinc sulfate, or apomorphine in the hospital.[1, 32] Many authorities recommended mechanical stimulation of the pharynx (finger-down-the-throat technique) as a quick-and-easy home remedy when induction of emesis was desirable.[1, 11] This method, however, is both ineffective and potentially traumatic, and is no longer encouraged.[11] Similarly, the use of saltwater emetics was abandoned after numerous cases of severe salt poisoning resulted from their administration.[4, 14] Mustard powder has never been proven effective.[8] The use of copper sulfate as an emetic[32] also fell out of favor because of its caustic properties, its potential to cause acute copper poisoning, and its unreliability.[29, 54] Zinc sulfate also is no longer used as an emetic.[8]

Until the 1980s, apomorphine was advocated as an emetic.[10, 43] One reason for its use was the thought that it was safer and more effective than copper sulfate.[29] It was supposed to be particularly useful for the combative or uncooperative patient because it could be administered parenterally, it had a rapid onset of action, and in this setting, was frequently used instead of syrup of ipecac.[44] Apomorphine's propensity to cause CNS depression, however, increased the risk of subsequent aspiration and made its use potentially very dangerous. Moreover, a sterile injectable form of apomorphine has not been available in the United States for many years. For all of these reasons, apomorphine is no longer used as

an emetic.[39]

The Universal Antidote

Two other â€œantidotesâ€• that were once commonly used for decontamination but that have fallen into disfavor are the â€œuniversal antidoteâ€• and burnt toast. For many years the universal antidote, sold

under the trade names Unidote and Res-Q, was a medical tradition[46] and was advocated by many textbooks as part of the standard management of the poisoned patient.[15, 22, 38] Commercial preparations consisted of one part magnesium oxide, one part tannic acid, and two parts activated charcoal. An alternative home recipe consisted of milk of magnesia, strong tea, and burnt toast. Combination therapy of this sort was thought to offer a broader spectrum of action than activated charcoal alone. It was theorized that the magnesium oxide would neutralize acids and the tannic acid would precipitate alkaloids and metals.[38] The use of the universal antidote declined by the mid-1980s and is no longer available. Studies demonstrated that activated charcoal was superior to the universal antidote in decreasing absorption[12, 46] and that the decreased efficacy of the universal antidote was caused by tannic acid interfering with activated charcoal's adsorbence of other toxins.[12] Furthermore, the potential hepatotoxicity of tannic acid was increasingly recognized.[46] Although burnt toast had been advocated as an activated charcoal substitute in the home,[3] its use was also abandoned because of its lack of significant adsorbent activity.[36]

Other Antiquated Antidotes

The use of drugs for the chemical restraint of agitated individuals has also undergone significant evolution during the past decades. Depressant agents, such as tribromoethanol (Avertin) and ether,

are no longer used because of the availability of safer alternative agents. Likewise, paraldehyde and ethanol, which were commonly used for the treatment of alcohol withdrawal,[24] have been replaced by the much safer and less toxic benzodiazepines. The use of analeptics to treat the depressive effects of ethanol is also obsolete.[56]

Another change in treatment involves the abandonment of neutralizing agents for caustic ingestions. Until the 1970s, typical recommendations for the treatment of alkali ingestions included the use of vinegar (acetic acid), lemon juice, or, in some cases, dilute hydrochloric acid.[38] Suggestions for neutralizing acid ingestions included the use of magnesium hydroxide, lime water, or calcium carbonate.[38] Because of the extremely rapid onset of action of caustic agents, concerns arose over whether it was already too late to reverse the caustic process. Furthermore, the addition of neutralizing agents could increase the potential for a consequential exothermic reaction and/or gas production.[51] Such reactions in an already weakened hollow viscus may be poorly tolerated and lead to extension of the tissue injury or perforation. For all of these reasons, the use of neutralizing agents is no longer recommended.

Other antiquated antidotes include ferric hydroxide (*antidotum arsenici*), which was used in the treatment of arsenic poisoning. Acetazolamide, which was advocated for alkalinizing the urine in salicylate poisoning,[52] causes a systemic acidemia that can worsen the salicylate toxicity, and is therefore no longer used. The use of sodium phosphate (Phospho-Soda) in the management of iron overdose in an attempt to create insoluble ferrous phosphate has also ceased because of problems with its marginal efficacy and resultant hyperphosphatemia.[20]

Some abandoned antidotes have found new uses. At one time potassium iodide was believed to be helpful as a means to enhance lead excretion, a practice that was later discarded. More recently,

potassium iodide has been touted as a specific blocker of thyroid radioiodine uptake which may reduce the risk of thyroid cancer after radiation exposure.[2]

Finally, enthusiasm has waned for raw rabbit brain, which was recommended as recently as the 1930s as a â€œchance of lifeâ€• for patients with *Amanita phalloides* poisoning.[37] The raw brain approach was pioneered in the early 1800s after it was observed that rabbits could eat poisonous mushrooms without ill effects.[5] Postulating that rabbits had some sort of protective mechanism that neutralized the mushroom toxin, investigators formulated an antidotal concoction consisting of seven rabbit brains and three rabbit stomachs. The preparation was minced and ground into pellets and administered with a sweetener. When patients who received the rabbit brain antidote survived the mushroom poisoning, it was erroneously concluded that these uncontrolled observations provided proof of efficacy.[5]

Many of our current antidotes have not undergone rigorous scientific evaluation regarding efficacy and safety. In time, some of these antidotes will undoubtedly join this list of antiquated antidotes. Lessons learned from the past, such as the abandonment of analeptics, help to optimize present-day patient care and to better prepare us to investigate and evaluate the next generation of antidotes.

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Chapter 2

Toxicologic Plagues and Disasters in History

Paul M. Wax

Throughout history, mass poisonings have caused suffering and misfortune. From the ergot epidemics of the Middle Ages to contemporary industrial disasters, these plagues have had great political, economic, social, and environmental ramifications. Particularly within the last 100 years, as the number of toxins and potential toxins has risen dramatically, toxic disasters have become an increasingly common event. The sites of some of these eventsâ€”Bhopal (India), Chernobyl (Ukraine), Jonestown (Guyana), Love Canal (New York), Minamata Bay (Japan), Seveso (Italy), West Bengal (India)â€”have come to symbolize our increasingly toxic habitat. This chapter provides an overview of some of the most consequential and historically important toxin-associated disasters. Globalization has led to the proliferation of toxic chemicals throughout the world. Many chemical factories are not secure despite their storage of large amounts of potentially lethal chemicals. Given the increasing attention to terrorism preparedness, an appreciation of chemicals as agents of

opportunity for terrorists to employ as weapons has suddenly assumed much greater importance.

Gas Disasters

Inhalation of toxic gases and oral ingestions resulting in food poisoning tend to subject the greatest number of people to adverse consequences of a toxic exposure. Toxic gas exposures may be the result of a natural disaster (volcanic eruption), industrial mishap (fire, chemical release), chemical warfare, or an intentional homicidal or genocidal endeavor (concentration camp gas chamber). Depending on the toxin, the clinical presentation may be acute, with a rapid onset of toxicity (cyanide), or subacute/chronic, with a gradual onset of toxicity (air pollution).

One of the earliest recorded toxic gas disasters resulted from the eruption of Mount Vesuvius near Pompeii, Italy, in 79 A.D. (Table 2-1). Poisonous gases generated from the volcanic activity reportedly killed thousands.[24] A much more recent natural disaster occurred in 1986 in Cameroon, when excessive amounts of carbon dioxide spontaneously erupted from Lake Nyos, a volcanic crater lake.[8] Seventeen hundred human and countless animal fatalities resulted from exposure to this asphyxiant.

A toxic gas leak at the Union Carbide pesticide plant in Bhopal, India, in 1984, resulted in one of the greatest civilian toxic disasters in modern history.[126] An unintended exothermic reaction at this carbaryl-producing plant caused the release of over 24,000 kg of methyl isocyanate. This gas was quickly dispersed through the air over the densely populated area surrounding the factory where many of the workers lived, resulting in at least 2500 deaths and 200,000 injuries.[74] The initial response to this disaster was greatly limited by a lack of pertinent information about the toxicity of this agent as well as the poverty of the residents. A followup study 10 years later showed persistence of small-airway obstruction among survivors.[20] Chronic eye problems also were

reported.[3] Calls for improvement in disaster preparedness and strengthened right-to-know laws regarding potential toxic exposures resulted from this tragedy.[43 , 126]

The release into the atmosphere of 26 tons of hydrofluoric acid at a petrochemical plant in Texas, in October 1987, resulted in 939 people seeking medical attention at nearby hospitals. Ninety-four people were hospitalized, but there were no deaths.[133]

More than any other single toxin, carbon monoxide has been involved with the largest number of toxic disasters. Catastrophic fires, such as the Cocoanut Grove Nightclub fire in 1943, have caused hundreds of deaths at a time, many of them from carbon monoxide poisoning.[27] The 1990 fire at the Happy Land Social Club in the Bronx, New York, claimed 87 victims, including a large number of nonburn deaths,[67] and the 2003 fire at The Station nightclub in West Warwick, Rhode Island, killed 98 people.[109] Carbon monoxide poisoning was a major toxin in many of these deaths, although hydrogen cyanide gas and simple asphyxiation may also have contributed to the overall mortality.

Another notable toxic gas disaster involving a fire occurred at the Cleveland Clinic, Cleveland, Ohio, in 1929, where a fire in the radiology department resulted in 125 deaths.[23] The burning of nitrocellulose radiographs produced nitrogen dioxide, cyanide, and carbon monoxide gases that were thought to be responsible for many of the fatalities. In 2003, at least 243 people died and 10,000 people became ill after a drilling well exploded in Gaogiao, China, releasing hydrogen sulfide and natural gas into the air.[136] A toxic gas cloud covered 25 square kilometers. Ninety percent of the villagers who lived in the village adjoining the gas well died.

The release of a dioxin-containing chemical cloud into the atmosphere from an explosion at a hexachlorophene production factory in Seveso, Italy, in 1976, resulted in one of the most serious exposures to dioxin (2,3,7,8-tetrachlorodibenzo-*p* -dioxin).[42] The

lethality of this agent in animals has caused considerable concern for acute and latent injury from human exposure. Despite this apprehension, chloracne was the only significant clinical finding related to the dioxin exposure at 5-year followup.[107]

Poisonous gas
Pompeii, Italy
79 A.D.
>2000 died from eruption of Mt. Vesuvius
Smog (SO_2)
London
1873
268 deaths from bronchitis
NO_2 , CO, CN
Cleveland Clinic, Cleveland, OH
1929
Fire in radiology department, 125 deaths
Smog (SO_2)
Meuse Valley, Belgium
1930
64 deaths
CO, CN
Cocoanut Grove Night Club, Boston
1942
498 deaths from fire
CO
Salerno, Italy
1944
>500 deaths on train stalled in tunnel
Smog (SO_2)
Donora, PA
1948
20 deaths, thousands ill
Smog (SO_2)

London
1952
4000 deaths attributed to the fog/smog
Dioxin
Seveso, Italy
1976
Unintentional industrial release of dioxin into environment; chloracne
Methyl isocyanate
Bhopal, India
1984
>2000 deaths; 200,000 injuries
Carbon dioxide
Cameroon
1986
>1700 deaths from release of gas from Lake Nyos
Hydrofluoric acid
Texas City, TX
1987
Atmospheric release, 94 hospitalized
CO, ?CN
Happy Land Social Club, Bronx, NY
1990
87 died in fire from toxic smoke
Hydrogen sulfide
Xiaoying, China
2003
243 died and 10,000 became ill from gas poisoning after a gas well exploded
CO, ?CN
West Warwick, RI
2003
98 died in fire

Xenobiotic Location Date Significance

TABLE 2-1. Gas Disasters

Air pollution is another source of toxic gases causing significant disease and death. Complaints about smoky air date back to at least 1272, when King Edward I banned the burning of sea-coal.[124] By the 19th centuryâ€"the era of rapid industrialization in Englandâ€"winter â€œfogsâ€• became increasingly problematic. An 1873 London fog was responsible for 268 deaths from bronchitis. Excessive smog in the Meuse Valley of Belgium in 1930, and in Donora, Pennsylvania, in 1948, was also blamed for excess morbidity and mortality. In 1952, another dense sulfur dioxide-laden smog in London was responsible for 4000 deaths.[65] Both the initiation of long-overdue air-pollution reform in England and Parliament's passing of the 1956 Clean Air Act resulted from this latter â€œfog.â€•

Warfare and Terrorism

Exposure to xenobiotics with the deliberate intent to inflict harm claimed an extraordinary number of victims during the 20th century (Table 2-2). During World War I, chlorine and phosgene gases and the liquid vesicant mustard were used as battlefield weapons, with mustard causing approximately 80% of the chemical casualties.[112] Reportedly, 100,000 deaths and 1.2 million casualties were attributable to these chemical attacks.[24] These toxic exposures resulted in severe airway irritation, acute lung injury, hemorrhagic pneumonitis, skin blistering, and ocular damage. Chemical weapons were used again in the 1980s during the Iran-Iraq war.

Chlorine, mustard gas, phosgene
Ypres, Belgium
1915â€“1918
100,000 dead and 1.2 million casualties from chemicals during

Toxin	Location	Date	Significance
World War I	Europe	1939â€“1945	Millions murdered by Zyklon-B (HCN) gas
CN, CO			
Agent Orange	Vietnam	1960s	Contains dioxin; excess skin cancer
Mustard gas	Iraq-Iran	1982	New cycle of war gas casualties
Possible toxin	Persian Gulf	1991	Gulf War syndrome
Sarin	Matsumoto, Japan	1994	First terrorist attack in Japan using sarin
Sarin	Tokyo	1995	Subway exposure; 5510 people seek medical attention
Dust and other particulates	New York City	2001	World Trade Center collapse from terrorist air strike resulted in persistent cough among some rescuers

TABLE 2-2. Warfare and Terrorism Disasters

The Nazis used poisonous gases during World War II to commit mass murder and genocide. Initially, the Nazis employed carbon monoxide to kill. To expedite the killing process, Nazi scientists developed Zyklon-B gas (hydrogen cyanide gas). As many as 10,000 people per day were killed by the rapidly acting cyanide, and millions of deaths were attributable to the use of these gases.

Agent Orange was widely used as a defoliant during the Vietnam War. This herbicide consisted of a mixture of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4-dichlorophenoxyacetic acid (2,4-D), as well as small amounts of a contaminant, 2,3,7,8-tetrachlorodibenzo-*p* -dioxin (TCDD), better known as dioxin. Over the years a large number of adverse health effects had been attributed to Agent Orange exposure. A 2002 Institute of Medicine study concluded that among Vietnam veterans there is sufficient evidence to demonstrate an association between this herbicide exposure and chronic lymphocytic leukemia, soft-tissue sarcomas, non-Hodgkin lymphomas, Hodgkin disease, and chloracne.[48]

Mass exposure to the very potent organic phosphorus compound sarin occurred in March 1995, when terrorists released this chemical warfare agent in three separate Tokyo subway lines.[91] Eleven people were killed, and 5510 people sought emergency medical evaluation at more than 200 hospitals and clinics in the area.[111] This mass disaster introduced the spectra of terrorism to the modern emergency medical services system, resulting in a

greater emphasis on hospital preparedness, including planning for the psychological consequences of such events. Sarin exposure also resulted in several deaths and hundreds of casualties in Matsumoto, Japan, in June 1994.[79 , 87]

During recent wars and terrorism events, a variety of physical and neuropsychologic ailments have been attributed to possible exposure to toxic agents.[16 , 47] Gulf War syndrome is a

constellation of chronic symptoms, including fatigue, headache, muscle and joint pains, ataxia, paresthesias, diarrhea, skin rashes, sleep disturbances, impaired concentration, memory loss, and irritability, noted in thousands of Persian Gulf War veterans without a clearly identifiable cause. A number of etiologies have been advanced to explain these varied symptoms, including exposure to the smoke from burning oil wells; chemical and biologic warfare agents, including nerve agents; and medical prophylaxis, such as the use of pyridostigmine bromide or anthrax and botulinum toxin vaccines, although the actual etiology remains unclear.[29 , 38 , 47 , 49 , 58 , 123]

Most recently, persistent cough and increased bronchial responsiveness was noted among 8% of New York City Fire Department workers who were exposed to large amounts of dust and other particulates following the collapse of World Trade Center in September 2001.[97] The risk of development of hyperreactivity and reactive airways dysfunction was clearly associated with the intensity of exposure.[6]

Food Disasters

Unintentional contamination of food and drink has led to numerous toxic disasters (Table 2-3). Ergot, produced by the fungus *Claviceps purpurea* , caused epidemic ergotism as the result of eating breads and cereals made from rye that was contaminated by *C. purpurea* . In some epidemics, convulsive manifestations predominated, and in others, gangrenous manifestations predominated.[76] Ergot-induced severe vasospasm was thought responsible for both types of presentations.[75] In 994 A.D., 40,000 people died in Aquitania, France, in one such epidemic.[63] Convulsive ergotism was initially described as a â€œfire which twisted the people,â€• and the term â€œSt. Anthony's fireâ€• (*ignis sacer*) was used to refer to the excruciating burning pain experienced in the extremities that is an early manifestation of

gangrenous ergotism. The events surrounding the Salem, Massachusetts witchcraft trials have also been attributed to the ingestion of contaminated rye. The bizarre neuropsychiatric manifestations exhibited by some of the individuals associated with this event may have been caused by the hallucinogenic properties of ergotamine, a lysergic acid diethylamide (LSD) precursor.[12 , 72]

Ergot
Aquitania, France
994 A.D.
40,000 died in the epidemic
Ergot
Salem, Massachusetts
1692
Neuropsychiatric symptoms may be attributable to ergot
Lead
Devonshire, England
1700s
Colic from cider contaminated during production
Arsenious acid
France
1828
40,000 cases of polyneuropathy from contaminated wine & bread
Lead
Canada
1846
134 men died during the Franklin expedition, possibly because of contamination of food stored in lead cans
Arsenic
Staffordshire, England
1900
Arsenic-contaminated sugar used in beer production
Cadmium
Japan

1939â€“1954
Itai-Itai (â€œouch-ouchâ€•) disease
Hexachlorobenzene
Turkey
1956
4000 cases of porphyria cutanea tarda
Methyl mercury
Minamata Bay, Japan
1950s
Consumption of organic mercury poisoned fish
Triorthocresyl phosphate
Meknes, Morocco
1959
Cooking oil adulterated with turbojet lubricant
Cobalt
Quebec City, Canada and others
1960s
Cobalt beer cardiomyopathy
Methylenedianiline
Epping, England
1965
Jaundice
Polychlorinated biphenyls
Japan
1968
Yusho (â€œrice oil diseaseâ€•)
Methyl mercury
Iraq
1971
>400 deaths from contaminated grain
Polybrominated biphenyls
Michigan
1973
97% of state contaminated through food chain

Polychlorinated biphenyls
Taiwan
1979
Yu-Cheng (â€œoil diseaseâ€•)
Rapeseed oil (denatured)
Spain
1981
Toxic oil syndrome affected 19,000 people
Arsenic
Buenos Aires
1987
Malicious contamination of meat; 61 people underwent chelation
Arsenic
Bangladesh and West Bengal, India
1990sâ€“present
Ground water contaminated with arsenic; millions exposed; 100,000s with symptoms; greatest mass poisoning in history
Nicotine
Michigan
2003
Deliberate contamination of ground beef; 92 people became ill

Xenobiotic Location Date Significance

TABLE 2-3. Food Disasters

During the last half of 20th century, unintentional mass poisoning from food and drink contaminated with toxic chemicals became all too common. One of the more unusual poisonings occurred in Turkey, in 1956, when wheat seed treated with the fungicide hexachlorobenzene and intended for planting was inadvertently used for human consumption. Approximately, 4000 cases of porphyria cutanea tarda were attributed to the ingestion of this wheat seed.[104]

Another example of chemical food poisoning took place in Epping, England, in 1965. In this incident, a sack of flour became contaminated with methylenedianiline when the chemical unintentionally spilled onto the flour during transport to a bakery. Subsequent ingestion of bread baked with the contaminated flour produced hepatitis in 84 people. This outbreak of toxic hepatitis became known as Epping jaundice.[55]

The manufacture of polybromated biphenyls (PBBs) in a factory that also produced food supplements for livestock resulted in the unintentional contamination of a large amount of livestock feed in Michigan in 1973.[13] Significant morbidity and mortality among the livestock population resulted. Increased human tissue levels of PBBs were reported,[134] although human toxicity seemed limited to vague constitutional symptoms and abnormal liver function tests.[2]

The chemical contamination of rice oil in Japan in 1968 caused a syndrome called Yusho (â€œrice oil diseaseâ€•). This occurred when heat-exchange fluid containing polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs) leaked from a heating pipe into the rice oil. More than 1600 people developed chloracne, hyperpigmentation, an increased incidence of liver cancer, and/or adverse reproductive effects. In 1979, 2000 people in Taiwan developed similar clinical manifestations after ingesting another batch of PCB-contaminated rice oil. This latter epidemic was referred to as Yu-Cheng (â€œoil diseaseâ€•).[50]

In another oil contamination epidemic, consumption of illegally marketed cooking oil in Spain, in 1981, was responsible for a mysterious poisoning epidemic that affected more than 19,000 people and resulted in at least 340 deaths. Exposed patients developed a multisystem disorder referred to as toxic oil syndrome (or toxic epidemic syndrome), which was characterized by pneumonitis, eosinophilia, pulmonary hypertension, scleroderma-like features, and neuromuscular changes. Although this syndrome

was associated with the consumption of rapeseed oil denatured with 2% aniline, the exact etiologic agent was never definitively identified.[53 , 121]

In 1999, an outbreak of Coca-Colaâ€“related health complaints occurred in Belgium, when 943 people, mostly children, complained of gastrointestinal symptoms, malaise, headaches, and palpitations, after consuming Coca-Cola.[88] Many of those affected complained of an off-taste or bad odor to the soft drink. Millions of cans and bottles were removed from the market at a cost of $103 million.[88] In some of the bottles the carbon dioxide was contaminated with small amounts of carbonyl sulfide, which hydrolyzes to hydrogen sulfide, and may have been responsible for odor-triggered reactions. Mass psychogenic illness may have contributed to the large number of medical complaints as the concentrations of the carbonyl sulfide (5â€“14 Âµg/L) and hydrogen sulfide (8â€“17 Âµg/L) were very low and unlikely to cause systemic toxicity.[31]

Epidemics of heavy metal poisoning from contaminated food and drink have also occurred throughout history. Epidemic lead poisoning is associated with many different vehicles of transmission, including leaden bowls, kettles, and pipes. A famous 18th-century epidemic was known as the Devonshire colic. Although the exact etiology of this disorder was unknown for many years, later evidence suggested that the ingestion of lead-contaminated cider was responsible.[127]

Intentional chemical contamination of food may also occur. Multiple cases of metal poisoning occurred in Buenos Aires, in 1987, when vandals broke into a butcher's shop and poured an unknown amount of acaricide (45% sodium arsenite solution) over 200 kg of partly minced meat.[101] The contaminated meat was purchased by 718 people. Of 307 meat purchasers who submitted to urine sampling, 49 had urine arsenic levels of 76â€“500 Âµg/dL, and 12 had urine arsenic levels above 500 Âµg/dL (normal urine

arsenic is <50â€“100 Âµg/dL).

In 2003, 92 people became ill after they ingested contaminated ground beef that was deliberately contaminated with a nicotine pesticide by a supermarket employee.[89] These mass poisoning have heightened concerns about food safety and security.

At the end of the 20th century and into the 21st century, what some observers call the greatest mass poisoning in history is occurring in Bangladesh and India's West Bengal State.[22, 81, 98, 116] In Bangladesh alone, 60 million people are routinely drinking arsenic-contaminated ground water. At least 220,000 inhabitants of India's West Bengal have been diagnosed with symptoms of arsenic poisoning.[80] Reported symptoms include melanosis, depigmentation, hyperkeratosis, hepatomegaly, splenomegaly, squamous cell carcinoma, intraepidermal carcinoma, and gangrene.[22] In a country that was long plagued with dysentery, attempts to purify the water supply led to the drilling of millions of wells into the superficial water table. Unknown to the engineers, this water was naturally contaminated with arsenic creating several thousand tube wells with extremely high concentrations of arsenicâ€”up to 40 times the acceptable concentration. Although toxicity from arsenic-contaminated groundwater was previously reported from other areas of the world, including Argentina, China, Mexico, Taiwan (Black Foot disease), and Thailand, the number of people at risk in Bangladesh and West Bengal is by far the largest.

Methyl mercury was the etiologic agent for several recent poisoning epidemics. During the 1950s, a Japanese chemical factory that manufactured vinyl chloride and acetaldehyde routinely discharged mercury into Minamata Bay, resulting in contamination of the aquatic food chain. An epidemic of methyl mercury poisoning ensued as the local people ate the poisoned fish.[96, 122] Chronic brain damage, tunnel vision, deafness, and severe congenital defects were associated with this outbreak.[96]

Another mass epidemic of methyl mercury poisoning occurred in

Iraq in 1971, when the local population consumed homemade bread prepared from wheat seed treated with a methyl mercury fungicide.[5] Six thousand hospital admissions and more than 400 deaths were associated with this disaster. As in the case of the hexachlorobenzene exposure in Turkey 25 years previously, the treated grain, intended for use as seed, was instead used as food.

Contamination of the local water supply with the wastewater runoff from a zinc-lead-cadmium mine in Japan, from 1939 to 1954, was believed responsible for causing Itai-Itai (â€œouch-ouchâ€•) disease, an unusual chronic syndrome manifested by extreme bone pain and osteomalacia. The local water was used for drinking and irrigation of the rice fields. Approximately 200 people who lived along the banks of the Jintsu River developed these peculiar symptoms, which were thought most likely to be caused by the cadmium.[10]

Medicinal Drug Disasters

Illness and death as a consequence of therapeutic drug use occur as sporadic events, usually affecting individual patients, or as mass disasters, affecting multiple (sometimes hundreds or thousands) patients. Sporadic single-patient medication-induced tragedies usually result from errors (Chap. 1) or unforeseen idiosyncratic reactions. Mass therapeutic drug disasters generally have occurred secondary to poor safety testing, a lack of understanding of diluents and excipients, drug contamination, or problems with unanticipated drugâ€“drug interactions or drug toxicity (Table 2-4).

In September and October 1937, more than 100 deaths were associated with the use of one of the early sulfa preparationsâ€”elixir of sulfanilamide-Massengillâ€”that contained 72% diethylene glycol as the vehicle for drug delivery. Little was known about diethylene glycol toxicity at the time, and many cases of renal failure and death occurred.[33] As a result of this

catastrophe, animal drug testing was mandated by the Food, Drug, and Cosmetic Act of 1938 to avoid similar tragedies in the future.[128] Unfortunately, diethylene glycol continues to be sporadically used in other countries as a medicinal diluent, resulting in additional deaths in South Africa (1969), India (1986), Nigeria (1990), Bangladesh (1990â€“1992), and Haiti (1995â€“1996).[129] In the most recent disaster in Haiti, at least 88 children died (case fatality rate 98% for those

who remained in Haiti) after ingesting an acetaminophen elixir formulated with diethylene glycolâ€“contaminated glycerin.[90 , 103]

Thallium
US
1920sâ€“1930s
Treatment of ringworm; 31 deaths
Diethylene glycol
US
1937
Elixir of sulfanilamide; renal failure
Thorotrast
US
1930sâ€“1950s
Hepatic angiosarcoma
Phenobarbital
US
1940â€“1941
Sulfathiazole contaminated with phenobarbital; 82 deaths
Diethylstilbestrol (DES)
US, Europe
1940sâ€“1970s
Vaginal adenocarcinoma in daughters
Stalinon
France
1954

Severe neurotoxicity from triethyltin
Clioquinol
Japan
1955â€“1970
Subacute myelooptic neuropathy (SMON); 10,000 symptomatic
Thalidomide
Europe
1960s
5000 cases of phocomelia
Isoproterenol 30%
Great Britain
1961â€“1967
3000 excess asthma deaths
Pentachlorophenol
US
1967
Used in hospital laundry; 9 neonates ill, 2 deaths
Benzyl alcohol
US
1981
Gasping syndrome
Acetaminophen-cyanide
Chicago
1982
Tampering incident resulted in 7 homicides
L-Tryptophan
US
1989
Eosinophilia-myalgia syndrome
Diethylene glycol
Haiti
1996
Acetaminophen elixir contaminated; renal failure; >88 pediatric deaths

Xenobiotic Location Date Significance

TABLE 2-4. Medicinal Disasters

A lesser-known drug manufacturing event, also involving an early sulfa antimicrobial, occurred in 1940â€“1941, when at least 82 people died from the therapeutic use of sulfathiazole that was contaminated with phenobarbital (Luminal).[117] The responsible pharmaceutical company, Winthrop Chemical, produced both sulfathiazole and phenobarbital, and the contamination likely occurred during the tableting process, because the tableting machines for the two medications were adjacent to each other and were used interchangeably. Each contaminated sulfathiazole tablet contained about 350 mg of phenobarbital (and no sulfathiazole), and the typical sulfathiazole dosing regimen was several tablets within the first few hours of therapy. Twenty-nine percent of the production lot was contaminated. Food and Drug Administration (FDA) intervention was required to assist with the recovery of the suspect sulfathiazole, although 22,000 contaminated tablets were never found.[117]

In the early 1960s, one of the greatest modern-day events occurred with the release of thalidomide as an antiemetic and sedative-hypnotic.[21] Its use as a sedative-hypnotic by pregnant women resulted in about 5000 babies born with severe congenital anomalies.[76] This tragedy was largely confined to Europe, Australia, and Canada, where the drug was initially marketed. Only the length of time required for review and the rigorous scrutiny of new drug applications by the FDA prevented a concurrent disaster in the United States.[73]

A major therapeutic drug event that did occur in the United States involved the widespread use of diethylstilbestrol (DES) for the treatment of threatened and habitual abortions. Despite the lack of convincing efficacy data, as many as 10 million Americans received

DES during pregnancy, or in utero, during a 30-year period, until the drug was prohibited in pregnancy in 1971. Adverse health effects associated with DES use include increased risk for breast cancer in â€œDES mothersâ€• and increased risk of a rare form of vaginal cancer, reproductive tract anomalies, and premature births in â€œDES daughters.â€•[35,41]

Thorotrast (thorium dioxide 25%) is an intravenous radiologic contrast medium that was widely used between 1928 and 1955. Its use was associated with the delayed development of hepatic angiosarcomas, as well as skeletal sarcomas, leukemia, and â€œthorotrastomasâ€•â€”malignancies at the site of extravasated thorotrast.[115,130]

The use of thallium to treat ringworm infections in the 1920s and 1930s also led to needless morbidity and mortality.[36] Understanding that thallium caused alopecia, dermatologists and other physicians prescribed thallium acetate, both as pills and as a topical ointment (Koremlu), to remove the infected hair. A 1934 study found 692 cases of thallium toxicity after oral and topical application and 31 deaths after oral use.[83] Medicinal thallium was subsequently taken off the market.

The â€œStalinon affairâ€• in France, in 1954 involved the unintentional contamination of a proprietary oral medication that was marketed for the treatment of staphylococcal skin infections, osteomyelitis, and anthrax. Although it was supposed to contain diethyltin diiodide and linoleic acid, triethyltin, a potent neurotoxin and the most toxic of organotin compounds, and trimethyltin were present as impurities. Of the approximately 1000 people who received this medication, 217 patients developed symptoms, and 102 patients died.[7,114]

An unusual syndrome, featuring a constellation of abdominal symptoms (pain and diarrhea), followed by neurologic symptoms (peripheral neuropathy and visual disturbances including blindness), was experienced by approximately 10,000 Japanese

between 1955 and 1970, resulting in several hundred deaths.[57] This presentation, subsequently labeled subacute myelooptic neuropathy (SMON), was associated with the use of the gastrointestinal disinfectant clioquinol, known in the West as Entero-Vioform and most often used for the prevention of travelers' diarrhea.[86] In Japan, this drug was referred to as â€œsei-cho-zaiâ€• (â€œactive in normalizing intestinal functionâ€•). It was incorporated into more than 100 nonprescription proprietary medications and was used by millions of people, often for weeks or months. The exact mechanism of toxicity has not been determined, but recent investigators theorize that clioquinol may enhance the cellular uptake of certain metals, particularly zinc, and that the clioquinol-zinc chelate may act as a mitochondrial toxin causing this syndrome.[4] New cases declined rapidly when clioquinol was banned in Japan.

In 1981, a number of premature neonates died with a â€œgasping syndrome,â€• manifested by severe metabolic acidosis, respiratory depression with gasping, and encephalopathy.[34] Prior to the development of these findings, the infants had all received multiple injections of heparinized bacteriostatic sodium chloride solution (to flush their indwelling catheters) and bacteriostatic water (to mix medications), both of which contained 0.9% benzyl alcohol.

Accumulation of large amounts of benzyl alcohol and its metabolite benzoic acid in the blood was thought responsible for this syndrome.[34]

A nursery mass poisoning occurred in 1967, when 9 neonates developed extreme diaphoresis, fever, and tachypnea, without rash or cyanosis. Two fatalities resulted, although the others responded dramatically to exchange transfusion. The illness was traced to sodium pentachlorophenate that had been used as an antimildew agent in the hospital laundry.[93]

In 1989 and 1990, eosinophilia-myalgia syndrome, a debilitating syndrome somewhat similar to toxic oil syndrome, developed in more than 1500 people who had taken the dietary supplement L-tryptophan.[52, 125] These patients presented with disabling myalgias and eosinophilia, often accompanied by extremity edema, dyspnea, and arthralgias. Skin changes, neuropathy, and weight loss sometimes developed. Intensive investigation revealed that all affected patients had ingested L-tryptophan produced by a single manufacturer that had recently introduced a new process involving genetically altered bacteria to improve L-tryptophan production. A contaminant produced by this process probably is responsible for this syndrome.[9] The banning of L-tryptophan by the FDA set in motion the passage of the Dietary Supplement Health and Education Act of 1994. This legislation, which attempted to regulate an uncontrolled industry, inadvertently facilitated industry marketing of dietary supplements bypassing FDA scrutiny.

In recent years, a number of therapeutic drugs, previously approved by the FDA, were withdrawn from the market because of concern about health risks. In a number of cases, the drugs that were withdrawn had been responsible for causing serious drugâ€“drug interactions (astemizole, cisapride, mibefradil, terfenadine).[82] Other drugs were withdrawn because of a propensity to cause hepatotoxicity (troglitazone), anaphylaxis (bromfenac sodium), valvular heart disease (fenfluramine, dexfenfluramine), rhabdomyolysis (cerivastatin), hemorrhagic stroke (phenylpropanolamine), and other adverse cardiac and neurologic effects (ephedra, rofecoxib). One of the most disconcerting drug problems to arise was the development of cardiac valvulopathy and pulmonary hypertension in patients taking the weight-loss drug-combination fenfluramine and phentermine (fen-phen) or dexfenfluramine.[18, 110] The histopathologic features observed with this condition were similar to the valvular lesions associated with ergotamine and carcinoid. Interestingly, appetite suppressant medications, as well as

ergotamine and carcinoid all increase available serotonin.

Triorthocresyl phosphate
US
1930â€“1931
Ginger Jake paralysis
Methanol
Atlanta, GA
1951
Epidemic from ingesting bootleg whiskey
Methanol
Jackson, MI
1979
Occurred in a prison
MPTP
San Jose, CA
1982
Illicit meperidine manufacturing resulting in drug-induced parkinsonism
3-Methyl fentanyl
Pittsburgh, PA
1988
â€œChina-whiteâ€• epidemic
Methanol
Baroda, India
1989
Moonshine contamination; 100 deaths
Fentanyl
New York City
1990
â€œTango and Cashâ€• epidemic
Methanol
New Delhi, India
1991
Antidiarrheal medication contaminated with methanol; >200

deaths
Methanol
Cuttack, India
1992
Methanol-tainted liquor; 162 deaths
Scopolamine
US East Coast
1995â€“1996
325 cases of anticholinergic poisoning in heroin users
Methanol
Cambodia
1998
>60 deaths

Xenobiotic Location Date Significance

TABLE 2-5. Alcohol and Illicit Drug Disasters

While many of these withdrawals involved drugs were only recently approved, the withdrawal of phenylpropanolamine in 2000 removed an over-the-counter agent that was consumed as a component of many cough and cold remedies for several decades. Despite the accumulation of increasing numbers of case reports and case series of medical problems associated with phenylpropanolamine use, drug production was only halted after a well-designed case-control study demonstrated that phenylpropanolamine use was an independent risk factor for hemorrhagic stroke.[51]

Alcohol and Illicit Drug Disasters

Unintended toxic disasters have also resulted from the use of alcohol and other drugs of abuse (Table 2-5). Arsenical neuropathy developed in an estimated 40,000 people in France in 1828, when wine and bread were unintentionally contaminated by

arsenious acid.[71] The use of arsenic-contaminated sugar in the production of beer in England in 1900 resulted in at least 6000 cases of peripheral neuropathy and 70 deaths (Staffordshire beer epidemic).[30]

During the early 20th century, and particularly during prohibition, the ethanolic extract of Jamaican ginger (sold as â€œthe Jakeâ€•) was a popular ethanol substitute in the southern and midwestern United States.[77] It was sold legally because it was considered a medical supplement to treat headaches and aid digestion and was not subject to prohibition. For years, the Jake was sold adulterated with castor oil, but in 1930, as the price of castor oil rose, the Jake was reformulated with an alternative adulterant, triorthocresyl phosphate (TOCP). Little was previously known about the toxicity of this compound, but TOCP proved to be a potent neurotoxin. From 1930 to 1931 at least 50,000 people who drank the Jake developed TOCP poisoning, which was manifested by upper and lower extremity weakness (â€œginger Jake paralysisâ€•) and gait impairment (â€œJake walkâ€• or â€œJake legâ€•).[77] A quarter century later, in Morocco, the dilution of cooking oil with a turbojet lubricant containing TOCP caused an additional 10,000 cases of TOCP-induced paralysis.[113]

In the 1960s, cobalt was added to several brands of beer as a foam stabilizer. Certain local breweries in Quebec City, Canada, Minneapolis, Minnesota, Omaha, Nebraska, and Louvain, Belgium, added 0.5â€“5.5 ppm cobalt to their beer. This resulted in epidemics of fulminant heart failure among heavy beer drinkers (cobalt-beer cardiomyopathy).[1,78]

Epidemic methanol poisoning among those seeking ethanol and other inebriants is well described. In one such incident in Atlanta, Georgia, in 1951, the ingestion of methanol-contaminated bootleg whiskey caused 323 cases of methanol poisoning, resulting in 41 deaths. In another epidemic in 1979, 46 prisoners became ill after

ingesting a methanol-containing diluent used in copy machines.[118]

In recent years, major mass methanol poisonings have continued to occur in developing countries where store-bought alcohol is often prohibitively expensive. In Baroda, India, in 1989, at least 100 people died and another 200 became ill after drinking a homemade liquor that was contaminated with methanol.[26] In New Delhi, India, in 1991, an inexpensive antidiarrheal medicine, advertised as containing large amounts of ethanol, was contaminated with methanol, and caused more than 200 deaths.[17] The following year, in Cuttack, India, 162 people died and an additional 448 were hospitalized after drinking methanol-tainted liquor.[119] A major epidemic of methanol poisoning occurred in 1998 in Cambodia, when rice wine was contaminated with methanol.[11] At least 60 deaths and 400 cases of illness were attributed to the methanol.

So-called designer drugs are responsible for several toxicologic disasters. In 1982, several injection drug users living in San Jose, California, who were attempting to use a meperidine analog MPPP (1-methyl-4-phenyl-4-propionoxy-piperidine), developed a peculiar, irreversible neurologic disease closely resembling parkinsonism.[60] Investigation revealed that these patients had unknowingly injected trace amounts of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), present as an inadvertent product of the clandestine MPPP synthesis. The subsequent metabolism of MPTP to MPP^+ resulted in a toxic compound that selectively destroyed cells in the substantia nigra, causing severe irreversible parkinsonism. The vigorous pursuit of the cause of this disaster led to a better understanding of the pathophysiology of parkinsonism and the development of possible future treatments.

Another example of a â€œdesigner-drugâ€• mass poisoning occurred in the New York City metropolitan area in 1991, when a sudden epidemic of opioid overdoses occurred among heroin users who bought envelopes labeled â€œTango and Cash.â€•[28]

Expecting to receive a new brand of heroin, the drug users instead purchased the much more potent fentanyl. Increased and unpredictable toxicity resulted from the inability of the dealer to adjust (â€œcutâ€•) the fentanyl dose properly. Some purchasers presumably received little or no fentanyl, while others received potentially lethal doses. A similar epidemic involving 3-methylfentanyl occurred in 1988 in Pittsburgh, Pennsylvania.[69]

Polycyclic aromatic hydrocarbons
England
1700s
Scrotal cancer among chimney sweeps; first description of occupational cancer
Mercury
New Jersey
Mid to late 1800s
Outbreak of mercurialism in hatters
White phosphorus
Europe
Mid to late 1800s
Phossy-jaw in matchmakers
Î²-Naphthylamine
Worldwide
Early 1900s
Bladder cancer in dye makers
Benzene
Newark, NJ
1916â€“1928
Aplastic anemia among artificial leather manufacturers
Asbestos
Worldwide
20th century
Millions at risk for asbestos-related disease
Vinyl chloride
Louisville, KY

1960sâ€“1970s
Hepatic angiosarcoma among polyvinyl chloride polymerization workers
Chlordecone
James River, VA
1973â€“1975
Neurologic abnormalities among insecticide workers
1, 2-Dibromochloropropane
California
1974
Infertility among pesticide makers

Xenobiotic Location Date Significance

TABLE 2-6. Occupational Disasters

At least 325 cases of anticholinergic poisoning occurred among heroin users in New York City, Newark, New Jersey, Philadelphia, Pennsylvania, and Baltimore, Maryland, from 1995 to 1996.[105] The â€œstreet drugâ€• used in these cases was adulterated with scopolamine. Whereas naloxone treatment was associated with increased agitation and hallucinations, physostigmine administration resulted in resolution of symptoms. Why the heroin was adulterated was unknown, although the use of an opiate-scopolamine mixture was reminiscent of the morphine-scopolamine combination therapy known as â€œtwilight sleepâ€• that was heavily used in obstetric anesthesia during the early 20th century.[94]

Another unexpected complication of heroin use was observed in the Netherlands in the 1980s, when 47 heroin users developed mutism and spastic quadriparesis that was pathologically documented to be spongiform leukoencephalopathy.[135] In these cases, as well as in subsequent cases in Europe and the United States, the users inhaled heroin vapors after the heroin powder

had been heated on aluminum foil, a drug administration technique known as â€œchasing the dragon.â€•[56,135] The exact toxic mechanism has not been elucidated.

Occupational-Related Chemical Disasters

Unfortunately, occupation-related toxic epidemics have become increasingly common (Table 2-6). These poisoning syndromes tend to have an insidious onset and may not be recognized clinically until years after the exposure. A specific toxin may cause a myriad of problems; among the most worrisome being the carcinogenic and mutagenic potentials.

Although the 18th-century observations of Ramazzini and Pott introduced the concept that certain diseases were a direct result of toxic exposures in the workplace, it was not until the height of the 19th-century industrial revolution that the problems associated with the increasingly hazardous workplace became apparent.[46] During the 1860s, a peculiar disorder, attributed to the effects of inhaling mercury vapor, was described among manufacturers of felt hats in New Jersey.[131] Mercury nitrate was used as an essential part of the felting process at the time. â€œHatter's shakesâ€• refers to the tremor that developed in an estimated 10â€“60% of hatters surveyed.[131] Extreme shyness, another manifestation of

mercurialism, also developed in many hatters in later studies. Five percent of hatters during this period died from renal failure.

Radium
Orange, NJ
1910sâ€“1920s
Increase in bone cancer in dial-painting workers
Radium

US
1920s
â€œRadithorâ€• (radioactive water) sold as radium-containing patent medication
Radiation
Hiroshima and Nagasaki, Japan
1945
First atomic bombs dropped at end of World War II; clinical effects still evident today
Radiation
Chernobyl, Ukraine
1986
Unintentional radioactive release; acute radiation sickness
Cesium
Goiania, Brazil
1987
Acute radiation sickness and radiation burns

Xenobiotic Location Date Significance

TABLE 2-7. Radiation Disasters

Other notable 19th-century and early 20th-century occupational tragedies included an increased incidence of mandibular necrosis (phossy jaw) among workers in the matchmaking industry who were exposed to white phosphorus,[44] an increased incidence of bladder tumors among synthetic dye makers who used Î²-naphthylamine,[37] and an increased incidence of aplastic anemia among artificial leather manufacturers who used benzene.[108] The epidemic of phossy jaw among matchmakers had a latency period of 5 years and a mortality rate of 20% and has been called the â€œgreatest tragedy in the whole story of occupational disease.â€•[14] The problem continued in the United States until Congress passed the White Phosphorus Match Act in 1912, which

established a prohibitive tax on white phosphorus matches.[85]

Since antiquity, occupational lead poisoning has been a constant threat. Workplace exposure to lead was particularly problematic during the 19th century and early 20th century, because of the large number of industries that relied heavily on lead. One of the most notorious of the â€œlead tradesâ€• was the actual production of white lead and lead oxides. Palsies, encephalopathy, and death from severe poisoning were reported.[40] Other occupations that entailed dangerous lead exposures included pottery glazing, rubber manufacturing, pigment manufacturing, painting, printing, and plumbing.[68] Given the increasing awareness of harm suffered in the workplace, the British Factory and Workshop Act was enacted in 1895, which required governmental notification of occupational diseases caused by lead, mercury, and phosphorus poisoning, as well as of occupational diseases caused by anthrax.[62]

Exposure to asbestos during the 20th century has become one of the most consequential occupational and environmental disasters in recent memory.[19 , 84] Despite the fact that the first case of asbestosis was reported in 1907, asbestos was heavily used in the shipbuilding industries in the 1940s as an insulating and fireproofing material. Since the early 1940s, 8â€“11 million individuals were occupationally exposed to asbestos,[64] including 4.5 million individuals who worked in the shipyards. Asbestos-related diseases include mesothelioma, lung cancer, and pulmonary fibrosis (asbestosis). A 3-fold excess of cancer deaths is observed in asbestos-exposed insulation workers, primarily as a consequence of excess lung cancer deaths.[106]

The manufacture and use of a variety of newly synthesized chemicals has also resulted in cases of mass occupational poisoning. In Louisville, Kentucky, in 1974, an increased incidence of angiosarcoma of the liver was first noticed among polyvinyl chloride polymerization workers who were exposed to vinyl

chloride monomer.[25] In 1975, chemical factory workers exposed to the organochlorine insecticide chlordecone (Kepone) experienced a high incidence of neurologic abnormalities, including tremor and chaotic eye movements.[120] An increased incidence of infertility among male Californian pesticide workers exposed to dibromochloropropane (DBCP) was noted in 1977.[132]

Radiation Disasters

A discussion of mass poisonings is incomplete without mention of a growing number of radiation disasters that have occurred during the 20th century (Table 2-7). The first significant mass exposure to radiation occurred among several thousand teenage girls and young women employed in the dial-painting industry.[15] These workers painted luminous numbers on watch and instrument dials with paint that contained radium. Exposure occurred by licking the paint brushes and inhaling radium-laden dust. Studies showed an increase in bone-related cancers, as well as aplastic anemia and leukemia, in exposed workers.[70 , 95]

At the time of the â€œwatchâ€• disaster, radium was also being sold as a nostrum touted to cure all sorts of ailments, including rheumatism, syphilis, multiple sclerosis, and sexual dysfunction. Referred to as â€œmild radium therapy,â€• in order to differentiate it from the higher-dose radium that was used in the treatment of cancer at that time, such Î±-particle-emitting isotopes were hailed as a powerful natural elixir that acted as a metabolic catalyst by delivering direct energy transfusions.[66]

During the 1920s, dozens of patent medications contained small doses of radium and were sold as radioactive tablets, liniments, or liquids. One of the most infamous preparations was Radithor. Each half-ounce bottle contained slightly more than 1 ÂµCi of radium-228 and radium-226. This radioactive water was sold all over the world â€œas harmless in every respectâ€• and was heavily promoted as a sexual stimulant and aphrodisiac, taking on the

glamour of a recreational drug for the wealthy.[66] More than 400,000 bottles were sold. The 1932 death of a prominent socialite and Radithor connoisseur from chronic radiation poisoning drew increased public and governmental scrutiny to this unregulated radium industry and helped end the era of radioactive patent medications.[66]

Concerns about the health effects of radiation have continued to escalate since the dawn of the nuclear age in 1945. Long-term followup studies 50 years after the atomic bombings at Hiroshima and Nagasaki show an increased incidence of leukemia, other cancers, radiation cataracts, hyperparathyroidism, delayed growth and development, and chromosomal anomalies in exposed individuals.[54]

The unintentional nuclear disaster at Chernobyl, Ukraine, in April 1986, again forced us to confront the medical consequences of 20th-century scientific advances that brought us the atomic age.[32] The release of radioactive material resulted in the hospitalization of more than 200 people for acute radiation sickness

and 31 deaths. By 2003, the predominant main long-term effects from the event appear to be childhood thyroid cancer and the psychological consequences.[99] In some areas with heavy contamination, the increase in childhood thyroid cancer has increased 100-fold.[102]

Another serious radiation event occurred in Goiania, Brazil, in 1987. When an abandoned radiotherapy unit was opened in a junkyard, 244 people were exposed to cesium-137. Of those people exposed to cesium-137, 104 showed evidence of internal contamination, 28 had local radiation injuries, and 8 developed acute radiation syndrome. There were at least 4 deaths.[92, 100]

In September 1999, a nuclear event at a uranium processing plant in Japan set off an uncontrolled chain reaction exposing 49 people to radiation.[25, 60] Radiation measured outside the facility reached

4000 times the normal ambient level. Two workers died from the effects of the radiation.

Mass Suicide by Poison

Toxic disasters have also manifested themselves as events of mass suicide. In 1978, in Jonestown, Guyana, 911 members of the Peoples Temple died when they ingested a beverage to which cyanide had been added.[39] Although the majority of those deaths may have been by suicide, some appear to have been involuntary.[61]

In 1997, phenobarbital and ethanol (sometimes assisted by physical asphyxiation) was the suicidal method favored by 39 members of the Heavens Gate cult in Rancho Santa Fe, California. This means of suicide was recommended in the book *Final Exit* .[45] Apparently, the cult members committed suicide in order to shed their bodies in hopes of hopping aboard an alien spaceship they believed was in the wake of the Hale-Bopp comet.[59]

Summary

Unfortunately, toxicologic plagues and disasters have had an all too prominent role in our history. An understanding of the pathogenesis of these toxic plagues that pertain to drug, food, and occupational safety is critically important if future disasters are to be prevented. These events teach us awareness that many of these toxic agents may have a potential role as agents of opportunity for terrorists and others who seek to harm. Given the practical and ethical limitations in studying the effects of many specific toxins in humans, lessons from these unfortunate tragedies must be fully mastered and retained for future generations.

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Chapter 3

Initial Evaluation of the Patient: Vita Signs and Toxic Syndromes

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For more than 200 years the American medical community has attempted standardize its approach to the assessment of patients. At the New York Hospital in 1865, pulse rate, respiratory rate, and temperature were incorporated into the bedside chart and called â€œvital signs.â€• [6] It was until the early part of the 20th century, however, that blood pressure determination also become routine. Additional components of the standar emergency assessment, such as oxygen saturation by pulse oximetry and severity using standardized scales, are now also beginning to be consider vital signs. Although both oxygen saturation and pain severity are essent components of the clinical assessment and are important considerations

throughout this text, neither is considered a vital sign here.

In the practice of medical toxicology, vital signs play an important role b assessing and monitoring the overall status of a patient, as they frequent provide valuable physiologic clues to the toxicologic etiology and severity illness. The vital signs also are a valuable parameter with which to assess monitor a patient's response to supportive treatment and antidotal therap

Table 3-1 presents the normal vital signs for various age groups. Howeve broad range of values considered normal should serve merely as a guide. a complete assessment of a patient can determine whether or not a parti vital sign is truly clinically normal. This table of normal vital signs is usef assessing children, as normal values for children vary considerably with a and knowing the range of variation is essential. The normal temperature defined as 95â€“100.4Â°F (35â€“38Â°C).

The difficulty in defining the â€œnormalcyâ€• of vital signs in an emerge setting has been inadequately addressed and may prove to be an impossi undertaking. Published normal values may have little relevance to an acu or anxious patient in the emergency setting, yet that is precisely the environment in which we need to define abnormal vital signs and address accordingly. For these reasons descriptions of vital signs as â€œnormalâ€ â€œstableâ€• are too nonspecific to be meaningful, and therefore should never be accepted as defining normalcy in an individual patient. Converse patient should be considered too agitated or too gravely ill to obtain a co set of vital signs; indeed, these patients urgently need a thorough evalua which includes all of the vital signs. Also the vital signs must be recorded accurately as possible first in the prehospital setting, and again with pre and reliability as soon as a patient arrives in the emergency department, serially thereafter.

Many xenobiotics affect the autonomic nervous system, which, in turn, a the vital signs via the sympathetic and/or parasympathetic pathways. Meticulous attention to both initial and repeated determinations of vital si of extreme importance in identifying a pattern of changes suggesting a particular xenobiotic or group of xenobiotics. The value of serial monitorin the vital signs is demonstrated by the patient who presents with an

anticholinergic overdose who is then given the antidote, physostigmine. I situation it is important to recognize when tachycardia becomes bradycar (ie, anticholinergic syndrome followed by physostigmine excess). Meticul attention to these changes assures that the therapeutic interventions can modified or adjusted accordingly.

Another common situation, perhaps, is the course of a patient who has o induced bradypnea (a decreased rate of breathing) who then develops tachypnea (an increased rate of breathing) following the administration of opioid antagonist naloxone. However the analysis becomes exceedingly complicated when the patient may have been exposed to two or more substances, such as an opioid and cocaine. In this situation the effects of cocaine may be â€œunmaskedâ€• by the naloxone used to counteract th opioid, and the clinician must then be forced to differentiate naloxone-in opioid withdrawal from cocaine toxicity. The assessment starts by analyzi combination of information, including history, vital signs, and physical examination.

Table 3-2 describes the most typical toxic syndromes. This table includes those vital signs that are thought to be characteristically abnormal or pathognomonic and directly related to the toxicologic effect of the xenob The primary purpose of the table, however, is to include many findings, i addition to the vital signs, that together constitute a toxic syndrome. Mo and Greensher[5] coined the term *toxidromes* from the words *toxic syndro* describe the groups of signs and symptoms that consistently result from particular toxins. These syndromes are usually best described by a comb of the vital signs and clinically obvious end-organ manifestations. The sig that prove most clinically useful are those involving the central nervous s (mental status); ophthalmic system (pupil size); gastrointestinal system (peristalsis); dermatologic system: skin (dryness vs. diaphoresis) and mu membranes

(moistness vs. dryness); and genitourinary system (urinary retention vs. incontinence). Table 3-3 includes some of the most important signs and symptoms and the xenobiotics most commonly responsible for these manifestations. A detailed analysis of each sign, symptom, and toxic syn

can be found in the pertinent chapters throughout the text. In this chapte most typical toxic syndromes (Table 3-2) are considered to enable the appropriate assessment and differential diagnosis of a poisoned patient.

Adult
120
80
60â€“100
16â€“24
16 years
120
80
80
16â€“30
12 years
119
76
85
16â€“30
10 years
115
74
90
16â€“30
6 years
107
69
100
20â€“30
4 years
104
65
110
20â€“30
2 years

102
58
120
25â€“30
1 year
100
55
120
25â€“30
6 months
90
55
120
30
4 months
90
50
145
30â€“35
2 months
85
50
145
30â€“35
Newborn
65
50
145
35â€“40
The normal rectal temperature is defined as 95â€“100.4Â°F (35â€“38Â°C)
all ages. For children â‰¤1 year of age these values are the mean value
the 50th percentile. For the older children these values represent the 90t
percentile at a specific age for the 50th percentile of weight in that age g
*These values were determined in the emergency department and may b

environment and situation dependent.

Age	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse (beats/min)	Respiration (breaths/mi

TABLE 3-1. Normal Vital Signs by Age

In considering a toxic syndrome the reader should always remember that actual clinical manifestations of an ingestion or exposure are far more va than the syndromes described in Table 3-2 . The concept of the toxic syr is most useful when thinking about a clinical presentation and formulating framework for assessment. Although some patients may present as â€œclassicâ€• cases, others will manifest partial toxic syndromes or *forr frustes.* Incomplete syndromes still may provide at least a clue to the co diagnosis. It is important to understand that partial presentations (partic in the presence of multiple toxins) do not necessarily imply less-severe c and, therefore, are no less important to appreciate.

In some instances, an unexpected combination of findings may be particu helpful in identifying a toxin or a combination of toxins. For example, a dissociation between such typically paired changes as an increase in pulse a decrease in blood pressure (cyclic antidepressants or phenothiazines), c presentation of a decrease in pulse with an increase in blood pressure (e alkaloids) may be extremely helpful in diagnosing a toxic etiology. The us these unexpected or atypical clinical findings is demonstrated in Chap. 23

Anticholinergics
â€“/â†‘
â†‘
=
â†‘
Delirium
â†‘
â†“
â†“

Dry mucous membranes, flush, urinary retention
Cholinergics
=
=
â€“/â†‘
â€“
Normal to depressed
=
â†‘
â†‘
Salivation, lacrimation, urination, diarrhea, bronchorrhea, fasciculations, paralysis
Ethanol or sedative-hypnotics
â†“
â†“
â†“
â€“/â†“
Depressed
=
â†“
â€“
Hyporeflexia, ataxia
Opioids
â†“
â†“
â†“
â†“
Depressed
â†“
â†“
â€“
Hyporeflexia
Sympathomimetics
â†‑

â†‘
â†‘
â†‘
Agitated
â†‘
â€“/â†‘
â†‘
Tremor, seizures
Withdrawal from ethanol or sedative-hypnotics
â†‘
â†‘
â†‘
â†‘
Agitated, disoriented
â†‘
â†‘
â†‘
Tremor, seizures
Withdrawal from opioids
â†‘
â†‘
â€“
â€“
Normal, anxious
â†‘
â†‘
â†‘
Vomiting, rhinorrhea, piloerection, diarrhea, yawning
â†‘ = increases; â†“ = decreases; Â± = variable; â€“ = change unlikely

Vital Signs

Group	BP	P	R	T	Mental Status	Puple Size	Peristaisis	Diaphoresls	C

TABLE 3-2. Toxic Syndromes

Blood Pressure

Xenobiotics cause hypotension by four major mechanisms: decreased peripheral resistance, decreased myocardial contractility, dysrhythmias, intravascular volume depletion. Many xenobiotics can initially cause seve orthostatic hypotension, without marked supine hypotension, and any xenobiotic that affects autonomic control of the heart or peripheral capa vessels may lead to orthostatic hypotension (Table 3-4).

Blood pressure and pulse rate may vary significantly as a result of change receptor responsiveness, degree of physical fitness, and degree of atherosclerosis, or general cardiovascular function. Changing patterns of pressure often assist in the diagnostic evaluation: exposure to a monoam oxidase inhibitor (MAOI) overdose characteristically causes an initial norr blood pressure, to be followed by severe hypertension which, in turn, may followed abruptly by severe hypotension (Chap. 69).

Agitation
Anticholinergics[a] , hypoglycemia, phencyclidine, sympathomimetics[b] , withdrawal from ethanol and sedative-hypnotics
Alopecia
Alkylating agents, radiation, selenium, thallium
Ataxia
Benzodiazepines, carbamazepine, carbon monoxide, ethanol, hypoglycem lithium, mercury, nitrous oxide, phenytoin
Blindness or decreased visual acuity
Caustics (direct), cocaine, cisplatin, mercury, methanol, quinine, thallium
Blue skin
Amiodarone, FD&C #1 dye, methemoglobin, silver
Constipation
Anticholinergics[a] , botulism, lead, opioids, thallium (severe)
Tinnitus, deafness

Aminoglycosides, cisplatin, metals, loop diuretics, quinine, salicylates

Diaphoresis

Amphetamines, cholinergics[c], hypoglycemia, opioid withdrawal, salicylat serotonin syndrome, sympathomimetics[b], withdrawal from ethanol and sedative-hypnotics

Diarrhea

Arsenic and other metals, boric acid (blue-green), botanical irritants, cathartics, cholinergics[c], colchicine, iron, lithium, opioid withdrawal, rac

Dysesthesias, paresthesias

Acrylamide, arsenic, ciguatera, cocaine, colchicine, thallium

Gum discoloration

Arsenic, bismuth, hypervitaminosis A, lead, mercury

Hallucinations

Anticholinergics[a], dopamine agonists, ergot alkaloids, ethanol, ethanol a sedative-hypnotic withdrawal, LSD, phencyclidine, sympathomimetics[b], tryptamines (eg, AMT)

Headache

Carbon monoxide, hypoglycemia, monoamine oxidase inhibitor/food inter (hypertensive crisis), serotonin syndrome

Metabolic acidosis (elevated anion, gap) [MUDPILES]

Methanol, uremia, ketoacidosis (diabetic, starvation, alcoholic), paraldeh phenformin, metformin, iron, isoniazid lactic acidosis, cyanide, protease inhibitors, ethylene glycol, salicylates, toluene

Miosis

Cholinergics[c], clonidine, opioids, phencyclidine, phenothiazines

Mydriasis

Anticholinergics[a], botulism, opioid withdrawal, sympathomimetics[b]

Nystagmus

Barbiturates, carbamazepine, carbon monoxide, ethanol, lithium, monoar oxidase inhibitors, phencyclidine, phenytoin, quinine

Purpura

Anticoagulant rodenticides, clopidogrel, corticosteroids, heparin, pit viper venom, quinine, salicylates, warfarin

Radiopaque ingestions

Arsenic, chloral hydrate, enteric coated tablets, halogenated hydrocarbor metals (eg, iron, lead)

Red skin

Anticholinergics[a] , boric acid, disulfiram, scombroid, vancomycin

Rhabdomyolysis

Carbon monoxide, doxylamine, HMG CoA reductase inhibitors, sympathomimetics[b] , *Tricholoma equestre*

Salivation

Arsenic, caustics, cholinergics[c] , ketamine, mercury, phencyclidine, stryc

Seizures

Bupropion, carbon monoxide, cyclic antidepressants, *Gyromitra* mushroor hypoglycemia, isoniazid, methylxanthines, withdrawal from ethanol and sedative-hypnotics

Tremor

Antipsychotics, arsenic, carbon monoxide, cholinergics[c] , ethanol, lithium mercury, methyl bromide, sympathomimetics[b] , thyroid replacement

Weakness

Botulism, diuretics, magnesium, paralytic shellfish, steroids, toluene

Yellow skin

Acetaminophen (late), pyrrolizidine alkaloids, Î² carotene, amatoxin mushrooms, dinitrophenol

[a] Anticholinergics: eg, antihistamines, atropine, cyclic antidepressants, scopolamine.

[b] Sympathomimetics: eg, amphetamines, Î² adrenergic agonists, cocaine, ephedrine.

[c] Cholinergics: eg, muscarinic mushrooms, organic phosphorus compounds carbamates including select Alzheimer drugs and physostigmine, pilocarp and other direct acting drugs.

TABLE 3-3. Clinical and/or Laboratory Findings in Poisoning

Î±$_1$ -Adrenergic antagonists

Ergot alkaloids

Î±$_2$ -Adrenergic agonists

Lead (chronic)
Î²-Adrenergic antagonists
Monoamine oxidase inhibitors (overdose early and drugâ€“food interactio
Nicotine (early)
Angiotensin converting enzyme inhibitors and angiotensin receptor blocke
Antidysrhythmics
Phencyclidine
Calcium channel blockers
Sympathomimetics
Cyanide
Yohimbine
Cyclic antidepressants
Ethanol and other alcohols
Iron
Methylxanthines
Nitrates and nitrites
Nitroprusside
Opioids
Phenothiazines
Phosphodiesterase-5â€² inhibitors
Sedative-hypnotics
Chap. 23 lists additional agents that affect hemodynamic function.

Hypotension Hypertension

TABLE 3-4. Common Xenobiotics That Affect Blood Pressure

Pulse Rate

Extremely useful clinical information can be obtained by evaluating the p rate (Table 3-5 and Chap. 23). Although the carotid artery is usually eas palpable, for reasons of both safety and reliability, the brachial artery is preferred in infants and adults greater than 60 years old. The normal hea

rate for adults was defined by consensus more than 50 years ago as a re rate >60 beats/min and <100 beats/min. More recent studies[7, 8] suggest 95% of the population have bradycardia and tachycardia thresholds of 50 beats/min and 90 beats/min, respectively. These lower limits are more consistent with our current understanding of the delicate balance imposed the sympathetic and parasympathetic nervous systems. In our text we ha chosen to retain the standard values although the lower values would de our sensitivity and increase our specificity with regard to the detection of clinically relevant bradycardias and tachycardias.

Because pulse rate is the net result of a balance between adrenergic and cholinergic (muscarinic and nicotinic) tone, many xenobiotics that exert therapeutic or toxic effects, cause pain syndromes, fever, or volume dep also cause pulse rate abnormalities.

There is a direct correlation between heart rate and temperature in that rate increases approximately 8 beats/min for each 1.8Â°F (1Â°C) elevatio temperature.[4]

Î±$_2$ -Adrenergic agonists
Anticholinergics
Î²-Adrenergic antagonists
Cyclic antidepressants
Baclofen
Disulfiram/ethanol
Calcium channel blockers
Ethanol and sedative hypnotic withdrawal
Cardioactive steroids
Iron
Ciguatera
Methylxanthines
Ergot alkaloids
Phencyclidine
Opioids
Phenothiazines

Sympathomimetics
Thyroid replacement
Yohimbine
Chap. 23 lists additional agents affecting heart rate.

Bradycardia Tachycardia

TABLE 3-5. Common Xenobiotics That Affect Pulse

The inability to differentiate easily between the sympathomimetic and anticholinergic xenobiotics by vital signs alone illustrates the principle tha single vital sign abnormality can definitively establish a toxicologic diagnc etiology. In trying to differentiate between sympathomimetic and anticholinergic toxicity, it should be understood that although a tachycar commonly results from both sympathomimetic and anticholinergic xenobi when tachycardia is accompanied by diaphoresis and/or increased bowel sounds, adrenergic toxicity is suggested, whereas when tachycardia is accompanied by decreased sweating, absent bowel sounds, and urinary retention, anticholinergic toxicity is likely.

Respirations

As always, establishment of an airway and evaluation of respiratory statu the initial priorities in patient stabilization. Although respirations are typ assessed initially for rate alone, careful observation of the depth and patt essential (Table 3-6) for establishing the etiology of a systemic illness o toxicity.[1] Unfortunately very few investigators have actually measured th respiratory rate in large populations of normal people, let alone in emerg department patients. Two papers[2] , [3] investigating respiratory rates in emergency department patients differ substantially in their determinations normal ranges from the remainder of the literature. The results of these investigations suggest â€œnormalâ€• respiratory rates are 16â€“24 breaths/min in adults with more rapid rates that are inversely related to a children. These respiratory rate ranges define normal in this text.

Î±2 -Adrenergic agonists
Cyanide
Botulinum toxin
Dinitrophenol and congeners
Ethanol and other alcohols
Epinephrine
Î³-Hydroxybutyric acid
Ethylene glycol
Neuromuscular blockers
Hydrogen sulfide
Opioids
Methanol
Organic phosphorus insecticides
Methemoglobin producers
Sedative-hypnotics
Methylxanthines
Nicotine (early)
Salicylates
Sympathomimetics
Chap. 22 lists additional agents affecting respiratory rate.

Bradypnea Tachypnea

TABLE 3-6. Common Xenobiotics That Affect Respiration

The term *hyperventilation* may mean tachypnea, or hyperpnea, (an increa tidal volume), or both. When hyperventilation results solely or predomina from hyperpnea, the less-astute clinician may miss this important finding entirely, instead erroneously describing such a hyperventilating patient a normally ventilating, or even *hypoventilating* , if bradypnea is also prese

Tachypnea may result from the direct effect of a CNS stimulant, such as salicylates, acting on the brainstem. However, salicylate poisoning can al result in only an increased tidal volume or hyperpnea without tachypnea. Pulmonary injury from any source, including aspiration of gastric contents

lead to hypoxemia with a resultant tachypnea. Later, tachypnea may char bradypnea and/or hypopnea (shallow breathing). Bradypnea can occur ev sooner when a CNS depressant acts on the brainstem. A progression from to slow breathing can also occur in a patient exposed to increasing levels cyanide or carbon monoxide.

The toxic alcohols methanol and ethylene glycol can transiently produce hypoventilation as a consequence of bradypnea or hypopnea from direct depression. In time, however, hyperventilation will predominate as meta acidosis develops.

Temperature

Temperature evaluation and control are critical. However, temperature assessment can be done only if safe and reliable equipment is used. The of inaccuracy are substantial when an oral temperature is taken in a tach patient, an axillary temperature is taken in any patient but especially in patients found outdoors, or a tympanic temperature is taken in a patient cerumen impaction. Obtaining rectal temperatures using a nonglass probe essential for safe and accurate temperature determinations in agitated individuals and is considered the standard method of temperature determination in this text.

The core temperature or deep internal temperature (T) is relatively stable (98.6 Â± 1.08Â°F; 37 Â± 0.6Â°C) under normal physiologic circumstance Both hypothermia (T <95Â°F; <35Â°C) and hyperthermia (T >100.4Â°F; >38Â°C) are common manifestations of xenobiotic toxicity. Severe or significant hypothermia and hyperthermia, unless immediately recognized managed appropriately, can result in grave complications and inappropria inadequate resuscitative efforts. Life-threatening hyperthermia (T >106Â >41.1Â°C) from any cause can lead to extensive rhabdomyolysis, myoglobinuric renal failure, and direct liver and brain injury, and must therefore be identified and corrected immediately.

Hyperthermia can result either from a distinct neurologic response to a s demanding thermal â€œupregulationâ€• or from an externally imposed

physical or environmental factor, such as the environmental conditions c heat stroke or the excessive swaddling in clothing causing hyperthermia i infants. Core temperatures higher than 106Â°F (41.1Â°C) are extremely unless normal feedback mechanisms are overwhelmed. Hyperthermia of t extreme nature is usually attributed to heat stroke, psychomotor agitation xenobiotic-related temperature disturbances such as malignant hyperthe and the neuroleptic malignant syndrome.

Drug-induced fevers coincide with the administration of a drug and disap within 48â€“96 hours of the discontinuation of the drug. A common xeno related hyperthermia pattern that frequently occurs in the emergency department is defervescence after an acute temperature elevation resulti from agitation or seizure activity. Table 3-7 is a representative list of xenobiotics that affect body temperature (Chap. 16 provides greater deta

Anticholinergics
Î ±$_2$ -Adrenergic agonists
Chlorphenoxy herbicides
Carbon monoxide
Dinitrophenol and congeners
Ethanol
Malignant hyperthermia
Hypoglycemic agents
Monoamine oxidase inhibitors
Opioids
Neuroleptic malignant syndrome
Sedative-hypnotics
Phencyclidine
Thiamine deficiency
Salicylates
Sedative-hypnotic or ethanol withdrawal
Serotonin syndrome
Sympathomimetics
Thyroid replacement

Chap. 16 lists additional agents affecting temperature.

Hyperthermia Hypothermia

TABLE 3-7. Common Xenobiotics That Affect Temperature

Hypothermia is probably less of an immediate threat to life than hyperth but it requires rapid appreciation, accurate diagnosis, and skilled manage Hypothermia will impair the metabolism of many xenobiotics, leading to unpredictable delayed effects when the patient is warmed. Many xenobio impair judgment and CNS function, thereby placing patients at great risk becoming hypothermic from exposure to cold climates. Most importantly, hypothermic patient should never be declared dead without both an exte assessment and a full resuscitative effort, particularly if the body temper remains less than 95Â°F (35Â°C) (Chap. 16).

Summary

Early, accurate determinations followed by serial monitoring of the vital s are as essential in medical toxicology as in any other type of emergency critical care medicine. For this reason, the vital signs are an essential par the initial evaluation of every case, and repeated vital signs are always necessary throughout the subsequent case management. Careful observat the vital signs helps to determine appropriate therapeutic interventions a guide the clinician in making necessary adjustments to initial and subseq therapeutic interventions. When pathognomonic clinical and laboratory fi are combined with accurate initial and sometimes changing vital signs, a syndrome may become evident, which will aid in both general supportive specific antidotal treatment. Toxic syndromes will also guide further diag testing.

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Chapter 4

Principles of Managing the Poisoned or Overdosed Patient

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Case 1

A 30-year-old woman was found unconscious in her apartment in the early afternoon. The paramedics found a suicide note alongside her, stating that the patient had ingested pills earlier in the morning. Reportedly, several empty bottles of pills were on the floor near her body, but unfortunately none were brought to the emergency department (ED).

The woman's initial vital signs in the ED were blood pressure, 120/75 mm Hg; pulse, 90 beats/min; respirations, 18 breaths/min; and

temperature, 98.6Â°F (37.0Â°C). Pulse oximetry was 99% while the patient was breathing room air. A rapid reagent bedside glucose test done prior to the patient's arrival in the ED was 95 mg/dL; consequently, dextrose was not administered. Physical examination demonstrated no trauma. The patient localized noxious cutaneous stimulation but did not open her eyes or respond verbally. Pupils were 4 mm and normally reactive. The neck was supple and the cardiopulmonary and abdominal examinations were normal. There were no lesions on the patient's extremities and, specifically, no signs of injection drug use. Neither flumazenil nor naloxone was administered.

An electrocardiogram revealed a sinus rhythm, normal electrical axis, and normal intervals without ectopy. A venous blood gas analysis was immediately available: pH, 7.35; PCO_2, 45 mm Hg; PO_2, 40 mm Hg. Serum acetaminophen and ethanol concentrations were zero. The patient was attached to a continuous cardiac monitor and pulse oximeter.

Case 2

A lethargic, 38-year-old woman presented to the ED at 6:45 A.M. According to her roommate, the patient had returned home from work at a nightclub at about 3 A.M. and â€œsmelled like alcohol.â€• At 5:30 A.M., the roommate saw the patient crying and then witnessed the patient ingest about 40 pills, possibly from the patient's bottle of quetiapine, before going into the bathroom. When the roommate went to check on her a short time later, she found the patient lethargic. The patient had a past history of depression, and was currently being treated with quetiapine and paroxetine. The patient also had a history of cocaine use.

In the ED, the patient was lethargic and had pinpoint pupils. Her vital signs were blood pressure, 90/60 mm Hg; pulse, 147 beats/min; respiratory rate, 20 breaths/min; and O_2 saturation was

90% on a 100% non-rebreather mask; in addition, she was afebrile. The patient was given naloxone 0.8 mg IV with no response. A nasogastric tube was inserted, and the patient vomited. After the tube was removed and then replaced, the patient was given a dose of activated charcoal (AC) through the nasogastric tube. The patient vomited again. The patient was observed to have increased lethargy and â€œKussmaul breathing.â€• Corresponding arterial blood gas (ABG) values at that time were: pH, 7.30; PCO_2, 57 mm Hg; PO_2, 105 mm Hg; and HCO_3, 30 mEq/L.

Intubating the patient was an extremely difficult-to-perform procedure, lasting 45 minutes. The endotracheal tube initially was inserted into the esophagus. Postintubation ABG values were pH, 7.4; PCO_2, 36 mm Hg; PO_2, 317 mm Hg; and HCO_3, 23 mEq/L. Chemistry values were sodium, 137 mEq/L; potassium, 3.6 mEq/L; chloride, 104 mEq/L; bicarbonate 23 mEq, BUN 10 mg/dL; creatinine 0.6 mg/dL; and glucose 150 mg/dL. The complete blood count (CBC) showed a white blood cell count (WBC) of 5100/mm^3; hemoglobin of 16 g/dL; hematocrit of 47%; and platelets of 192,000/mm^3. Ethanol was 79 mg/dL; acetaminophen and salicylates were negative. Urine toxicology studies were sent. ECG revealed normal ST segments and normal intervals.

The patient's vital signs were: blood pressure, 139/86 mm Hg; pulse 132 beats/min, and O_2 saturation 88% on 100% FiO_2. She was receiving IV fluids and lorazepam as needed for agitation. She also received clindamycin empirically for possible aspiration pneumonitis. The patient was then admitted to the ICU.

At this point the poison center (PC) was consulted and recommended supportive care, continued IV fluids, and benzodiazepines for sedation.

The patient remained intubated and sedated with a continuous propofol infusion until the next day, at which time her vital signs were blood pressure, 148/82 mm Hg; pulse, 126 beats/min; respiration, 32 breaths/min; and temperature, 102.3Â°F (39Â°C).

Chemistries were normal. CBC revealed a WBC of 14,000/mm^3. Chest radiography revealed an infiltrate and clindamycin was continued. The patient was extubated and continued to do well afterwards. Four days after the patient arrived, she was transferred out of the intensive care unit to a regular floor bed.

Case 3

A 16-month-old girl was given a bottle of ferrous sulfate â€œas a toy.â€• The mother felt that the cap was firmly in place and was childproof. After an absence from the room for several minutes, the mother noted on returning that the child had opened the bottle and that several tablets were missing. The child was asymptomatic en route to the hospital and on arrival the child had a blood pressure of 80/40 mm Hg; a pulse of 100 beats/min; respirations of 28 breaths/min; and a temperature of 99.7Â°F (37.6Â°C). Examination of the head, eyes, ears, nose, and throat was unremarkable. The mouth was free of tablets or obvious red discoloration from the iron tablets. The heart and lungs were normal. The abdomen was soft and nontender with no masses; bowel sounds were normal. The neurovascular examination was normal.

Prior to the trip to the hospital, the child had been given 15 mL of syrup of ipecac and had vomited up several partially digested pills 30 minutes later. However, an abdominal radiograph revealed at least 4 tablets in the GI tract. At 3 hours following ingestion the serum iron concentration was 286 Âµg/dL. Although the child had already vomited several times, whole-bowel irrigation with polyethylene glycol electrolyte solution was administered via a nasogastric tube at 500 mL/h. Guaiac-negative, red-tinged stool and fluid with tablet fragments were passed via the rectum.

Other than crying and persistent vomiting for an additional hour, the child remained asymptomatic and the clinical parameters remained

stable. A repeat abdominal radiograph taken 4 hours after the initial radiograph showed no remaining tablets. During the 24 hours that the child was hospitalized, she remained asymptomatic.

The 3 cases above illustrate several principles in the modern management of poisonings and overdoses. In all confirmed or suspected cases, thorough but rapid evaluation and reevaluation are always required, even when no specific interventions are subsequently indicated (case 1). In other cases, although some interventions may be appropriate, others are either unnecessary, harmful, or counterproductive (case 2). The prehospital use of syrup of ipecac is no longer recommended in almost any instance, and its use may not obviate the need for a more effective and less dangerous procedure, such as whole-bowel irrigation, to achieve intestinal evacuation (the iron tablets in case 3).

Overview

For almost 4 decades, medical toxicologists and information specialists at poison centers have used a clinical approach to the poisoned or overdosed patient that emphasizes treating the patient rather than treating the poison. Too often in the past, patients were initially all but neglected while attention was focused on the ingredients listed on the containers of the product(s) to which they presumably were exposed. Although the astute clinician must always be prepared to administer a specific antidote immediately in those instances when nothing else will save a patient, all poisoned or overdosed patients will benefit from an organized, rapid, clinical management plan (Fig. 4-1).

In the past 15 years, some basic tenets and long-held beliefs regarding the initial therapeutic interventions in toxicologic management have been questioned and subjected to an â€œevidence-basedâ€• analysis. For example, in the mid-1970s most medical toxicologists began to advocate a standardized

approach to a comatose and possibly overdosed adult patient, typically calling for the intravenous administration of 50 mL of $D_{50}W$, 100 mg of thiamine, and 2 mg of naloxone, as well as 100% oxygen at high flow rates. The rationale for this approach was to compensate for the previously idiosyncratic style of overdose management encountered in different healthcare settings and for the unfortunate likelihood that omitting any one of these measures at the time that care was initiated in the emergency department would result in omitting it altogether. It was not unusual then to discover from a laboratory chemistry report more than an hour after a supposedly overdosed comatose patient had arrived in the ED, that the initial blood glucose was 30 or 40 mg/dLâ€”a critical delay in the management of unsuspected and consequently untreated hypoglycemic coma. Today, however, with the widespread availability of accurate rapid reagent bedside testing for blood glucose and pulse oximetry for oxygen saturation, coupled with a much greater appreciation by all physicians of what needs to be done for each suspected overdose patient, clinicians can safely provide a more rational, individualized approach to determine the need for and in some instances more precise amounts of dextrose, thiamine, naloxone, and oxygen.

A second major approach to providing more rational individualized early treatment for toxicologic emergencies involves a closer examination of the actual benefits and risks of various gastrointestinal emptying interventions. Appreciation of the potential for significant adverse effects associated with all types of gastrointestinal emptying interventions and recognition of the absence of clear evidence-based support of efficacy, have led to a significant reduction in the routine use of syrup of ipecac-induced emesis or orogastric lavage as well as cathartic-induced intestinal evacuation. In 2004, the American Academy of Pediatricians (AAP) all but entirely abandoned its recommendations for the use of syrup of ipecac in the home. The efficacy of orogastric lavage, even when indicated by the nature or type of ingestion, is limited by the amount

of time elapsed since the ingestion. The value of whole-bowel irrigation (WBI) with polyethylene glycol electrolyte solution (PEG-ELS) appears to be much more specific and limited than originally thought. Some of the limitations and (uncommon) adverse effects of AC are now more widely recognized.

Similarly, interventions to eliminate absorbed xenobiotics from the body are now much more narrowly defined or, in some cases, abandoned: Multiple-dose activated charcoal (MDAC) is useful for some but not all xenobiotics. Ion-trapping in the urine is only beneficial, achievable, and relatively safe when the urine can be maximally alkalinized after a significant salicylate, phenobarbital, or chlorpropamide poisoning. Finally, the roles of hemodialysis, hemoperfusion and other extracorporeal techniques are now much more specifically defined. With the foregoing in mind, this chapter represents our current efforts to formulate a logical and effective approach to managing a patient with probable or actual toxic exposure.

Table 4-1 provides a recommended stock list of antidotes and therapeutics for the treatment of poisonings and overdoses.

Managing the Poisoned or Overdosed Patient

The 3 cases at the beginning of this chapter illustrate many of the problems clinicians face in managing ill patients with possible xenobiotic exposures. Rarely, if ever, are all of the circumstances known: the history may be incomplete, unreliable, or unobtainable; multiple drugs, xenobiotics may be involved; and even when a xenobiotic etiology is identified, it may not be easy to determine whether the

problem is an overdose, an allergic or idiosyncratic reaction, or a drugâ€“drug interaction. Similarly, it is sometimes difficult or

impossible to differentiate between adverse effects of a correct dose of medication or the consequences of a deliberate or unintentional overdose. The patient's presenting signs and symptoms may force an intervention at a time when there is almost no information available about the etiology of the patient's condition, and as a result therapeutics must be thoughtfully chosen empirically to treat or diagnose a condition without exacerbating the situation.

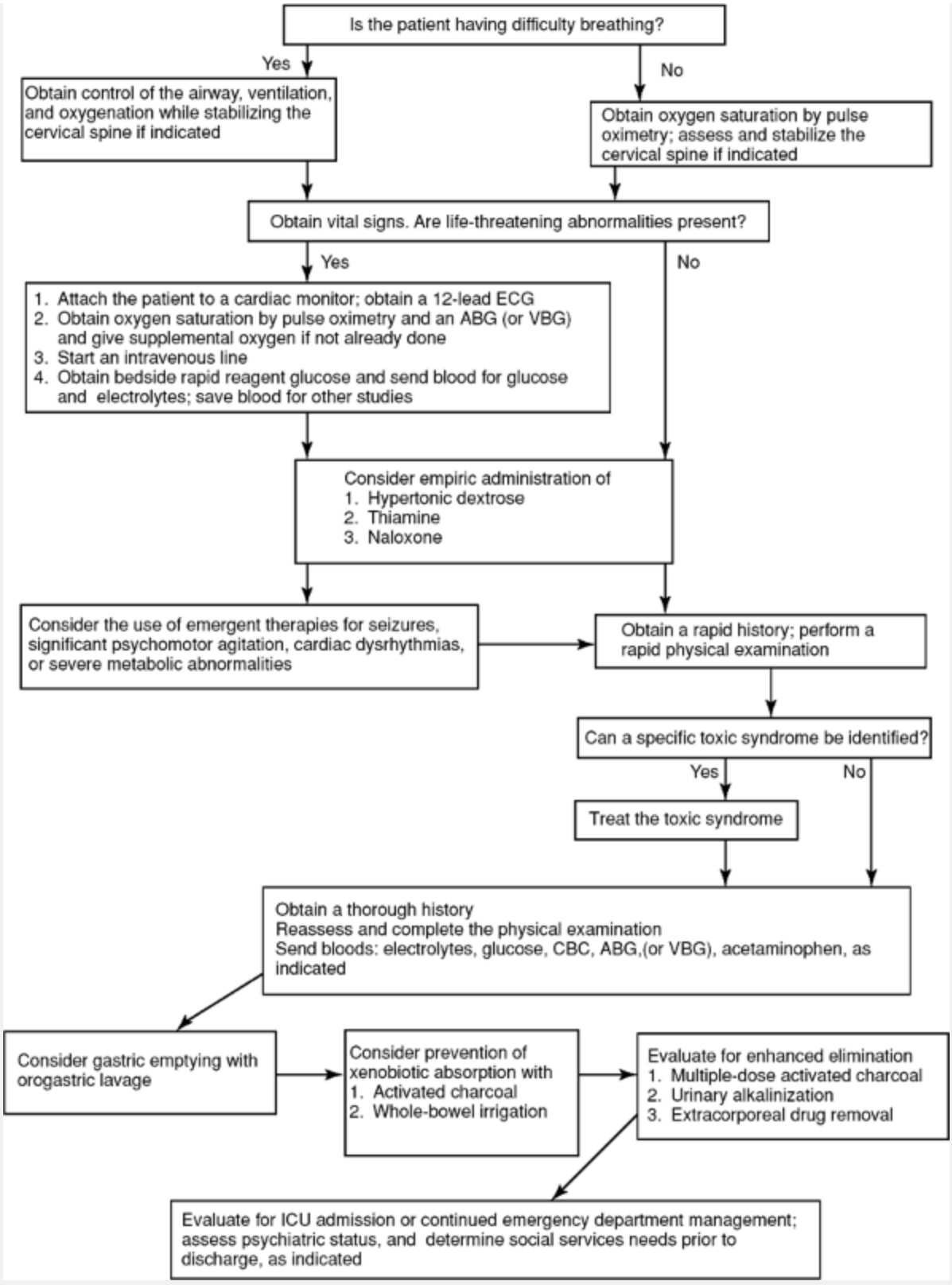
Is the patient having difficulty breathing?
Yes
No
Obtain control of the airway, ventilation, and oxygenation while stabilizing the cervical spine if indicated
Obtain oxygen saturation by pulse oximetry; assess and stabilize the cervical spine if indicated
Obtain vital signs. Are life-threatening abnormalities present?
Yes
No
1. Attach the patient to a cardiac monitor; obtain a 12-lead ECG
2. Obtain oxygen saturation by pulse oximetry and an ABG (or VBG) and give supplemental oxygen if not already done
3. Start an intravenous line
4. Obtain bedside rapid reagent glucose and send blood for glucose and electrolytes; save blood for other studies
Consider empiric administration of
1. Hypertonic dextrose
2. Thiamine
3. Naloxone
Consider the use of emergent therapies for seizures, significant psychomotor agitation, cardiac dysrhythmias, or severe metabolic abnormalities
Obtain a rapid history; perform a rapid physical examination
Can a specific toxic syndrome be identified?
Yes
No
Treat the toxic syndrome
Obtain a thorough history
Reassess and complete the physical examination
Send bloods: electrolytes, glucose, CBC, ABG,(or VBG), acetaminophen, as indicated
Consider gastric emptying with orogastric lavage
Consider prevention of xenobiotic absorption with
1. Activated charcoal
2. Whole-bowel irrigation
Evaluate for enhanced elimination
1. Multiple-dose activated charcoal
2. Urinary alkalinization
3. Extracorporeal drug removal
Evaluate for ICU admission or continued emergency department management; assess psychiatric status, and determine social services needs prior to discharge, as indicated

Figure 4-1. This algorithm is a basic guide to the management of poisoned patients. A more detailed description of the steps in management may be found in the accompanying text. This algorithm is only a guide to actual management, which must, of course, consider the patient's clinical status.

TABLE 4-1. Antidotes and Therapeutics for the Treatment of Poisonings and Overdoses[a]

Therapeutics[b]	Uses
Activated charcoal (p. 128)	Adsorbs xenobiotics in GI tract
Antivenom *(Crotalinae)* (p. 1657)	Crotaline snake envenomations
Antivenom *(Latrodectus mactans)* (p. 1623)	Black widow spider envenomations
Antivenom *(Elapidae)* (p. 1657)	Coral snake envenomations
Atropine (p. 1519)	Bradydysrhythmias, cholinesterase inhibitors (organic phosphorus agents, physostigmine) muscarinic mushrooms *(Clitocybe*, *Inocybe)* ingestions

Botulinum antitoxin (ABE-trivalent) (p. 728)	Botulism
Calcium chloride, calcium gluconate (p. 1424)	Fluoride, hydrofluoric acid, ethylene glycol, calcium channel blockers, hypomagnesemia, Î²-adrenergic antagonists
L-Carnitine (p. 746)	Valproic acid
Cyanide kit (nitrites, p. 1725, sodium thiosulfate, p. 1728)	Cyanide
Dantrolene (p. 1037)	Malignant hyperthermia
Deferoxamine mesylate (Desferal) (p. 638)	Iron
Dextrose in water (50% adults; 20% pediatrics; 10% neonates) (p. 764)	Hypoglycemia
Diazepam or lorazepam	Seizures, agitation, stimulants, ethanol and sedative-hypnotic withdrawal
Digoxin-specific antibody fragments (Digibind and Digifab) (p. 983)	Cardioactive steroids

Dimercaprol (BAL, British anti-Lewisite) (p. 1265)	Arsenic, mercury, gold, and lead
Diphenhydramine	Dystonic reactions, allergic reactions
Edetate calcium disodium (calcium disodium versenate, $CaNa_2$ EDTA) (p. 1331)	Lead, and other selected metals
Ethanol (oral and parenteral dosage forms) (p. 1465)	Methanol and ethylene glycol
Flumazenil (Romazicon) (p. 1112)	Benzodiazepine
Folinic acid (Leucovorin) (p. 826)	Methotrexate, methanol
Fomepizole (Antizole) (p. 1460)	Ethylene glycol, methanol
Glucagon (p. 942)	Î²-Adrenergic antagonists and calcium channel blockers
Hydroxocobalamin (p. 1731)	Cyanide

Ipecac, syrup of (p. 124)	Induces emesis
Magnesium sulfate or magnesium citrate (p. 135)	Induces catharsis
Magnesium sulfate injection	Cardioactive steroids, hydrofluoric acid, hypomagnesemia, ethanol withdrawal, torsades de pointes
Methylene blue (1% solution) (p. 1746)	Methemoglobinemia
N-acetylcysteine (Mucomyst and Acetadote) (p. 544)	Acetaminophen and other causes of liver failure
Naloxone hydrochloride (Narcan) (p. 614)	Opioids, clonidine
Norepinephrine (Levarterenol)	Hypotension (preferred for cyclic antidepressants)
Octreotide (Sandostatin) (p. 770)	Oral hypoglycemic agent-induced hypoglycemia
Oxygen (oxygen, hyperbaric) (p. 1705)	Carbon monoxide, cyanide, hydrogen sulfide

D-Penicillamine (Cuprimine) (p. 1303)	Copper, lead
Phenobarbital	Seizures, agitation, stimulants, ethanol and sedative-hypnotic withdrawal
Phentolamine (p. 1140)	MAOI interactions, cocaine, epinephrine, and ergot alkaloids
Physostigmine salicylate (Antilirium) (p. 794)	Anticholinergics
Polyethylene glycol electrolyte solution (p. 135)	Decontaminates GI tract
Pralidoxime chloride (2-PAM-chloride) (Protopam) (p. 1513)	Acetylcholinesterase inhibitors (organic phosphorus agents and carbamates)
Protamine sulfate (p. 907)	Heparin anticoagulation
Prussian blue (Radiogardase) (p. 1373)	Thallium and radioactive cesium
Pyridoxine hydrochloride (Vitamin B_6) (p. 872)	Ethylene glycol, isoniazid, gyromitrin-containing mushrooms

Sodium bicarbonate (p. 565)	Ethylene glycol, methanol, salicylates, cyclic antidepressant, methotrexate, phenobarbital, quinidine, chlorpropamide, type 1 antidysrhythmics, chlorphenoxy herbicide
Sorbitol (p. 135)	Induces catharsis
SSKI (p. 1816)	Radioactive iodine
Starch (p. 1388)	Iodine
Succimer (Chemet) (p. 1325)	Lead, mercury, arsenic
Thiamine hydrochloride (p. 1162)	Thiamine deficiency, ethylene glycol, chronic ethanol consumption (â€œalcoholismâ€•)
Vitamin K_1 (Aquamephyton) (p. 903)	Warfarin or rodenticide anticoagulant

[a]Each emergency department should have all the above agents readily available to its staff. Some of these antidotes may be stored in the pharmacy, and others may be available from the Centers for Disease Control and Prevention, but the precise mechanism for locating each one must be known by each staff member.

[b]A detailed analysis of each of these agents is found in the

text, in the Antidotes in Depth section on the page cited to the right of each therapeutic agent listed.

P.45

P.46

Patients with a suspected overdose or poisoning and an altered mental status present some of the most serious initial challenges. Conscious patients, asymptomatic patients, and pregnant patients with possible xenobiotics exposures raise additional management issues, as do the victims of toxic cutaneous or ophthalmic exposures. One of the most frequent toxicologic emergencies that clinicians must deal with is a patient with a suspected toxic exposure to an unidentified xenobiotic (medication or substance), sometimes referred to as an *unknown overdose.* Considering not only those patients who have an altered mental status but those who are suicidal, those who use illicit drugs, or those who are exposed to xenobiotics that they are unaware of, many toxicologic emergencies at least partly involve an unknown component.

Initial Management of a Patient with a Suspected Exposure

Similar to the management of any seriously compromised patient, the clinical approach to the patient potentially exposed to a xenobiotic begins with the recognition and treatment of life-threatening conditions: airway compromise, breathing difficulties, and circulatory problems such as hemodynamic instability and serious dysrhythmias. Once the â€œABCsâ€• (airway, breathing, and circulation) are addressed, the patient's level of consciousness should be assessed, as this helps determine the techniques to be used for further management of the exposure.

The Patient with an Altered Mental

Status

After airway patency is established or secured and, when indicated, cervical spine trauma either excluded or the cervical spine protected, an initial bedside assessment should be made regarding the adequacy of respiration. If it is not possible to assess the depth and rate of respiration, then at least the presence or absence of regular breathing should be determined. In this setting, any irregular breathing pattern should be considered a possible sign of the incipient cessation of breathing requiring ventilation with 100% oxygen by bag-valve-mask followed, as soon as possible, by endotracheal intubation and mechanical ventilation. Endotracheal intubation may be indicated for some cases of coma resulting from a toxic exposure in order to insure and maintain control of the airway and to enable safe performance of procedures to prevent gastrointestinal absorption or eliminate previously absorbed xenobiotics.

Although the widespread availability of pulse oximetry to determine O_2 saturation has in many instances made an ABG analysis less of an immediate priority, pulse oximetry has not eliminated the importance of ABG analysis entirely: an ABG determination will more accurately define the adequacy not only of oxygenation (PO_2, O_2 saturation) and ventilation (PCO_2), but may also alert the physician to possible toxic-metabolic etiologies of coma characterized by acid base disturbances (pH, PCO_2) (Chap. 17). In addition, when clinically indicated, a carboxyhemoglobin determination is necessary to diagnose or exclude carbon monoxide poisoning (Chap. 120). In all cases, a bedside rapid reagent blood glucose determination should be obtained as soon as possible.

After the patient's respiratory status is assessed and managed appropriately, the strength, rate, and regularity of the pulse should be evaluated, the blood pressure determined, and a rectal temperature obtained. Both a 12-lead ECG and continuous ECG monitoring are essential. Monitoring will alert the clinician to

dysrhythmias that are related to toxic exposures either directly, or indirectly via hypoxemia or electrolyte imbalance. A 12-lead ECG demonstrating QRS widening and a right axis deviation might indicate a life-threatening exposure to a cyclic antidepressant, an IA or IC antidysrhythmics, or another xenobiotic with sodium-channel-blocking properties. In these cases, the physician can anticipate such serious sequelae as ventricular tachydysrhythmias, seizures, and cardiac arrest, and consider both the early use of specific treatment (antidotes), such as intravenous sodium bicarbonate, and avoiding medications, such as procainamide and other IA and IC antidysrhythmics, that could exacerbate the situation. Other ECG changes such as PR and QTc interval lengthening or shortening, baseline changes, and T- and U-wave abnormalities may point to cardioactive drug toxicity or serious electrolyte abnormalities (Chap. 5).

Extremes of core body temperature must be addressed early in the evaluation and treatment of a comatose patient. Life-threatening hyperthermia (temperature >105Â°F; >40.5Â°C) is usually appreciated when the patient is touched (although the widespread use of gloves as part of standard precautions has made this less apparent than previously). Most of these individuals, regardless of the etiology, should have their temperatures immediately reduced to about 101.5Â°F (38.7Â°C) by ice water immersion to prevent catastrophic complications or death (Chap. 16). Hypothermia is probably easier to miss than hyperthermia, especially in northern regions during winter months, when most arriving patients feel cold to the touch. Early recognition of hypothermia, however, helps to avoid administering a variety of medications that may be ineffective until the patient becomes relatively euthermic when iatrogenic drug toxicity may result.

For the hypotensive patient with clear lungs and an unknown overdose, a fluid challenge with intravenous 0.9% sodium chloride or lactated Ringer solution may be started. If the patient remains hypotensive or cannot tolerate fluids, a vasopressor or an inotropic

agent may be indicated, as well as more invasive monitoring.

At the time that the IV catheter is inserted, blood samples for glucose, electrolytes, BUN, a CBC, and any indicated toxicologic analysis can be drawn. If the patient has an altered mental status, there may be a temptation to send blood and urine specimens to identify any CNS depressants and/or so-called drugs of abuse, along with other medications, but the indiscriminate ordering of these tests rarely provides clinically useful information. For the potentially suicidal patient, an acetaminophen concentration should be routinely requested, along with tests affecting the management of any specific xenobiotic such as carbon monoxide, lithium, theophylline, iron, salicylates, and digoxin (or other cardioactive steroids), as suggested by history, physical examination, or bedside diagnostic tests. In the vast majority of cases, the blood tests that are most useful in diagnosing toxicologic emergencies are not the toxicologic assays but the â€œnontoxicologicâ€• routine metabolic profile tests such as BUN, glucose, electrolytes, and ABGs or venous blood gases (VBGs).

Xenobiotic-related seizures may broadly be divided into three categories: (a) those that respond to standard anticonvulsant treatment (typically a benzodiazepine); (b) those that either require specific antidotes to control seizure activity or that do not respond consistently to standard anticonvulsant treatment, such as isoniazid-induced seizures requiring pyridoxine administration; and (c) those that may *appear* to respond to initial treatment with cessation of tonicâ€“clonic activity, but which leave the patient exposed to the underlying, unidentified toxin or to continued electrical seizure activity in the brain, such as carbon monoxide or hypoglycemia.

Within the first 5 minutes of managing a patient with an altered mental status, 4 therapeutic agents should be *considered*, and if indicated, administered: (a) hypertonic dextrose 0.5â€“1.0 g/kg of $D_{50}W$ for an adult, or a more dilute dextrose solution ($D_{10}W$ or $D_{25}W$)

for a child. The dextrose is administered to diagnose and treat or exclude hypoglycemia; (b) thiamine 100 mg IV for an adult (usually unnecessary for a child) to prevent or treat Wernicke encephalopathy; (c) naloxone 0.05 mg IV for an adult or child with opioid (or clonidine)-induced respiratory compromise; and (d) high-flow oxygen (8â€“10 L/min) to treat a variety of xenobiotic-induced hypoxic conditions.

The clinician must consider that hypoglycemia may be the sole or contributing cause of coma even when the patient manifests focal neurologic findings and therefore dextrose administration should only be omitted when hypoglycemia can be definitely excluded by accurate rapid reagent bedside testing. Also, while examining a patient with an altered mental status (AMS) for clues to the etiology of a presumably toxic-metabolic form of AMS, it is important to search for any indication that trauma may have caused, contributed to, or resulted from the patient's condition. Conversely, the possibility of a concomitant drug ingestion or toxic metabolic disorder in the patient with obvious head trauma should also be considered.

The remainder of the physical examination should be performed rapidly, but thoroughly. In addition to evaluating the patient's level of consciousness, the physician should note abnormal posturing (decorticate or decerebrate), abnormal or unilateral withdrawal responses, and pupil size and reactivity. Pinpoint pupils suggest exposure to opioids or organic phosphorus insecticides, and widely dilated pupils suggest anticholinergic or sympathomimetic poisoning. The presence or absence of nystagmus, abnormal reflexes, and any other focal neurologic findings may provide important clues to a structural cause of AMS. For those clinicians accustomed to applying the Glasgow Coma Score (GCS) to all patients with altered mental status, assigning a score to the overdosed or poisoned patient may provide a useful measure for assessing changes in neurologic status, but in this situation, *the GCS should never be used for prognostic purposes*, because complete recovery from properly managed toxic-metabolic coma despite a low GCS is the rule rather than the

exception.

Characteristic breath or skin odors may identify the etiology of coma. The fruity odor of ketones on the breath suggests diabetic or alcoholic ketoacidosis, but also the possible ingestion of acetone or isopropyl alcohol, which is metabolized to acetone. The pungent, minty odor of oil of wintergreen on the breath or skin suggests methyl salicylate poisoning. The odors of other substances such as cyanide (â€œbitter almondsâ€•), hydrogen sulfide (â€œrotten eggsâ€•), and organic phosphorus compounds (â€œgarlicâ€•) are described in detail in Chap. 21 and summarized in Table 21-1.

Further Evaluation of all Patients with Suspected Xenobiotic Exposures

Reauscultation of breath sounds, particularly after a fluid challenge, helps to diagnose pulmonary edema, acute lung injury, or aspiration pneumonia when present. Coupled with an abnormal breath odor of hydrocarbons or organic phosphorus compounds, for example, crackles and rhonchi may point to a pulmonary *etiology* instead of a cardiac etiology; this is important because the administration of cardiac medications may be inappropriate or dangerous in these circumstances.

Heart murmurs in an injection drug user, especially when accompanied by fever, may indicate bacterial endocarditis. Dysrhythmias may suggest overdoses or inappropriate use of cardioactive medications (such as digoxin and other cardioactive steroids, Î²-adrenergic antagonists, calcium channel blockers, and cyclic antidepressants).

The abdominal examination may reveal signs of trauma or alcohol-related hepatic disease. The presence or absence of bowel sounds helps to exclude or to diagnose anticholinergic toxicity and is important in considering whether to manipulate the gastrointestinal tract in an attempt to remove toxin.

Examination of the extremities might reveal clues to current or former drug use (track marks, skin-popping scars), metal poisoning (Mees lines, arsenical dermatitis), and the presence of cyanosis or edema suggesting preexisting cardiac, pulmonary, or renal disease.

Repeated evaluation of the patient suspected of an overdose is essential for identifying new or developing findings or toxic syndromes, and for early identification and treatment of a deteriorating condition. Until the patient is completely recovered or considered no longer at risk for the consequences of a xenobiotic exposure, frequent reassessment must be provided, even as the procedures described below are carried out. Toxicologic etiologies of abnormal vital signs and physical findings are summarized in Tables 3-1, 3-2, 3-3, 3-4, 3-5, 3-6 and 3-7. Toxic syndromes, sometimes called â€œtoxidromes,â€• are summarized in Table 3-2.

Typically in the management of patients with toxicologic emergencies, there is both a necessity and an opportunity to obtain various diagnostic studies and ancillary tests interspersed with stabilizing the patient's condition, obtaining the history, and performing the physical examination exist. Chaps. 5, 6, and 7 discuss the timing and indications for qualitative and quantitative diagnostic laboratory studies, the use and interpretation of the electrocardiogram, and diagnostic imaging procedures in evaluating and managing the poisoned or overdosed patient.

The Role for Gastrointestinal Evacuation

A series of highly individualized treatment decisions must now be made. As noted previously and as discussed in detail in Chap. 8, the decision to evacuate the GI tract and/or administer AC can no longer be considered standard or routine toxicologic care for all patients. Instead, the decision should be based on the type of ingestion; estimated quantity and size; time since ingestion; concurrent ingestions; ancillary medical conditions; and age and size of the patient. The indications, contraindications, and procedures for

performing orogastric lavage and for administering WBI, AC,

MDAC, and cathartics are listed in Tables 8-1, 8-2, 8-3 and 8-4 and discussed both in Chap. 8 and in the specific Antidotes in Depth sections immediately following Chap. 8.

Eliminating Absorbed Xenobiotics from the Body

After deciding whether or not an intervention to try to *prevent* absorption of a xenobiotic is indicated, the clinician must next consider the applicability of techniques available to eliminate xenobiotics already absorbed. Detailed discussions of the indications for and techniques of manipulating urinary pH (ion trapping), diuresis, hemodialysis, hemoperfusion, hemofiltration, and exchange transfusion are found in Chap. 10. Briefly, patients who may benefit from these procedures are those who have systemically absorbed xenobiotics amenable to one of these techniques and whose clinical condition is both serious (or potentially serious) and unresponsive to supportive care, or whose physiologic route of elimination (liverâ€“stools, kidneyâ€“urine) is impaired.

Alkalinization of the urinary pH for acidic xenobiotics has only limited applicability. Commonly, sodium bicarbonate can be used to alkalinize the urine (as well as the blood) and enhance salicylate, phenobarbital, and chlorpropamide elimination and prevent toxicity from methotrexate (see Antidotes in Depth: Sodium Bicarbonate). Attempts to acidify the urine in order to hasten the elimination of alkaline substances is difficult to accomplish, probably useless, possibly dangerous, and therefore has no role in poison management. *Forced diuresis* has no indication and may endanger the patient by causing pulmonary or cerebral edema.

If extracorporeal elimination is contemplated, consider *hemodialysis* (HD) for salicylates, methanol, ethylene glycol, lithium, and drugs

that are both dialyzable and cause fluid and electrolyte problems. If available, consider *hemoperfusion* (HP) for theophylline, phenobarbital, phenytoin, and carbamazepine (though rarely, if ever, for the last three). When HP is the method of choice (as for a theophylline overdose) but not available, HD is a logical, effective alternative and certainly preferable to delaying treatment until HP becomes available. *Peritoneal dialysis* (PD) is too ineffective to be of practical utility, and *hemofiltration* (HF) is not as efficacious as HD or HP, although it may play a role between multiple runs of dialysis. In theory, both HD and HP *in series* may be useful for certain life-threatening overdoses such as salicylates.

Avoiding Pitfalls

The history alone is not a reliable indication of which patients require naloxone, hypertonic dextrose, thiamine, and oxygen. Instead, these therapies should be *considered* for all patients with altered mental status, unless specifically contraindicated. The physical examination should be used to guide the use of naloxone. If dextrose or naloxone is indicated, sufficient amounts should be administered to exclude and/or treat hypoglycemia or opioid toxicity, respectively.

In a patient with a suspected or unknown overdose, avoid the use of vasopressors in the initial management of hypotension prior to administering fluids or assessing filling pressures.

Attributing an altered mental status to alcohol because of its odor on a patient's breath is potentially dangerous and misleading: Small amounts of alcohol and its congeners generally produce the same breath odor as do intoxicating amounts. Conversely, even when an extremely high blood-ethanol concentration is *confirmed* by the laboratory, it is dangerous to ignore other possible etiologies of an altered mental status; chronic alcoholics may be awake and seemingly alert with ethanol concentrations in excess of 500 mg/dL, a concentration that would result in coma and possibly apnea and death in a nonalcoholic patient.

The metabolism of ethanol is fairly constant at 15â€“30 mg/dL/h. Therefore, as a general rule, regardless of the initial blood alcohol concentration, a presumably â€œinebriatedâ€• comatose patient who is still unarousable 3â€“4 hours after arrival should be considered to have structural CNS damage (head trauma) and/or another toxic-metabolic etiology for the alteration in consciousness, until proven otherwise. Careful neurologic evaluation supplemented by a head CT scan is frequently indicated in such a case. This is especially important in dealing with a seemingly â€œintoxicatedâ€• patient who appears to have only a minor bruise, as the early treatment of a subdural or epidural hematoma or subarachnoid hemorrhage is critical to a successful outcome.

Additional Considerations in Managing a Patient with a Normal Mental Status

As in the case of the patient with AMS, vital signs must be obtained and recorded. Initially, an assumption may have been made that the patient was breathing adequately, and if the patient is alert, talking and in no respiratory distress, all that remains to document is the respiratory rate and rhythm. Because the patient is alert, additional history should be obtained, keeping in mind that information regarding the number and types of xenobiotics ingested, time elapsed, prior vomiting and other critical information may be unreliable, depending in part on whether the ingestion was intentional or unintentional.

When indicated for the potential benefit of the patient, another history should be privately and independently obtained from a friend or relative after the patient has been initially stabilized. Recent emphasis on compliance with the federal Health Insurance Portability and Accountability Act (HIPAA) may inappropriately discourage clinicians from attempting to obtain information necessary to evaluate and treat patients. Obtaining such information from a friend or relative without unnecessarily giving that person information

about the patient may be the key to successfully helping such a patient without violating confidentiality.

Speaking to a friend or relative of the patient may provide an opportunity to learn useful and reliable information regarding the ingestion, the patient's frame of mind, a history of previous ingestions, and the type of support that is available should the patient be discharged from the ED. At times, it may be essential to initially separate the patient from any relatives or friends in order to obtain greater cooperation from the patient, avoid violating confidentiality and also because their anxiety may interfere with therapy. Even if the history obtained from a patient with an overdose proves to be unreliable, it may nevertheless provide clues to an overlooked possibility or a second ingestant or reveal the patient's mental and emotional condition. As is often true of the history, physical examination, or laboratory assessment in other clinical situations, the information obtained may confirm but never exclude possible etiologies.

At this point in the management of a conscious patient, a focused physical examination should be performed, concentrating on the pulmonary, cardiac and abdominal examinations. A neurologic survey should emphasize reflexes and/or any focal findings.

Approaching the Patient with an Intentional Exposure

Initial efforts at establishing rapport with the patient by indicating to the patient concern about the problems that led to the ingestion and the availability of help after the xenobiotic is removed (if such procedures are planned), may help make management easier. If gastrointestinal decontamination is deemed necessary, the reason for and nature of the procedure should be clearly explained to the patient together with reassurance that after the procedure is

completed, there will be ample time to discuss related problems and provide additional care. These considerations are especially important in managing the patient with an intentional overdose who may be seeking psychiatric help or emotional support. In deciding on the necessity of gastrointestinal decontamination, it is important to consider that a resistant patient may transform a procedure of only potential value into one with predictable adverse consequences.

Special Considerations for Managing the Pregnant Patient

In general, a successful outcome for both mother and fetus is dependent on optimum management of the mother and proven effective treatment for a potentially serious toxic exposure to the mother should never be withheld based on theoretical concerns regarding the fetus.

Physiologic Factors

A pregnant woman's total blood volume and cardiac output are elevated through the second trimester and into the later stages of the third trimester. This means that signs of hypoperfusion and hypotension will manifest later than they would in a woman who is not pregnant and when they do, uterine blood flow may already be compromised. For these reasons, the possibility of hypotension in the pregnant woman must be more aggressively sought and, if found, more rapidly treated. Maintaining the patient in the left-lateral decubitus position will help prevent supine hypotension resulting from impairment of systemic venous return by compression of the inferior vena cava. The left lateral decubitus position is also the preferred position for orogastric lavage, deemed necessary.

Because the tidal volume is increased in pregnancy, the baseline PCO_2 will normally be lower by approximately 10 mm Hg. Appropriate adjustment for this effect should be made when interpreting arterial

blood gas results.

Use of Antidotes

Few data are available on the use of antidotes in pregnancy. In general, antidotes should not be used if the indications for use are equivocal. On the other hand, antidotes should not be withheld if their use may reduce potential morbidity and mortality. Risks and benefits of either decision must be considered. For example, reversal of opioid-induced respiratory depression calls for the use of naloxone, but in an opioid-dependent woman, the naloxone can precipitate acute withdrawal, including uterine contractions and possible induction of labor. Very slow, careful, intravenous titration starting with 0.05 mg naloxone may be indicated, unless apnea is present, cessation of breathing appears imminent, or the PO_2 or O_2 saturation is already grossly inadequate. In these instances, naloxone may have to be administered in higher doses (ie, 0.4â€“2.0 mg) or assisted ventilation provided or a combination of assisted ventilation and small doses of naloxone used.

An acetaminophen overdose is a serious *maternal* problem when it occurs throughout pregnancy, but the *fetus* is at greatest risk in the third trimester. Although acetaminophen crosses the placenta easily, *N*-acetylcysteine has somewhat diminished transplacental passage. During the third trimester, when both the mother and the fetus may be at substantial risk from a significant acetaminophen overdose, immediate delivery of a mature or viable fetus may need to be considered.

In contrast to the situation with acetaminophen, the fetal risk from iron poisoning is less than the maternal risk. Because deferoxamine is a large charged molecule with little transplacental transport, deferoxamine should never be withheld out of unwarranted concern for fetal toxicity when indicated to treat the mother.

Carbon monoxide (CO) poisoning is particularly threatening to fetal

survival. The normal PO_2 of the fetal blood is approximately 15â€“20 mm Hg. Oxygen delivery to fetal tissues is impaired by the presence of carboxyhemoglobin, which shifts the oxyhemoglobin dissociation curve to the left, potentially compromising an already tenuous balance. For this reason, hyperbaric oxygen (HBO) is recommended for much lower carboxyhemoglobin concentrations in the pregnant compared to the nonpregnant woman (Chap. 120 and Antidotes in Depth: Hyperbaric Oxygen). Early notification of the obstetrician and close cooperation among involved physicians are essential for best results in all of these instances.

Management of Patients with Cutaneous Exposure

The xenobiotics that people are commonly exposed to externally include household cleaning materials; organic phosphorus or carbamate insecticides from crop dusting, gardening, or pest extermination; acids from leaking or exploding batteries; alkalis, such as lye; and lacrimating agents that are used in crowd control. In all cases, the principles of management are as follows:

- Avoid secondary exposures by wearing protective (rubber or plastic) gowns, gloves, and shoe covers. Cases of serious secondary poisoning have occurred in emergency personnel after contact with xenobiotics such as organic phosphorus compounds on the victim's skin or clothing.
- Remove the patient's clothing and place it in plastic bags, then seal it.
- Wash the patient with soap and copious amounts of water *twice*, regardless of how much time has elapsed since the exposure.
- Make no attempt to neutralize an acid with a base, or a base with an acid. Further tissue damage may result from the heat generated by this reaction.

- Avoid using any greases or creams as they will only keep the xenobiotic in close contact with the skin and ultimately make removal more difficult.

Chap. 29 discusses the principles of managing cutaneous exposures.

Management of Patients with Ophthalmic Exposures

Although the vast majority of toxicologic emergencies result from ingestion, injection, or inhalation, the eyes are occasionally the routes of systemic absorption or are the organs at risk. The eyes should be irrigated with lids fully retracted for no less than 20 minutes. To facilitate irrigation, a drop of an anesthetic (eg, proparacaine) in each eye may be used and the eyelids should be kept open with a lid retractor. An adequate irrigation stream may be obtained by running 1 L of normal saline through regular IV tubing held a few inches from the eye or by using an irrigating lens. Checking the lid fornices with pH paper strips is important to ensure adequate irrigation; the pH should normally be 6.5â€“7.6 if accurately tested, although when using paper test strips, the measurement will often be near 8.0. Chap. 20 describes the management of toxic ophthalmic exposures in more detail.

Identifying the Patient with a Nontoxic Exposure

There is ample opportunity to needlessly subject a patient to potential harm when the patient with a nontoxic exposure is treated aggressively with gastrointestinal evacuation techniques and other forms of management indicated for serious exposures. More than 40% of exposures reported to poison centers annually are judged to be nontoxic. The following general guidelines for considering an

exposure nontoxic or minimally toxic will assist clinical decision making:

- Identification of the product and its ingredients is possible.
- None of the US Consumer Product Safety Commission â€œsignal wordsâ€• â€”CAUTION, WARNING, or DANGERâ€”appear on the product label.
- The history permits the route(s) of exposure to be determined.
- The history permits a reliable approximation of the maximum quantity involved with the exposure.
- Based on the available medical literature and clinical experience, the potential effects related to the exposure are expected to be at most benign and self-limited, and do not require referral to health care.
- The patient is asymptomatic, or has developed the expected benign self-limited toxicity.

(Adapted from McGuigan MA, Guideline Consensus Panel: Guideline for the out-of-hospital management of human exposures to minimally toxic substances. J Toxicol Clin Toxicol 2003;41:907â€“917; and Mofenson HC, Greensher J: The nontoxic ingestion. Pediatr Clin North Am 1970;17:583â€“590.)

Assuring Optimal outcome for the Patient

The best way to assure an optimal outcome for the patient with a suspected toxic exposure is to apply the principles of basic and advanced life support in conjunction with a planned and staged approach, always bearing in mind that a toxicologic etiology or coetiology for any abnormal conditions necessitates modifying whatever standard approach is brought to the bedside of a severely

ill patient. For example, it is extremely important to recognize that xenobiotic-induced dysrhythmias and cardiac instability require alterations in standard protocols that assume a primary cardiac or nontoxicologic etiology (Chap. 23).

Typically, only some of the xenobiotics to which a patient is exposed will ever be confirmed by laboratory analysis. The thoughtful combination of stabilization, general management principles, and specific treatment when indicated, will result in successful outcomes in the vast majority of patients with actual or suspected exposures.

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Chapter 5
Electrocardiographic Principles

Cathleen Clancy

The electrocardiogram (ECG) is ubiquitous in emergency departments and intensive care units and its interpretation is widely understood by physicians of nearly all disciplines. It is an invaluable diagnostic tool for patients with acute cardiovascular complaints. However, it is also a valuable source of information in poisoned patients and has the potential to enhance and direct their care. Although it seems obvious that an ECG would be required following exposure to a drug used for cardiovascular indications, many drugs with no overt cardiovascular effects with therapeutic dosing become cardiotoxic in overdose. In patients with unknown exposures, the ECG can suggest specific xenobiotics or demonstrate electrolyte abnormalities, long before blood is even drawn. For example, oropharyngeal or dermal burns in a patient whose ECG has evidence of hyperkalemia or hypocalcemia suggests exposure to hydrofluoric acid.[47, 48] Alternatively, a patient manifesting signs of the opioid toxidrome with runs of ventricular tachycardia might have been exposed to propoxyphene.[25] QTc prolongation may be a clue to the etiology of an overdose with an atypical antipsychotic agent such as

quetiapine. The ECG can also be used to predict complications of poisoning, such as seizures following a tricyclic antidepressant overdose. Therefore, an ECG should be examined critically early in the initial evaluation of most poisoned patients.

History

The knowledge of a relationship between electricity and muscular movement can be traced back to 1790, when Luigi Galvani electrically stimulated an ex vivo preparation of the legs of a frog, and made them â€œdance.â€• In 1887, Waller developed a â€œcapillary electrometerâ€• that transmitted electrical impulses from a man's skin to a capillary tube. Pulsations similar to the patient's heartbeat were visible in the tube.[43] In the 1900s, Willem Einthoven graphically displayed the electrical activity of the heart and named the different wavesâ€”P, QRS, and T. He called this tracing an â€œelektrokardiogramme.â€• In 1924, he was awarded a Nobel Prize for his efforts. The acronym *EKG* , still employed by some authors, was derived from Einthoven's spelling. The acronym *ECG* , which is consistent with our current spelling of electrocardiogram, is used throughout this text.

Since this initial description, both the normal electrophysiology of the heart and the pharmacologic effects of various xenobiotics on the ECG have been described. Despite the large number, diversity, and complexity of the various cardiac toxins, there are only a limited number of electrocardiographic manifestations.

Basic Electrophysiology of the Myocardial Cell

The resting myocardial cell, or myocyte, is negatively charged, or polarized. When the myocytes in the sinus node depolarize, ion channels in the nearby myocardium open and allow a net influx of positively charged sodium and calcium ions. This influx raises the

electrical potential of the cell toward and then past neutral and initiates an impulse that propagates throughout the myocardium, producing electrical and mechanical systole. The membrane depolarization is maintained by an outward potassium current and an inward calcium current throughout systole. After a well-defined time period the myocardial membrane is repolarized by a growing outward current of potassium and a reduction in the inward calcium current. Final repolarization requires the repartitioning of sodium out of the cell and potassium into the cell by an adenosine triphosphate (ATP)-using pump [ATPase] (Table 5-1).

Figure 5-1 shows schematically the relationship of the major ion flux across the myocardial cell membrane, the phases of the action potential, and the surface ECG recording. Chap. 23 provides a more detailed description of ion fluxes and channels.

Basic Electrophysiology of an Electrocardiogram

Simplistically, a positive or upward deflection on the oscilloscope is generated when an electrical force moves toward an electrical sensor or electrode, and a downward deflection occurs if the force moves away. An ECG represents the sum of movement of all electrical forces in the heart in relation to the surface electrode, and the height above baseline represents the magnitude of the force

(Fig. 5-2). Only during depolarization or repolarization does the ECG tracing leave the isoelectric baseline, because it is only during these periods that measurable currents are flowing in the heart. During the other periods, mechanical effects are occurring in the myocardium, but large amounts of current are not flowing.

Calcium
Positive

Inward
Inward
Depolarization
Sodium
Positive
Inward
Inward
Depolarization
Potassium
Positive
Outward
Outward
Repolarization
Chloride
Negative
Inward
Outward
Repolarization
Reproduced, with permission, from Katz AM: Cardiac ion channels. N Engl J Med

Ion	Charge	Direction of Passive Flux	Current Generated	Effect of Membrane Potential

TABLE 5-1. Ions as Charge Carriers Across Cell Membranes

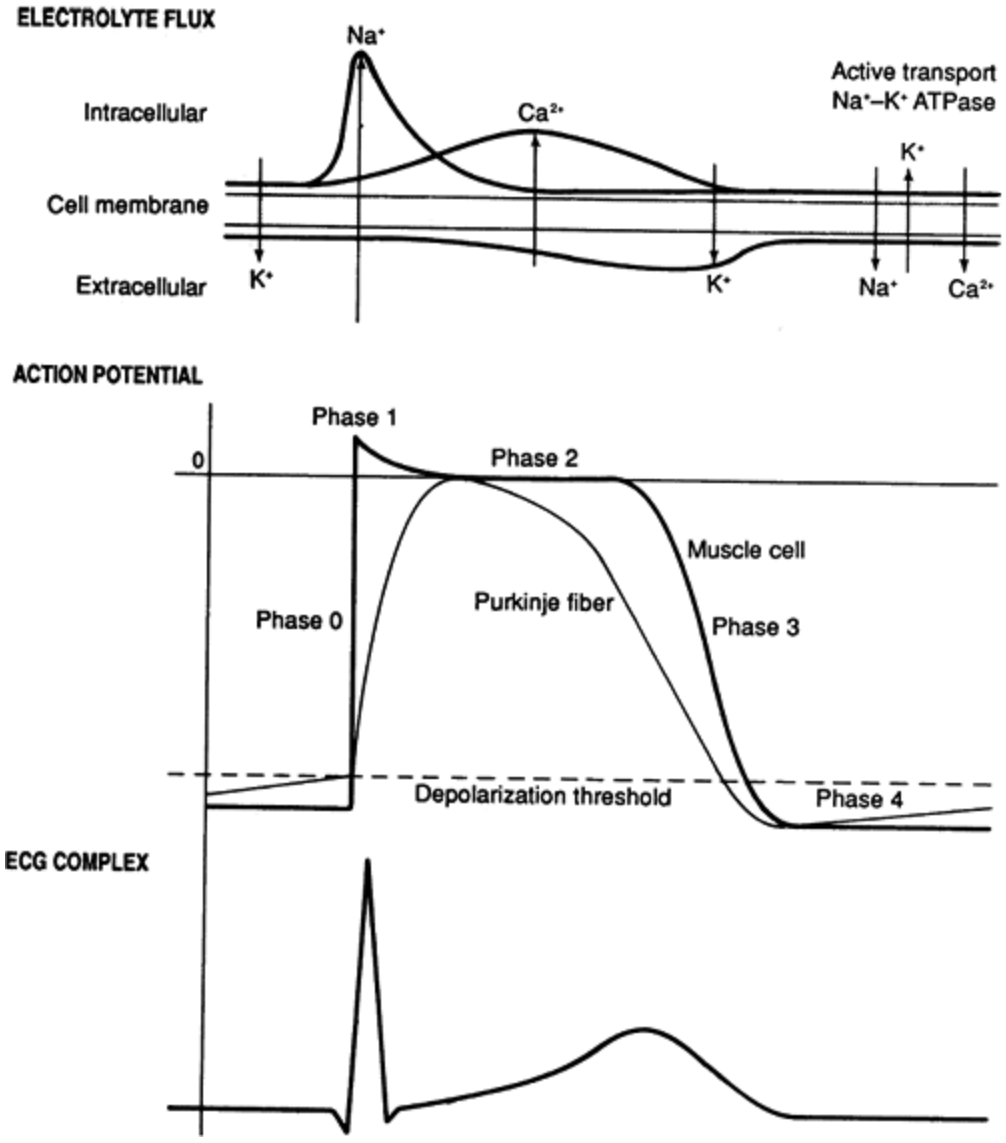

Figure 5-1. Relationship of electrolyte movement across the cell membrane to the action potential and the surface ECG recording.

Leads

Although the reading from a single electrocardiogram lead provides an immense amount of information, to visualize the heart in a nearly three-dimensional perspective, multiple leads must be assessed simultaneously. Given the cylindrical nature of both the heart and thorax, at any given moment some of these leads will

record positive voltage and others negative. The lead placement that was described and refined in the early 1900s by Einthoven forms the basis for the bipolar or limb leads, described as I, II, and III (Fig. 5-3). The Einthoven triangle is an equilateral triangle formed by the sum of these leads. Unipolar limb leads and precordial leads were subsequently added to the standard electrocardiogram. Wilson and colleagues connected limb leads, called V_R , V_L , and V_F , to a common point where the sum of the potentials from

leads I, II, and III was zero. A unipolar potential was measured.[44] The currently used, augmented (a) leads (aV_R , aV_L , and aV_F) are based on these unipolar leads (Fig. 5-4).[16] The precordial leads, called V_1 through V_6 , are also unipolar measurements of the change in electric potential measured from a central point to the 6 anterior and left lateral chest positions (Fig. 5-5). If V_2 is placed over the right ventricle, part of the initial positive ventricular deflection (QRS complex) reflects right ventricular activation, with electrical forces moving toward the electrode. The majority of the subsequent terminal negative deflection reflects activation of other muscle tissue (septum, left ventricular wall) when the electrical forces are moving away from the electrode. Recordings from each of these 12 leads (I, II, III, aV_R , aV_L , aV_F , $V_{1â€“6}$) evaluate the heart from two different planes in 12 different positions, yielding a three-dimensional electrical â€œpictureâ€• of the heart, with respect to time and voltage.

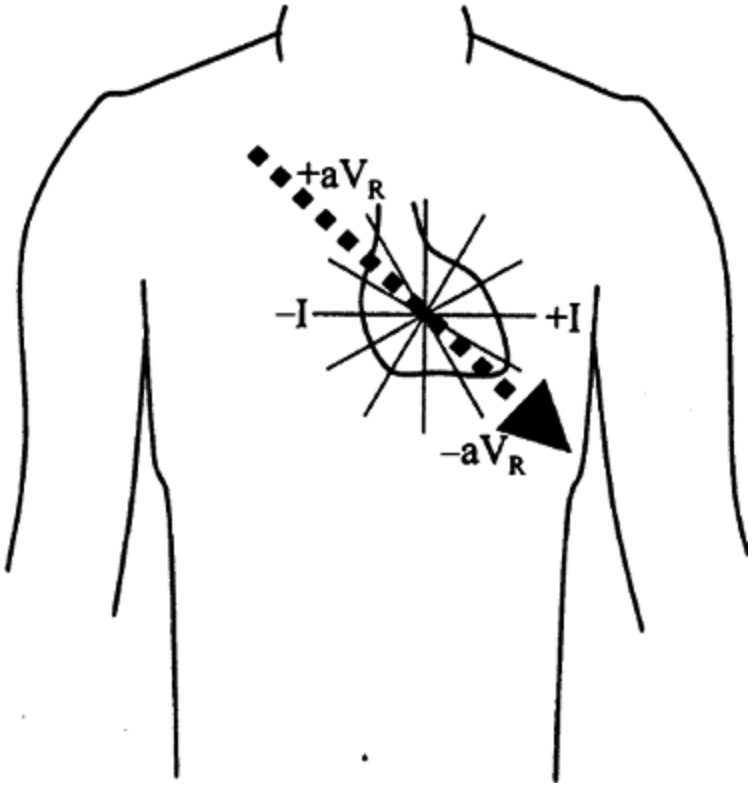

Figure 5-2. A simplistic correlation between cardiac anatomy and electrocardiographic representation.

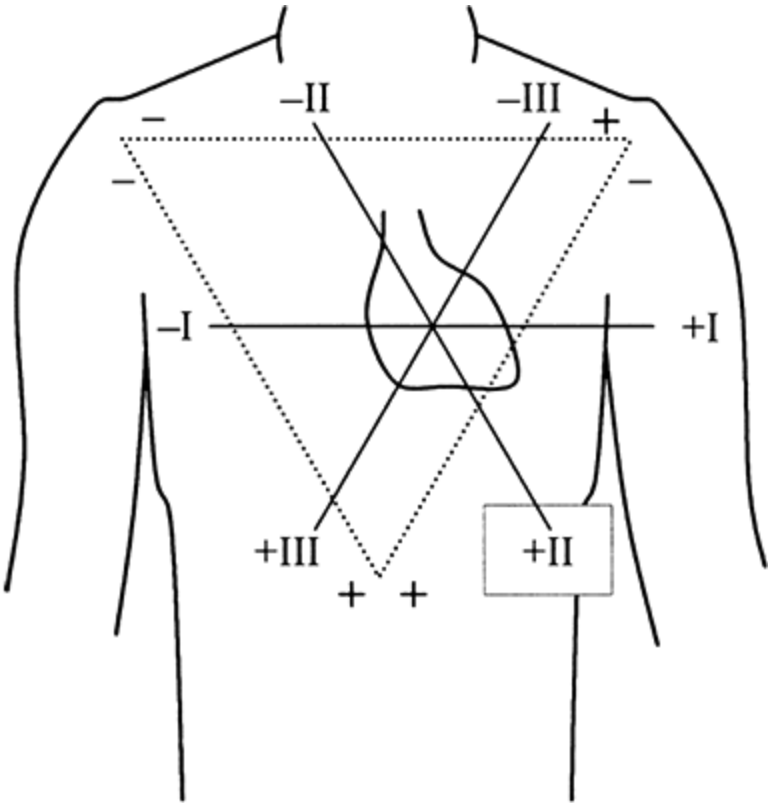

Figure 5-3. The relationships of the original three limb leads are illustrated. The equiangular (60Â°) Einthoven triangle formed by leads I, II, and III is shown *(dotted lines)* with positive and negative poles of each of the leads indicated. Leads I, II, and III are also presented as a triaxial reference system that intersects in the center of the ventricles.

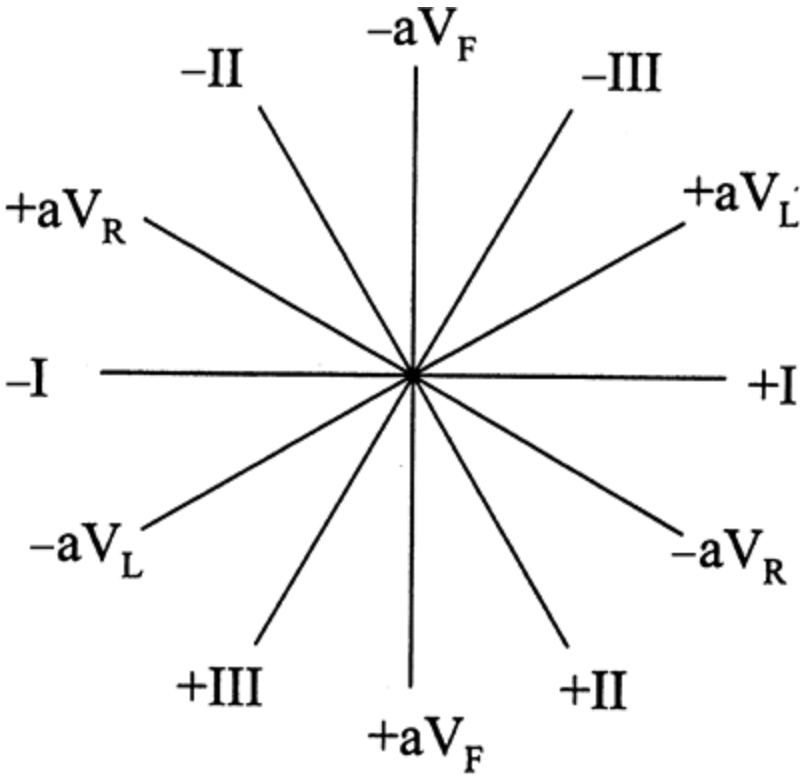

Figure 5-4. The hexaxial reference system derived from the Einthoven equilateral triangle defining the electrical potential vectors of electrocardiography.

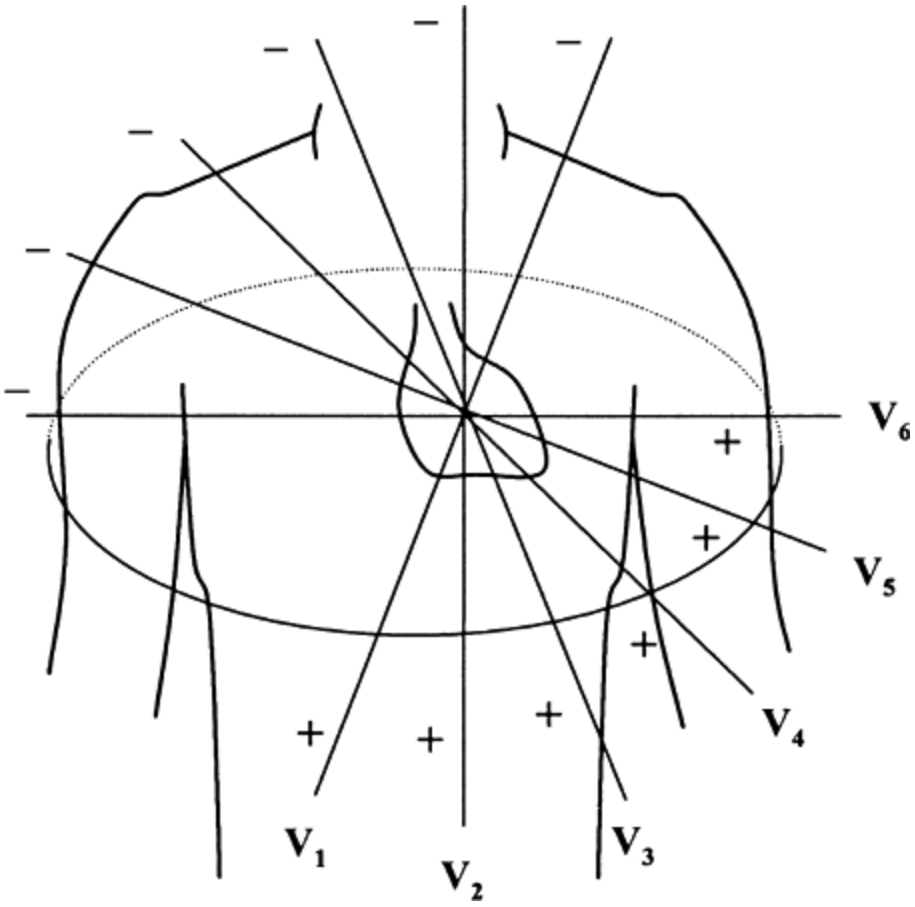

Figure 5-5. Visualized as a cross-section, each of the chest leads is oriented through the atrioventricular (AV) node and exits through the patient's back, which is negative.

A continuous cardiac monitor usually relies on recordings from one of two bipolar leads: a modified left chest lead (MCL_1) or a lead II. The recording from an MCL_1 , in which the positive electrode is in the V_1 position, is similar in appearance to a V_1 recording on a 12-lead ECG. This lead visualizes ventricular activity well; however, lead II shows atrial activity (ie, the P wave) much more clearly.

The Various Intervals and Waves

The ECG tracing has specific nomenclature to define the

characteristic patterns. Waves refer to positive or negative deflections from baseline, such as the P, T, or U wave. A segment is defined as the distance between two waves, such as the ST segment, and an interval measures the duration of a wave plus a segment, such as QT or PR interval. Complexes are a group of waves without intervals or segments between them (QRS). Electrophysiologically, the P wave and PR interval on the ECG tracing represent the depolarization of the atria. The QRS complex represents the depolarization of the ventricles. The plateau is depicted by the ST segment and repolarization is visualized as the T wave and the QT interval (QTc). The U wave, when present, generally represents an afterdepolarization (Fig. 5-6).

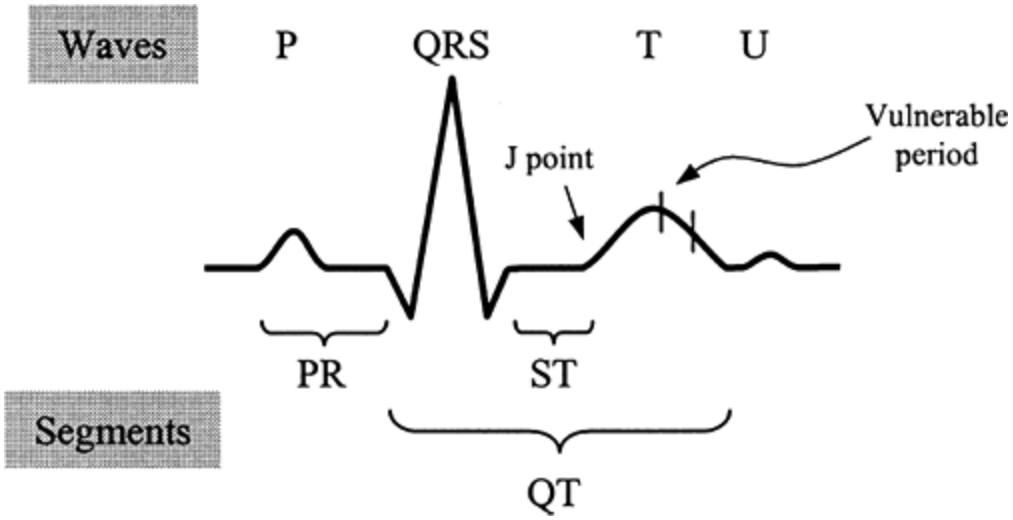

Figure 5-6. The normal ECG: P wave, atrial depolarization; QRS, ventricular depolarization; ST segment, T wave, QT interval, and U wave, ventricular repolarization. The U wave is the small, positive deflection following the T wave.

The P Wave

The P wave is the initial deflection on the ECG that occurs with the initiation of a new cardiac cycle.

Electrophysiology

The early, middle, and late portions of the P wave are represented sequentially by the electrical potential initiated by the sinus node. The impulse is propagated directly through the right atrial muscle, producing contraction. The impulse is also propagated by specialized conduction tissue across the interatrial septum, to produce contraction of the left atrium. Additionally, internodal pathways rapidly conduct the impulse to the atrioventricular (AV) node. The electrical excitation of the sinus node differs from that of the ventricular myocardium in that current is mediated primarily by calcium ion influx via slow T-type calcium channels, not by sodium entering through fast sodium channels. Furthermore, the vagus nerve exerts a profound suppressive influence on the nodal tissues.

The Abnormal P Wave

Clinically, abnormalities of the P wave occur with xenobiotics that depress automaticity of the sinus node, causing sinus arrest and nodal or ventricular escape rhythms (Î²-adrenergic antagonists, calcium channel blockers). The P wave is absent in rhythms with sinus arrest, such as occurs with xenobiotics that produce vagotonia such as cardioactive steroids and cholinergic agents. A notched P wave suggests delayed conduction across the atrial septum and is characteristic of quinidine poisoning. P waves decrease in amplitude as hyperkalemia becomes more severe until they become indistinguishable from the baseline (Chap. 17).

The PR Interval

The PR interval is measured from the beginning of the P wave to the beginning of the QRS complex (normal is 120â€“200 milliseconds).

Electrophysiology

Despite rapid conduction by specialized conduction tissue from the sinoatrial (SA) to the AV node, the AV node delays transmission of the impulse into the ventricles, ostensibly to allow for complete atrial emptying. Thus, the PR interval represents the interval between the onset of atrial depolarization and the onset of ventricular depolarization. Children usually have more rapid conduction and a shorter PR interval, and older adults generally have a longer PR interval. The segment between the end

of the P wave and the beginning of the QRS complex (the PQ segment) reflects atrial contraction and is usually isoelectric. Atrial repolarization coincides with the Q wave, but its ECG findings, or atrial T waves, are obscured by the QRS complex.

The Abnormal PR Interval

Xenobiotics that decrease interatrial or AV nodal conduction cause marked lengthening of the PR segment until such conduction completely ceases. At this point, the P wave no longer relates to the QRS complex; this is AV dissociation, or complete heart block. Some xenobiotics suppress AV nodal conduction by blocking calcium channels in nodal cells, as does magnesium, antagonizing at the Î²-adrenergic receptors, or enhancing vagal tone. Although the therapeutic use of digoxin, as well as early cardioactive steroid poisoning, causes PR prolongation through vagotonic effects, direct electrophysiologic effects account for the bradycardia of poisoning (see â€œBradydysrhythmias â€• section later in this chapter, as well as Chap. 62 and Antidotes in Depth: Digoxin-Specific Antibody Fragments [Fab]).

The QRS Complex

The QRS complex is the second and typically larger deflection on

the ECG. The normal QRS duration in adults varies between 60 and 120 msec. The normal range for the QRS axis in the frontal plane is between -30Â° and 90Â°, although most people will have values between 30Â° and 75Â°. This axis will vary with the weight and age of the patient. Alterations in myocardial function may also alter the electrical axis of the heart.

Electrophysiology

The QRS complex reflects the electrical forces generated by ventricular depolarization mediated primarily by sodium influx into the myocardial cells. Although under normal conditions both ventricles depolarize nearly simultaneously, the greater mass of the left ventricle causes it to contribute the majority of the electrical forces. The QRS complex is primarily positive in leads I and aV_L on the surface ECG recording because under normal conditions the depolarization vector is directed at 60Â° and is thus moving toward the positive electrodes in these leads.

The simultaneous and rapid depolarization of the ventricles results in a very short period of electrical activity recorded on the electrocardiogram. Of course, mechanical systole lasts well past the end of the QRS complex and is maintained by continued depolarization during the plateau phase of the action potential. The return and maintenance of the baseline, or isoelectric potential, is simply a result of the fact that the entire heart is depolarized and there is no significant flow of current during this period.

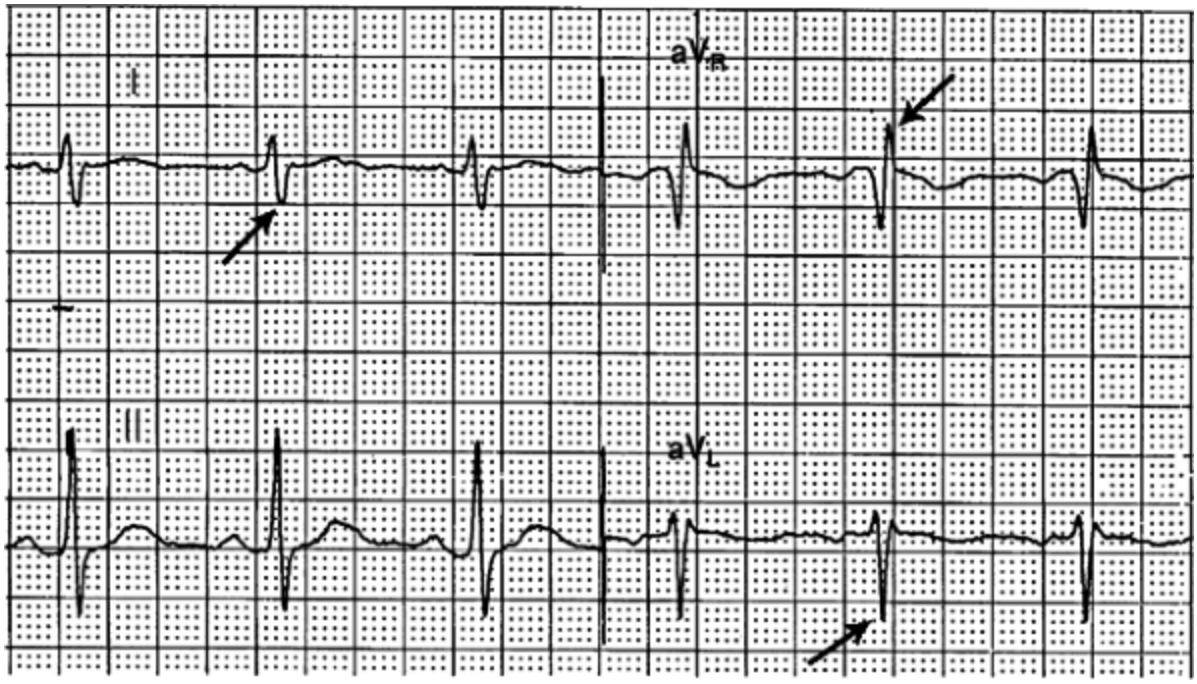

Figure 5-7. ECG showing leads I, II, aV_R , and aV_L of a patient with a tricyclic antidepressant overdose. The prominent S wave in leads I and aV_L and R wave in aV_R demonstrate the terminal 40-msec rightward axis shift.

The axis of the terminal 40 msec (0.04 seconds) of the QRS complex represents the late stages of ventricular depolarization and generally follows the direction of the overall axis. This axis is determined by examining the last box (0.04 seconds or 40 msec) of the QRS complex on the electrocardiogram paper.

The Abnormal QRS Complex

In the presence of a bundle-branch block, the two ventricles depolarize sequentially rather than concurrently. Although, conceptually, conduction through either the left or right bundle may be affected, many xenobiotics preferentially affect the right bundle. This effect typically results in the left ventricle depolarizing slightly more rapidly than the right. The consequence on the ECG is both a widening of the QRS complex and the

appearance of the right ventricular electrical forces that were previously obscured by those of the left ventricle. These changes are a result of the effects of a xenobiotic that blocks fast sodium channels. Implicated xenobiotics include cyclic antidepressants, quinidine and other type IA and IC antidysrhythmic agents, phenothiazines,[3] amantadine, diphenhydramine,[11] carbamazepine, and cocaine. In the setting of tricyclic antidepressant poisoning, this finding has both prognostic and therapeutic value (Chap. 71).[1 , 14 , 18 , 19 , 34] Specifically, in a prospective analysis of ECGs the maximal limb lead QRS duration was prognostic of seizures (0% if <100 msec; 30% if greater) and ventricular dysrhythmias (0% if <160 msec; 50% if greater).[7]

This terminal 40-msec axis of the QRS complex contains critical information regarding the likelihood, but not the extent, of poisoning by sodium channel blocking agents. In a poisoned patient, the terminal portion of the QRS has a rightward deviation greater than 120Â°. The common abnormalities include, an R wave (positive deflection) in lead aV_R and an S wave (negative deflection) in leads I and aV_L .[21] The combination of a rightward axis shift in the terminal 40 msec of the QRS complex (Fig. 5-7) with a prolonged QTc and a sinus tachycardia is highly specific and sensitive for cyclic antidepressant poisoning. Absence of these findings, in one study at least, excluded serious tricyclic antidepressant (TCA) poisoning.[31 , 45] Another study suggests that although ECG changes, like a prolonged QRS duration, are better at predicting severe outcomes than the TCA level, neither is very accurate.[1] One prospective study

suggests that an absolute height of the terminal portion of aV_R that is greater than 3 mm, predicted seizures or dysrhythmias in TCA-poisoned patients.[20] In infants younger than 6 months old, however, a rightward deviation of the terminal 40-msec QRS axis is physiologic and not predictive of tricyclic antidepressant toxicity.[6] In older children, retrospective chart review of 37

children diagnosed with tricyclic antidepressant overdose and 35 controls (all younger than 11 years old) found interpatient variability, unrelated to age, so great that a rightward deviation of the terminal 40-msec QRS axis could not distinguish between poisoned and healthy children.[6]

An apparent increase in QRS duration and morphology, which is actually an elevation or distortion of the J point called a J wave or an Osborn wave (Fig. 16-2), is a common finding in patients with hypothermia.[33] Hypermagnesemia is also associated with a widening the QRS duration and a slight narrowing of the QRS complex may occur with hypomagnesemia.[29] Significant elevation in the serum concentrations of potassium may also cause widening and distortion of the QRS complex.

The ST Segment

The ST segment is defined as the distance between the end of the QRS complex and the beginning of the T wave.

Electrophysiology

This segment reflects the period of time between depolarization and the start of repolarization, or the plateau phase of the action potential. During this period, no major currents flow within the myocardium, which explains why under normal circumstances the ST segment is isoelectric. Although both the degree of displacement from the baseline and the length of this segment are important, the ST segment duration is usually measured by its effects on the QT duration (see â€œThe QT Interval â€• section, below).

The Abnormal ST Segment

Displacement of the ST segment from its baseline typically characterizes myocardial ischemia or infarction (Fig. 5-8). The

subsequent appearance of a Q wave is diagnostic of myocardial infarction. The ECG patterns of these entities reflect the different underlying electrophysiologic states of the heart. Ischemic regions are highly unstable and produce currents of injury because of inadequate repolarization, which is related to lack of energy substrate to power the Na^+ -K^+ ATPase. Infarction represents the loss of electrical activity from the necrotic, inactive ventricular tissue, allowing the contralateral ventricular forces to be predominant on the ECG. Patients who are poisoned by xenobiotics that cause vasoconstriction, such as cocaine (Chap. 74), other Î±-adrenergic agonists, or the ergot alkaloids, are particularly prone to develop focal myocardial ischemia and infarction. The specific electrocardiographic manifestations help to identify the region of injury and may, to some extent, be correlated with an arterial flow pattern: inferior (leads II, III, aV_F ; right coronary artery); anterior (leads I, aV_L ; left anterior descending artery); or lateral (leads aV_L , $V_{5â€“6}$; circumflex branch). However, any poisoning that results in profound hypotension or hypoxia may also result in ECG changes of ischemia and injury. In this situation, the injury may be more global, involving more than one arterial distribution. Diffuse myocardial damage may not be identifiable on the electrocardiogram because of global, symmetric electrical abnormalities. In this situation, the diagnosis is made by other noninvasive testing, such as by echocardiogram or by finding elevations in serum markers for myocardial injury (eg, troponin).

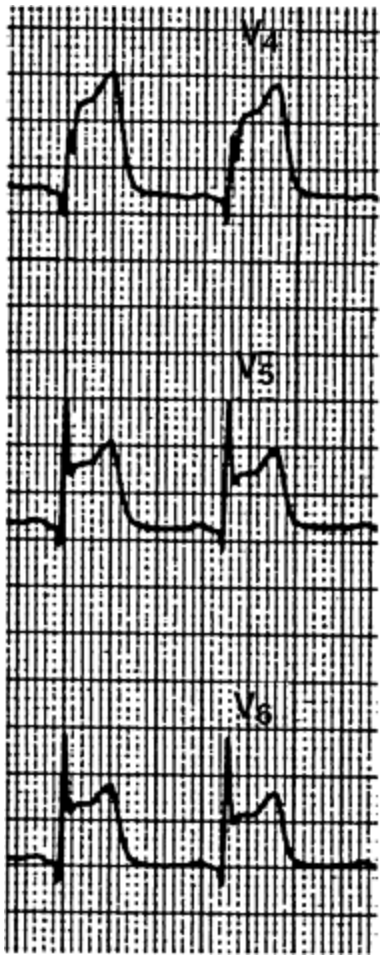

Figure 5-8. Leads V_4 â€“ V_6 are shown from the ECG of a 27-year-old man with substernal chest pain after using crack cocaine.

Many young, healthy patients have ST segment abnormalities that mimic those of myocardial infarction. The most common normal variant is termed â€œearly repolarizationâ€• or â€œJ-point elevation,â€• and is identified as diffusely elevated, upwardly concave ST segments, located in the precordial leads and typically with corresponding T waves of large amplitude.[9] The J point is located at the beginning of the ST segment just after the QRS complex. Because this electrocardiographic variant is common in patients with cocaine-associated chest pain (Chap. 74),[17] its recognition is critical to instituting appropriate therapy.

The Brugada electrocardiographic pattern (Fig. 5-9) is characterized by terminal positivity of the QRS complex and ST-segment elevation in the right precordial leads. The Brugada pattern is found in some patients with mutations of the gene that codes for the sodium channel Î± subunit. These patients are at risk for sudden death, but a similar ECG pattern often occurs in patients who are poisoned by sodium channel blocking xenobiotics, including TCAs,[5] cocaine,[32] class IA (procainamide), and class IC (flecainide, encainide) antidysrhythmic agents.[23 , 28] In TCA-poisoned patients this pattern is associated with an increased risk of hypotension, but not sudden death or dysrhythmias.[4 , 28] Sagging ST segments, inverted T waves, and normal or shortened QT intervals are characteristic effects of cardioactive steroids, such as digoxin, on the ECG. These repolarization abnormalities are sometimes identified by their similar appearance to â€œSalvador Dali's mustache.â€• As a group, these findings, along with PR prolongation, are commonly described as the â€œdigitalis effectâ€• (Chap. 62). They are found in patients with therapeutic drug levels and in patients with cardioactive steroid poisoning. As the serum level or, more precisely, the tissue concentration increases,

clinical and electrocardiographic manifestations of toxicity will appear (Chap. 62), which include profound bradycardia or ventricular dysrhythmias.

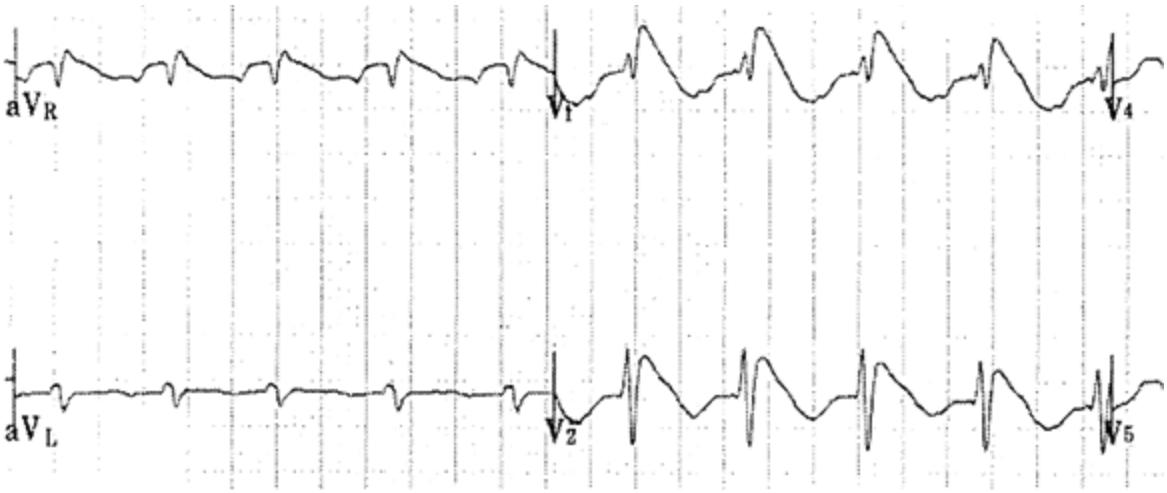

Figure 5-9. The Brugada pattern is characterized by terminal positivity of the QRS complex and ST-segment elevation in the right precordial leads and is a similar ECG pattern to that noted in patients poisoned by sodium channel blocking agents such as tricyclic antidepressants.[4] *(Reproduced with permission of Vikhyat Bebarta, MD.)*

Changes in the ST segment duration are frequently caused by abnormalities in the serum calcium concentration. Hypercalcemia causes shortening of the ST segment through enhanced calcium influx during the plateau phase of the cardiac cycle speeding the onset of repolarization. For practical purposes this effect is more commonly identified by reduction of the QTc (Fig. 5-10 ; see The QT Interval below). In patients with hypercalcemia, the morphology and duration of the QRS complex and T and P waves remain essentially unchanged. Xenobiotic-induced hypercalcemia may result from exposure to antacids (milk alkali syndrome), diuretics (eg, hydrochlorothiazide), cholecalciferol (vitamin D), vitamin A, and other retinoids. Hypocalcemia causes prolongation of the ST segment and QTc (Fig. 5-10).

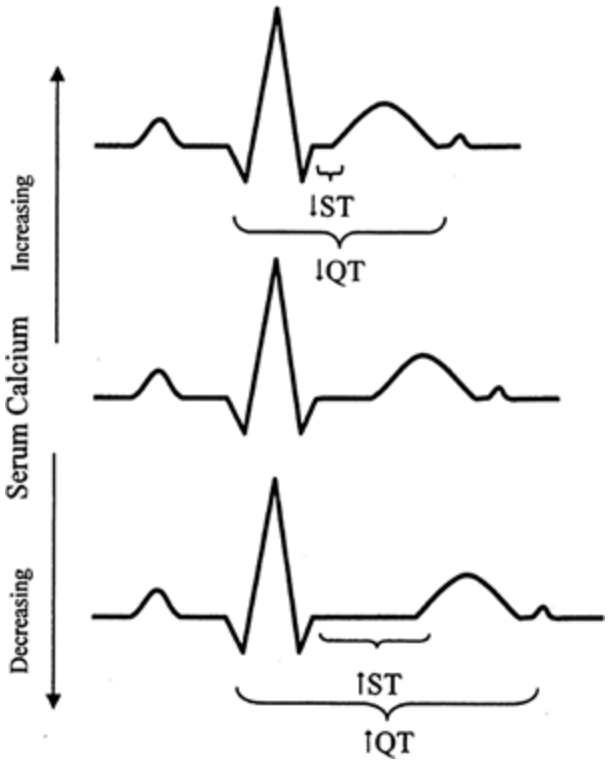

Figure 5-10. Electrocardiographic findings associated with changes in serum calcium.

The T Wave

The T wave is the third deflection that occurs on the ECG.

Electrophysiology

The T wave represents ventricular repolarization, during which current is again flowing, although at a cellular level in the opposite direction from that during depolarization. Cardiac repolarization on the larger level generally follows the same pattern as depolarization and thus the deflection is usually in the same direction as the QRS complex. During repolarization, the intracellular potential of the cardiac myocyte becomes more negative as a result of a net loss of positive charge because of the increasing outward flow of potassium ions. As repolarization

progresses, the voltage-dependent ion channels â€œresetâ€• themselves as the intracellular potential falls past their set points. Thus, the initial part of the T wave represents the absolute refractory period of the heart, because at this time there are an insufficient number of reset voltage-dependent calcium channels to allow an impulse to cause a contraction. The latter part of the T wave represents the relative refractory period of the heart, during which time a sufficient number of these calcium channels are available to open with an aberrant depolarization and initiate a contraction.

The Abnormal T Wave

Isolated peaked T waves are usually evidence of early hyperkalemia.[27] Hyperkalemia initially causes tall, tented T waves with normal QRS, QTc, and P wave (Fig. 5-11). As the measured potassium rises to 6.5â€“8 mEq/L, the P wave diminishes in amplitude and the PR and QRS intervals prolong. Progressive widening of the QRS complex causes it to merge with the ST segment and T wave, forming a â€œsine wave.â€• Electrocardiographic manifestations of hyperkalemia may occur following chronic exposure to numerous therapeutic agents, including potassium-sparing diuretics, angiotensin-converting enzyme inhibitors (Chap. 60), or potassium supplements. Either fluoride or cardiac glycoside poisoning produces acute hyperkalemia, but the latter rarely produces hyperkalemic ECG changes (Chap. 62). Peaked T waves also occur following myocardial ischemia and may also be confused with early repolarization effects (see The ST Segment above). Consequently, the ability to properly identify electrolyte abnormalities by electrocardiography is often limited.

Hypokalemia typically reduces the amplitude of the T wave and, ultimately, causes the appearance of prominent U waves (Fig. 5-11). Its effects on the electrocardiogram are manifestations of

altered myocardial repolarization. Lithium similarly affects myocardial ion fluxes and causes reversible changes on the electrocardiogram that may mimic mild hypokalemia, although documentation of

low cellular potassium levels is lacking.[12, 37, 46] Patients chronically poisoned with lithium have more T-wave abnormalities (typically flattening) than do those who are acutely poisoned, but these abnormalities are rarely of clinical significance.[8, 22, 38]

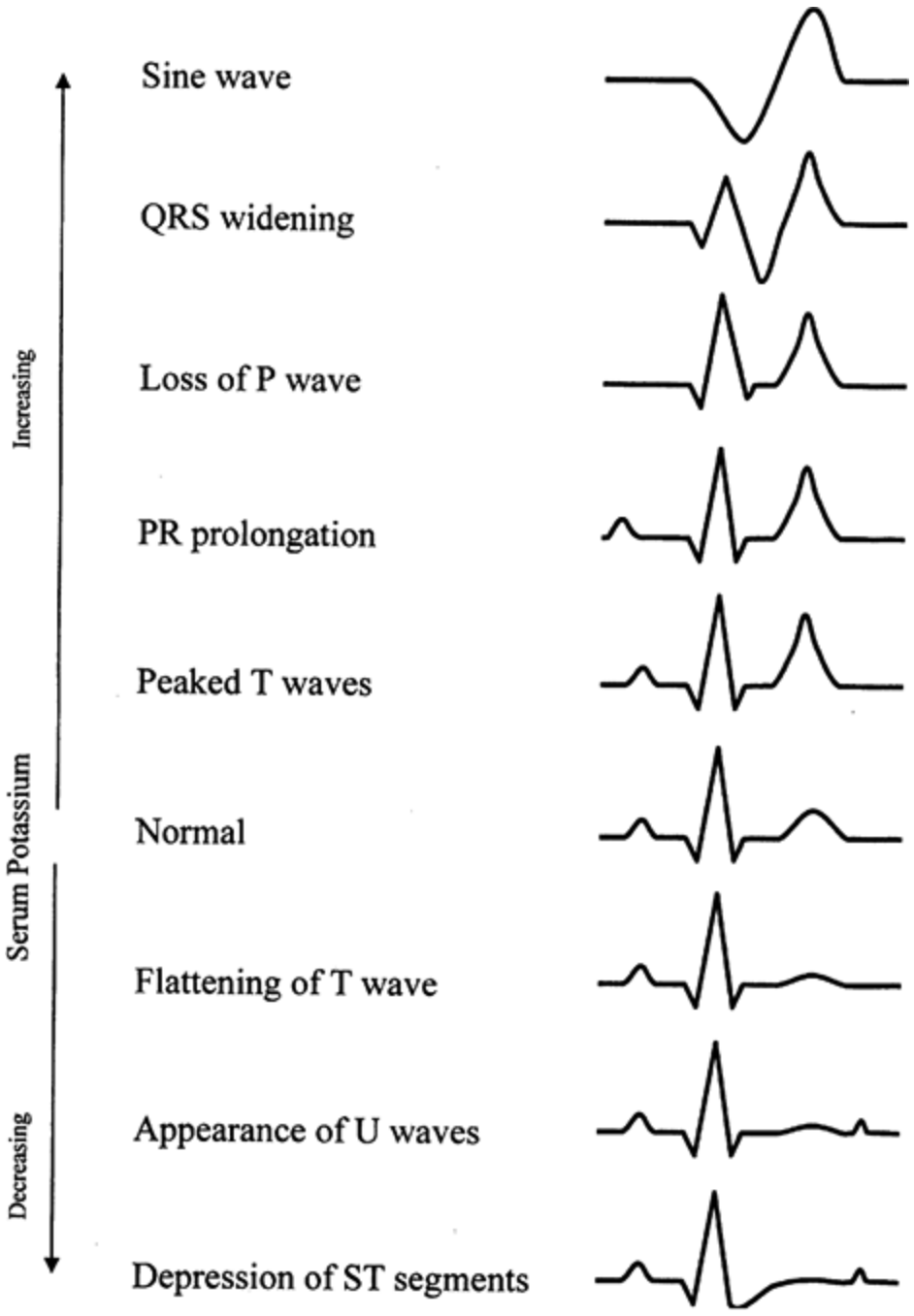

Figure 5-11. Electrocardiographic manifestations associated with changes in serum potassium.

The QT Interval

The QT is measured from the beginning of the QRS complex to the end of the T wave. The bipolar limb lead with the largest T wave should be used for this measurement. As the normal QT varies with the heart rate, numerous formulas (eg, the QT divided by $\sqrt{\text{R-R interval}}$ in seconds) and tables are available to obtain the corrected QT, known as the QTc.[15] Using the QTc allows the determination of the appropriateness of the QTc independent of the heart rate. With slow heart rates, a prominent U wave can obscure the terminal portion of the T wave and with fast heart rates the subsequent P wave can obscure the terminal portion of the T wave. In these cases the QTc should be estimated by following the downslope of the T wave. The QTc is often measured to approximate repolarization, although this is not fully appropriate because alterations in depolarization, such as excess Na^+ entry, may affect it.

Electrophysiology

The QT represents the entire duration of ventricular systole and thus is made up of several electrophysiologic periods. Although as noted above depolarization abnormalities can affect the QT, these are uncommon, and the plateau phase and repolarization are primarily reflected by the QT.

The Abnormal QT Interval

A prolonged QTc reflects an increase in the time period that the heart is â€œvulnerableâ€• to the initiation of ventricular dysrhythmias[36] (Fig. 5-6). This occurs because although some myocardial fibers are refractory during this time period, others are not (i.e., relative refractory period). Early afterdepolarizations may occur in patients with lengthened repolarization time (Table 5-2).[30] An early afterdepolarization (EAD) occurs when a

myocardial cell spontaneously depolarizes before its repolarization is complete (Fig. 23-4). If this depolarization is of sufficient magnitude, it may capture and initiate a premature ventricular contraction, which itself may initiate ventricular tachycardia, ventricular fibrillation, or torsades de pointes. There are two types of EADs that occur when the membrane potential is decreased either during phase 2 (type 1) or phase 3 (type 2) of the cardiac action potential. The ionic basis of EADs is unclear, but may be via the L-type calcium channel; EADs are suppressed by magnesium.[2, 39]

Xenobiotics that cause sodium channel blockade (Chap. 61), prolong the QT duration by slowing cellular depolarization during phase 0. Thus, the QT duration increases because of a prolongation of the QRS complex duration, and the ST segment duration remains near normal. Xenobiotics that cause potassium channel blockade similarly prolong the QT, but through prolongation of the plateau and repolarization phases. This specifically prolongs the ST segment duration. Although at a cellular level these agents are antidysrhythmic, the multicellular effects may be prodysrhythmic.[32]

Hypocalcemia is caused by a number of xenobiotics, including fluoride, calcitonin, ethylene glycol, phosphates, and mithramycin (Table 17-9). Hypokalemia alone does not usually prolong the QTc. Arsenic poisoning may cause prolongation of the QTc and

torsades de pointes.[5, 40, 41] The mechanism is unknown, although either a direct dysrhythmogenic effect or an autoimmune myocarditis are postulated.

Antidysrhythmics
- Class IA and class IC drugs
- Class III

Electrolyte disturbances
- Hypokalemia

Hypomagnesemia

Nonantidysrhythmics

Psychotropics: phenothiazines, haloperidol, atypical antipsychotics tricyclic and tetracyclic antidepressants

Antihypertensives: bepridil, ketanserin

Antimicrobials: erythromycin, trimethoprim-sulfamethoxazole, pentamidine, amantidine, chloroquine

Antifungals: ketoconazole, itraconazole

Antihistaminics: terfenadine, astemizole

Other drugs: cisapride, cocaine, organic phosphorus insecticides, arsenic, vasopressin

Other conditions

Cardiac disorders; myocarditis, ventricular tumor

Endocrine disorders: hypothyroidism, hypoparathyroidism, pheochromocytoma, hyperaldosteronism

Intracranial disorders; subarachnoid hemorrhage, cerebrovascul accident, encephalitis, head injury

Nutritional disorders: liquid protein diet, starvation

Severe bradycardia

TABLE 5-2. Classification and Causes of an Acquired Long QTc

The U Wave

The U wave is a small deflection that occurs after the T wave and usually with a similar orientation. Distinguishing a U wave from a notched T wave is difficult. The apices of a notched T wave are usually less than 150 msec apart, and the peaks of a TU complex are greater than 150 msec apart.

Electrophysiology

U waves occur when there is fluctuation in the membrane potential

following myocardial repolarization. Although they may be physiologic, when prominent, U waves are generally representative of an underlying electrophysiologic abnormality. Physiologic U waves may be caused by repolarization of the Purkinje fibers.

The Abnormal U Wave

Abnormal U waves are typically caused by spontaneous afterdepolarization of membrane potential that occurs in situations where repolarization is prolonged. EAD occurs in situations where the prolonged repolarization period allows calcium channels (which are both time and voltage dependent) to close and spontaneously reopen because they may close at a membrane potential that is above their threshold potential for opening. In this situation, the opening of the calcium channels produces a slight membrane depolarization that is identified as a U wave. Delayed afterdepolarization occurs when the myocyte is overloaded with calcium, as in the setting of cardioactive steroid toxicity. The excess intracellular calcium can trigger the ryanodine receptors on the myocyte sarcoplasmic reticulum to release calcium, causing slight depolarization that is recognized as a U wave. If the U waves are of sufficient magnitude to reach threshold, the cell may depolarize and initiate a premature ventricular contraction. Transient U-wave inversion can also be caused by myocardial ischemia or systemic hypertension.

The Abnormal QU Interval

The QU interval is the distance between the end of the Q wave and the end of the U wave. Differentiation between the QU and the QT intervals is difficult if the T and U waves are superimposed. When hypomagnesemia coexists with hypokalemia, as is usually the case, QU prolongation and torsades de pointes may occur.[40]

Electrocardiogram Disturbances

The distinction between xenobiotics that cause a rapid rate and those that cause a slow rate on the ECG is somewhat artificial, because many can do both. For example, patients poisoned by tricyclic antidepressants almost always develop sinus tachycardia, but most die with a wide complex bradycardia. In either case, abnormalities in the pattern or rate on the electrocardiogram can provide the clinician with immediate information about a patient's cardiovascular status. Any rhythm other than normal sinus rhythm is referred to as a dysrhythmia in this text. Electrocardiographic disturbances in many poisoned patients may be categorized in more than one manner (abnormal pattern, fast rate, slow rate). In any case, when electrocardiographic abnormalities are detected, appropriate interpretation, evaluation, and therapy must be rapidly performed.

Tachydysrhythmias

The intrinsic pacemaker cells of the heart undergo spontaneous depolarization and reach threshold at a predictable rate. Under normal circumstances the sinus node is the most rapidly firing pacemaker cell of the heart; because of this, it controls the heart rate. Spontaneous depolarization occurs via ion entry through potassium, sodium, and calcium channels via phase 4 of the action potential. Other potential pacemakers exist in the heart, but their rate of spontaneous depolarization is considerably slower than that of the sinus node. Thus, they are reset during depolarization of the myocardium and they never spontaneously reach threshold. Xenobiotics that speed the rate of rise of phase 4, or diastolic depolarization, speed the rate of firing of the pacemaker cells. As long as the sinus node is preferentially affected, it maintains the pacemaker activity of the heart. If the firing rate of another intrinsic pacemaker exceeds that of the sinus node, ectopic rhythms may develop. This effect may be either pathologic or lifesaving, depending on the clinical circumstances.

Because the rate of impulse formation at the sinus node is regulated by the balance between parasympathetic and sympathetic tone, varying the influences of these parts of the autonomic nervous system is responsible for regulating the heart rate under normal conditions. Sympathomimetic agents, such as cocaine and amphetamines, increase sympathetic tone, producing sinus tachycardia and enhancing AV nodal conduction. Sinus tachycardia may be the first manifestation of exposure to a sympathomimetic agent. However, other supraventricular or ventricular dysrhythmias may develop if an abnormal rhythm is generated in another part of the heart. Similarly, xenobiotics that antagonize acetylcholine released from the vagus nerve onto the sinus node enhance the rate of firing, producing sinus tachycardia. Such xenobiotics include the belladonna alkaloids atropine and scopolamine, antihistamines, and the tricyclic antidepressants. Table 23-7 lists a wide variety of agents that often cause tachydysrhythmias.

Certain xenobiotics are more highly associated with ventricular tachydysrhythmias following poisoning. Those that alter myocardial repolarization and prolong the QTc predispose to the development of afterdepolarization-induced contractions during the relative refractory period (R on T phenomena), which initiates ventricular tachycardia. If torsades de pointes is noted (Fig. 5-12) this is undoubtedly the mechanism, and the QTc should be carefully assessed and appropriate treatment initiated. Alternatively, xenobiotics that increase the adrenergic tone on the heart, either directly or indirectly, may cause ventricular dysrhythmias. Whether a result of excessive circulating catecholamines observed with cocaine and sympathomimetics, myocardial sensitization secondary to halogenated hydrocarbons or thyroid hormone, or increased second messenger activity secondary to theophylline, the extreme inotropic and chronotropic effects cause dysrhythmias. Altered repolarization, increased intracellular calcium concentrations, or myocardial ischemia can

cause the dysrhythmia. Additionally, xenobiotics that produce focal myocardial ischemia, such as cocaine or ephedrine, can lead to malignant ventricular dysrhythmias. Finally, an uncommon cause of xenobiotic-induced ventricular dysrhythmias is persistent activation of sodium channels, without distinguishing

electrocardiographic findings that occur following aconitine poisoning.[37] Not all wide QRS complex tachydysrhythmias are ventricular in origin, but making this assumption is generally considered to be prudent. For example, in a patient known to be poisoned with tricyclic antidepressants, cocaine, or similar agents (see The QRS Complex above), the differentiation of aberrantly conducted sinus tachycardia (common) from ventricular tachycardia (rare) is important, but difficult. Although guidelines for determining the origin of a wide complex tachydysrhythmia exist,[10] they are imperfect, difficult to apply, and unstudied in poisoned patients.

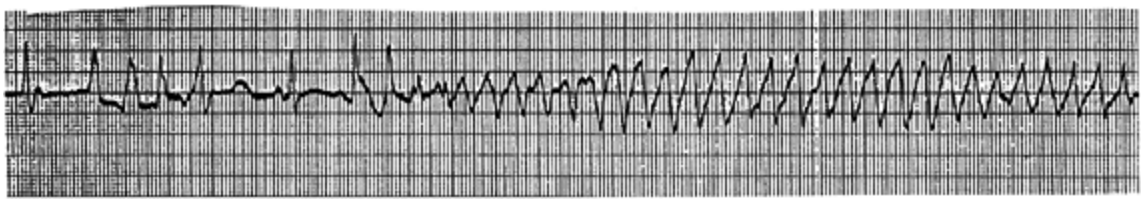

Figure 5-12. Torsades de pointes in a patient who ingested an unknown amount of thioridazine.

Bidirectional ventricular tachycardia is associated with severe cardioactive steroid toxicity and results from alterations of intraventricular conduction, junctional tachycardia with aberrant intraventricular conduction, or, on rare occasions, alternating ventricular pacemakers (Fig. 5-13). The only other xenobiotic that commonly causes this dysrhythmia is aconitine, usually obtained from traditional or alternative therapies that contain the plant Aconitum (Chaps. 43 and 114).

Bradydysrhythmias

Bradycardia and asystole are the terminal events following fatal ingestions of many xenobiotics, but some xenobiotics tend to cause sinus bradycardia (Table 23-7) and conduction abnormalities (Table 23-2) early in the course of toxicity. Sinus bradycardia with an otherwise normal electrocardiogram is characteristic of xenobiotics that reduce central nervous system outflow. Examples include benzodiazepines, ethanol, and clonidine. Differentiating among these agents is not possible based on electrocardiographic criteria alone. Xenobiotics that directly affect ion flux across myocardial cell membranes cause abnormalities in AV nodal conduction. Calcium channel blockers, Î²-adrenergic receptor antagonists, and cardioactive steroids (Chaps. 58 , 59 , and 62) are the leading causes of sinus bradycardia and conduction disturbances.

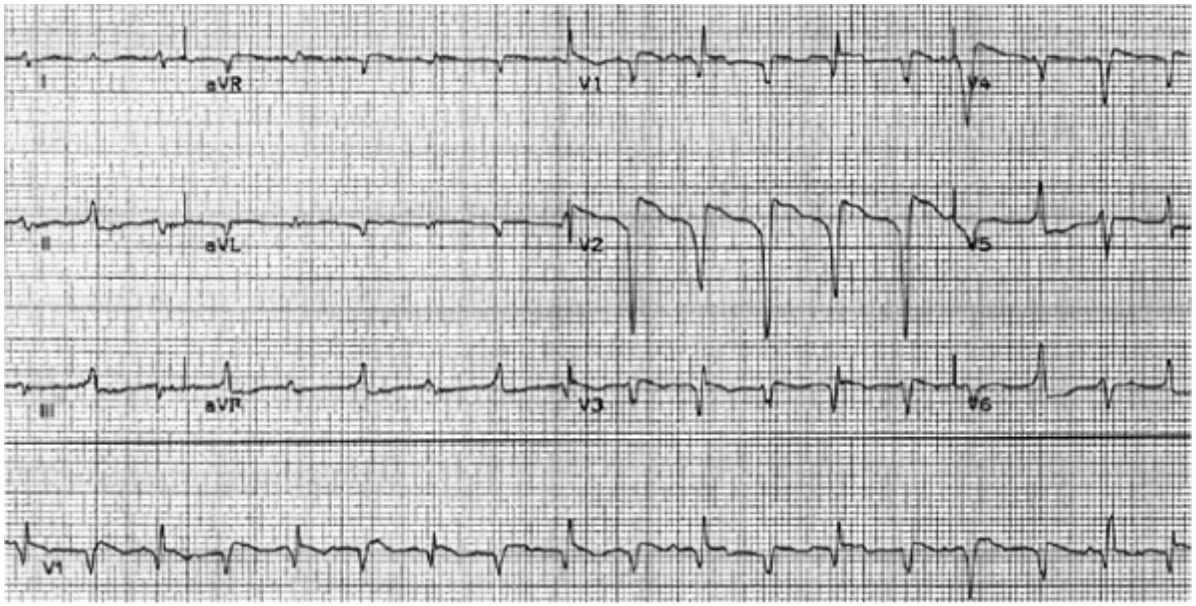

Figure 5-13. Digoxin-induced bidirectional ventricular tachycardia. The ECG demonstrates the alternating QRS axis characteristic of bidirectional ventricular tachycardia and is nearly pathognomonic for cardioactive steroid poisoning. The 89-year-old patient's serum digoxin concentration was 4.0 ng/mL. *(Courtesy of*

Ruben Olmedo, MD, Mount Sinai School of Medicine.)

The ECG manifestations of calcium channel blocker and Î²-adrenergic antagonist overdoses are difficult to distinguish. In general, both drug classes cause decreased dromotropy (conduction), although the specific pharmacologic actions of the drugs differ even within the class (Chaps. 58 and 59). For example, most members of the dihydropyridine subclass of calcium channel blockers do not have any antidromotropic effect, whereas verapamil and diltiazem routinely produce PR prolongation. Similarly, while most Î²-adrenergic antagonists produce sinus bradycardia and first-degree heart block, certain members of this group, such as propranolol, may prolong the QRS complex through their sodium channel blocking abilities.[24] Others, such as sotalol, which have properties of the class III agents, block myocardial potassium channels and prolong the QTc duration. The bradycardia produced by cardioactive steroids is typically accompanied by signs of â€œdigitalis effect,â€• including PR prolongation and ST segment depression (Chap. 62).

Ectopy

Ectopy is the electrocardiographic manifestation of myocardial depolarization initiated from a site other than the sinus node. Ectopy may be lifesaving under circumstances in which the atrial rhythm cannot be conducted to the ventricles, as during high-degree AV blockade induced by cardioactive steroids. Alternatively, ectopy may lead to dramatic alterations in the physiologic function of the heart or deteriorate into lethal ventricular dysrhythmias (Fig. 5-14).

Several mechanisms by which ectopic rhythms may develop are noted. An impulse that occurs after completion of repolarization (phase 4) is called a *delayed afterdepolarization* (DAD) (Fig. 23-4 and Table 5-3). The mechanism of DADs is related to increases in

intracellular calcium that activate a nonselective cation channel or an electrogenic Na^+ -Ca^{2+} exchanger that causes a transient inward current carried primarily by sodium ions. This inward sodium current generates the DAD. The increased calcium concentrations may come from extensive sympathetic stimulation,[26] large doses of cardioactive steroids, or other abnormal physiologic conditions. DADs are the likely cause of some dysrhythmias induced by cardioactive steroid poisoning (Chap. 62). Compared with EADs, DADs generally arise when the membrane potential is more negative.

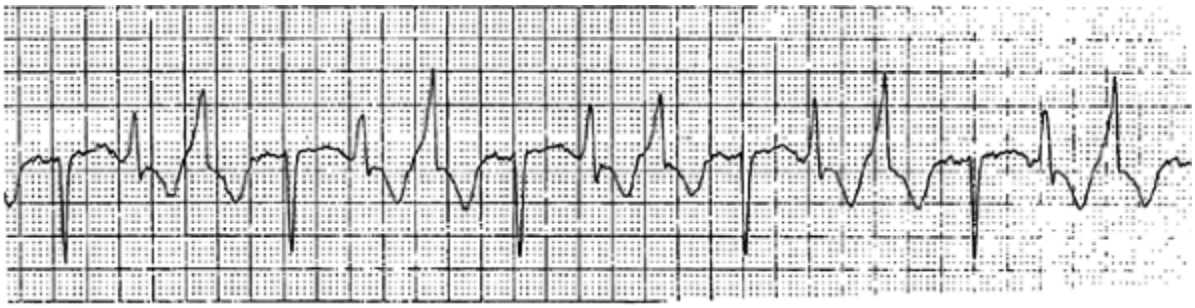

Figure 5-14. This rhythm strip shows ventricular ectopy in a patient following a chloral hydrate overdose. Following the administration of propranolol the ectopy resolved.

The Pediatric Electrocardiogram

The Normal Pediatric ECG

The normal pediatric ECG differs in many ways from the normal adult ECG. The resting heart rate of infants and children is substantially higher than that of adults and, in general, conduction is faster. In a term infant, the right ventricle is substantially larger than the left, and the ECG demonstrates prominent R waves in the right precordium and deep S waves in the left lateral precordium.[13] An adult ratio of left-right ventricular size is usually

reached by the age of 6 months. In infants, Q waves commonly exist in the inferior and lateral precordial leads, but are abnormal in leads I and aV_L . The T waves are the most notable difference between pediatric and adult electrocardiograms. The T waves in the right precordial leads in children are deeply inverted until age 7 years and sometimes beyond (persistent juvenile T-wave pattern).

The Abnormal Pediatric ECG

Although congenital heart disease is the most common cause of electrocardiographic abnormalities in children, electrolyte disorders and drugs may also cause changes in electrophysiology that are reflected on the ECG. Abnormalities that are useful markers on the adult ECG may not always be as useful in the pediatric population.

Delayed after depolarization (DAD)
Phase 4
Cardioactive steroidâ€“induced dysrhythmias
â†‘Intracellular Ca^{2+} â†’ Activation of a nonselective cation channel
or Na^{+} -Ca^{2+} exchanger â†’ Transient inward current carried mostly by Na^{+} ions
Early after depolarization (EAD)

â†‘Repolarization time
Long QT syndrome (hereditary and acquired
Possibly via L-type calcium channels
Type 1
Phase 2
Drug-induced torsades de pointes, ventricular tachycardia
Suppressed by magnesium
Type 2
Phase 3

Phase of Action Potential Affected by Depolarization	Clinical Effect	Mechanism

TABLE 5-3. The Electrophysiologic Basis for Delayed Afterdepolarization and Early Afterdepolarization

Summary

The ECG is one of the few widely available diagnostic procedures that reveal immediate, useful clinical information. This has far-reaching implications in toxicology, where other diagnostic test results often return too late to effectively impact the care of an acutely poisoned patient.

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Chapter 6
Diagnostic Imaging

David T. Schwartz

Diagnostic imaging can play a significant role in the management of many toxicologic emergencies. In some cases, radiographic studies can directly visualize the xenobiotic, whereas in others, they reveal the xenobiotic's effect on various organ systems (Table 6-1). Radiography can confirm a diagnosis, assist in such therapeutic interventions as monitoring gastrointestinal decontamination, and detect complications of the xenobiotic exposure.[165]

Conventional radiography is readily available in the emergency department (ED) and is the imaging modality most frequently used in acute patient management. However, many other imaging modalities are employed in toxicologic emergencies including computed tomography (CT), enteric and intravascular contrast studies, ultrasonography, magnetic resonance imaging (MRI), and nuclear scintigraphy.

Visualizing the Xenobiotic

A number of xenobiotics are *radiopaque* and can potentially be

detected by conventional radiography. If ingested, the xenobiotic may be seen on an abdominal radiograph. Injected radiopaque xenobiotics are also amenable to radiographic detection. If the toxic material is available for examination, it can be radiographed outside of the body to detect any radiopaque contents (Fig. 99-1 and Case Studies Fig. 2).

The radiopacity of a xenobiotic is determined by several factors. First, the *intrinsic radiopacity* of a substance depends on its physical density (g/cm^3) and the atomic numbers of its constituent atoms. Biologic tissues are composed mostly of carbon, hydrogen, and oxygen, and have an average atomic number of approximately 6. Substances that are more radiopaque than soft tissues include bone, which contains calcium (atomic number 20); radiocontrast agents containing iodine (atomic number 53) and barium (atomic number 56); iron (atomic number 26); and lead (atomic number 82). Some medications and xenobiotics have constituent atoms of high atomic number, such as chlorine (atomic number 17), potassium (atomic number 19), and sulfur (atomic number 16), that contribute to their radiopacity.

The thickness of an object affects its radiopacity. Small particles of a moderately radiopaque xenobiotic are often not visible on a radiograph. The radiographic appearance of the surrounding area also affects the detectability of an object. A moderately radiopaque tablet is easily seen against a uniform background, but in a patient, overlying bone or bowel gas often obscures the tablet.

Ultrasonography

In comparison to conventional radiography, ultrasonography theoretically is a useful tool for detecting ingested xenobiotics because it depends on *echogenicity* rather than radiopacity for visualization. Solid pills within the fluid-filled stomach have an

appearance similar to gallstones within the gallbladder. In one in vitro study using a water-bath model, virtually all intact pills could be seen.[4] These authors were also successful at detecting pills within the stomachs of human volunteers who ingested pills. Nonetheless, reliably finding pills scattered throughout the gastrointestinal tract, which often contains air and feces that block the ultrasound beam, is a formidable task. Ultrasonography, therefore, has limited clinical practicality.

Ultrasonography has been used in persons suspected of smuggling drugs by â€œbody packing.â€• Sonography was able to visualize the numerous uniform drug-containing packages in the gastrointestinal tract in a large proportion of cases.[68 , 122]

Ingestion of an Unknown Xenobiotic

Although a clinical policy issued by the American College of Emergency Physicians in 1995 suggested that an abdominal radiograph should be obtained in the unresponsive overdosed patient in an attempt to identify the involved xenobiotic,[2] the role of abdominal radiography in screening patients who have ingested an unknown xenobiotic is questionable. The number of potentially ingested xenobiotics that are radiopaque is limited. In addition, the radiographic appearance of an ingested xenobiotic is not sufficiently distinctive to determine its identity (Fig. 6-1).[189] However, when ingestion of a radiopaque xenobiotic such as iron tablets or metals is suspected, abdominal radiographs are helpful.[3] In addition, knowledge of potentially radiopaque xenobiotics is useful in suggesting diagnostic possibilities when a radiopaque xenobiotic is discovered on an abdominal radiograph that was obtained for reasons other than suspected xenobiotic ingestion, such as in a patient with abdominal pain (Fig. 6-2).[164 , 170]

Several investigators have studied the radiopacity of various medications.[45 , 52 , 70 , 77 , 86 , 133 , 161 , 173 , 180] The investigators used an in vitro water-bath model to simulate the

radiopacity of abdominal soft tissues.[161] These studies found that only a small number of medications exhibit some degree of radiopacity. A short list of the more consistently radiopaque xenobiotics is summarized in the mnemonic CHIPESâ€“â€“chloral hydrate, heavy metals, iron, phenothiazines, and enteric-coated and sustained-release preparations.

Amiodarone
Chest
Phospholipidosis (Interstitial and alveolar filling), pulmonary fibrosis
72, 76
Asbestos
Chest
Interstitial fibrosis (asbestosis), calcified pleural plaques, mesothelioma
72, 76
Beryllium
Chest
Acute: airspace filling; chronic: hilar adenopathy
74
Body packer
Abdominal
Ingested packets, ileus, bowel obstruction
64, 69
Enteric contrast or abdominal CT
Retained packets
Carbon monoxide
Head CT, MRI
Bilateral basal ganglion lucencies, white matter demyelinization
78, 80
SPECT, PET
Cerebral dysfunction
Caustic ingestion
Enteric contrast

Esophageal perforation or stricture
76
Chemotherapeutics (busulfan, bleomycin)
Chest
Interstitial pneumonitis
72
Cholinergics
Chest
Diffuse airspace filling (bronchorrhea)
71
Cocaine
Chest, abdominal
Diffuse airspace filling, pneumomediastinum, pneumothorax aortic dissection ileus, bowel infarction, perforation
77, 80, 82
Head CT, MRI, TEE
SAH, intracerebral hemorrhage, infarction
SPECT, PET
Cerebral dysfunction, dopamine receptor down-regulation
Corticosteroids
Skeletal
Avascular necrosis (femoral head)
68, 73
Ethanol
Chest
Dilated cardiomyopathy, aspiration pneumonitis
78, 82
Head CT, MRI
Cortical atrophy, cerebellar atrophy, SDH (head trauma)
SPECT, PET
Cerebellar and cortical dysfunction
Fluorosis
Skeletal
Osteosclerosis, osteophytosis, ligament calcification

68
Hydrocarbons (low viscosity)
Chest
Aspiration pneumonitis
65, 70
Inhaled allergens
Chest
Hypersensitivity pneumonitis
72
Iron
Abdominal
Radiopaque tablets
63, 65
Irritant gases
Chest
Diffuse airspace filling thorax
71
IDU (injection drug use)
Chest, skeletal, head CT
Septic emboli, pneumothorax, osteomyelitis (axial skeleton), AIDS-related infections
68, 72, 73
Lead
Skeletal
Metaphyseal bands in children (proximal tibia, distal radius), bullets (dissolution near joints)
64, 65, 67
Abdominal
Ingested leaded paint chips or other leaded compounds
Mercury (elemental)
Abdominal, skeletal, or chest
Ingested, injected, or embolic deposits
64, 67
Metals (Pb, Hg, TI, As)

Abdominal
Ingested xenobiotic
64
Nitrofurantoin
Chest
Hypersensitivity pneumonitis
72
Opioids
Chest
Acute lung injury
71

Abdominal
Ileus

Phenytoin
Chest
Hilar lymphadenopathy
74
Procainamide, INH, hydralazine
Chest
Pleural and pericardial effusions (drug-induced lupus syndrome)
72
Salicylates
Chest
Acute lung injury
71
Silica, coal dust
Chest
Interstitial fibrosis, hilar adenopathy (egg-shell calcification)
72
Thorium dioxide
Abdominal
Hepatic and splenic deposition

76, 79

[a] Conventional radiography unless otherwise stated.

Xenobiotic	Imaging Study[a]	Finding	Page

TABLE 6-1. Xenobiotics with Diagnostic Imaging Findings

The CHIPES mnemonic has several limitations.[161] It does not include all of the pills that are radiopaque in vitro (eg, acetazolamide and busulfan). Most of these medications, however, are only moderately radiopaque and, when ingested, dissolve rapidly and become difficult or impossible to detect. Psychotropic medications include a wide variety of compounds of varying radiopacity.[133, 161] For example, trifluoperazine (containing fluorine, atomic number 9) is radiopaque in vitro, whereas chlorpromazine (containing chlorine, atomic number 17) is not.[161] Finally, sustained-release preparations and those with enteric coatings have variable composition and radiopacity. Pill formulations of fillers, binders, and coatings vary between manufacturers, and even a specific product can change depending on the date of manufacture. The insoluble matrix of some sustained-release preparations is radiopaque; however, when

seen on a radiograph these pills may no longer contain active medication. Some sustained-release cardiac medications such as verapamil and nifedipine have inconsistent radiopacity.[106, 172, 181]

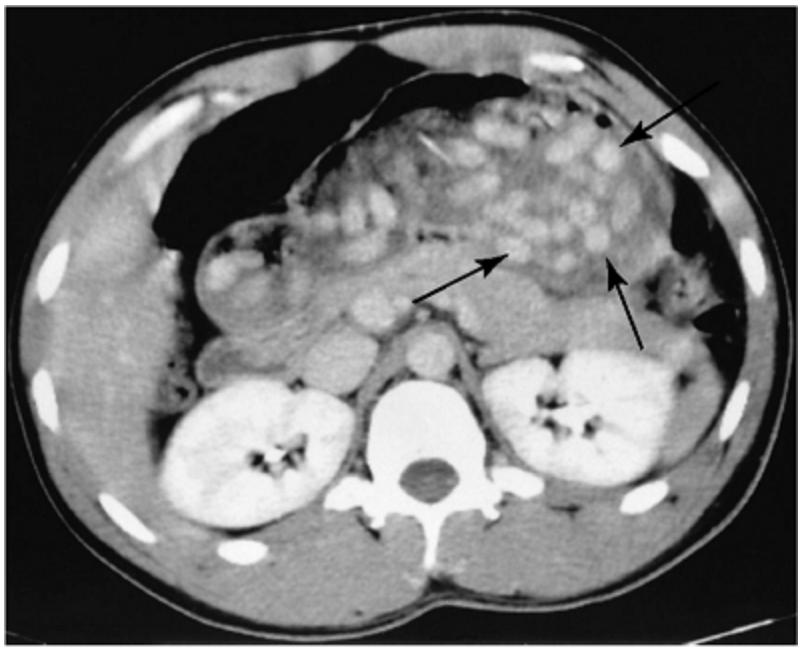


Figure 6-1. Ingestion of an unknown substance. A 46-year-old male presented to the ED with a depressed level of consciousness. Because he also complained of abdominal pain and mild diffuse abdominal tenderness, a CT scan of the abdomen was obtained. The CT revealed innumerable tablet-shaped densities within the stomach (*arrows*). The CT finding was suspicious for an overdose of an unknown medication. Orogastric lavage was attempted and the patient vomited a large amount of whole navy beans. CT is able to detect small, nearly isodense structures such as these, which cannot be seen using conventional radiography. *(Courtesy of Earl J. Reisdorff, MD, Michigan State University, Lansing, Michigan.)*

Exposure to a Known Xenobiotic

When a xenobiotic that is known to be radiopaque is involved in a poisoning, radiography plays an important role in patient care.[3] Radiography can confirm the diagnosis of a radiopaque xenobiotic exposure, quantify the approximate amount of xenobiotic involved, and monitor its removal from the body. Examples include

sustained-release potassium chloride,[176] ferrous sulfate, and heavy metals.

Iron Tablet Ingestion

Ferrous sulfate tablets are readily detected radiographically because they are highly radiopaque and disintegrate slowly when ingested. Radiographs repeated after whole-bowel irrigation help to determine whether further gastrointestinal decontamination is needed (Fig. 6-3).[44 , 54 , 90 , 132 , 137 , 139 , 188] However, caution must be exercised in using radiography to exclude an iron ingestion. Some iron preparations are not radiographically detectable. Liquid, chewable, or encapsulated (â€œSpansuleâ€•) iron preparations rapidly fragment and disperse after ingestion. Even when intact, these preparations are less radiopaque than ferrous sulfate tablets.[45]

Metals

Metals of high atomic number, such as lead, mercury, arsenic, and thallium, can be detected radiographically. Examples of metal exposure include leaded ceramic glaze (Fig. 6-4);[152] paint chips containing lead (Fig. 91-5);[99 , 119] mercuric oxide (Fig. 92-1);[109] thallium salts (atomic number 81; Case Studies Fig. 2);[37 , 120] Zinc (atomic number 30);[20] and arsenic (atomic number 33; Fig. 6-5);[67 , 103 , 186] with lower atomic numbers are also radiopaque.

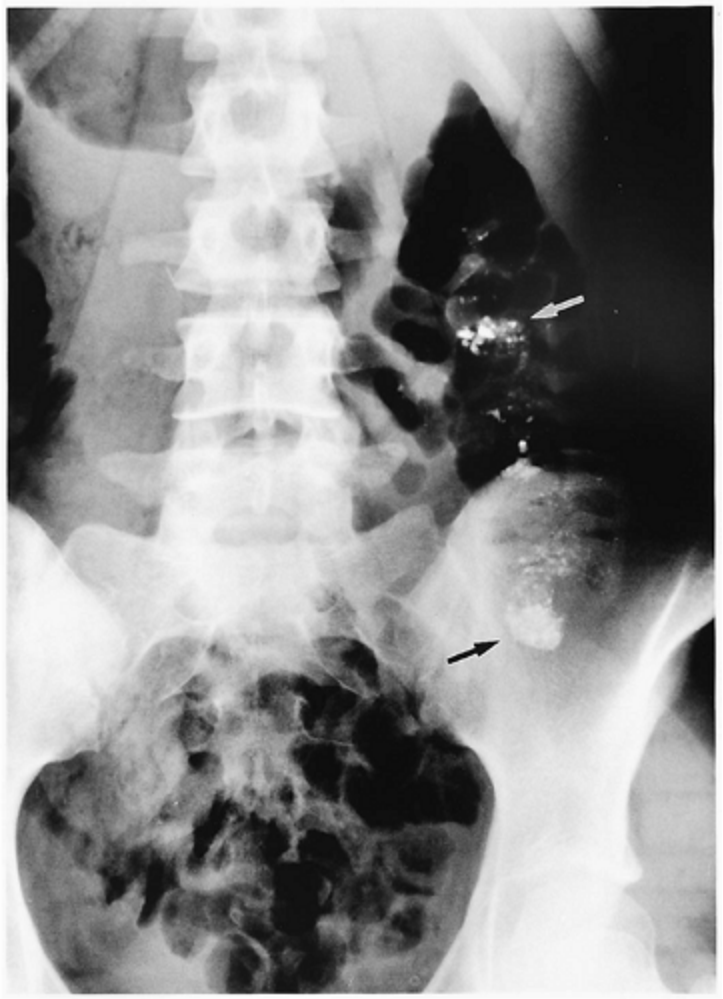


Figure 6-2. Detection of a radiopaque substance on an abdominal radiograph. An abdominal radiograph obtained on a patient with upper abdominal pain revealed radiopaque material throughout the intestinal tract (*arrows*). Further questioning of the patient revealed that he had been consuming bismuth subsalicylate (Pepto-Bismol) tablets to treat his peptic ulcer (bismuth, atomic number 83). The identification of radiopaque material does not allow determination of the nature of the substance.

Mercury

Unintentional ingestion of elemental mercury can occur when a

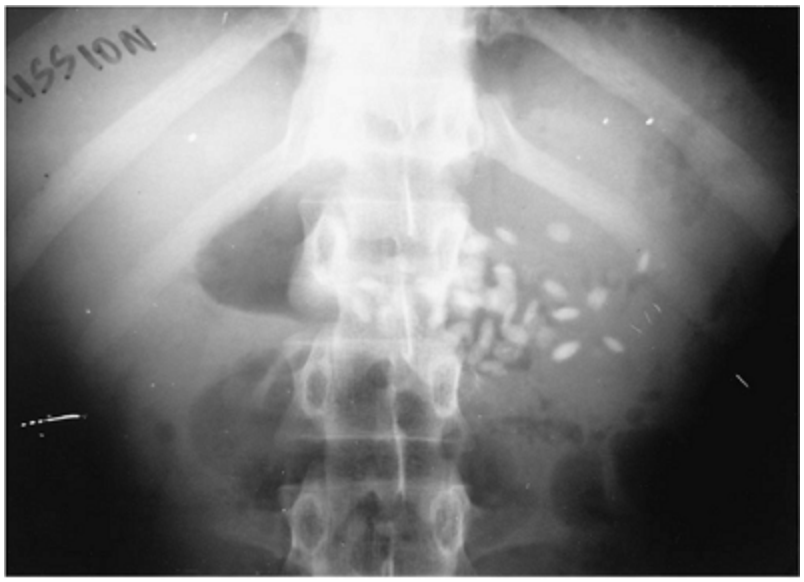
glass thermometer or a long intestinal tube with a mercury containing balloon breaks. Liquid elemental mercury can be injected subcutaneously or intravenously. Radiographic studies assist dÃ©bridement by detecting mercury that remains after the initial excision. Elemental mercury that is injected intravenously produces a dramatic radiographic picture of pulmonary embolization (Fig. 6-6).[20 , 23 , 99 , 112 , 116 , 129]

Lead

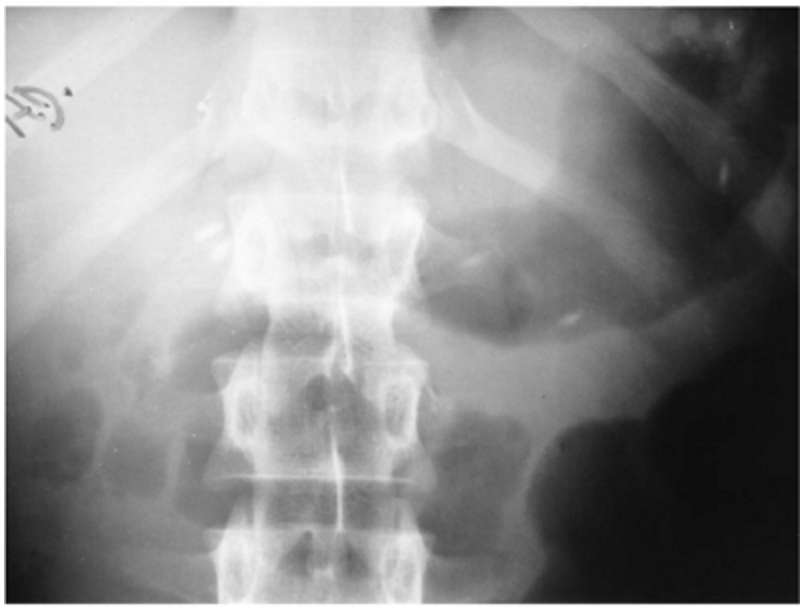
Although metallic lead (eg, a bullet) that is embedded in soft tissues is not usually systemically absorbed, when the bullet is in contact with an acidic environment such as synovial fluid or cerebrospinal fluid (CSF), there can be significant absorption. Over many years, mechanical and chemical action within the joint causes the bullet to fragment and to gradually dissolve.[36 , 38 , 46 , 175 , 179] Radiography can confirm the source of lead poisoning by revealing metallic material in the joint or CSF (Fig. 6-7). An abdominal radiograph in a child with lead poisoning can confirm the source of lead as ingested paint chips.

Xenobiotics in Containers

In some circumstances, ingested xenobiotics can be seen even though they are of similar radiopacity to surrounding soft tissues. If a xenobiotic is ingested in a container, the container itself may be visible.



A



B

Figure 6-3. Iron tablet overdose. A . The identification of the large amount of radiopaque tablets confirms the diagnosis in a patient with a suspected iron overdose and permits rough quantification of the amount ingested. B. Following emesis and whole-bowel irrigation, a second radiograph revealed some remaining tablets and indicated the need for further intestinal decontamination. A third radiograph after additional bowel

irrigation demonstrated clearing of the intestinal tract. *(Courtesy of the Toxicology Fellowship of the New York City Poison Control Center.)*

Body Packers

â€œBody packersâ€• are individuals who smuggle large quantities of illicit drugs across international borders in securely sealed packets.[12, 13, 22, 30, 49, 85, 96, 111, 118, 167, 183] The uniformly shaped oblong packets can be seen on abdominal radiographs either because there is a thin layer of air or metallic foil within the container wall or because the packets are outlined by bowel gas (Fig. 6-8). In some cases, a â€œrosetteâ€• representing the knot at the end of the packet is seen.[167] In other cases, intraabdominal calcifications (pancreatic calcifications and bladder stones) have been misinterpreted as drug-containing packets.[184, 201]

The sensitivity of abdominal radiography for such packets is high, in the range of 85â€“90%. The major role of radiography is as a rapid screening test to confirm the diagnosis in individuals highly suspected of smuggling drugs. However, because packets are occasionally not visualized and the risk of rupture can be fatal, abdominal radiography should not be relied on to exclude the diagnosis of body packing. Ultrasonography has also been used to rapidly detect packets in persons being held by airport customs agents. It was able to confirm 40 of 42 cases (sensitivity 95%), although the negative predicative value was approximately 77%; consequently, sonography should not be relied on to exclude such a life-threatening ingestion.[68, 122]

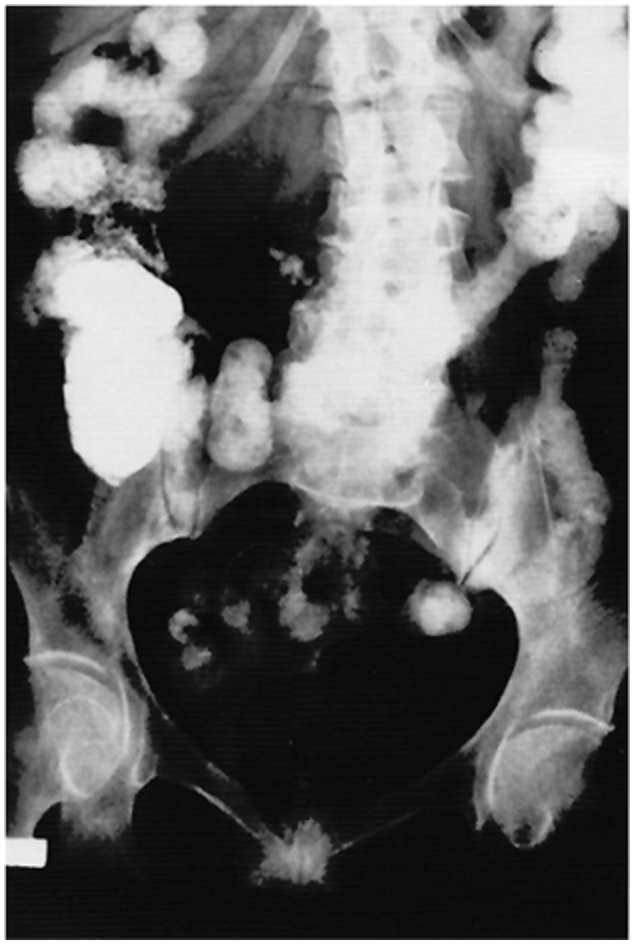


Figure 6-4. An abdominal radiograph of a patient who intentionally ingested ceramic glaze containing 40% lead. *(Courtesy of the Toxicology Fellowship of the New York City Poison Control Center.)*

Because rupture of a single container can be fatal, care must be taken to ensure that all packets are removed. One or two retained packets can be difficult to detect on an abdominal radiograph, and an upper GI series with oral contrast can reveal any remaining packets.[81] CT with enteric contrast is also capable of disclosing remaining packets.[134] However, in one reported case, a single retained packet was not seen on CT and was identified on a subsequent abdominal film with oral contrast.[69]

Body Stuffers

The â€œbody stufferâ€• is an individual who, in an attempt to avoid imminent arrest, hurriedly ingests contraband in insecure packaging.[155] The risk of leakage from such haphazardly constructed containers is high. Unfortunately, radiographic studies cannot reliably confirm or exclude an ingestion. In one series, none of 98 patients had a positive abdominal radiograph.[171]

Occasionally, a radiograph will demonstrate the ingested material (Fig. 6-9). If the drug is in a glass or in a hard-plastic crack vial, the container may be seen. However, only a small number of crack vials are detected radiographically, and the radiograph cannot determine whether the vial still contains any drug. In one series, crack vials were seen on abdominal radiographs in only 2 of

11 patients (18%).[80] If the body stuffer swallows soft plastic bags containing the drug, the containers are not usually visible. However, in three reported cases, â€œbaggiesâ€• were visualized by abdominal CT.[72, 92, 142, 165] Occasional reports have noted that some crack cocaine â€œrocksâ€• can be detected by radiography or CT because they contain radiopaque contaminants.[31, 72, 75] However, CT is not always able to detect such packets.[41]

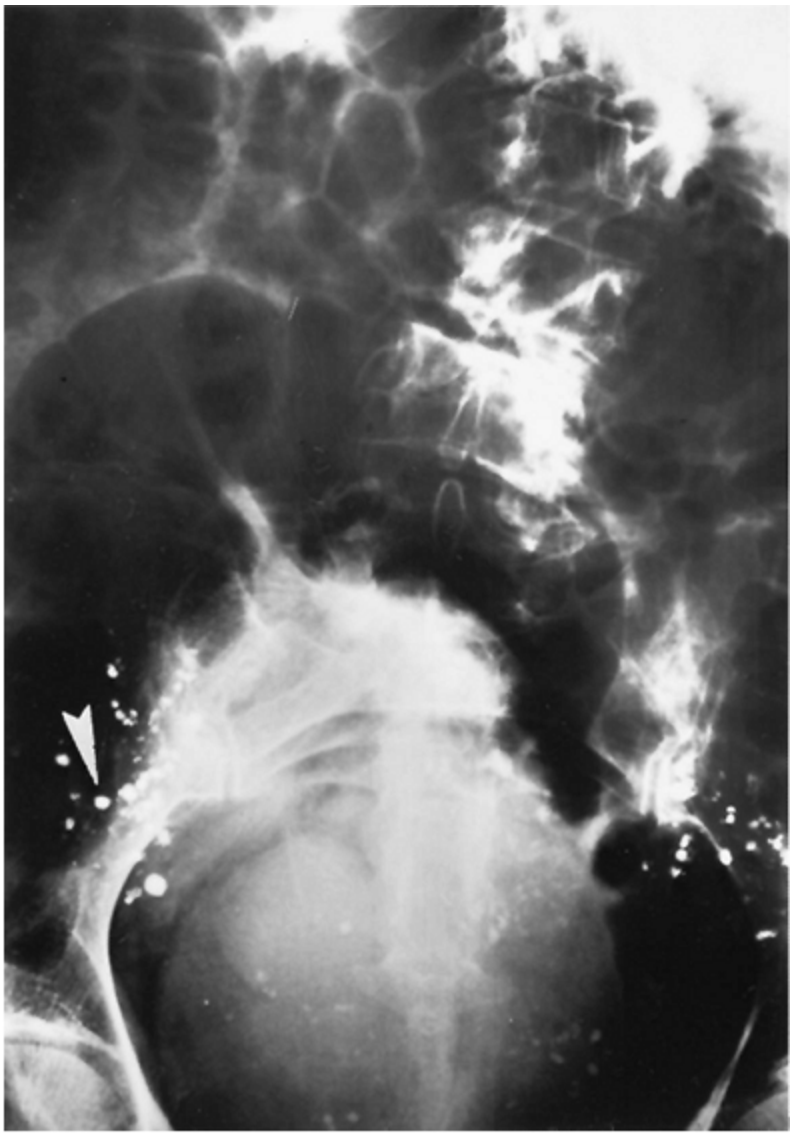


Figure 6-5. An abdominal radiograph in an elderly woman incidentally revealed radiopaque material in the pelvic region. This was residual from gluteal injection of antisyphilis therapy she had received 35â€“40 years earlier. The injections may have contained an arsenical. (*Courtesy of Dr. Emil J. Balthazar, Professor of Radiology, New York University* .)

Halogenated Hydrocarbons

Some halogenated hydrocarbons can be visualized

radiographically.[32] Radiopacity is proportionate to the number of chlorine atoms, and both carbon tetrachloride (CCl_4) and chloroform ($CHCl_3$) are radiopaque. Because these liquids are immiscible in water, a triple layer is seen within the stomach on an upright abdominal film: an uppermost air bubble, a middle radiopaque chlorinated hydrocarbon layer, and a lower gastric fluid layer. However, these ingestions are rare and the quantity ingested is usually too small to show this effect. Other halogenated hydrocarbons such as methylene iodide are highly radiopaque.[200]

Mothballs

Different types of mothballs can be distinguished by radiography. Relatively nontoxic paradichlorobenzene mothballs (containing chlorine, atomic number 17) are moderately radiopaque, whereas more toxic naphthalene mothballs are radiolucent.[177] Radiographs of mothballs outside of the patient can help distinguish these two types (Fig. 99-1).

Radiolucent Xenobiotics

A radiolucent substance may be visible because it is less radiopaque than surrounding soft tissues. Hydrocarbons such as gasoline are relatively radiolucent when embedded in soft tissues. The radiographic appearance resembles subcutaneous gas as seen in a necrotizing soft-tissue infection (Fig. 6-10).

Summary

Obtaining an abdominal radiograph in an attempt to identify pills or other xenobiotics in a patient with an unknown ingestion is unlikely to be helpful and is, in general, not warranted. Radiography is most useful when the suspected substance is known to be radiopaque, as is the case with iron tablets and heavy

metals. The xenobiotic can be radiographed either within the patient's abdomen, elsewhere in the patient's body, or outside of the patient if the material is available.

Extravasation of Intravenous Contrast Material

Extravasation of radiographic contrast material is a common occurrence. In most cases, the volume extravasated is small and there are no clinical sequelae.[14, 29, 47, 154] Rarely, there is an extravasation large enough to cause cutaneous necrosis and ulceration. In the past, the most common radiographic procedure associated with contrast extravasation was lower extremity venography. This is because in venography a small peripheral vein of an edematous leg or foot is injected and often a metal needle rather than a plastic intravenous cannula is used.

Recently, the incidence of sizable extravasations has increased because of the use of rapid-bolus automated power injectors for spiral CT studies. Fortunately, nonionic low-osmolality contrast solutions are currently nearly always used for these studies. These solutions are far less toxic to soft tissues than older ionic high-osmolality contrast materials.

The treatment of contrast extravasation has not been studied in a large series of human subjects and is therefore controversial. Various strategies have been proposed. The affected extremity should be elevated to promote drainage. Although topical application of heat causes vasodilation and could theoretically promote absorption of extravasated contrast material, the intermittent application of ice packs is shown to lower the incidence of ulceration.[29] Rarely, an extremely large volume of liquid is injected into the soft tissues, which requires surgical decompression when there are signs of a compartment syndrome. A radiograph of the extremity will demonstrate the extent of

extravasation.[29]

Precautions should be taken to prevent extravasation. A recently placed, well-running intravenous catheter should be used. The distal portions of the extremities (hands, wrist, and feet) should be avoided. Patients at greater risk, such as infants, debilitated patients, and those with an impaired ability to communicate, must be closely monitored to determine if extravasation occurs.

Visualizing the effects of a Xenobiotic on the Body

The lungs, central nervous system, gastrointestinal tract, and skeleton are the organ systems most amenable to diagnostic imaging. Disorders of the lungs and skeletal system are seen by plain radiography. For abdominal pathology, contrast studies and computed

tomography are more effective, although plain radiographs can diagnose intestinal obstruction, perforation, and radiopaque foreign bodies. Imaging of the central nervous system employs CT, MRI, and nuclear scintigraphy (PET and SPECT).

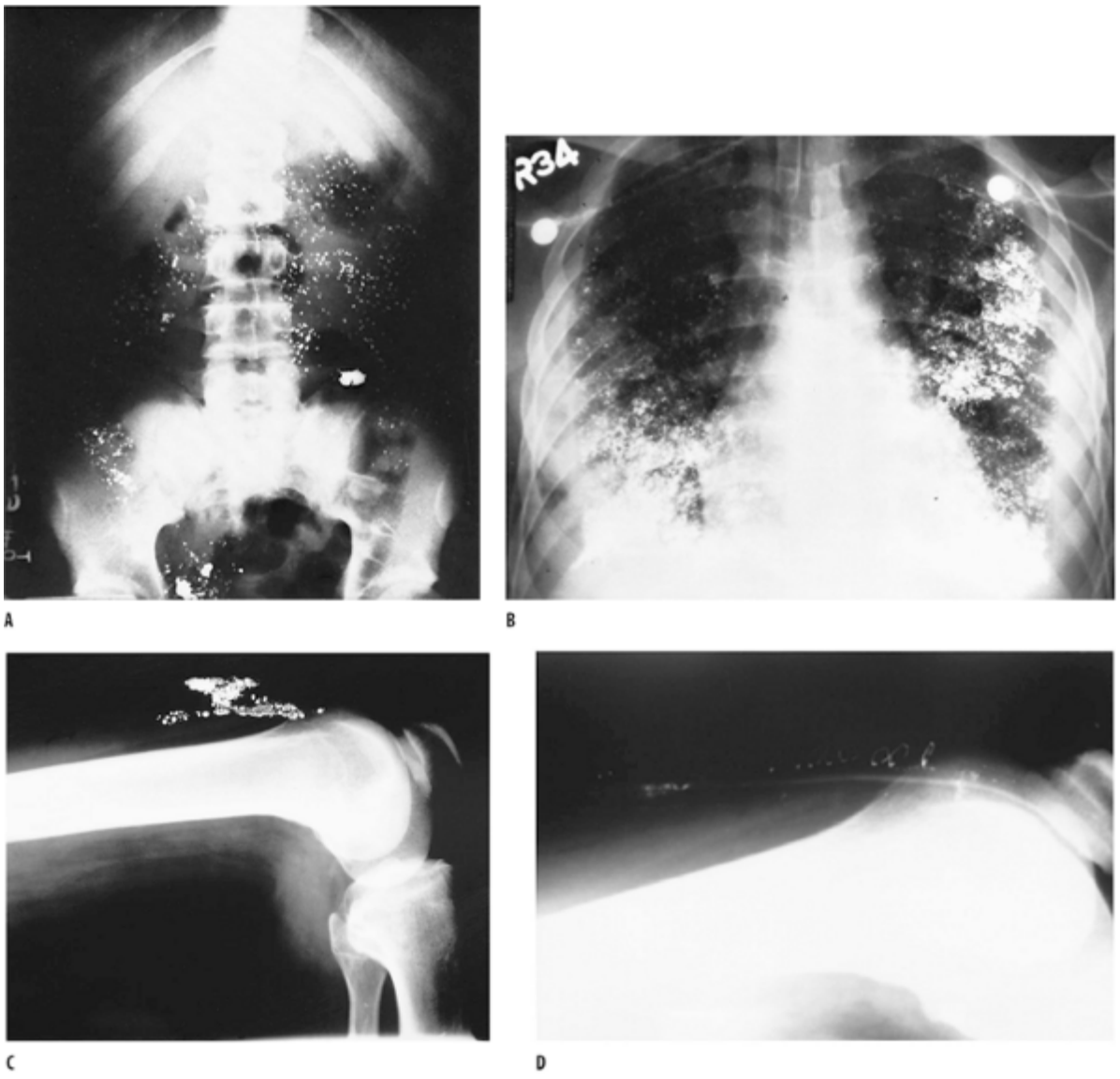


Figure 6-6. Liquid elemental mercury exposures. A. Unintentional rupture of a Cantor intestinal tube distributed mercury throughout the bowel. (Courtesy of Dr. Richard Lefleur, Associate Professor of Radiology, New York University.) B. The chest radiograph in a patient following intravenous injection of elemental mercury showing metallic pulmonary embolism. The patient developed respiratory failure, pleural effusions, and uremia, and expired despite aggressive therapeutic interventions. (*Courtesy of Dr. N. John Stewart.*) C. Subcutaneous injection of liquid elemental mercury is readily detected radiographically. Because mercury is

systemically absorbed from subcutaneous tissues, it must be removed by surgical excision. (*Courtesy of the Toxicology Fellowship of the New York City Poison Control Center.*) D. A radiograph following surgical dÃ©bridement reveals nearly complete removal of the mercury deposit. Surgical staples and a radiopaque drain are visible. *(Courtesy of the Toxicology Fellowship of the New York City Poison Control Center.)*

Skeletal Changes Caused by Xenobiotics

A number of xenobiotics affect bone mineralization. Toxicologic effects on bone result in either increased or decreased density (Table 6-2). Some xenobiotics produce a characteristic radiographic picture, although the exact diagnosis usually depends on correlation with the clinical scenario.[7 , 131] Furthermore, alterations in skeletal structure develop gradually and are usually not visible unless the exposure continues for at least 2 weeks.

Lead Poisoning

Skeletal radiography can support the diagnosis of chronic lead poisoning before the blood lead concentration

is obtained. With lead poisoning, the metaphyseal regions of rapidly growing long bones develop transverse bands of increased density along the growth plate (Fig. 6-11).[18 , 145 , 148 , 159] Characteristic locations are the distal femur and proximal tibia. Flaring of the distal metaphysis also occurs. Lead lines are also seen in the vertebral bodies and iliac crest. Lead lines are detected in approximately 80% of children with a mean lead level of 49 Â± 17 Âµg/dL.[18] They usually occur in children 2â€“9 years of age. It usually takes several weeks for lead lines to appear,

although in very young infants (2â€“4 months old) lead lines can develop within days of exposure.[205] After exposure ceases, lead lines diminish and may eventually disappear. Lead lines are caused by lead's toxic effect on bone growth and do not represent deposition of lead in bone. Lead impedes resorption of calcified cartilage in the zone of provisional calcification adjacent to the growth plate. This is termed *chondrosclerosis* .[18 , 40] Other xenobiotics that cause metaphyseal bands are yellow phosphorus, bismuth, and vitamin D (Chap. 41).

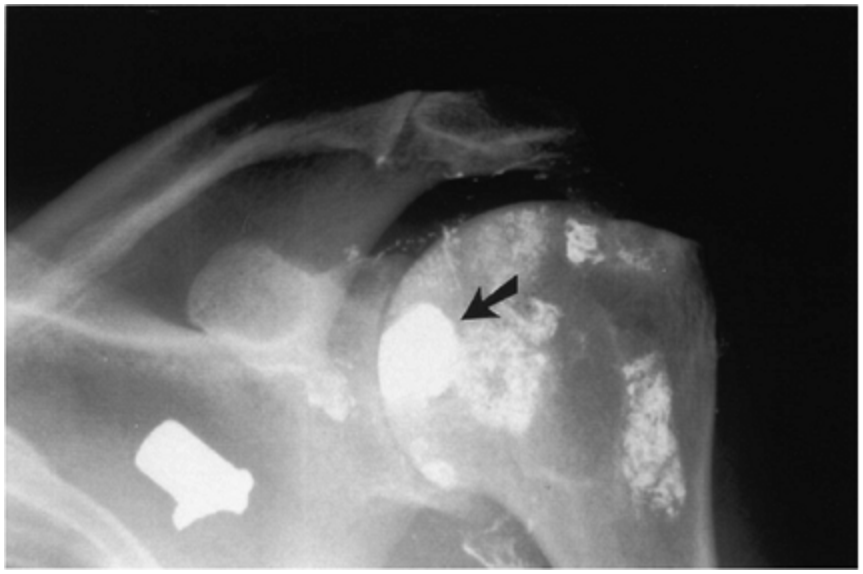


Figure 6-7. A â€œlead arthrogramâ€• discovered many years after a bullet wound to the shoulder. At the time of the initial injury, the bullet was embedded in the articular surface of the humeral head (*arrow*). The portion of the bullet that protruded into the joint space was surgically removed, leaving a portion of the bullet exposed to the synovial space. A second bullet is embedded in the muscles of the scapula. Eight years after the injury, the patient presented with weakness and anemia. Extensive lead deposition throughout the synovium is seen. Lead level was 91 Âµg/dL. *(Courtesy of the Toxicology Fellowship of the New York City Poison Control Center.)*

Fluorosis

Fluoride poisoning causes a diffuse increase in bone mineralization. Endemic fluorosis occurs where drinking water contains very high levels of fluoride (at least 2 or more parts per million) or as an occupational exposure for aluminum workers handling cryolite (sodium-aluminum fluoride). The skeletal changes associated with fluorosis are osteosclerosis, osteophytosis, and ligament calcification. Fluorosis primarily affects the axial skeleton, especially the vertebral column and pelvis, and the teeth. Thickening of the vertebral column can cause compression of the spinal cord and nerve roots. Without a history of fluoride exposure, the clinical and radiographic findings can be mistaken for osteoblastic skeletal metastases. The diagnosis of fluorosis is confirmed by histologic examination of the bone and measurement of fluoride levels in the bone and urine.[19, 193]

Focal Loss of Bone Density

Skeletal disorders associated with focal diminished bone density (or mixed sclerosis and rarefaction) include osteonecrosis, osteomyelitis, and osteolysis. *Osteonecrosis* , also known as avascular necrosis, most often affects the femoral head, the humeral head, and proximal tibia.[113] There are many causes of osteonecrosis. Xenobiotic causes include long-term corticosteroid use and alcoholism. Radiographically, there are focal skeletal lucencies and sclerosis, with loss of bone volume and collapse (Fig. 6-12A).

Acroosteolysis refers to bone resorption of the distal phalanges and is associated with occupational exposure to vinyl chloride monomer. Protective measures have reduced its incidence since it was first described in the early 1960s.[149]

Osteomyelitis is a serious complication of injection drug use. It

usually affects the axial skeleton, especially the vertebral bodies, and the sternomanubrial and sternoclavicular joints (Fig. 6-12B). Back pain or neck pain in intravenous drug users warrants careful consideration. A spinal epidural abscess causing spinal cord compression can accompany vertebral osteomyelitis.[82 , 111] Plain films are negative early in the disease course, and the diagnosis is confirmed by CT or MRI (Fig. 6-12C).

Soft Tissue Changes

Various abnormalities in soft tissues, predominantly as a consequence of infectious complications of injection drug use, are amenable to radiographic diagnosis.[66 , 88] In an injection drug user who presents with signs of local soft-tissue infections, radiography is indicated to detect a retained metallic foreign body, such as a

needle fragment or subcutaneous gas, as may be seen in a necrotizing soft-tissue infection such as necrotizing fasciitis or gas gangrene. CT is more sensitive at detecting soft-tissue gas than conventional radiography. CT and ultrasonography can distinguish subcutaneous or deeper abscess formation that will require surgical or guided percutaneous drainage.

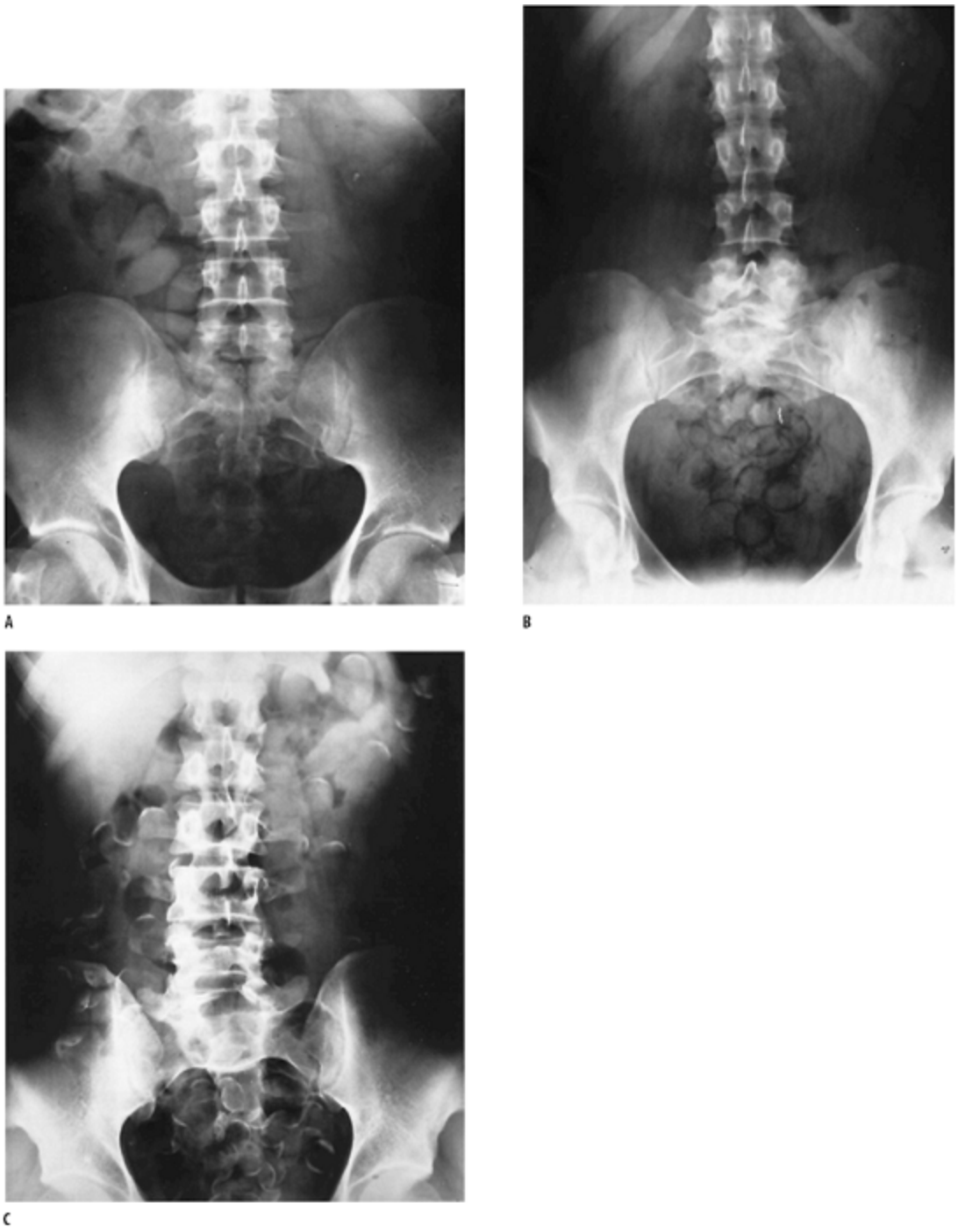


Figure 6-8. Radiographs of three â€œbody packersâ€• showing the various appearances of drug packets. Drug smuggling is accomplished by packing the gastrointestinal tract with large numbers of manufactured, well-sealed containers. A. Multiple oblong packages of uniform size and shape are seen throughout

the bowel. B. The packets are visible in this patient because they are surrounded by a thin layer of air within the wall of the packet. C. Metallic foil is part of the packet's container wall in this patient. *(Courtesy of Dr. Emil J. Balthazar, Professor of Radiology, New York University.)*

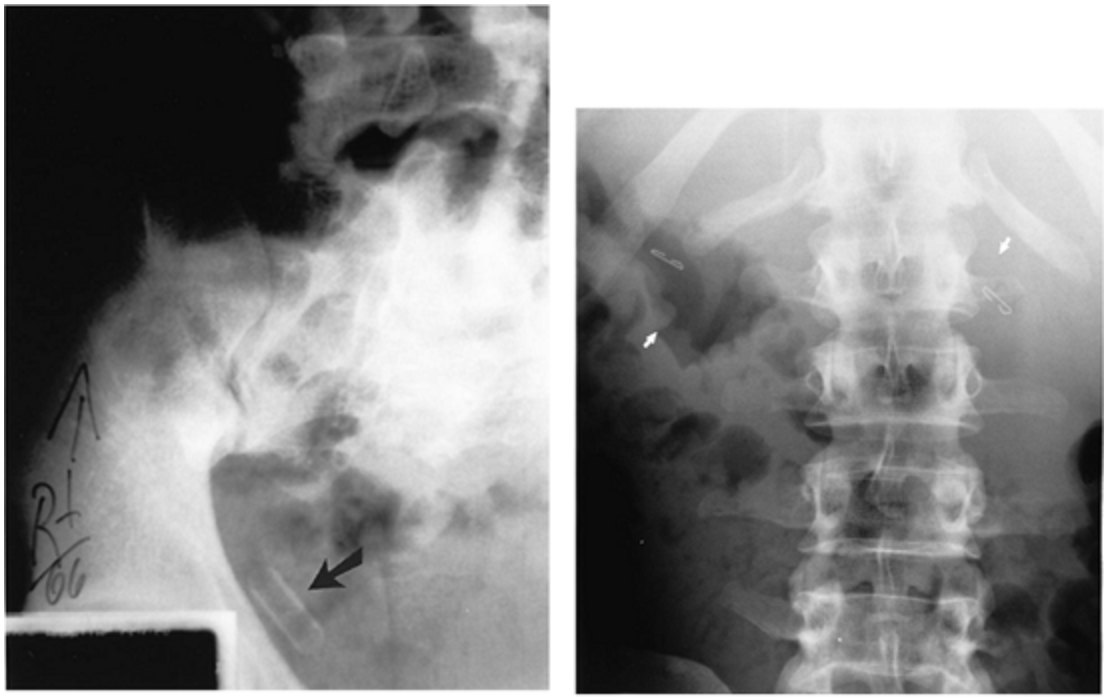


Figure 6-9. Two â€œbody stuffers.â€• Radiography infrequently helps with the diagnosis. A. An ingested glass crack vial is seen in the distal bowel (*arrow*). The patient had ingested his contraband several hours earlier at the time of a police raid. Only the tubular-shaped container, and not the drug, is visible radiographically. The patient did not develop signs of cocaine intoxication during 24 hours of observation. B. Another patient in police custody was brought to the ED for allegedly ingesting his drugs. The patient repeatedly denied this. The radiographs revealed â€œnonsurgicalâ€• staples in his abdomen (*arrows*). When questioned again, the patient admitted that he had swallowed several plastic bags that were stapled closed. *(Courtesy of the*

Toxicology Fellowship of the New York City Poison Control Center.)

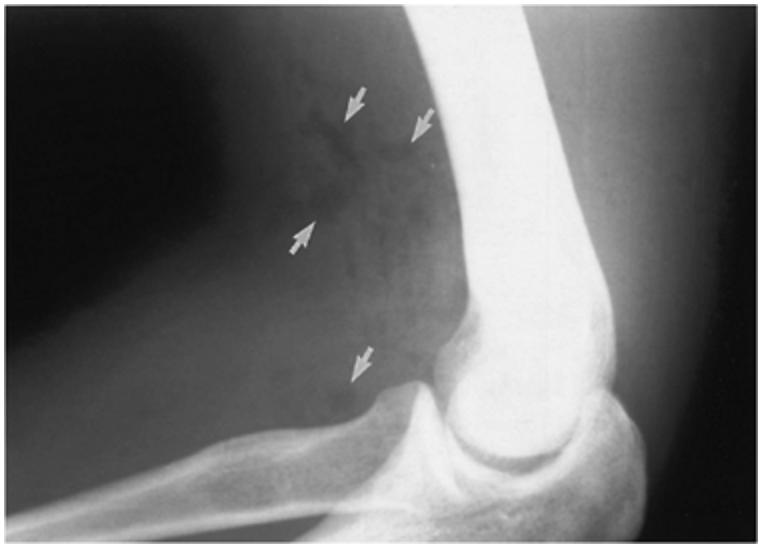


Figure 6-10. Subcutaneous injection of gasoline into the antecubital fossa. The radiolucent hydrocarbon mimics gas in the soft tissues that is seen with a necrotizing soft-tissue infection such as necrotizing fasciitis or gas gangrene (*arrows*). *(Courtesy of the Toxicology Fellowship of the New York City Poison Control Center.)*

Metaphyseal bands (children)
Corticosteroids:
Lead, bismuth, phosphorus:
Osteoporosis: diffuse.
Chondrosclerosis caused by toxic effect on bone growth.

Diffuse increased bone density
Fluorosis:
Osteonecrosis: focal lesions, eg. avascular necrosis of the femoral head; loss of volume with both increased and decreased bone density; osteonecrosis also occurs in alcoholism, bismuth arthropathy, Caisson disease (dysbarism), trauma.

Osteosclerosis, osteophytosis, ligament calcification. Usually involves the axial skeleton (vertebrae and pelvis) and can cause compression of the spinal cord and nerve roots.

Hypervitaminosis D (adult):

Focal or generalized osteoporosis.

Injection drug use:

Osteomyelitis (focal lytic lesions) caused by septic emboli; usually affects vertebral bodies and sternomanubrial joint.

Hypervitaminosis A (pediatric):

Vinyl chloride monomer:

Cortical hyperostosis and sub-periosteal new bone formation.

Diaphyses of long bones have an undulating appearance.

Acroosteolysis (distal phalanges).

Hypervitaminosis D (pediatric):

Generalized osteosclerosis, cortical thickening, and metaphyseal bands.

Increased Bone Density	Diminished Bone Density (Either Diffuse Osteoporosis or Focal Lesions)

TABLE 6-2. Xenobiotic Causes of Skeletal Abnormalities

Pulmonary and Other Thoracic Complications

Many xenobiotics that affect intrathoracic organs produce pathologic changes that can be detected on chest radiographs.[6, 9, 21, 42, 55, 66, 126, 157, 203] The lungs are most often affected, but the pleura, hilum, heart, and great vessels may also be involved.[2] Patients with chest pain may have a pneumothorax, pneumomediastinum, or aortic dissection. Patients with fever, with

or without respiratory symptoms, may have a focal infiltrate, pleural effusion, or hilar lymphadenopathy.

The chest radiographic findings will suggest certain diseases, although the diagnosis ultimately depends on a thorough clinical history. When a specific xenobiotic exposure is known or suspected, the chest radiograph can confirm the diagnosis and assess its severity. If the history of xenobiotic exposure is not known, a patient with an abnormal chest radiograph may initially be misdiagnosed as having pneumonia or another disorder that is more common than xenobiotic-mediated lung disease.[150] Therefore, all patients with chest radiographic abnormalities must be carefully questioned regarding possible xenobiotic exposures at work or at home, as well as the use of medications or other drugs.

Many pulmonary disorders are radiographically detectable because they result in fluid accumulation within the normally air-filled lung. The fluid accumulates within the alveolar spaces or interstitial tissues of the lung, producing the two major radiographic patterns of pulmonary disease: airspace filling and interstitial lung disease (Table 6-3). Most xenobiotics are widely distributed throughout the lungs and produce a diffuse rather than a focal radiographic abnormality.

Diffuse Airspace Filling

Overdose with various compounds, including salicylates, opioids, and paraquat, causes *acute lung injury* , which is characterized pathologically by leaky capillaries (Figs. 6-13 and 111-2).[66 , 74 , 79 , 168 , 174 , 202] There are many other causes of acute lung injury, including sepsis, anaphylaxis, and major trauma.[196] Other xenobiotic exposures resulting in diffuse airspace filling include inhalation of irritant gases that are of low water solubility such as phosgene ($COC1_2$), nitrogen dioxide (silo filler's disease), chlorine, and sulfur dioxide (Chaps. 119 and 123). Organic phosphorus insecticide poisoning causes cholinergic

hyperstimulation, resulting in bronchorrhea (Chap. 109). Smoking â€œcrackâ€• cocaine is associated with diffuse alveolar hemorrhage.[53 , 66 , 203]

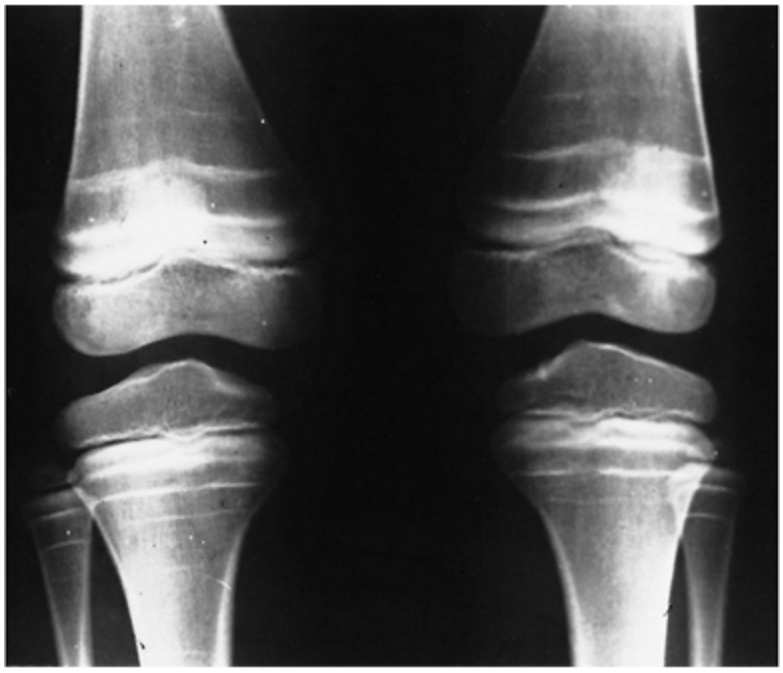
Focal Airspace Filling

Most focal infiltrates are caused by bacterial pneumonia, although aspiration also causes localized airspace disease.[66 , 178] Aspiration of gastric contents can occur during sedative-hypnotic or alcohol intoxication, or during a seizure. Low-viscosity hydrocarbons often enter the lungs when they are swallowed (Figs. 6-14 and 102-2). Because of the delay in development of radiographic abnormalities, the chest radiograph may not be abnormal until 6 hours after the ingestion.[5] During aspiration, the most dependent portions of the lung are affected. When the patient is upright at the time of aspiration, the lower lung segments are involved. When the patient is supine, the posterior segments of the upper and lower lobes are affected.

Multifocal Airspace Filling

Multifocal airspace filling occurs with septic pulmonary emboli, a complication of injection drug

use and right-sided bacterial endocarditis. The foci of pulmonary infection often undergo necrosis and cavitation (Fig. 6-15).[66]



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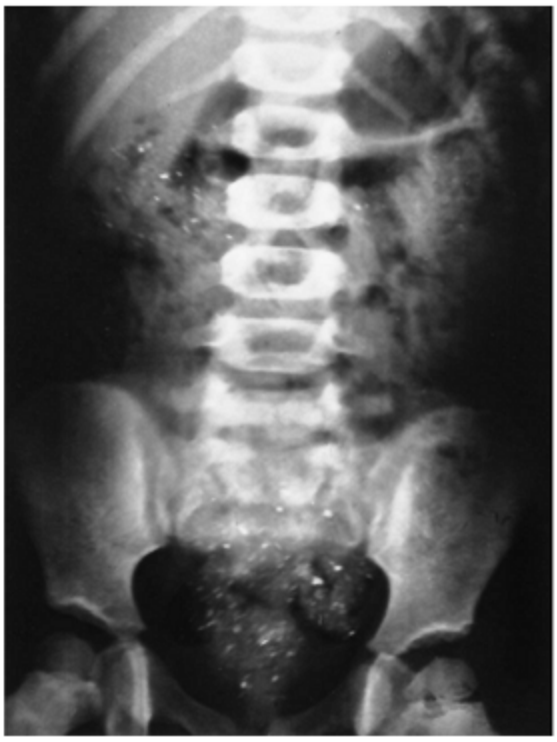


B

Figure 6-11. A. A radiograph of the knees of a child with lead poisoning. The metaphyseal regions of the distal femur and proximal tibia have developed transverse bands representing bone

growth abnormalities caused by lead toxicity. The multiplicity of lines implies repeated exposures to lead. B. The abdominal radiograph of the child shows many radiopaque flakes of ingested leaded paint chips. Lead poisoning also caused abnormally increased cortical mineralization of the vertebral bodies, which gives them a boxlike appearance. *(Courtesy of Dr. Nancy Genieser, Professor of Radiology, New York University.)*

Interstitial Lung Diseases

Toxicologic causes of interstitial lung disease include hypersensitivity pneumonitis, medications with direct pulmonary toxicity, and inhalation or injection of inorganic particulates.[66] Interstitial lung diseases can have an acute, subacute, or chronic course. On the chest radiograph, acute and subacute disorders cause a fine reticular or reticulonodular pattern (Fig. 6-16). Chronic interstitial disorders cause a coarse reticular â€œhoneycombâ€• pattern.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis is a delayed-type hypersensitivity reaction to an inhaled or ingested allergen.[34 , 150] Inhaled organic allergens such as those in moldy hay (farmer's lung) and bird droppings (pigeon breeder's lung) cause hypersensitivity pneumonitis in sensitized individuals. There are two clinical syndromes: an acute, recurrent illness and a chronic, progressive disease. The acute illness presents with fever and dyspnea. The chest radiograph is normal or may show fine interstitial or alveolar infiltrates. Chronic hypersensitivity pneumonitis causes progressive dyspnea. The radiograph shows interstitial fibrosis.

The most common medication causing hypersensitivity pneumonitis is nitrofurantoin. Respiratory symptoms occur after taking the medication for 1â€“2 weeks. Other medications that can cause

hypersensitivity pneumonitis include sulfonamides and penicillins.

Chemotherapeutic Agents

Various chemotherapeutic agents, such as busulfan, bleomycin, cyclophosphamide, and methotrexate, cause pulmonary injury by their direct cytotoxic effect on alveolar cells.[33, 57] The radiographic pattern is usually interstitial (reticular or nodular), but can include airspace filling or mixed patterns. The patient presents with dyspnea, fever, and pulmonary infiltrates that begin after several weeks of therapy. The clinical and radiographic findings must be distinguished from opportunistic infection, pulmonary carcinomatosis, pulmonary edema, and intraparenchymal hemorrhage. Symptoms usually resolve with discontinuation of the offending medication.

Amiodarone

Amiodarone toxicity causes phospholipid accumulation within alveolar cells and can cause pulmonary fibrosis. An interstitial radiographic pattern is seen, although airspace filling can also occur (Fig. 6-16). (See Chap. 61 .)

Particulates

Inhaled inorganic particulates such as asbestos, silica, and coal dust cause *pneumoconiosis.* This is a chronic interstitial lung disease characterized by interstitial fibrosis and loss of lung volume.[124, 151, 199] The intravenous injection of illicit drugs that have particulate contaminants, such as talc, causes a chronic interstitial lung disease.[48, 195]

Pleural Disorders

Asbestos-related calcified pleural plaques develop many years after asbestos exposure (Fig. 6-17). These lesions do not cause

clinical symptoms and have only a minor association with malignancy and interstitial lung disease. Asbestos-related pleural plaques should not be called asbestosis because that term refers specifically to the interstitial lung disease caused by asbestos. Pleural plaques must be distinguished from a mesothelioma, which is not calcified, enlarges at a rapid rate, and erodes into nearby structures such as the ribs.

Pleural effusions occur in drug-induced systemic lupus erythematosus.[126] The medications most frequently implicated are procainamide, hydralazine, isoniazid, and methyldopa. The patient presents with fever and other symptoms of systemic lupus erythematosus.

Pneumothorax pneumomediastinum are associated with illicit drug use, and are related to the route of administration rather than to the particular drug. Barotrauma and pneumocardium associated with

Valsalva maneuver or intense inhalation with breath holding during the smoking of â€œcrackâ€• cocaine or marijuana results in pneumomediastinum (Fig. 6-18A).[17 , 43 , 66 , 136] Pneumomediastinum is one cause of cocaine-related chest pain that can be diagnosed by chest radiography. Forceful vomiting after ingestion of syrup of ipecac or alcohol can produce esophageal tears, pneumomediastinum, and mediastinitis.[204] Attempted injection into the subclavian and internal jugular veins is a cause of pneumothorax in intravenous drug users.[39]

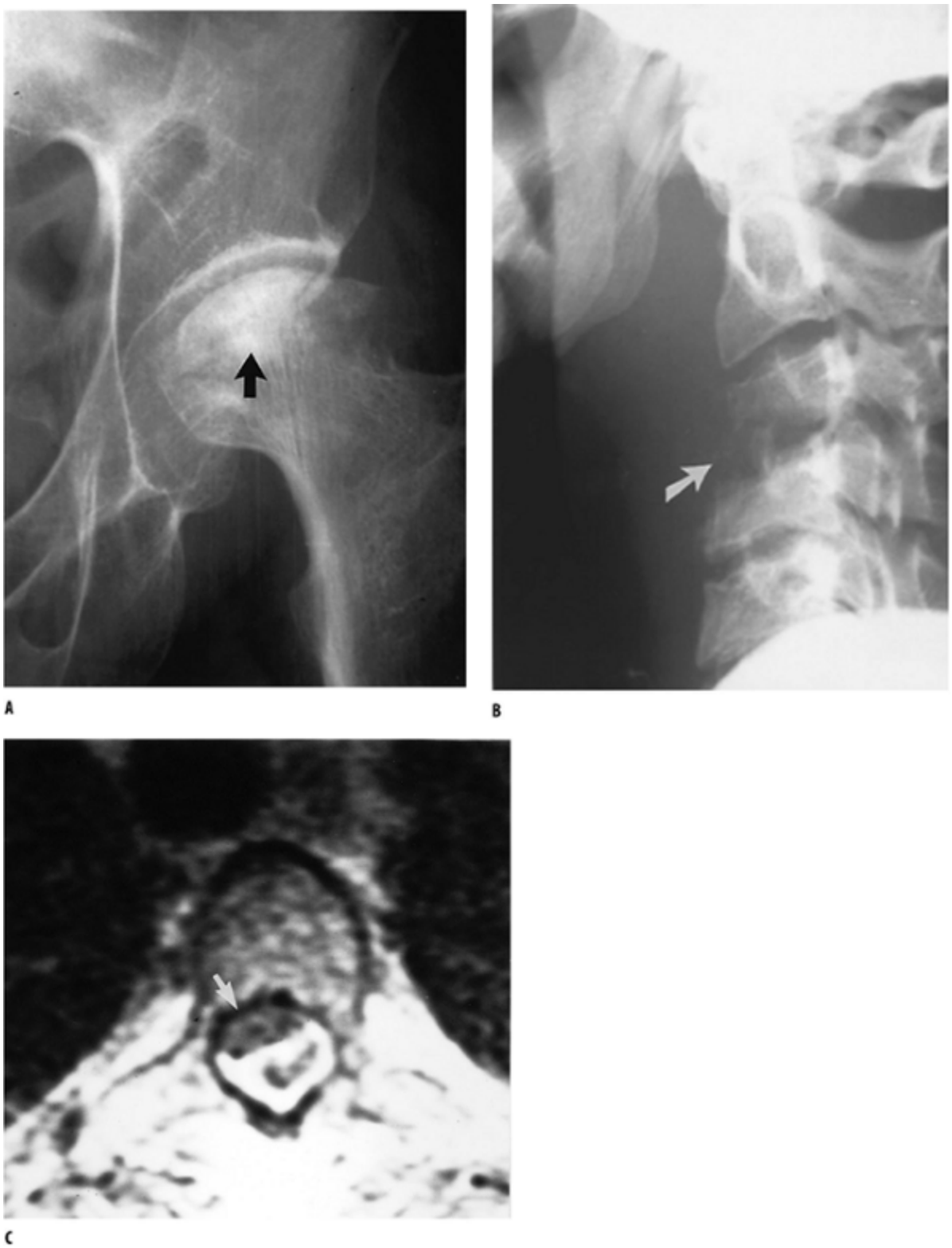


Figure 6-12. A. Avascular necrosis causing collapse of the

femoral head in a patient with long-standing steroid-dependent asthma (*arrow*). B. A patient with vertebral body osteomyelitis complicating injection drug use. Destruction of the intervertebral disk and endplates of C3 and C4 are seen (*arrow*). Operative culture of the bone grew *Staphylococcus aureus.* C. An injection drug user with thoracic back pain, leg weakness, and low-grade fever. Radiographs of the spine were negative. MRI showing an epidural abscess (*arrow*) compressing the spinal cord. The cerebral spinal fluid in the compressed thecal sac is bright white on this T2-weighted image. *(From Levitan R: Thoracolumbar spine. In: Schwartz DT, Reisdorff EJ, eds: Emergency Radiology. New York, McGraw-Hill, 2000, p. 343, with permission.)*

Diffuse airspace filling
Salicylates
Acute lung injury
Opioids
Paraquat
Irritant gases: NO_2 (silo filler's disease), phosgene ($COCl_2$), Cl_2 , H_2S
Organic phosphorus agents, carbamates
Cholinergic stimulation (bronchorrhea)
Alcoholic cardiomyopathy, cocaine, doxorubicin, cobalt
Congestive heart failure
Focal airspace filling
Low-viscosity hydrocarbons
Gastric contents aspiration: CNS depressants, alcohol, seizures
Aspiration pneumonitis
Multifocal airspace filling
Injection drug user
Septic emboli
Interstitial patterns
Inhaled organic allergens: farmer's lung, pigeon-breeder's lung
Hypersensitivity pneumonitis

Fine or coarse reticular or reticulonodular pattern.
Patchy airspace filling is seen in some cases.
Nitrofurantoin, penicillamine
Chemotheraputic agents: busulfan, bleomycin, carmustine, cyclophosphamide, methotrexate
Cytotoxic lung damage

Amiodarone
Phospholipidosis

Talcosis (illicit drug contaminant)
Injected particulates

Pneumoconiosis: asbestosis, silicosis, coal dust, berylliosis (chronic)
Inhaled inorganic particulates
Pleural effusion
Procainamide, hydralazine, INH, methyldopa
Drug-induced systemic lupus erythematosus
Pneumomediastinum Pneumothorax
â€œCrackâ€• cocaine and marijuana (forceful inhalation), ipecac and alcoholism (forceful vomiting), attempted subclavian vein injection
Barotrauma
Pleural plaques (calcified)
Asbestos exposure

Lymphadenopathy
Phenytoin, methotrexate (rare)
Pseudolymphoma

Silicosis (eggshell calcification), berylliosis
Pneumoconiosis
Cardiomegaly

	Ethanol, doxorubicin, cocaine (chronic), amphetamine (chronic), ipecac syrup	Dilated cardiomyopathy
	Drug-induced systemic lupus erythematosus (procainamide, hydralazine, INH)	Pericardial effusion
		Aortic enlargement
	Cocaine	Aortic dissection

TABLE 6-3. Chest Radiographic Findings in Toxicologic Emergencies

Lymphadenopathy

Phenytoin can cause drug-induced lymphoid hyperplasia with hilar lymphadenopathy.[126] Chronic beryllium exposure results in hilar lymphadenopathy that mimics sarcoidosis, and granulomatous changes in the lung parenchyma. Silicosis is associated with â€œeggshellâ€• calcification of hilar lymph nodes.

Cardiovascular Abnormalities

Dilated cardiomyopathy occurs in chronic alcoholism and exposure to cardiotoxic medications such as doxorubicin (Adriamycin). Enlargement of the cardiac silhouette can also be caused by a pericardial effusion, which can accompany a drug-induced systemic lupus erythematosus. *Aortic dissection* is associated with use of cocaine.[58, 66, 101, 138, 147] The chest radiograph may show an enlarged or indistinct aortic knob or ascending or descending aorta (Fig. 6-18B).

Abdominal Complications

Abdominal imaging modalities include conventional radiography, CT, GI contrast studies, and angiography.[60] Conventional radiography is limited in its capability to detect most intraabdominal pathology because most pathologic processes involve soft-tissue structures that are not well seen. Plain radiography readily visualizes gas in the abdomen and is therefore usable to diagnose pneumoperitoneum (free intraperitoneal air) and bowel distension caused by mechanical obstruction or diminished gut motility (adynamic ileus). Other abnormal gas collections, such as intramural gas associated with intestinal infarction, are seen infrequently (Table 6-4).[65 , 107 , 114 , 123 , 170]

Pneumoperitoneum

Gastrointestinal perforation is diagnosed by seeing free intraperitoneal air under the diaphragm on an upright chest radiograph. Peptic ulcer perforation is associated with

crack cocaine use.[1 , 26 , 94] Esophageal or gastric perforation can be a complication of large-bore orogastric tube placement and forceful emesis induced by syrup of ipecac or alcohol intoxication (Fig. 6-19).[204] Esophageal and gastric perforation can also occur following the ingestion of caustics such as iron, alkali, or acid. Esophageal perforation causes pneumomediastinum and mediastinitis.

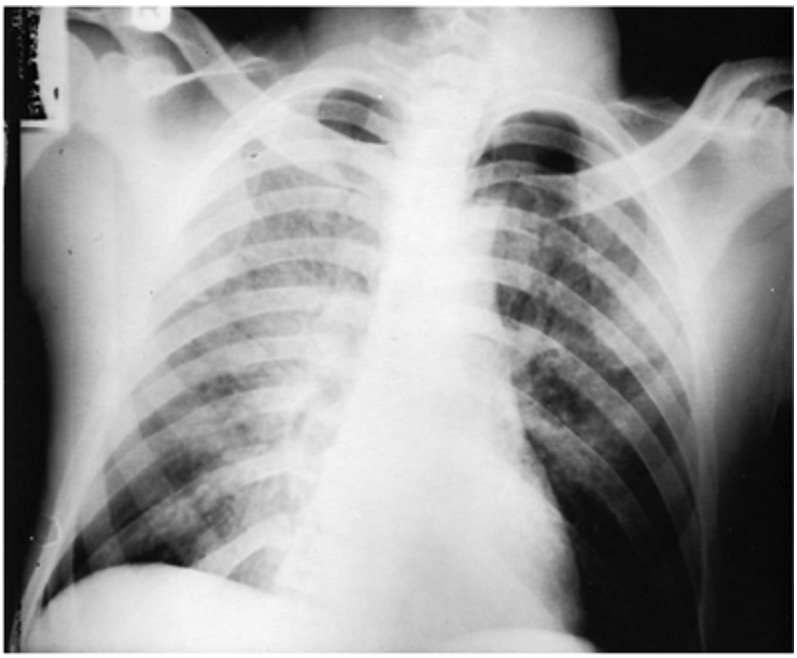


Figure 6-13. Diffuse airspace filling. The chest radiograph of a patient who had recently injected heroin intravenously presented with respiratory distress and acute lung injury. The heart size is normal.

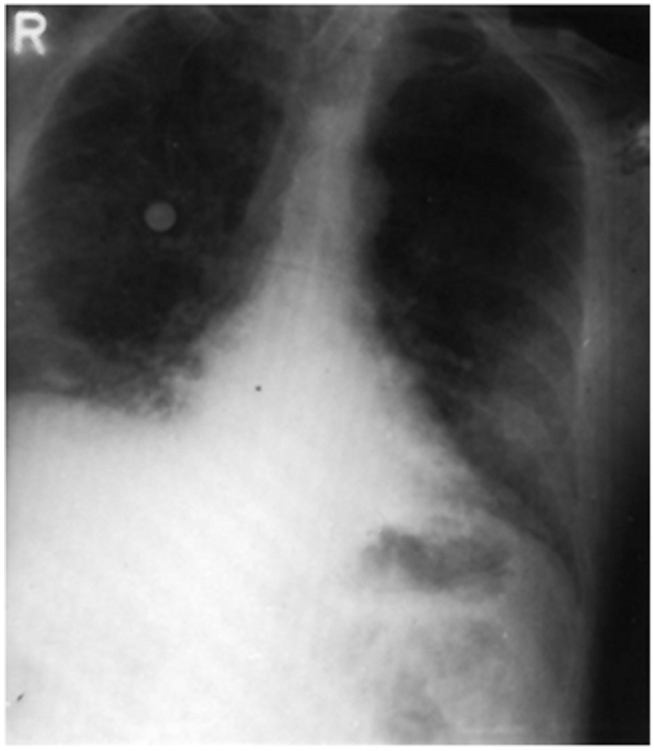


Figure 6-14. Focal airspace filling as a result of hydrocarbon aspiration. A 34-year-old male aspirated gasoline. The chest radiograph shows bilateral lower lobe infiltrates.

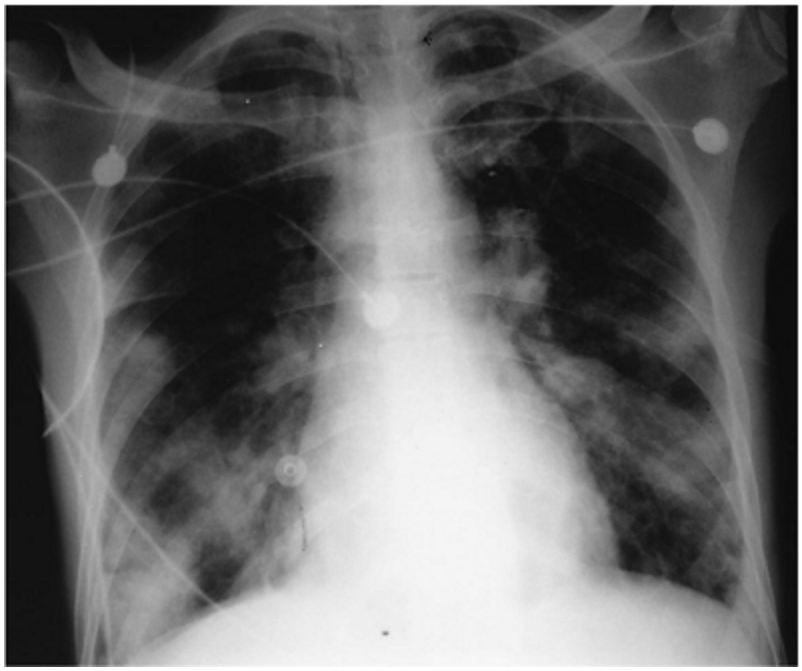


Figure 6-15. Multifocal airspace filling. The chest radiograph in an injection drug user who presented with high fever but without pulmonary symptoms. There are multiple ill-defined pulmonary opacities throughout both lungs, which are characteristic of septic pulmonary emboli. His blood cultures grew *Staphylococcus aureus* .

Obstruction and Ileus

Both mechanical bowel obstruction and adynamic ileus cause bowel distension. With mechanical obstruction, there is a greater amount of intestinal distension proximal to the point of obstruction and a relative paucity of gas and intestinal collapse distal to the point of obstruction. In adynamic ileus, the bowel distension is relatively uniform throughout the entire intestinal tract. On the upright abdominal radiograph, both mechanical obstruction and adynamic ileus show air-fluid levels. In mechanical obstruction, air-fluid levels are seen at different heights and produce a â€œstep-ladderâ€• appearance.

Mechanical bowel obstruction can be caused by large intraluminal foreign bodies such as a body packer's packets or a medication bezoar.[56, 180] Adynamic ileus can complicate ingestions of opioids, anticholinergics, and tricyclic antidepressants (Fig. 6-20).[12, 60] Because adynamic ileus is seen in many diseases, the radiographic finding of an ileus is not helpful diagnostically. When the diagnosis of obstruction is uncertain based on the abdominal radiographs, abdominal CT can clarify the diagnosis.[121]

Mesenteric Ischemia

In most patients with intestinal ischemia, plain abdominal radiographs show only a nonspecific or adynamic ileus pattern. In a small proportion of patients with ischemic bowel (5%), intramural gas is seen.[12] Rarely, gas is also seen in the hepatic portal venous system. CT is better able to detect signs of mesenteric ischemia (Case Studies Fig. 9).[11]

Intestinal ischemia and infarction can be caused by cocaine, ergot alkaloids, and other sympathomimetic agents which induce mesenteric vasoconstriction.[97, 116] Calcium channel blocker overdoses cause splanchnic vasodilation and hypotension that may result in intestinal ischemia and infarction.[197] Superior mesenteric vein thrombosis can be caused by hypercoagulability associated with oral contraceptives.

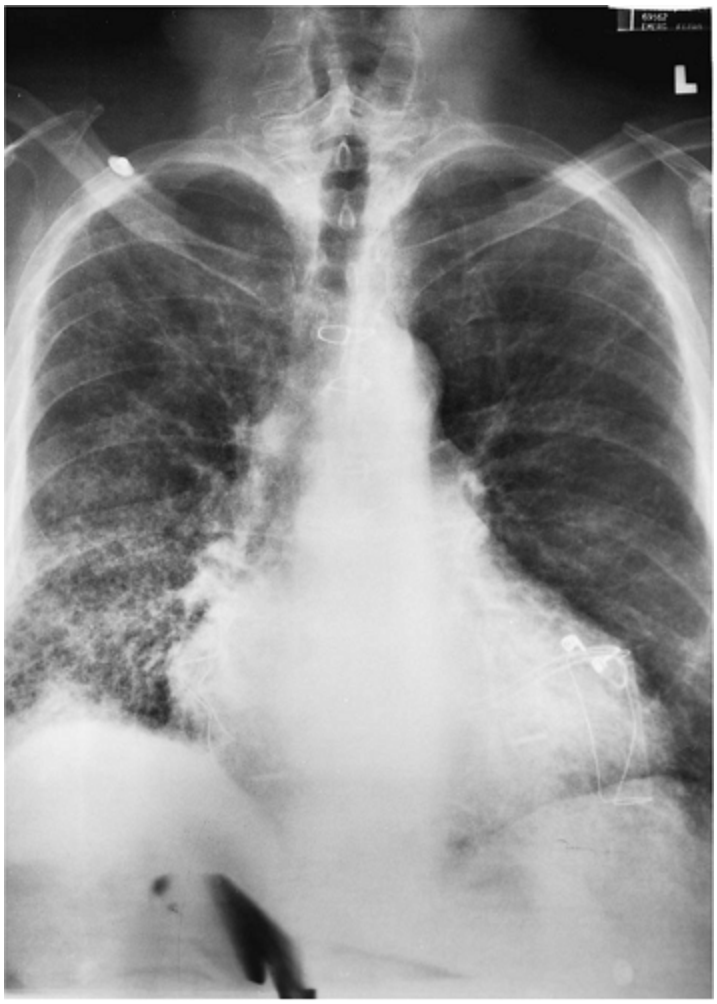


Figure 6-16. Reticular interstitial pattern. The chest radiograph of a patient with cardiac disease who presented to the ED with progressive dyspnea. The initial diagnostic impression was interstitial pulmonary edema. The patient was on amiodarone for malignant ventricular dysrhythmias (note the implanted automatic defibrillator). The lack of response to diuretics and the high-resolution CT pattern suggested that this was toxicity to amiodarone. The medication was stopped and there was partial clearing over several weeks. *(Courtesy of Dr. Georgeann McGuinness, Department of Radiology, New York University.)*

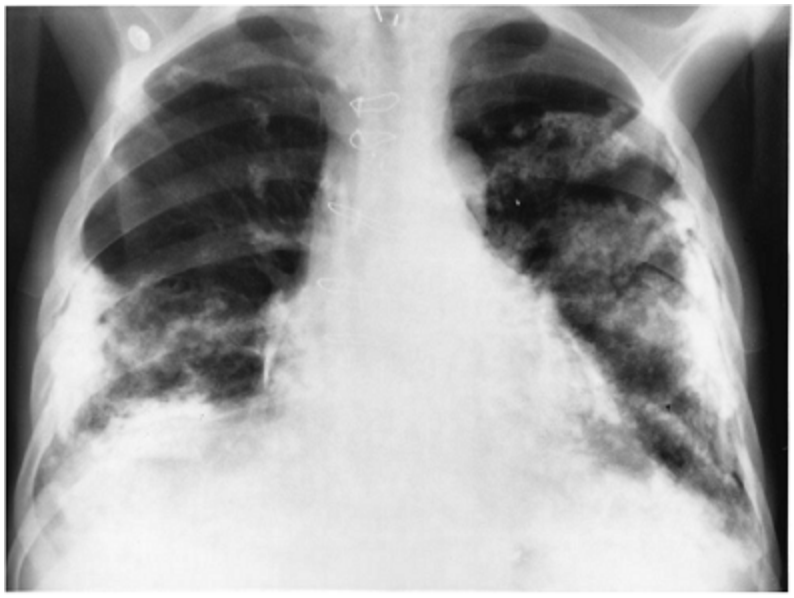
GI Hemorrhage and Hepatotoxicity

Radiography is not usually helpful in the diagnosis of such common abdominal complications as gastrointestinal bleeding and hepatotoxicity.

The now obsolete radiocontrast agent *thorium dioxide* (Thorotrast; thorium, atomic number 90) provides a unique example of pharmaceutical-induced hepatotoxicity. It was used as an angiographic contrast agent until 1947, when it was found to cause hepatic malignancies. The radioactive isotope of thorium has a half-life of 400 years. It accumulates within the reticuloendothelial system and remains there for the life of the patient. It has a characteristic radiographic appearance with multiple punctate densities in the liver, spleen, and lymph nodes (Fig. 6-21). These patients are at risk for hepatic malignancies and pneumococcal sepsis.[15 , 187]

Contrast Esophagram and Upper GI Series

Ingestion of a caustic substance can cause severe damage to the mucosal lining of the esophagus. This can be demonstrated by a contrast esophagram. However, in the acute setting, upper endoscopy should be performed because it provides more information about the extent of injury and prognosis.[98] In addition, administration of barium will coat the mucosa, making endoscopy difficult. For later evaluation, a contrast esophagram identifies mucosal defects, scarring, and stricture formation (Figs. 6-22 and 100-3).[115]



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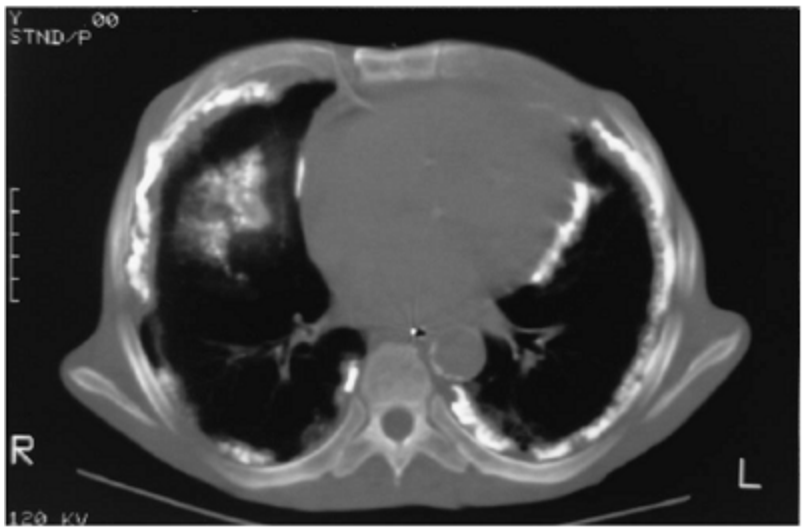


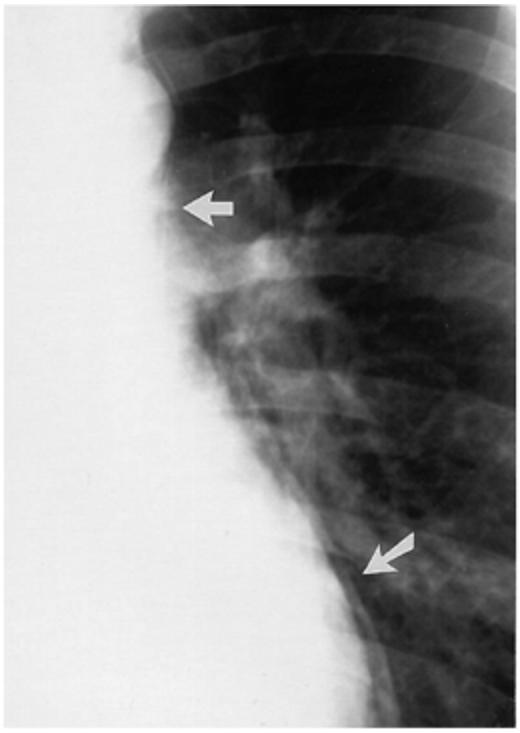
B

Figure 6-17. A. Calcified plaques typical of asbestos exposure are seen on the pleural surfaces of the lungs, diaphragm, and heart. The patient was asymptomatic; this was an incidental radiographic finding. B. The CT scan demonstrates that the opacities seen on the chest radiograph do not involve the lung itself. A lower thoracic image shows calcified pleural plaques (the diaphragmatic plaque is seen on the right). The CT confirms that there is no interstitial lung disease (â€œasbestosisâ€•).

The choice of radiographic contrast agent (barium or water-soluble material) depends on the clinical situation. If the esophagus is severely strictured and there is risk of aspiration, barium should be used because water-soluble contrast material is damaging to the pulmonary parenchyma. If, on the other hand, esophageal or gastric perforation is suspected, water-soluble contrast is safer because extravasated barium is highly irritating to mediastinal and peritoneal tissues.

Ingested objects can cause esophageal and gastric outlet obstruction. Esophageal obstruction because of a drug packet can be demonstrated by a contrast esophagram. Concretions of ingested

material in the stomach can cause gastric outlet obstruction. This has been reported with potassium chloride tablets and enteric-coated aspirin.[8, 169]



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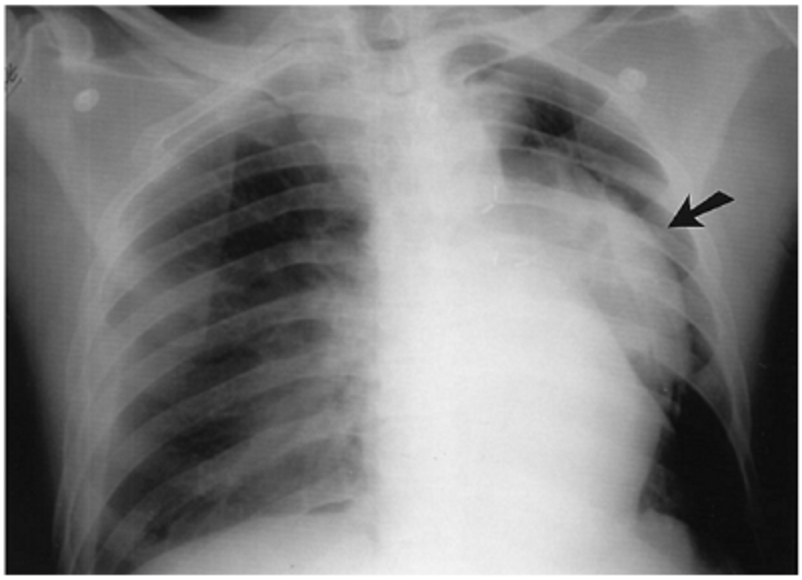

B

Figure 6-18. Two patients with chest pain following cocaine use. A. Pneumomediastinum after forceful inhalation while smoking â€œcrackâ€• cocaine. A fine white line representing the pleura elevated from the mediastinal structures is seen (*arrows*). The

patient's chest pain resolved during a 24-hour period of observation. B. Thoracic aortic dissection and rupture following cocaine use. The patient presented with chest pain radiating to the back. Chest radiography reveals a wide and indistinct aortic contour (*arrow*). *(Courtesy of the Toxicology Fellowship of the New York City Poison Control Center.)*

Abdominal Computed Tomography

CT provides great anatomic definition of intraabdominal organs and plays an important role in the diagnosis of a wide variety of abdominal disorders. In most cases, both oral and intravenous contrast are administered. Oral contrast delineates the intestinal lumen. Intravenous contrast is needed to reliably detect lesions in hepatic and splenic parenchyma, the kidneys, and bowel wall.

Certain abdominal complications of poisonings are amenable to CT diagnosis. Intestinal ischemia causes bowel wall thickening, intramural hemorrhage, and, at a later stage, intramural gas and hepatic portal venous gas (Case Studies Fig. 9).[11] Splenic infarction and splenic and psoas abscesses are complications of intravenous drug use that can be diagnosed on CT.[12] Radiopaque foreign substances can be detected and accurately localized by CT such as intravenously injected elemental mercury.[112] Radiolucent foreign bodies, such as a body packer's packets, can be detected by using enteric contrast.[72 , 75] However, in one case, a retained packet was missed by CT and detected on an upper GI oral contrast study.[69]

Vascular Lesions

Angiography can detect such complications of injection drug use as venous thrombosis and arterial laceration causing pseudoaneurysm formation (Figs. 6-23 and 6-24). Intravenous injection of amphetamine, cocaine, or ergotamine causes necrotizing angiitis

that is associated with microaneurysms, segmental stenosis, and arterial thrombosis. These lesions are seen in the kidneys, small bowel, liver, pancreas, and cerebral circulation (Fig. 6-25).[28 , 146] Complications include aneurysm rupture and visceral infarction. Renal lesions cause severe hypertension and renal failure.[160]

Neurologic Complications

Imaging studies have revolutionized the diagnosis of central nervous system (CNS) disorders.[50 , 63] Both acute focal brain lesions and chronic degenerative changes can be detected (Table 6-5).[105] Some xenobiotics have a direct effect on the CNS, whereas with others, neurologic injury is an indirect sequela of the xenobiotic exposure caused by hypoxia, hypotension, hypertension, cerebral vasoconstriction, head trauma, or infection.

Imaging Modalities

Computed tomography can directly visualize brain tissue and many intracranial lesions.[62] CT is the imaging study of choice in the emergency setting because it readily detects acute intracranial hemorrhage as well as parenchymal lesions that are causing mass effect. Infusion of intravenous contrast further delineates intracerebral mass lesions such as tumors and abscesses. CT is fast, widely available on an emergency basis, and can accommodate critical support and monitoring devices.

Magnetic resonance imaging has supplanted CT in nearly all areas of nonemergency neurodiagnosis. It offers greater anatomic discrimination of brain tissues and of areas of cerebral edema and demyelination. However, in the emergency setting, the disadvantages of MRI outweigh its strengths. MRI is no better than CT in detecting acute blood collections. Furthermore, MRI is usually not readily available on an emergency basis, image acquisition time is long, and critical care supportive and monitoring devices are often incompatible with MR scanning

machines.[108]

Nuclear scintigraphy that uses computed tomography technology (SPECT and PET, discussed later under Nuclear Scintigraphy) is being employed as a tool to elucidate functional characteristics of the central nervous system. Examples include both immediate and long-term effects of various xenobiotics on regional brain metabolism, blood flow, and neurotransmitter function.[102, 140, 191]

Emergency Head CT Scanning

An emergency noncontrast head CT scan is obtained to detect acute intracranial hemorrhage and focal brain lesions causing cerebral edema and mass effect. Patients

with these lesions present with focal neurologic deficits, seizures, headache, or altered mental status. Toxicologic causes of intraparenchymal and subarachnoid hemorrhage include cocaine or other sympathomimetics (Fig. 6-26).[100, 104] Cocaine-induced vasospasm can cause ischemic infarction, although this is not seen by CT until 6 to 24 or more hours after onset of the neurologic deficit. Drug-induced CNS depression, most commonly ethanol intoxication, predisposes the patient to head trauma, which can result in a subdural hematoma or cerebral contusion (Fig. 6-27). Toxicologic causes of intracerebral mass lesions include septic emboli complicating injection drug use and HIV-associated CNS toxoplasmosis and lymphoma (Fig. 6-28).[16, 135] On a contrast CT, such tumors and focal infections exhibit a pattern of â€œring enhancement.â€•

Radiographic Finding	Xenobiotic
Pneumoperitoneum (hollow viscus perforation)	Caustics: iron, alkali, acids Cocaine GI decontamination (ipecac, lavage tube)
Mechanical obstruction (intraluminal foreign body) Intestinal Gastric outlet } Upper GI Esophageal } series	Foreign-body ingestion: body packer, enteric-coated pills (bezoar)
Ileus (diminished gut motility)	Opioids Anticholinergics Tricyclic antidepressants Mesenteric ischemia caused by cocaine, oral contraceptives, cardioactive steroids, induced hypokalemia, hypomagnesemia
Intramural gas (intestinal infarction) Bowel wall thickening Hepatic portal venous gas (CT is more sensitive)	Cocaine Ergot alkaloids Oral contraceptives Calcium channel blockers Systemic hypotension
Foreign-body ingestion	Iron pills Metals (Hg, Pb, Tl, As) Body packers and stuffers Bismuth subsalicylate Calcium carbonate Enteric-coated and sustained-release tablets Pica (calcareous clay)

TABLE 6-4. Plain Abdominal Radiography in Toxicologic Emergencies

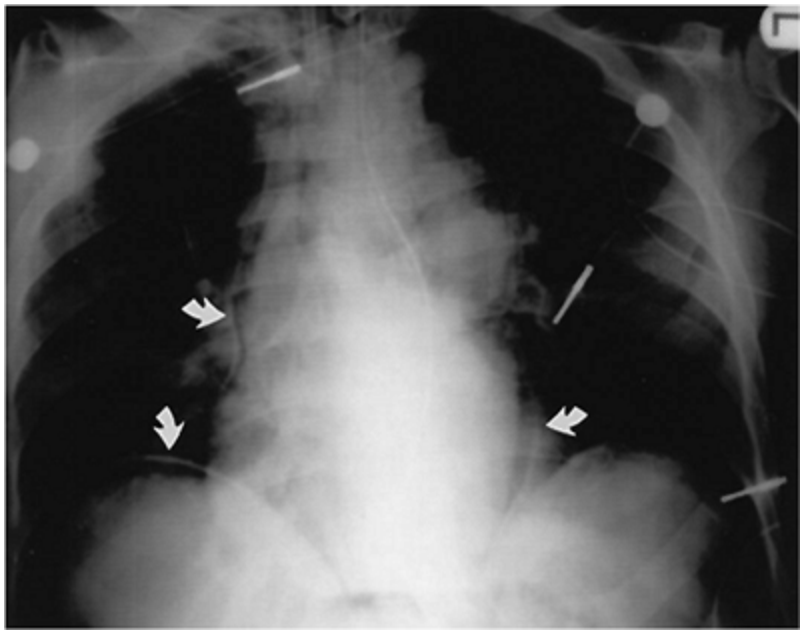

Figure 6-19. GI perforation following gastric lavage with a large-bore orogastric tube. The upright chest radiograph shows air under

the right hemidiaphragm and pneumomediastinum (*arrows*). An esophagram with water-soluble contrast did not demonstrate the perforation. Laparotomy revealed perforation of the anterior wall of the stomach.

Xenobiotic-Mediated Neurodegenerative Disorders

A number of xenobiotics directly damage brain tissue, which produces morphologic changes that are detectable using CT and MRI. Such changes include generalized atrophy, focal areas of neuronal loss, demyelinization, and cerebral edema. Imaging abnormalities can help establish a diagnosis or predict prognosis in a patient with neurologic dysfunction following a xenobiotic exposure. In some cases, the imaging abnormality will suggest a toxicologic diagnosis in a patient with a neurologic disorder in whom a xenobiotic exposure was not suspected clinically.[10 , 50 , 89 , 91 , 141 , 198]

Atrophy

Ethanol is the most widely used neurotoxin. With long-term ethanol use, there is a widespread loss of neurons with resultant atrophy. In some alcoholics, the loss of brain tissue is especially prominent in the cerebellum. However, the amount of cerebral or cerebellar atrophy does not always correlate with the extent of cognitive impairment or gait disturbance.[35 , 59 , 73 , 76 , 93 , 192 , 194] Chronic toluene exposure (occupational and illicit use) also causes diffuse cerebral atrophy.[83 , 156]

Focal Degenerative Lesions

Carbon monoxide poisoning produces focal degenerative lesions in the brain. In about half of

patients with severe neurologic dysfunction following carbon monoxide poisoning, CT scans show bilateral symmetric lucencies in the basal ganglia, particularly the globus pallidus (Figs. 6-27 and 120-1).[25 , 84 , 89 , 127 , 141 , 143 , 144 , 162 , 163 , 166 , 182 , 190] The basal ganglia are especially sensitive to hypoxic damage because of their limited blood supply and high metabolic requirements. Subcortical white matter lesions also occur following carbon monoxide poisoning. Although less frequent than lesions of the basal ganglia, white matter lesions are more clearly associated with poor neurologic outcome. MRI is more sensitive than CT at detecting these CNS lesions, especially at detecting white matter abnormalities.[25 , 50 , 91 , 144 , 182]

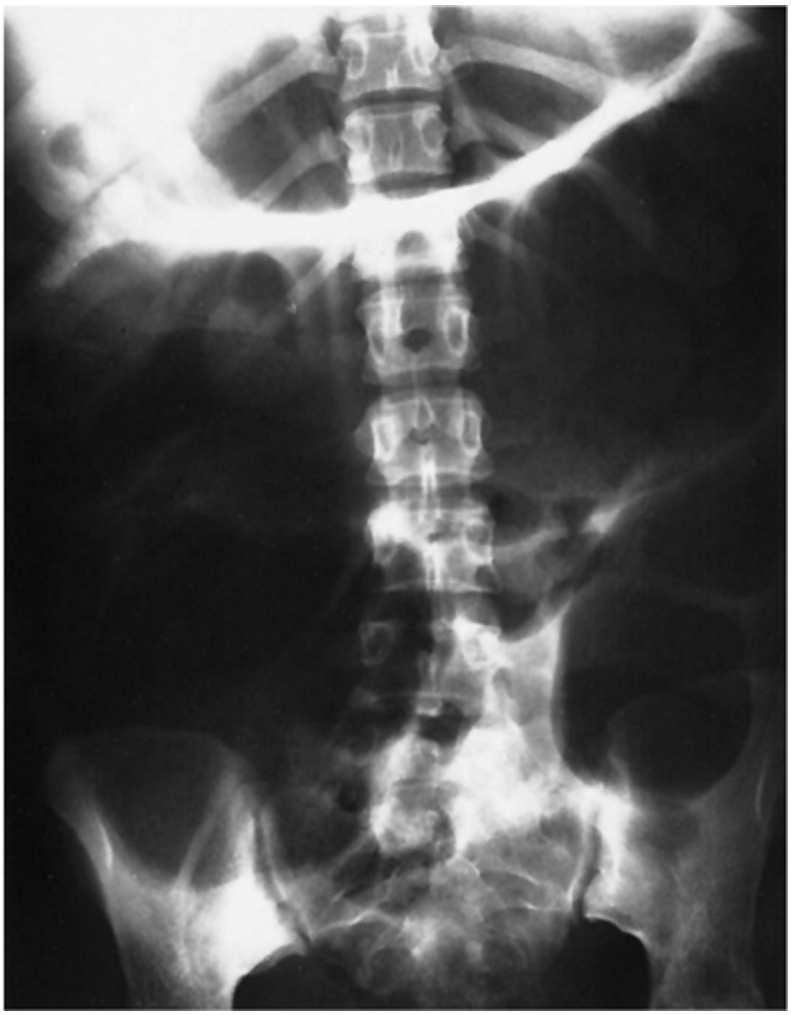

Figure 6-20. Methadone maintenance therapy causing marked abdominal distension. The radiograph reveals striking large bowel dilatation, termed colonic ileus, caused by chronic opioid use. A similar radiographic picture is seen with anticholinergic poisoning. A contrast enema can clarify the diagnosis. *(Courtesy of Dr. Emil J. Balthazar, Professor of Radiology, New York University.)*

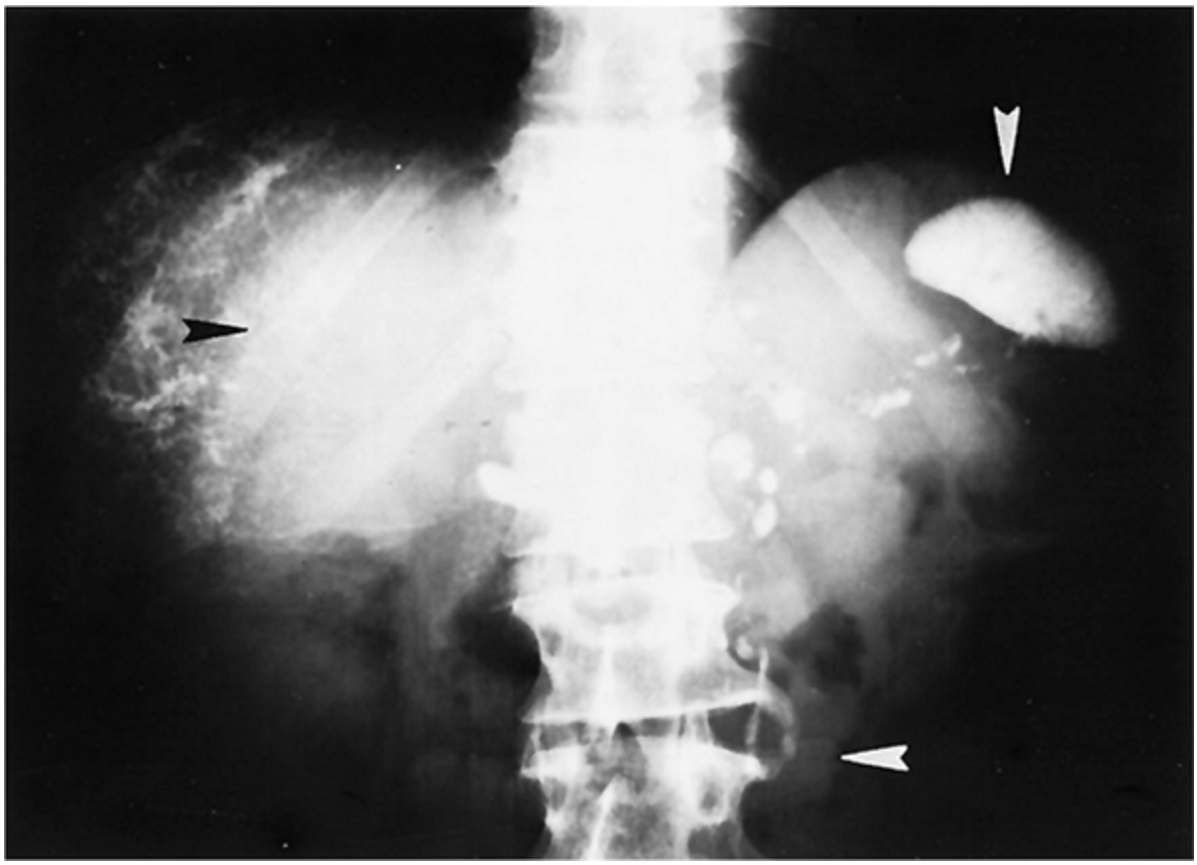

Figure 6-21. The abdominal radiograph of a patient who had received thorium dioxide (Thorotrast) for a radiocontrast study many years previously. The spleen (*vertical white arrow*), liver (*horizontal black arrow*), and lymph nodes (*horizontal white arrow*) are demarcated by thorium retained in the reticuloendothelial system. *(Courtesy of Dr. Emil J. Balthazar, Professor of Radiology, New York University.)*

Basal ganglion lucencies, white matter lesions, and atrophy are caused by other xenobiotics such as methanol (putaminal lesions),[9 , 61 , 71 , 128 , 153 , 158] ethylene glycol, cyanide,[51 , 125] hydrogen sulfide, inorganic and organic mercury,[117] manganese,[10] heroin,[91 , 95] barbiturates, chemotherapeutic agents, solvents such as toluene,[50 , 83 , 156] and podophyllin.[24 , 130] Similar imaging abnormalities can be caused by nontoxicologic disorders including hypoxia, hypoglycemia, and infectious encephalitis.[71 , 78]

Nuclear Scintigraphy

Both CT and MRI display cerebral anatomy, whereas nuclear medicine studies provide functional information about the brain. Nuclear scintigraphy uses radioactive isotopes that are bound to carrier molecules (ligands). The choice of ligand depends on the biologic function being studied. Brain cells take up the radiolabeled ligand in proportion to their physiologic activity or the regional blood flow. The radioactive emission from the isotope is detected by a scintigraphic camera, which produces an image showing the quantity and distribution of tracer. Better anatomic detail is provided by using computed tomography techniques to generate cross-sectional images. There are two such technologies: *single photon emission computed tomography* (SPECT) and *positron emission tomography* (PET). These imaging

modalities have been used in the research and clinical settings to study the neurologic effects of particular xenobiotics and the mechanisms of xenobiotic-induced neurologic dysfunction.

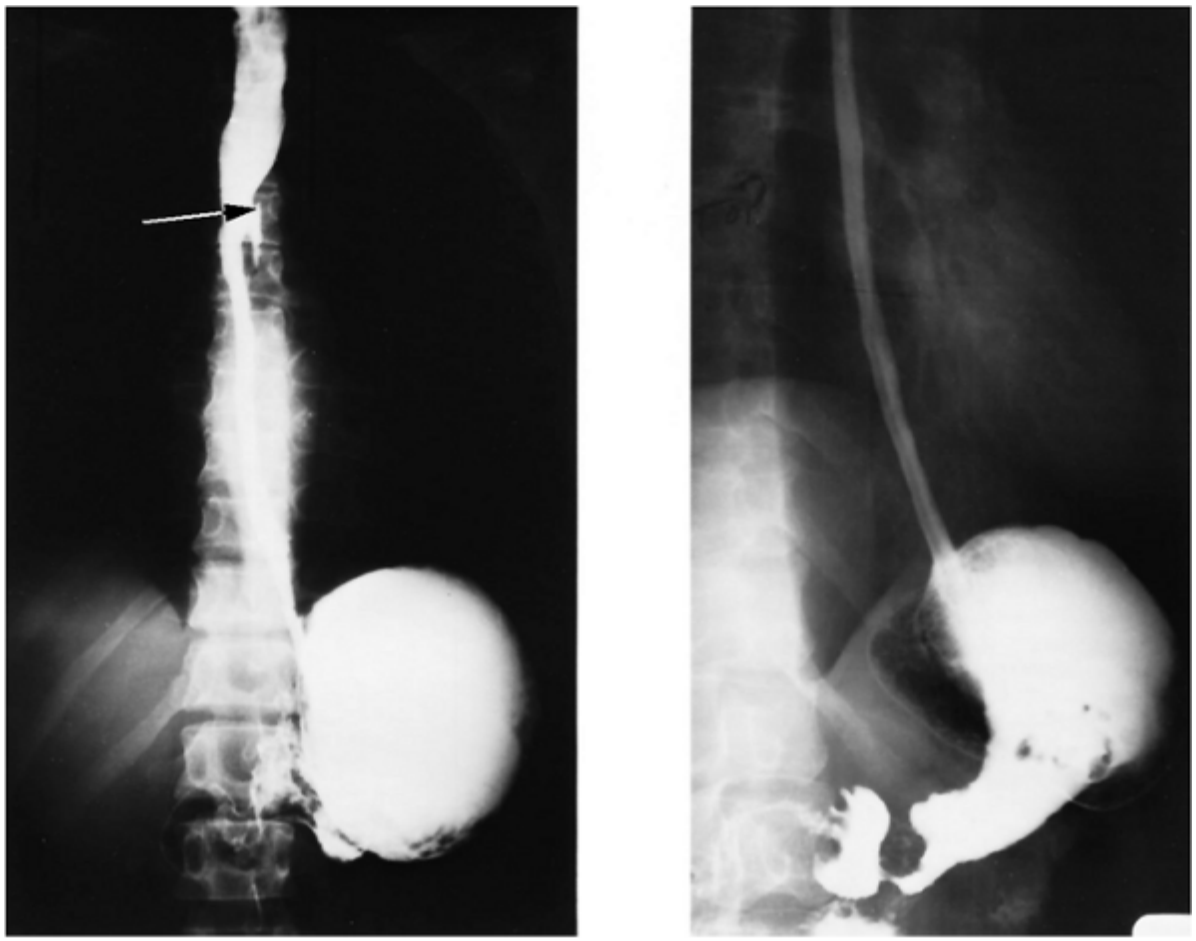

Figure 6-22. A. A barium swallow performed several days after ingestion of liquid lye shows intramural dissection and extravasation of barium with early stricture formation. B. At 3 weeks' postingestion, there is an absence of peristalsis, diffuse narrowing of the esophagus, and reduction in size of the fundus and antrum of the stomach as a result of scarring. *(Courtesy of Dr. Emil J. Balthazar, Professor of Radiology, New York University.)*

SPECT employs conventional isotopes such as technetium-99m and iodine-123.[102] These isotopes are bound to ligands that are taken up in the brain in proportion to regional blood flow, reflecting the local metabolic rate.

PET uses radioactive isotopes of biologic elements such as carbon-

11, oxygen-15, nitrogen-13, and fluoride-18 (a substitute for hydrogen).[140] These radioisotopes have very short half-lives so that PET scanning requires an onsite cyclotron to produce the isotope. The isotopes are incorporated into molecules such as glucose, oxygen, water, various neurotransmitters, and drugs. Labeled glucose is taken up in proportion to the local metabolic rate for glucose. Uptake of labeled oxygen demonstrates the local metabolic rate for oxygen. Labeled neurotransmitters generate images reflecting their concentration and distribution within the brain.

Both PET and SPECT have been used to study the effects of various xenobiotics on cerebral function. For example, although both CT and MRI can detect cerebellar atrophy in chronic alcoholics, there is a poor correlation between the magnitude of cerebellar atrophy and the clinical signs of cerebellar dysfunction. PET scans can demonstrate diminished cerebellar metabolic rate for glucose, which correlates more accurately with the patient's clinical status.[64 , 192]

In patients with severe neurologic dysfunction following carbon monoxide poisoning, SPECT regional blood flow measurements show diffuse hypometabolism in the frontal cortex.[27] In one patient, severe perfusion abnormalities improved slightly over several months in proportion with the patient's gradual clinical improvement.[87] In another patient treated with hyperbaric oxygen, a SPECT scan revealed increased blood flow in the frontal lobes, although the blood flow still remained significantly less than normal.[110]

In patients who chronically use cocaine, SPECT blood flow scintigraphy demonstrates focal cortical perfusion defects. The extent of these perfusion defects correlates with the frequency of drug use. Focal perfusion defects probably represent local vasculitis or small areas of infarction.[82 , 185] PET scanning has been used to demonstrate the effects of cocaine on cerebral blood

flow and regional glucose metabolism. PET neurotransmitter studies show

promise in elucidating potential mechanisms of action of cocaine. Using radiolabeled dopamine analogs, downregulation of dopamine (D_2) receptors has been noted following a cocaine binge. This finding may be responsible for cocaine craving that occurs during cocaine withdrawal. Using ^{11}C-labeled cocaine, uptake of cocaine can be demonstrated in the basal ganglia, a region rich in dopamine receptors.[191]

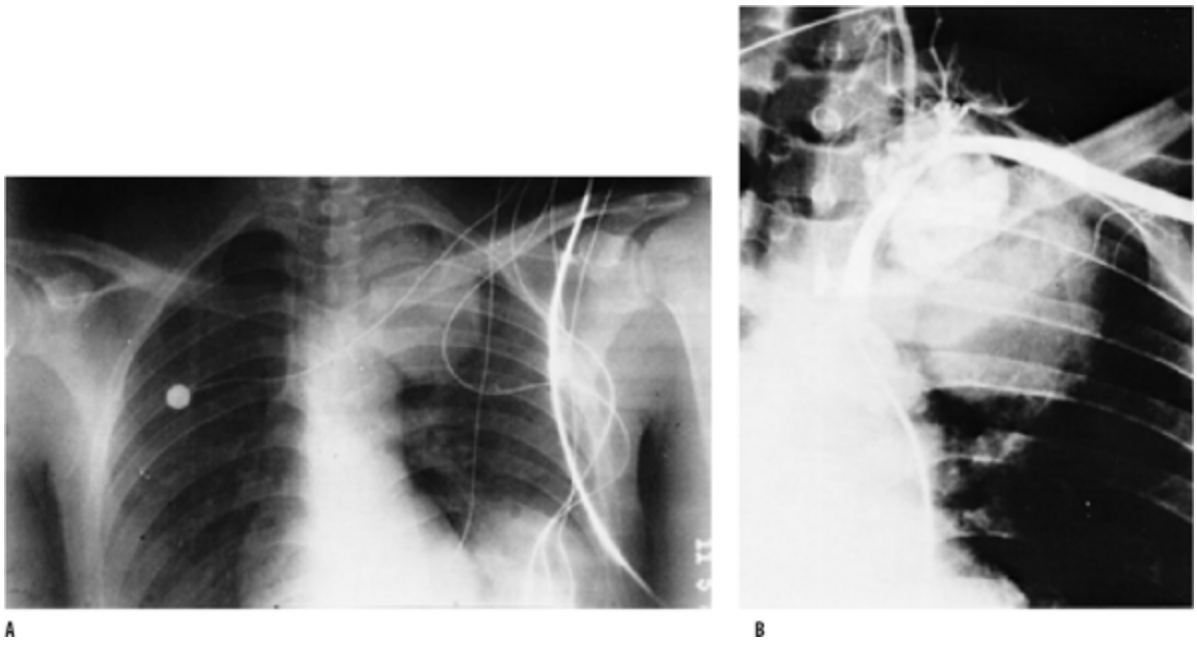

Figure 6-23. A. Chest radiograph of a young drug abuser who used the supraclavicular approach for heroin injection. The large mass in the left chest was suspicious for a pseudoaneurysm. B. An arch aortogram performed on the patient revealed a large pseudoaneurysm and hematoma subsequent to an arterial tear during attempted injection. Surgical repair was performed. *(Courtesy of Richard Lefleur, Department of Radiology, Bellevue Hospital.)*

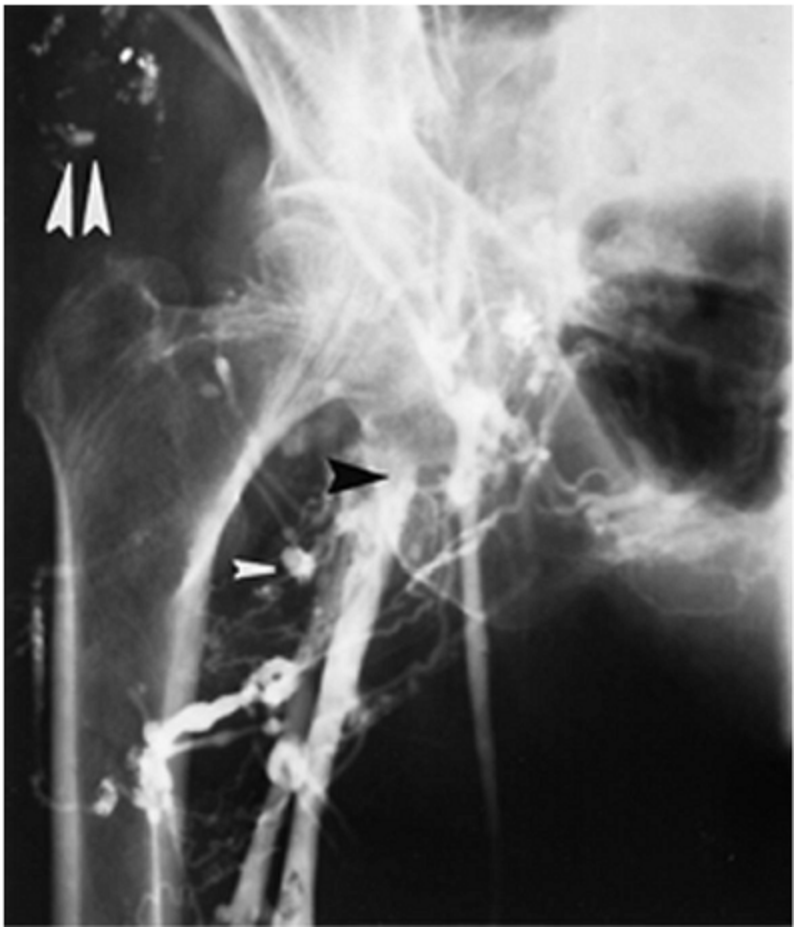

Figure 6-24. Venogram of a 50-year-old patient who routinely injected heroin into his groin. Occlusion of the femoral vein *(black arrow)* with diffuse aneurysmal dilation *(small arrow)* and extensive collaterals are shown. Incidental radiopaque materials are noted in the right buttock *(double arrow)* . By history, this represents either bismuth or arsenicals he received as antisyphilitic therapy. *(Courtesy of Richard Lefleur, Department of Radiology, New York University.)*

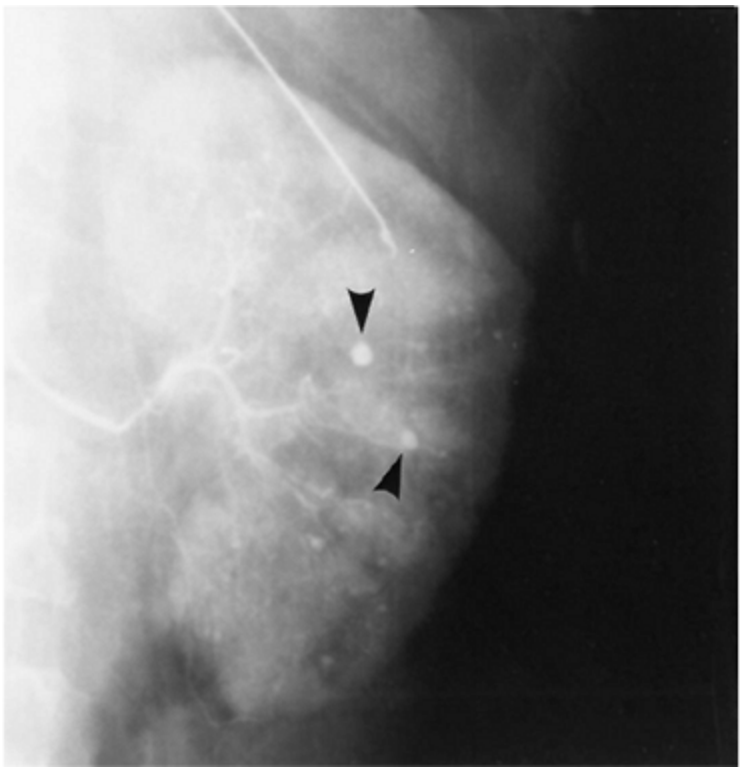

Figure 6-25. A selective renal angiogram in an injection methamphetamine user demonstrating multiple small and large aneurysms (*arrows*). *(Courtesy of Dr. Richard Lefleur, Associate Professor of Radiology, New York University.)*

Hemorrhage
Intraparenchymal hemorrhage
Subarachnoid hemorrhage
Sympathomimetics: cocaine (â€œcrackâ€•), amphetamine, phenylpropanolamine, phencyclidine, ephedrine, pseudoephedrine
Mycotic aneurysm rupture (IDU)
Subdural hematoma
Trauma secondary to ethanol, sedative-hypnotics, seizures
Anticoagulants
Brain lucencies
Basal ganglia local necrosis (also subcortical white matter lucencies)

Carbon monoxide, cyanide, hydrogen sulfide, methanol
Strokeâ€”vasoconstriction
Sympathomimetics: cocaine (â€œcrackâ€•), amphetamine, phenylpropanolamine, phencyclidine; ephedrine, pseudoephedrine; ergotamine
Mass lesionâ€”tumor, abscess
Septic emboli, AIDS-related
CNS toxoplasmosis or lymphoma
Loss of brain tissue
Atrophyâ€”cerebral, cerebellar
Alcoholism, toluene

CT Finding Brain Lesion Xenobiotic Etiology

TABLE 6-5. Head CT (Noncontrast) in Toxicologic Emergencies

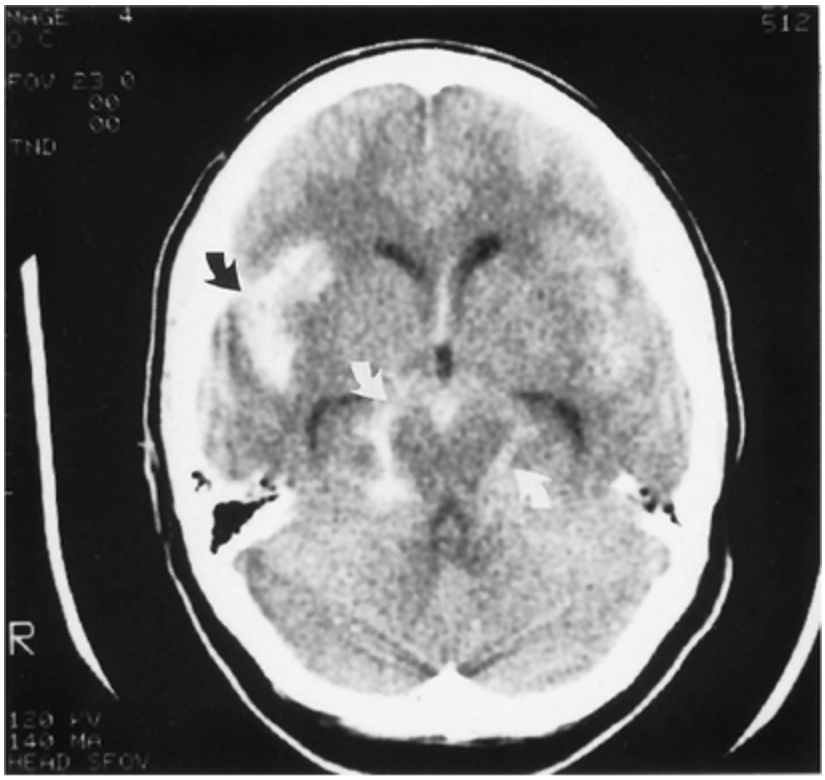

Figure 6-26. Subarachnoid hemorrhage following intravenous cocaine use. The patient had sudden severe headache followed by a generalized seizure. Extensive hemorrhage is seen surrounding the midbrain (*white arrows*) and in the right sylvian fissure (*black arrow*). Angiography revealed an aneurysm at the origin of the right middle cerebral artery.

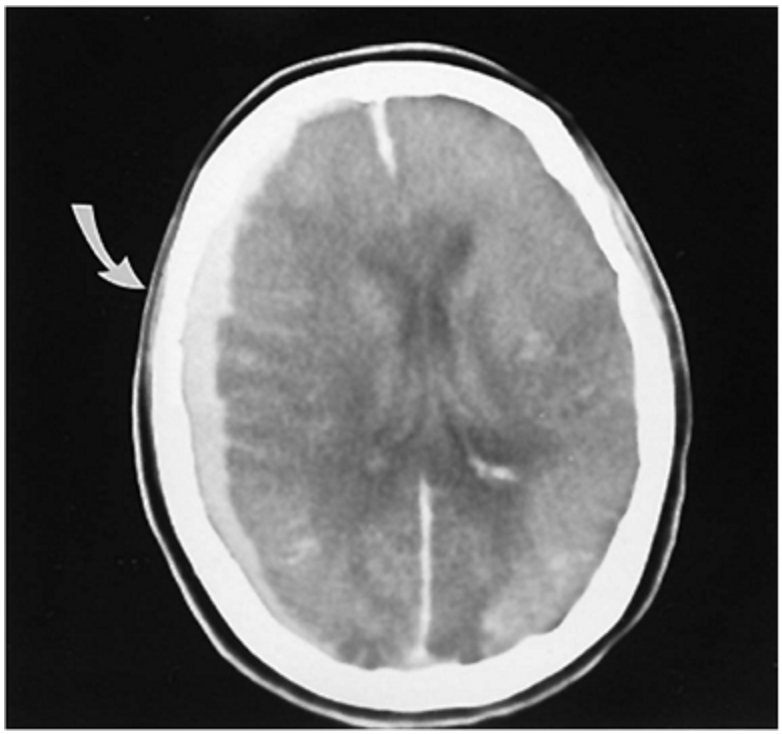

Figure 6-27. An acute subdural hematoma in an alcoholic patient following an alcohol binge. A crescent-shaped blood collection is seen between the right cerebral convexity and the inner table of the skull (*arrow*).

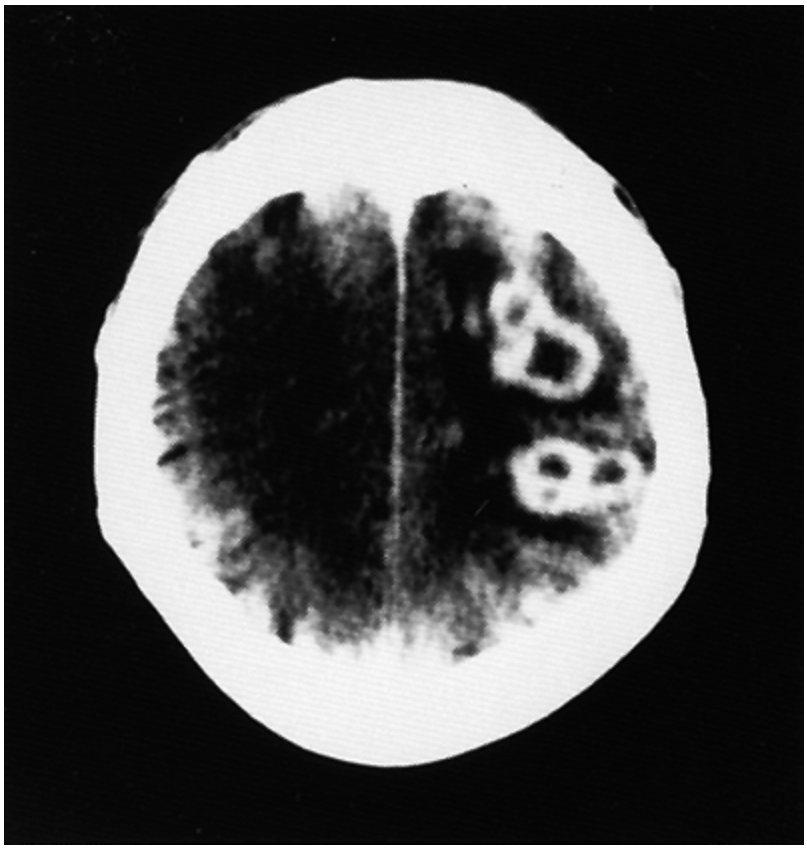

Figure 6-28. An injection drug user with ring-enhancing intracerebral lesions. The patient presented with fever and altered mental status. In this patient, the lesions represent multiple septic emboli complicating acute *Staphylococcus aureus* bacterial endocarditis. A similar ring-enhancing appearance is seen with lesions caused by toxoplasmosis or primary CNS lymphoma in patients with AIDS. This patient was HIV-negative.

P.82

P.83

Much has been learned about these imaging modalities and initial applications can be applied to patient care. They are capable of demonstrating abnormalities in many patients with xenobiotic exposures, although other patients with significant cerebral dysfunction have normal studies.

Summary

This chapter has highlighted a variety of situations in which diagnostic imaging studies are useful in toxicologic emergencies. Imaging can be an important tool in establishing a diagnosis, assisting in the treatment of patients, or in detecting complications of a toxicologic emergency. The imaging modalities include plain radiography, CT, enteric or intravascular contrast studies, nuclear scintigraphy, and ultrasonography. Effective use of a diagnostic test requires understanding of the clinical situations in which the test can be useful, knowledge of the test's capabilities and limitations, and how the results should be applied to the care of an individual patient.

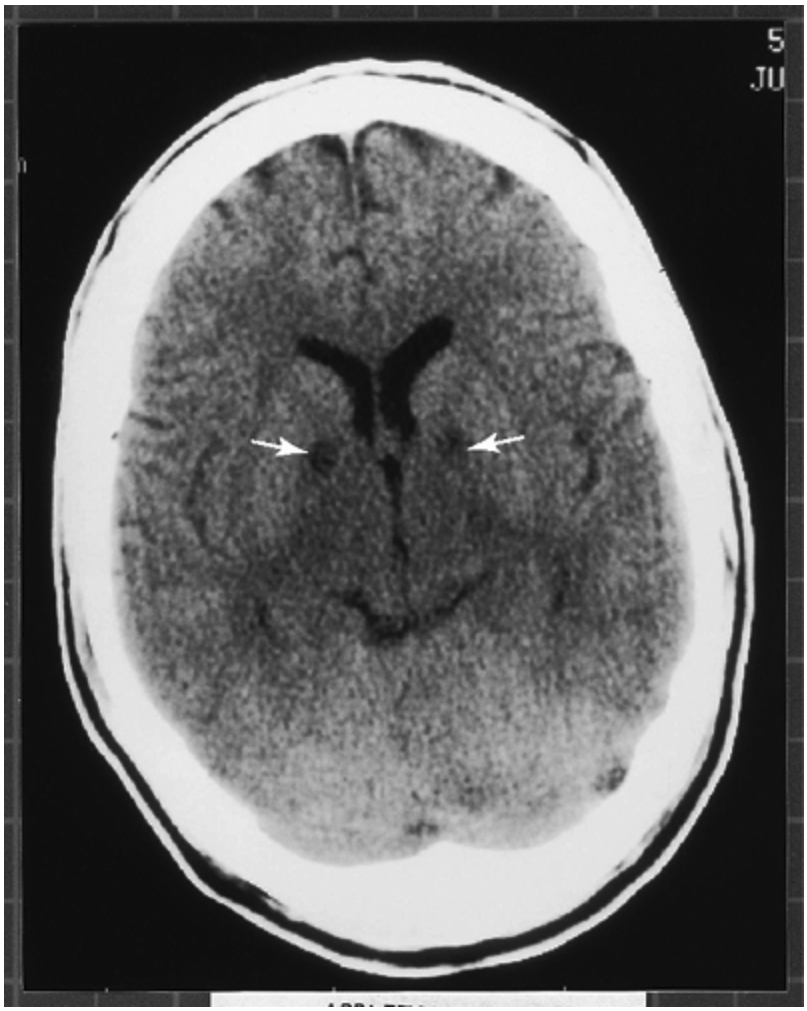

Figure 6-29. A head CT of a patient with mental status changes following carbon monoxide poisoning. The scan shows characteristic bilateral symmetrical lucencies of the globus pallidus (*arrows*). *(Courtesy Dr. Paul Blackburn, Maricopa Medical Center, Arizona.)*

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Chapter 7
Laboratory Principles

Petrie M. Rainey

Medical toxicology addresses harm caused by acute and chronic exposures excessive concentrations of a substance. The management of toxicologic emergencies is a major component of medical toxicology. Detecting the presence or measuring the concentration of drugs and other acutely toxic substances is the primary activity of the medical toxicology laboratory. S testing is closely intertwined with therapeutic drug monitoring, in which concentrations are measured as an aid to optimizing drug-dosing regimen addition to drugs, measurements may be made of substances that lack a therapeutic purpose; for example pesticides, herbicides, and naturally oc plant and animal poisons. The unify characteristic of the substances typic measured is their common presentation in patients with toxicologic emergencies, and the subsequent need for testing results within a relativ short time frame.

The toxicology laboratory is frequently viewed in much the same way as clinical laboratories often areâ€”as a black box that converts orders into results. Because toxicology testing volumes are relatively low and menus extensive, testing is not as highly automated as other clinical laboratorie Many results may be â€œhand-made the old-fashioned way.â€• The dov

of this may be somewhat longer turnaround times. But the upside is that toxicology personnel have the incentive and flexibility to develop substar expertise, as well as the desire to share that expertise. The medical toxi who learns how toxicology testing is done will be able to use the results effectively. The toxicologist who invests the time to get to know the local toxicology laboratory will have developed an invaluable resource.

Recommendations for Routinely Available Toxicology Tests

Despite a common focus, there is remarkable variability in the range of t offered by medical toxicology laboratories. Test menus may range from c daily testing for routinely monitored drugs and common drugs of abuse to around-the-clock availability of a broad array of assays with the theoretic potential to identify several thousand compounds. Recently, consensus documents have been developed that recommend tests that should be av to support management of poisoned patients presenting to emergency departments.[24, 35] While making specific recommendations, these guide recognize that no set of recommendations will be universally appropriate also note that it is impossible for a clinical laboratory to offer a full spect toxicology testing in real time. Decisions on the menu of tests to be offer any specific laboratory should be decided by the laboratory director in consultation with clinicians who will use the service, and should take into account regional patterns of use of licit and illicit drugs, as well as resou available and competing priorities.

The recommendations in Table 7-1 were developed by the National Acade Clinical Biochemists (NACB) from a consensus process that involved clinic biochemists, medical toxicologists, forensic toxicologists and emergency physicians.[35] Although these tests should be readily available in the clinic laboratory, they should not be considered as a test panel for possibly po patients. As with all laboratory tests, they should be selectively ordered on presentation. Suggested turnaround time for reporting serum concent was 1 hour or less. Quantitative tests for serum methanol and ethylene g were also recommended, with the reservations that these tests are not n

in all settings and that a realistic turnaround time is 2â€“4 hours. Serum cholinesterase testing with a turnaround time of less than 4 hours was proposed by some participants, but did not achieve a general consensus. United Kingdom, the National Poisons Information Service and the Assoc of Clinical Biochemists have recommended a nearly identical list of tests, omitting the anticonvulsants.[24]

Although the consensus for the menu of serum assays was generally exc there was less agreement as to the need for qualitative urine assays. This largely a result of issues of poor sensitivity and specificity, poor correlati with clinical effects, and infrequent alteration of patient management. Wh these were potential issues for all of the urine drug tests, they led to exp omission of tests for tetrahydrocannabinol (THC) and benzodiazepines fro recommended list, despite their wide use. THC results were thought to ha little value in managing acute problems, and tests for benzodiazepines w believed to have an inadequate spectrum of detection. Testing for amphetamines, propoxyphene, and phencyclidine were only recommended areas where use was prevalent. It was also suggested that diagnosis of t antidepressant toxicity not be based solely on the results of a urine scree immunoassay, because a number of other drugs may cross-react. The significance of tricyclic antidepressant results should always be correlated electrocardiographic findings. The only urine test included in the United Kingdom guidelines was a spot test for paraquat.[24] Paraquat testing was omitted in the NACB guidelines because of a very low incidence of paraqu exposure in North America.[35]

Acetaminophen
Amphetamines
Carbamazepine
Barbiturates
Cooximetry (carboxyhemoglobin, methemoglobin, oxygen saturation)
Cocaine
Opiates
Digoxin
Propoxyphene

Serum Assays, Quantitative	Urine Assays, Qualitative
Ethanol	
Phencyclidine	
Iron (plus transferrin or unfilled iron-binding capacity)	
Tricyclic antidepressants	
Lithium	
Phenobarbital	
Salicylate	
Theophylline	
Valproic acid	

TABLE 7-1. Toxicology Assays Recommended by the National Aca of Clinical Biochemists

The NACB guidelines also recommend the availability of broad-spectrum toxicology testing, to be used for selected patients with presentations compatible with poisoning, but who remain undiagnosed by using the test Table 7-1 , and who are not improving. In general, such testing should nc ordered until the patient is stabilized and input obtained from a medical toxicologist or poison control center. This second level of testing may be provided directly by the local laboratory or by referral to a reference lab or a regional toxicology center.

Many physicians will order a broad-spectrum toxicology screen on a poisc patient if one is readily available, but only approximately 3% of clinical laboratories provide relatively comprehensive toxicology services (as est from proficiency testing data[4]). Although broad-spectrum toxicology scr can identify most drugs present in overdosed patients,[13] the results of b spectrum screens infrequently alter management or outcomes.[12 , 13 , 17 25 , 26] Consequently, many laboratories provide a more limited menu of toxicologically useful tests.

The extent to which the NACB recommendations are being followed may l

estimated from the numbers of laboratories participating in various types proficiency testing. Result summaries from the 2003 series of proficiency surveys administered by the College of American Pathologists suggest tha quantitative serum assays for acetaminophen, salicylate, cooximetry, theophylline, valproic acid, carbamazepine, digoxin, phenobarbital, iron, ethanol are available in 50â€“60% of laboratories that offer routine clinic testing, as are screening tests for drugs of abuse in urine. About one-thir laboratories offer testing for lithium, while only 1 in 6 offers measuremen transferrin and/or unfilled iron-binding capacity.[4]

Only 3% of laboratories participated in proficiency testing for a full range toxicology services. These laboratories typically offer quantitative assays additional therapeutic drugs, particularly tricyclic antidepressants, as well assays that are designated as broad-spectrum or comprehensive toxicolo screens. About half of these full-service toxicology laboratories (less than of all clinical laboratories) offer testing for volatile alcohols other than e

While relatively few laboratories offer a wide range of in-house testing, r laboratories will send out specimens to reference laboratories that offer l toxicology menus. The turnaround time for such â€œsendoutâ€• tests ca range from a few hours to several days, depending on the proximity of th reference laboratory and the type of test requested.

Even in full-service toxicology laboratories, the test menu may vary substantially from institution to institution. Larger laboratories typically o one or more broad-spectrum testing choices, often referred to as â€œtox screens.â€• There is as much variety in the range of compounds detecte various toxicologic screens as there is in the total menu of toxicologic tes Routinely available tests are usually listed in a printed or online laborato manual. Laboratories with comprehensive services may be able to offer ad chromatographic assays for additional substances that are not listed. Tes that is sent to a reference laboratory is often not listed in the laboratory manual. The best way to determine if a particular substance can be detec quantitated is to ask the director or supervisor of the toxicology section, laboratory clerical staff may only be aware of testing listed in the manual

Using the Toxicology Laboratory

There are many reasons for toxicologic testing. The most common functio confirm or exclude toxic exposures suspected from the history and physic examination. A laboratory result provides a level of confidence not readil obtained otherwise and may avert other unproductive diagnostic investig driven by the desire for completeness and medical certainty. Testing incr diagnostic certainty in more than half of cases.[2,12,17] In some instance diagnosis may be based primarily on the results of testing. This can be particularly important in poisonings with substances having delayed onset clinical toxicity, such as acetaminophen, or in patients with ingestion of multiple substances. In these instances, characteristic clinical findings ma have not yet developed at the time of presentation, or may be obscured altered by the effects of coingestants.

Testing can provide two key parameters that will have a major impact on clinical course, namely, the poison involved and the intensity of the expo This information can assist in triage decisions, such as whether to admit a patient or to observe the individual for expectant discharge. Serum concentrations can facilitate decisions to employ specific antidotes or spe interventions to hasten elimination. Well-defined exposure information ca facilitate provision of optimum advice by poison control centers, whose personnel do not have the ability to make decisions based on direct obse of the patient. Serum concentrations can be used to determine when to institute and when to terminate interventions such as hemodialysis or an administration, and can support the decision to transfer from intensive ca discharge from the hospital. Finally, positive findings for ethanol or drugs abuse in trauma patients may serve as a risk marker for the likelihood of trauma.[12]

The confirmation of a clinical diagnosis of poisoning provides an importan feedback function, whereby the physician may evaluate the diagnosis aga â€œgold standard.â€• Another important benefit is reassurance; for exa reassurance that an unintentional ingestion did not result in absorption of toxic amount of drug. Such reassurance can allow a physician to avoid sp excessive time with patients who are relatively stable. It can allow admis

to be made and interventions undertaken more confidently and efficiently would be likely based solely on a clinical diagnosis. This can be especially beneficial in a setting where multiple cases are competing for the physici attention.

Testing may also be indicated for medicolegal reasons. Diagnoses with le implications should be established â€œbeyond a

reasonable doubt.â€• While testing for illicit drugs is often done for mec purposes, it is almost impossible to dissociate such testing from legal considerations. Documentation is also important in malevolent poisonings intentional or unintentional child abuse involving therapeutic or illicit drug pharmacologic elder abuse. Where test results may be used to document criminal activity, consideration should be given to having testing done in forensic laboratory maintaining full chain of custody.

The documentation function is also important outside the medicolegal are Results of testing in a central laboratory are almost invariably entered int patient's medical record and can often provide definitive confirmation of a problem. Documentation has an additional importance that goes beyond t individual cases. Medical toxicology does not lend itself readily to experi human investigation. Much of toxicologic knowledge has been derived fro experiments of nature, recorded in case reports and case series. Hard da such as drug concentrations, can serve as key quantitative variables in summarizing and correlating the data. That laboratory results can be reli and generally easily found in the medical record makes them particularly valuable in retrospective reviews. A related service that the toxicology laboratory may provide is testing in support of experimental investigation

The key to optimum use of the toxicology laboratory is communication. T begins with learning the laboratory's capabilitiesâ€”what drugs are on its menus, which ones can be measured and which merely detected, and wha anticipated turnaround times. For screening assays, one should know whi drugs are routinely detected, which ones can be detected if specifically requested, and which ones cannot be detected, even when present at tox levels.

A key item is learning which specimens are appropriate for the test requ
A general rule is that quantitative tests require serum (red stopper) or
heparinized plasma (green stopper), but not ethylenediamine tetraacetic
(EDTA) plasma (lavender stopper) or citrate plasma (light-blue stopper).
and citrate bind divalent cations that may serve as cofactors for enzymes
as reagents or labels in various assays. Additionally, liquid EDTA and citr
anticoagulants dilute the specimen. Serum separator tubes or plasma se
tubes, identifiable by the separator gel in the tube, should be avoided, b
some drugs may diffuse into the gel, leading to falsely low results. A ran
clean urine specimen is generally preferred for toxicology screens, becaus
higher drug concentrations usually found in urine can compensate for the
sensitivity of the broadly focused screening techniques. A urine specimen
mL is usually optimal. Requirements for all specimens may vary from lab
to laboratory.

Spot test
+
Â±
No
Few
Fast
$
Spectrochemical
+
+
Yes
Few
Medium
$
Immunoassay
++
++
Yes
Moderate
Medium

$$
TLC
+
++
No
Broad
Slow
$$
HPLC
++
++
Yes
Broad
Medium
$$
GC
++
++
Yes
Broad
Medium
$$
GC/MS
+++
+++
Yes
Broad
Slow
$$$
LC/MS/MS
+++
+++
Yes
Broad

Medium
$$$$
GC, gas chromatography; GC/MS, gas chromatographymass spectroscopy HPLC, high-performance liquid chromatography; LC/MS/MS, liquid chromatography-tandem mass spectroscopy; TLC, thin-layer chromatogra

Method	Sensitivity	Specificity	Quantitation	Analyte Range	Speed

TABLE 7-2. Relative Comparison of Toxicology Methods

An important, and often overlooked, item of communication is specifying that are particularly suspected when making a request for a screening tes knowledge can allow the laboratory to set up the tests for those drugs fir possibly adjust the protocols to increase sensitivity or specificity. This ma an hour or more in the time needed to receive the critical information.

Consultation with the laboratory regarding puzzling cases or unusual need allow consensus on an effective and feasible testing strategy. The full capabilities of a toxicology laboratory are often not apparent from publish lists of tests available. Most full-service laboratories will devote substant efforts to meeting reasonable requests, and will provide consultations at charge.

The laboratory should also be contacted whenever results are inconsisten clinical presentation. The most common causes for this are interferences preanalytical errors. Analytical interference is caused by materials in the specimen that interfere with the measurement process, leading to falsely or low results. For example, hemoglobin can interfere with a variety of spectrophotometric tests by absorbing the light used to make the measurement. Preanalytical errors are events that occur prior to laborato analysis and produce incorrect or misleading results, such as mislabeling, specimen contamination by intravenous solutions, and incorrect collection or technique. The laboratory will be familiar with the common sources of discrepancies. If the discrepancy is the result of laboratory error, it is cri that the laboratory be informed, so that steps can be taken to understand

source of the error and avoid a recurrence.

Methods used in the Toxicology Laboratory

Most tests in the toxicology laboratory are directed toward the identificat and/or quantitation of drugs and poisons. The primary techniques used i spot tests, spectrochemical tests, immunoassays and chromatographic techniques. Mass spectrometry may also be used, usually in conjunction gas chromatography or liquid chromatography. Table 7-2 compares the b features of these methodologies. Other methodologies include ion-selecti electrode measurements of lithium, atomic absorption spectroscopy or inductively coupled plasma mass spectroscopy for lithium and heavy met and anodic stripping methods for heavy metals. There are also many adj tests that may be useful in the management of the poisoned patient, incl glucose, creatinine, electrolytes, osmolality, metabolic products, and enz activities. The focus here is on the major methods used for directly meas drugs and poisons.

Spot Tests

The simplest tests are spot tests. These rely on the rapid reaction of a dr with a chemical reagent to produce a colored product; for example, the formation of a colored complex between salicylate and ferric ions. Becaus reagents may cause precipitation of serum proteins, spot tests are more commonly performed on urine specimens or gastric aspirates. Such tests once a mainstay of toxicologic testing. Because of the poor selectivity of chemical reagents, as well as substantial variability in visual interpretatic these assays suffer from fairly frequent false-positive results and occasic false-negative results. As more sensitive and more specific methods have become available, spot tests have waned in popularity. Only a few are sti use, largely to fill gaps in testing menus, or to rapidly exclude some com poisonings. The introduction of point-of-care testing devices that have be sensitivity and specificity and are designed to facilitate compliance with regulations is likely to further reduce the use of spot tests.

Spectrochemical Tests

Spectrochemical tests are sophisticated versions of spot tests. They also a chemical reaction to form a light-absorbing substance. They differ in th reaction conditions and reagent concentrations are carefully controlled an amount of light absorbed is quantitatively measured at one or more spec wavelengths. The use of specific wavelengths enhances the sensitivity an particularly, the specificity of the detection, and the measurement of the amount of light absorbed under controlled conditions allows quantitation c substance.

When an analyte is intrinsically light absorbing, no reaction may be nece Cooximetry represents a sophisticated application of spectrophotometry to measurement of various forms of hemoglobin in a hemolyzed blood samp Measurement of light absorbance at several wavelengths allows multiple hemoglobin species to be simultaneously quantitated. For mathematical reasons, the number of wavelengths used must be greater than the numb different types of hemoglobin present. This is why pulse oximetry, which only two wavelengths, yields spurious results in the presence of significa amounts of methemoglobin or carboxyhemoglobin (Chaps. 22 and 122).

Most analytes are neither as deeply colored, nor as highly concentrated, hemoglobin species. Their detection requires the generation of an intense light-absorbing product, as is done in spot tests. Most spot test reactions been used for spectrochemical assays; for example, salicylate assays usi Trinder reagent (a variation on ferric chloride). The difference between a test and a spectrochemical one lies in whether the colored product is vis observed or quantitatively measured in a spectrophotometer. Because spectrophotometers can also measure ultraviolet and infrared light, it is necessary that the product have a visible color. Early spectrochemical as typically measured the absorbance after conversion of all of the analyte t light-absorbing product. Modern assays usually employ rate spectrophoto taking multiple absorbance measurements over time to determine the rat change in light absorbance as the reaction proceeds. During the initial ph the reaction, this rate is constant and proportional to the initial concentr

of the analyte. This significantly reduces the time needed to obtain a res because the reaction does not have to go to completion first, and it allow averaging of multiple measurements, improving precision. Furthermore, it unaffected by nonreacting substances that absorb light at the test wavel because the absorbance of the nonreacting substances is constant and do contribute to the rate of change in the absorbance.

Rate spectrophotometry remains subject to interference by substances th react to produce a light-absorbing product, thereby falsely increasing the apparent concentration. Substances that inhibit the assay reaction, or tha consume reagents without producing a light-absorbing product, will give low results. For example, ascorbic acid produces negative interference in spectrophotometric assays that use oxidation reactions to generate color products.

Cooximetry is generally relatively free of interferences because the concentrations of the hemoglobins are so much higher than other substar the blood. However, the presence of intensely colored substances may lea spurious answers. Methylene blue, which is used to treat methemoglobin typically causes falsely increased methemoglobin measurements by coox This interference does not occur when methemoglobin is measured by oth methods, such as electrophoresis.

One way to improve the selectivity of a spectrochemical assay is to increa selectivity of the reaction that generates the light-absorbing product. En which can catalyze highly selective reactions, are often used for this purp For example, many assays for ethanol use alcohol dehydrogenase to cata the oxidation of ethanol to acetaldehyde, with concomitant reduction of t cofactor NAD^+ (oxidized form of nicotinamide adenine dinucleotide) to NA (reduced form of nicotinamide adenine dinucleotide). The initial rate of i in light absorption produced by the conversion of NAD^+ to NADH is propo to the concentration of ethanol. Although other alcohols such as isopropa and methanol can also be oxidized by alcohol dehydrogenase, they are m poorer substrates with low rates of reaction and correspondingly low leve interference.

Many other enzymatic assays also rely on measuring the change in light

absorption at 340 nm when NAD^+ is converted to NADH or vice versa. Th include enzymatic assays for ethylene glycol, as well as some enzyme-lin immunoassays, such as EMIT (enzyme-multiplied immunoassay technique assays. All such assays are potentially subject to interference by specime with high concentrations of lactate. Lactate dehydrogenase, which is natu present in serum, will oxidize this lactate to pyruvate if NAD^+ becomes available for simultaneous reduction to NADH. When a serum specimen w high lactate is mixed with assay reagents that contain NAD^+ , oxidation o lactate contributes to the total rate of NADH production. The increased ra NADH production results in a false increase in the measured concentration the target analyte.

Immunoassays

The need to measure very low concentrations of an analyte with a high d of specificity led to the development of immunoassays. The combination o affinity and high selectivity makes antibodies ideal assay reagents. There two common types of immunoassays: noncompetitive and competitive. In noncompetitive immunoassays, the analyte is sandwiched between two antibodies, each of which recognizes a different epitope on the analyte. I competitive immunoassays, analyte from the patient's specimen competes limited number of antibody binding sites with a labeled version of the an provided in the reaction mixture. Because most drugs are too small to ha distinct antibody binding sites, drug immunoassays are usually competiti

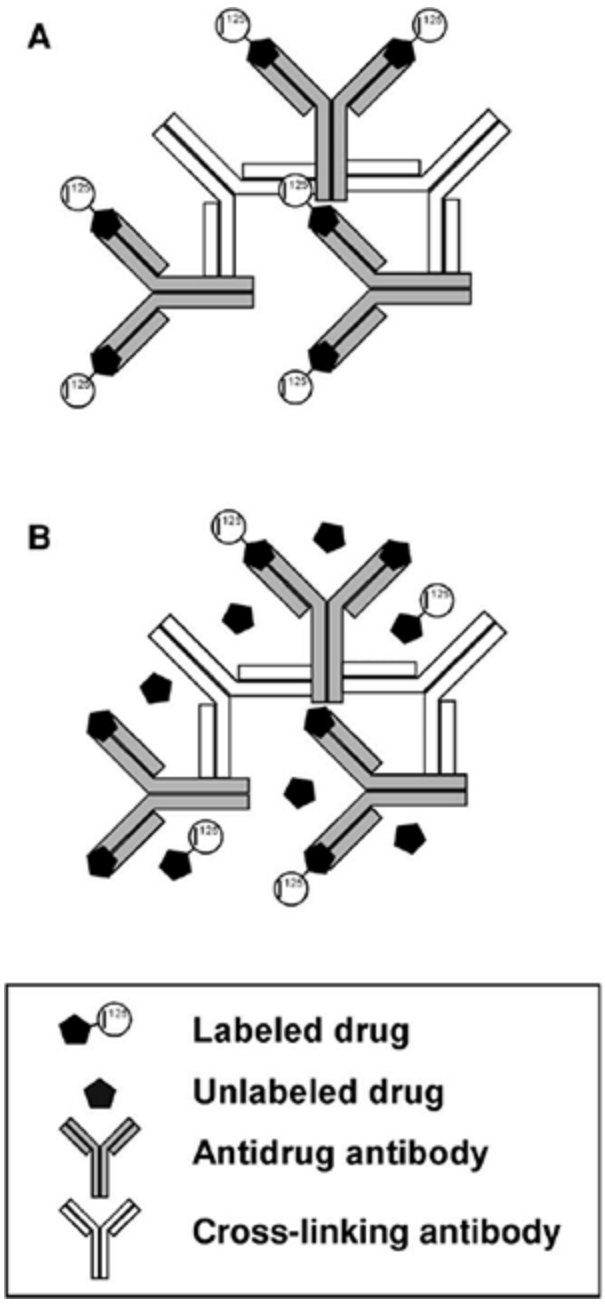

Figure 7-1. Competitive radioimmunoassay. A. No drug from the specime present to displace the ^{125}I-labeled drug. Adding the cross-linking antib precipitates the assay antibody, along with high amounts of bound radio B. Unlabeled drug in the specimen displaces some of the labeled drug. Th displaced label is left in solution when the cross-linking antibody is added resulting in less radioactivity in the precipitate.

In competitive immunoassays, increasing the concentration of drug in the specimen results in increased displacement of labeled drug from the anti The amount of drug in the specimen can be determined by measuring eith amount of label remaining bound to the assay antibodies or the amount o free in solution. In the earliest immunoassays, the label was a radioisoto typically iodine-125, tritium, or carbon-14. The bound and free radioactiv were physically separated; for example, by using a second antibody to cr link and precipitate the assay antibody, along with its bound radioactivity 7-1), or by adsorbing the free label with activated charcoal. Today, radioimmunoassays are relatively uncommon because of problems associ with handling and disposal of radioactivity. They are primarily used for a with insufficient demand to justify the development costs of more sophis nonisotopic assays.

Nonisotopic immunoassays are currently the most widely used methodolo for the measurement of drugs. They offer high selectivity and good preci and are readily adapted to automated analyzers, thereby decreasing both cost and the turnaround time of the assays. The effort involved in develo these assays is substantial. Accordingly, the drugs for which immunoassa available are limited to those for which there is a high demand, such as monitored therapeutic drugs and the drugs of abuse included in workplac screening. However, after assay development is completed, production co are relatively low, allowing the tests to be widely distributed at reasonab prices.

The most widely used nonisotopic drug immunoassays are in the category homogenous immunoassays. Homogenous immunoassays measure differe in the properties of bound and free labels, rather than directly measuring or the other after their physical separation. Avoiding a separation step al homogenous immunoassays to be readily adapted to automated analysis. Homogenous techniques that are in wide use include EMIT (Fig. 7-2), fluorescence polarization immunoassay (FPIA, Fig. 7-3), kinetic inhibition microparticles in solution (KIMS), and cloned enzyme donor immunoassay (CEDIA).

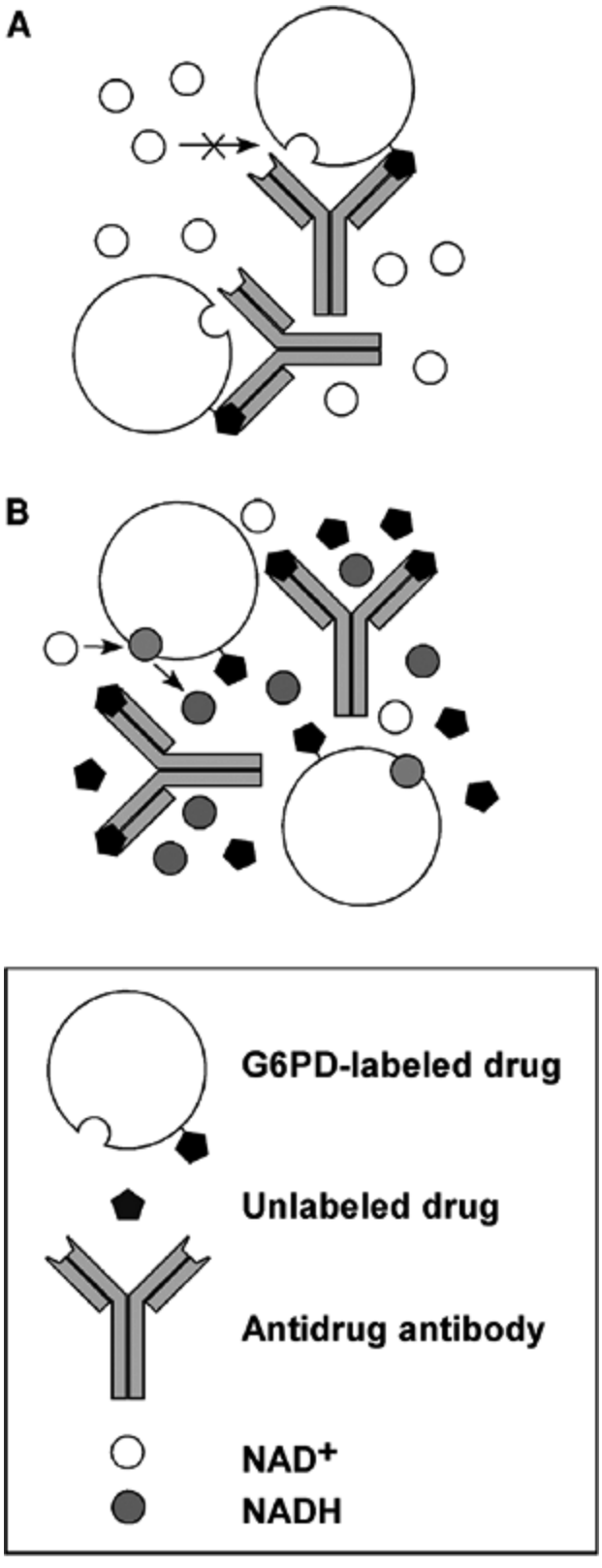

Figure 7-2. EMIT immunoassay. The drug to be measured is labeled by l

attached to the enzyme, glucose-6-phosphate dehydrogenase (G6PD), nea active site. A. Binding of the enzyme-labeled drug to the assay antibody the active site, inhibiting conversion of NAD^+ to NADH. B. Unlabeled drug the specimen can displace the drug-enzyme conjugate from the antibody, thereby unblocking the active site and increasing the rate of reaction.

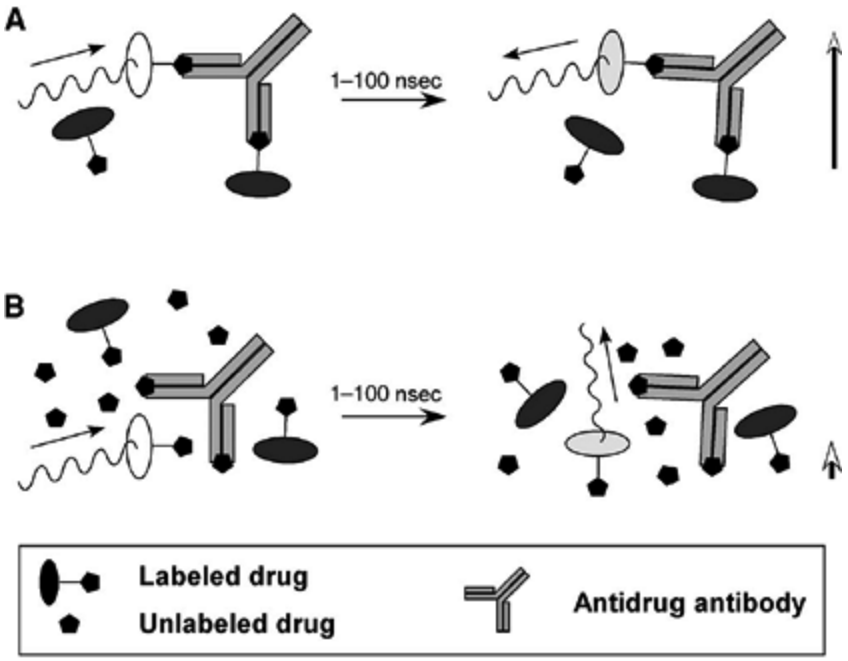

Figure 7-3. FPIA immunoassay. A. After drug labeled with fluorescein competes with unlabeled drug from the specimen for assay antibodies, th fluorescein is photoexcited with a flash of polarized light. Fluorescein mo aligned with the plane of polarization can absorb the light, entering an e state (*white fill*). The excited fluorescein decays over a few nanoseconds lower energy state (*light-gray fill*) and reemits the light at a lower wave The polarization of the emitted light is determined by the orientation of fluorescein. Fluorescein that is attached by the drug to the large assay a move little before reemission, so the emitted light retains most of the polarization (*vertical arrow at right*). B. Drug from the specimen can pre binding of the drugâ€“fluorescein conjugates. The unbound conjugates ca tumble rapidly and randomize their orientation prior to reemission of ligh resultant loss of polarization. The residual polarization of the emitted ligh

inversely proportional to the drug concentration in the specimen.

Some of the newest automated immunoassays are again using physical separation techniques. In these assays, the detection antibody is physica attached to a solid support and separation occurs by a simple wash step. wash step removes the patient's serum along with many potentially inter substances. Newer solid supports consist of fine glass fibers or latex microparticles. These have very high total surface areas that allow for ra equilibration and short assay times. Older assays of this type used antibo bound to large plastic beads or wells of microtiter plates, and required lo incubation steps because of substantial times required for diffusion of the reactants to the antibodies. These new techniques are readily automated allow the measurement of bound label with more sensitive methods, such chemiluminescent, electroluminescent, and total fluorescence labels, than available with homogenous immunoassays.

Microparticle capture assays are a type of competitive immunoassays that become very popular, especially for urine drug screening tests. The use o colored microparticles, either latex or colloidal gold, as the label enables result to be read visually as the presence or absence of a colored band, w special instrumentation required. Competitive binding occurs as the assay mixture is drawn by capillary action through a porous membrane. This de feature is responsible for alternate names for the technique: lateral flow immunoassay or immunochromatography.

The simplest design employs an antidrug antibody bound to colored microparticles and a capture zone consisting of immobilized drug (Fig. 7-4 the specimen is drug-free, the beads will bind to the immobilized analyte forming a colored band. When the amount of drug in the patient specimen exceeds the detection limit, all of the antibody sites will be occupied by d from the specimen, and no labeled antibody will be retained in the captur zone. The use of multiple antibodies and discrete capture zones with diff immobilized analytes can allow several drugs to be detected with a single device.

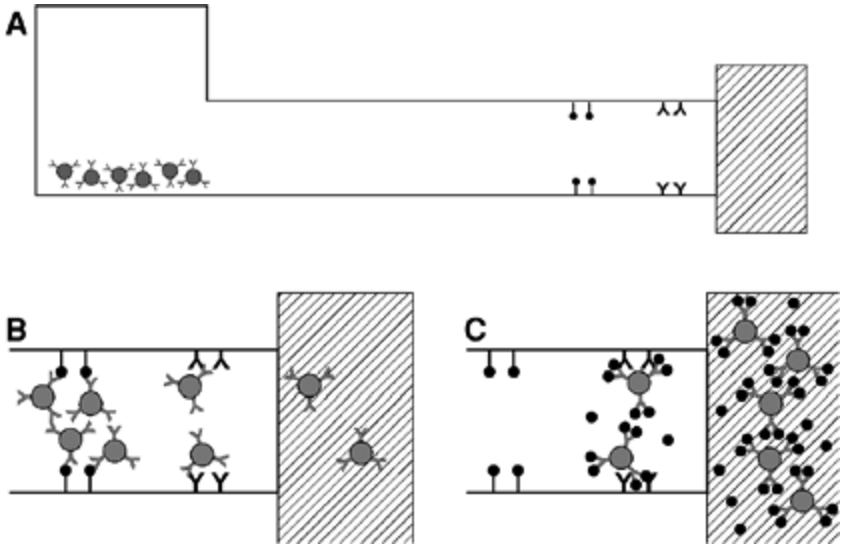

Figure 7-4. Microparticle capture immunoassay. A. Diagram of a device to specimen addition. Colored microbeads (about the size of red blood ce coated with antidrug antibodies (Y) are in the specimen well. At the far er porous strip are capture zones with immobilized drug molecules (â€¢) and control zone with antiantibodies recognizing the antibodies that coat the microbeads. B. Adding the urine specimen suspends the microbeads, whic drawn by capillary action through the porous strip and into an absorbent reservoir (*hatched area*) at the far end of the strip. In the absence of dr the urine, the antibodies will bind the beads to the capture zone containir immobilized drug and form a colored band. Excess beads will be bound by antibodyâ€“antibody interactions in the control zone, forming a second c band that verifies the integrity of the antibodies in the device. C. If the u contains the drug (â€¢) in concentrations exceeding the detection limit, a the antibodies on the microbeads will be occupied by drug from the speci and the microbeads will not be retained by the immobilized drug in the c zone. No colored band will form. However, the beads will be bound and fo band in the control zone.

A disadvantage of this design is the potential for causing confusion, becau positive result is indicated by the absence of a band. More complex (and expensive) variations have been developed in which a colored band denot positive result.

Although immunoassays have a high degree of sensitivity and selectivity, are also subject to interferences and problems with cross-reactivity. Cros reactivity refers to the ability of the assay antibody to bind to molecules than the target analyte. Molecules with similar chemical structures may b efficiently bound, which can lead to falsely elevated results. In some situ cross-reactivity can be beneficially exploited. For example, some immun effectively detect classes of drugs rather than one specific drug. Immun for opiates employ antibodies that recognize various molecules that are structurally related to morphine, including codeine, hydrocodone, and hydromorphone. However, they have little or no cross-reactivity with structurally unrelated synthetic opioids, such as meperidine or methadon Immunoassays for the benzodiazepine class react with a wide variety of benzodiazepines, but with varying degrees of sensitivity.[19]

Class specificity can be a two-edged sword. Assays for the tricyclic antidepressant family have similar reactivity with amitriptyline, nortripty imipramine, and desipramine, and can be used to provide a semiquantita estimate of the total concentration of any combination of these. However, large number of other drugs with tricyclic structures, including carbamaz many phenothiazines, and diphenhydramine, also cross-react and generat signal, particularly at concentrations found in patients who overdose on s drugs. Qualitative tests, such as microparticle capture assays, may then false-positive results, if the signal generated by the cross-reacting drug (carbamazepine) exceeds the detection limit of the immunoassay. With quantitative or semiquantitative assays, however, the apparent tricyclic antidepressant concentration generated by a cross-reacting drug is gene well below concentrations associated with toxicity.

Even when an antibody is selected to be specific to a single drug, it is co that metabolites of the target drug show some cross-reactivity. This too r beneficial. When the metabolite is an active one (eg, carbamazepine epo the contribution of its cross-reactivity may yield results that correlate be with the drug effect than the true concentration of the parent drug alone.

Immunoassays are also subject to interference by substances that impair

detection of the label. The mechanism by which elevated lactate concent may lead to spuriously increased drug concentrations in specimens tested EMIT is described above. Immunoassays that rely on enzyme labels are particularly sensitive to nonspecific interference because enzyme activity highly dependent on reaction conditions. A number of substances that car inhibit the enzyme reaction in EMIT assays are used to adulterate urine submitted for drug-abuse testing with the intent of producing false-negat results (see the discussion of drug-abuse screening tests under Special Considerations for Drug-Abuse Screening Tests below). Such adulteration be detected when the rate of reaction is lower than the rate observed wit drug-free control.

Chromatography

Chromatography encompasses several related techniques in which analyt specificity is achieved by physical separation. The unifying mechanism fo separation is the partition of the analytes and other substances between stationary phase and a moving phase (mobile phase). In most instances, stationary phase consists of very fine particles arranged in a thin layer or enclosed within a column. The mobile phase flows through the spaces be the particles. Analytes are in a rapid equilibrium between solution in the phase and adsorption to the surfaces of the particles. They move when in mobile phase and stop when adsorbed to the stationary phase. The avera velocity of the analyte molecules depends on the relative time spent in th moving versus stationary phase. Molecules that partition primarily into th mobile phase have average velocities slightly less than the mobile phase velocity. Average velocity decreases as the proportion of time adsorbed t stationary phase increases. Under controlled conditions, these average velocities are highly reproducible. Substances may be provisionally ident based on their characteristic velocity. This is measured as the distance t relative to the solvent migration distance in thin-layer chromatography, o amount of time required to traverse the length of a chromatography colu These characteristic parameters are referred to as the R_F value and rete time, respectively.

Chromatography is a separation method and must be combined with a de method to allow identification and measurement of the separated substa The sensitivity of chromatographic methods depends on both the amount specimen available and the sensitivity of the detection method. The dete limit may range from less than 10 ng with mass spectrometric detection t more than 10 Âµg when detection is achieved by forming a colored produ using a postchromatographic chemical reaction. Chromatographic behavio sufficiently reproducible that the failure to detect a signal at an R_F value retention time characteristic of a compound effectively excludes the prese that compound in amounts greater than the detection limit. On the other a number of different substances may have migration velocities that are identical or nearly so. A positive finding is therefore not completely speci Definitive identification depends on having additional information, which r obtained through selective detection techniques or by confirmatory testin using a second method.

A major advantage of chromatographic techniques is that multiple substa may be detected and measured in a single procedure. It is not always necessary to know in advance the specific material to be looked for. For reason, chromatographic techniques have a major role in the performance screening tests.

Most chromatographic procedures require extraction and concentration of substances to be analyzed prior to the chromatography. Extraction results removal of salts, proteins and other materials that may exhibit unfavorab interactions with either of the chromatographic phases. Concentration all the substances to be introduced in a narrow â€œband,â€• so that compo with slightly different relative mobilities become completely resolved, or separated from one another, rather than overlapping. This also results in more intense signal as a band passes through the detector and increases sensitivity.

Extraction of drugs is most commonly done with organic solvents, but â€ phase extractionâ€• is also very popular.[11] Solid-phase extraction is a modified chromatographic procedure in which a urine or serum specimen passed through a short chromatography column with a hydrophobic stati

phase. Most drugs are sufficiently hydrophobic that they partition almost completely into the stationary phase and are retained on the column. Subsequently, the retained compounds are eluted with an organic solvent organic solvents from either extraction technique are evaporated to conc the extracted substances. The extraction process allows the analyte from large volume of specimen to be concentrated. Detection sensitivity can t be increased, provided large volume specimens can be readily obtained, a true with urine.

Often there is a preextraction treatment to increase the hydrophobicity of substances to be extracted. The most common manipulation is pH adjust either upward or downward, to convert charged forms of drugs into unch extractable ones. In other instances, enzymatic or chemical hydrolysis ma employed to convert water-soluble glucuronide metabolites back to their readily extracted parent compounds; for example, conversion of morphin glucuronide to morphine.

In thin-layer chromatography (TLC), the concentrated extracts are redis in a small amount of solvent and spotted onto a thin layer of silica gel tha supported on a glass or plastic plate, or embedded in a fiber matrix. A ty TLC plate will have room for several different spots of extracts from sam and controls. The plates are placed vertically in closed tanks containing a shallow layer of an organic solvent mixture. As the solvent is drawn upwa through the silica gel by capillary action, various compounds are carried at characteristic velocities determined by

their partition between the moving organic solvent and the stationary silic (Fig. 7-5). Silica gel is polar, so hydrophobic compounds migrate rapidly hydrophilic ones more slowly. Adjusting the composition of the solvent m allows optimization of the migration rates. After sufficient solvent migrat the plates are removed from the tanks, dried and sprayed with a series o reagents that convert the drugs to be detected into various colored deriv The drugs are thereby visualized as colored spots and identified by their migration distance (R_F value), as well as by the various colors produced each spray. Drugs that are metabolized can be further confirmed by the of additional spots corresponding to characteristic metabolites. Identifica

can be most confidently made when an authentic sample of the drug has included as a control on the plate.

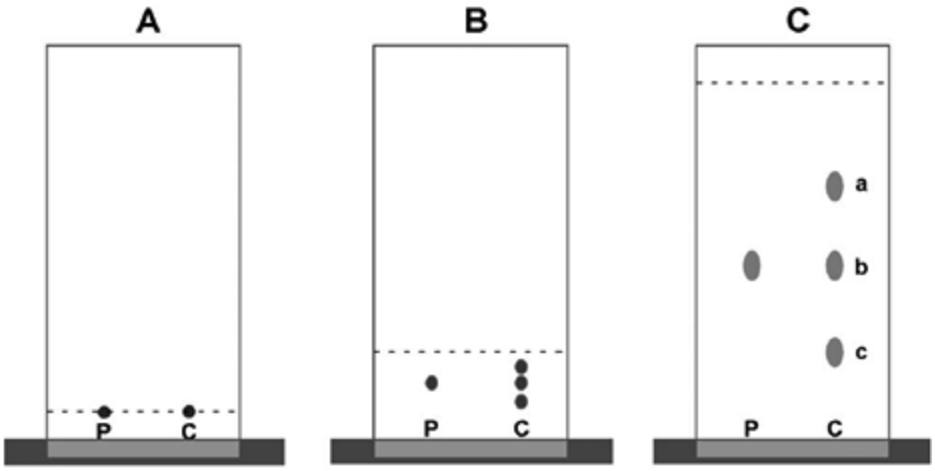

Figure 7-5. Thin-layer chromatography. A. Concentrated extracts from p (*P*) and control (*C*) specimens are dried in small spots on a plate coated a thin layer of silica gel particles. The plate is placed vertically into an or solvent mixture, which is being drawn up the plate by capillary action. Th leading edge (or solvent front, shown by the *dotted line*) reaches the ex and begins to dissolve them. B. Various substances are moving at differe rates, depending on the relative proportion of time spent in the moving s (mobile phase) and adsorbed to the silica gel (stationary phase). C. The development of the chromatogram is stopped when the solvent front near top. Various substances are seen at characteristic positions relative to th solvent front. The patient specimen contains a substance that can be tentatively identified as compound *b* in the control mixture, based on its relative mobility. Although shown as shaded spots here for clarity, most are colorless and are visualized at the end of the chromatography by beir dipped or sprayed with reagents that form colored products. The tentativ identification of the unknown drug as compound *b* requires that it show t same behavior with the visualizing reagents.

TLC has the ability to identify the presence of a large number of drugs an widely used in â€œdrug screens.â€• Visualization as colored spots gene requires fairly large amounts of material. For this reason, TLC is usually

with urine and gastric aspirate specimens because they typically have hig concentrations of many drugs than do corresponding serum specimens, a because they are readily available in large volumes.

Drawbacks to TLC include the need for multiple steps: extraction, concentration, chromatography, and a series of detection reactions. This TLC a relatively slow and labor-intensive procedure. Interpretation of the requires a skilled technologist who knows the TLC behavior of commonly encountered drugs. Quantitation of the drugs detected is difficult and rar attempted. Therefore, TLC is primarily used to demonstrate the presence drug. It is of limited value in identifying a drug not previously seen by th chromatographer, unless a possible candidate is suggested to the laborat and an authentic sample (ie, a standard) can be obtained to verify its be in the TLC system. Drugs that have limited excretion in the urine might n readily detected.

In the past, full-service toxicology laboratories used classical TLC procedu screen urine for a variety of drugs. The development of a commercial kit TLC of drugs in urine (Toxilab, Varian, Inc., Palo Alto, CA) has reduced th time, labor, and expertise required, and has extended its practicability to broader range of laboratories.[14] The use of a standardized procedure also allows tentative identification of a drug not previously encountered by comparing its characteristics with those of a broad range of drugs provide compendium by the manufacturer. Identifications made solely on the basi agreement with characteristics described in the compendium should be considered provisional until confirmed by additional testing.

In the related technique of high-performance liquid chromatography (HPL the stationary phase is packed into a column and the mobile phase is pur through under high pressure (Fig. 7-6). This allows good flow rates to be achieved, even when solid phases with very small particle sizes are used. Smaller particle size increases surface area, decreases diffusion distances improves resolution, but the spaces between the particles are also smalle increasing the resistance to flow. The use of high pressure and small par allows better separations in a fraction of the time required for TLC.

Another way that HPLC often differs from TLC is that HPLC typically empl

â€œreverse-phaseâ€• chromatography. Reverse-phase chromatography employs stationary phases in which the silica gel particles have had hydrocarbon molecules covalently linked to the outer surface. This reduce surface charge on the silica, thereby reducing its hydrophilicity, and simultaneously coats the particles with a permanently bonded oil-like laye the same time, solvent polarity is increased by using a primarily aqueous mobile phase with varying amounts of organic solvent. Because of these modifications, hydrophobic molecules are more strongly adsorbed by the stationary phase, whereas hydrophilic ones tend to remain in the mobile This results in an order of elution from the column that is approximately reverse of that seen with organic solvents and unmodified silica gel. Thus term â€œreverse-phase chromatographyâ€• is used. (Both TLC and HPLC be done using either â€œnormal-phaseâ€• or â€œreverse-phaseâ€• conditions. However, TLC is more commonly done in normal phase and HI more commonly in reverse phase.) A variety of hydrocarbons can be used derivatize the silica gel. By far the most common reverse phase columns octadecyl hydrocarbon as the outer coating and are often referred to as C columns.

In HPLC, the drugs are detected after they exit the chromatographic colu this case, they are identified by their retention time (the characteristic ti required to traverse the column). Because most drugs absorb ultraviolet detection is commonly by ultraviolet spectroscopy using specially designe flow-through cuvettes. Measuring light absorbance at a selected wavelen allows the amount of the drug to be determined. Accuracy is often enhan comparing the absorbance of the target analyte with absorbance of an in standard; that is, a compound with a different retention time that is adde fixed amount to all specimens. The ratio of the drug absorbance to the in standard absorbance is proportional to the drug concentration in the spe

Although most HPLC detectors allow a selection of the detection wavelen commonly only one wavelength is used during a

given run. Some detectors, however, allow absorbance at multiple wavel to be determined, either by rapidly and repeatedly scanning through a ra wavelengths, or by breaking white light into its component wavelengths c

after it has passed through the detection cuvette and then using an array photodiode detectors to make measurements at multiple wavelengths simultaneously. These techniques can allow the absorbance spectrum of a compound to be determined as it elutes from the column. This information supplement the retention time and allow more specific identifications to b made.

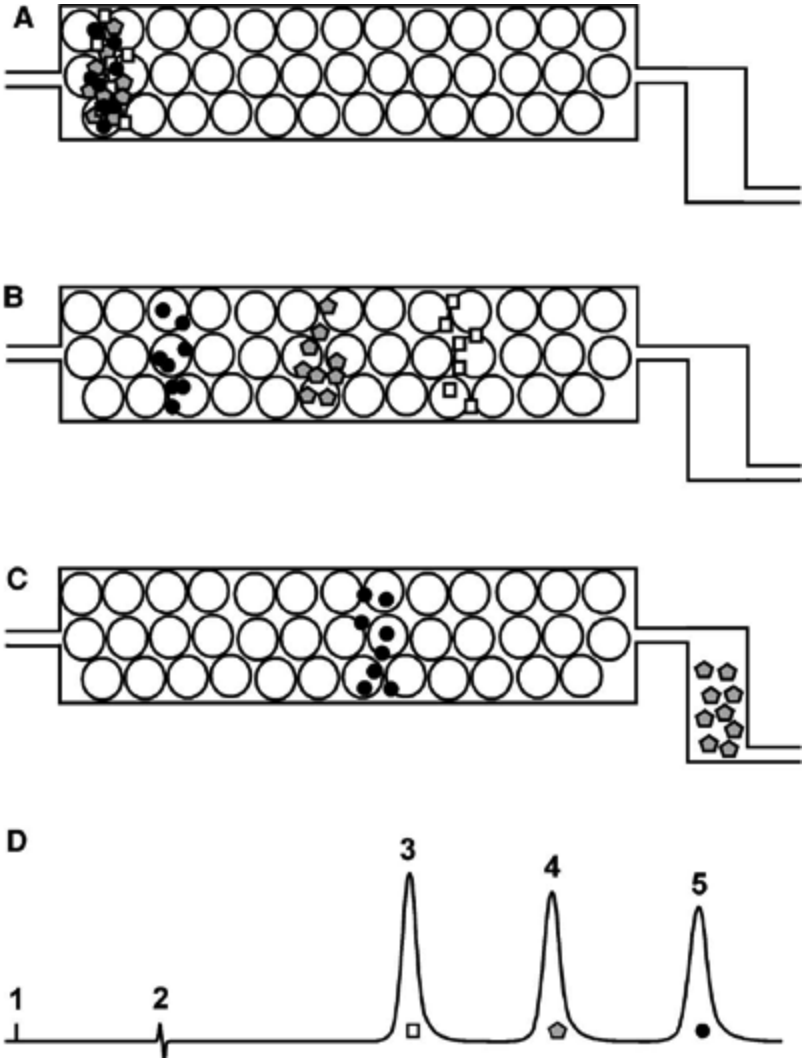

Figure 7-6. High-performance liquid chromatography. HPLC is schematic shown. A. A mixture of three compounds is injected into a column with a reversed-phase packing (⬟). B. The compounds move through the columr characteristic speeds. The most hydrophilic compound (â–¡) moves most quickly, whereas the most hydrophobic compound (⬟) moves most slowly The compound of intermediate polarity (⬟) has reached the detection cel

where it absorbs light directed through the cell and generates a signal proportional to its concentration. D. Illustration of the HPLC tracing that result: *1* indicates the time of injection. The artifact at *2* results when the injection solvent reaches the detector, and indicates the retention time of completely unretained compound. The peaks at *3, 4* , and *5* correspond to separated compounds. For example, peak *4* might be amitriptyline; peak might be the more polar metabolite, nortriptyline; and peak *5* could be th more hydrophobic internal standard *N* -ethylnortriptyline. Later-emerging are typically wider and shorter, because of more time for diffusive forces spread out the molecules.

TLC generally requires one or more hours to complete and provides qual identification of drugs present at concentrations of 1 mg/L or higher in contrast, HPLC can routinely provide quantitation of drugs at 10-fold lowe concentrations in less than 1 hour (provided the calibration was done in advance). Thus, HPLC is often the method of choice for measuring serum concentrations of drugs for which no immunoassay is available. Relative disadvantages of HPLC in comparison with TLC are the much higher costs equipment, the inability to analyze multiple samples simultaneously, and relative inability to analyze drugs with a wide range of polarities with a s assay. The latter limitation inhibits the use of HPLC as a broad drug-scre technique.

Gas chromatography (GC) is similar in principle to HPLC, except that the moving phase is a gas, usually the inert gas helium but occasionally nitro The schematic illustration of HPLC in Figure 7-6 is also applicable to GC. low flow resistance of gas allows high flow rates that make possible substantially longer columns than are used in HPLC. This offers the dual advantages of high resolution and fast analysis. As was true in HPLC, mos assays incorporate an internal standard to increase precision.

Because the inert carrier gas does not engage in intermolecular interacti partition of the analytes into the moving gas phase depends primarily on natural volatility. Elevated column temperatures are required to achieve sufficient volatility for analysis of most substances. The use of a tempera gradient (the column temperature is programmed to increase throughout course of the analysis) can allow compounds with a wide range of volatilit

be analyzed in a single run. This feature makes GC suitable for screening assays encompassing a broad range of drugs.

Gas chromatography is limited to molecules that are reasonably volatile a temperatures below 572Â°F (300Â°C), above which the stationary phase begin to break down. Two principal attributes of a molecule limit its vola its size and its ability to form hydrogen bonds. Molecules that form hydro bonds via amino, hydroxyl, and carboxylate moieties can be made more by replacing hydrogens on oxygen and nitrogen atoms with a nonbonding preferably large, substituent. (Large substituents sterically hinder access acceptor electron pairs on the nitrogen and oxygen atoms.) A number of derivatizing agents can be used to add appropriate substituents. The mos common derivatives involve the trimethylsilyl (TMS) group. Although derivatization with TMS substantially increases the molecular weight, the resulting derivative is much more volatile as a consequence of the loss of hydrogen bonding.

In traditional packed-column GC, the packing may consist of inert suppor particles with a fine coating of nonvolatile, high-molecular-weight oil that comprises the stationary phase. It is increasingly common for the station phase to be covalently bonded to the support particles. A highly useful v of GC is capillary chromatography. A long, fine capillary tube of fused silic coated on the inside with a covalently bonded stationary phase. The mobi phase flows through the tiny channel in the middle. These capillaries are flexible, allowing very long columns (10 meters or longer) to be coiled int small space. The long column length, coupled with highly uniform conditi throughout the column, results in extremely high resolution. The fineness column allows rapid thermal equilibration and the use of steep temperatu gradients that can speed analysis. The major drawback to capillary chromatography is a very limited column capacity. Special techniques are needed to restrict the amount of material introduced into the column and avoid overloading it. High-sensitivity detectors are required to measure t small quantities that can be chromatographed.

A number of detectors are available for GC. The most common detector,

particularly for packed columns, is the flame ionization detector. This inv directing the outflow of the column into a hydrogen flame. Organic molec emerging from the column are burned, creating charged combustion intermediates that can be measured as a current. The amount of current largely determined by the mass of carbon that is being burned. Nitrogen-phosphorus detectors are also widely used in drug analysis. In this modi of a flame ionization detector, a heated bead coated with an alkali metal used to selectively generate ions from compounds containing nitrogen or phosphorus. These devices detect broad ranges of substances, but do not identify them. The identity of the compounds detected must be inferred f the retention time.

The mass spectrometer can serve as a highly sensitive GC detector and possesses, in addition, the ability to generate highly characteristic mass from the compounds it is detecting. A special requirement of the mass spectrometer is that it requires a high vacuum in order to prevent the ion particles that it creates from interacting with other molecules or ions. Thi requires removal of the inert carrier gas and is easiest when there is a lo gas flow, such as occurs with capillary GC. The mass spectrometer, in tur provides good sensitivity for the small amounts of analyte that can be accommodated in capillary GC.

This detection process also begins by generating ions from the analyte molecules. This is usually done using electron impact ionization. The gas analyte is separated from the bulk of the carrier gas and introduced into ionization chamber, where it is bombarded by a stream of electrons. Elec impact can dislodge an electron from the analyte, creating a positively cl ion and frequently imparting sufficient energy to the ion to break it into If fragmentation occurs, conservation of charge requires that one of the resulting fragments be a positively charged ion. The fragments into which molecular ion breaks are characteristic of the molecule, as is the relative probability that a given fragment will carry the positive charge.

The mass spectrometer then uses electromagnetic filtering to direct only a specified mass-to-charge (m/z) ratio to a detector. Because most of th produced have a single positive charge, the observed peaks generally

correspond to the mass of the ions. The detector has sufficient electronic amplification that a single ion could theoretically be detected, accounting the high sensitivity of mass spectrometric detection. By rapidly scanning through a range of masses that are sequentially allowed to reach the det a mass spectrum may be generated. The mass spectrum records the mas the pieces produced by fragmentation of the parent ion, as well as the re frequency with which these fragments are produced and detected. The hi mass observed in the spectrum usually corresponds to the mass of intact ions generated from collisions that were not energetic enough to cause fragmentation.

Figure 7-7 shows the mass spectrum obtained from a gas chromatograph time when the trimethylsilyl derivative of the cocaine metabolite benzoylecgonine was emerging from the capillary column. The mass spec of any compound is highly distinctive and usually unique. The primary ex involves optical enantiomers, both of which have the same mass spectrur Toxicologically significant examples of enantiomers include *d* -methamphetamine, a drug of abuse, and *l* -methamphetamine, found in decongestant inhalers; and dextrorphan, the major metabolite of the cou suppressant dextromethorphan, and levorphan (levorphanol), a controlle substance.

To avoid the need to scan the full range of masses in a typical mass spec selected ion monitoring is often used. Here, the mass spectrometer is ty programmed to filter and detect only three of the larger and more chara peaks in the spectrum. In the case of trimethylsilyl benzoylecgonine (TMS BZE), the peaks at *m/z* 240, 256, and 361 are used. The concentration of BZE in the specimen is determined from the ratio of the peak height at *m* to a peak height at *m/z* 243 that results from a corresponding fragment o triply deuterium-labeled internal standard, d_3 -TMS-BZE (see Fig. 7-7). T specificity of the identification is verified by finding peaks at *m/z* 256 and 361, with peak height ratios to the peak at *m/z* 240 comparable to the ra seen with authentic TMS-BZE. The detection at the correct retention time substance producing all three peaks in the correct ratios produces an ex specific identification.

The high sensitivity and specificity afforded by gas chromatography/mass spectroscopy is being further extended by the related hybrid technique of chromatography/tandem mass spectroscopy, often abbreviated as LC/MS Initially restricted to research settings, the technique is now available in toxicology laboratories.[20] In LC/MS/MS, a tandem mass spectrometer is u the detector for liquid chromatography system. The initial ionization is do under conditions that do not promote fragmentation and yield primarily th intact parent ions of the molecules emerging from the HPLC. The first ma spectrometer is used to selectively filter only those ions with the molecul mass of the intact molecule of interest. As the selected ions exit the first spectrometer, they are allowed to collide with molecules of an inert gas. collisions cause the ions to break apart to create the mass spectrum that detected by the second mass spectrometer. The additional selection step provided by the first mass spectrometer greatly enhances specificity, and reduces background signal, enhancing sensitivity.

Quantitative Drug Measurements

When properly used to guide dosing adjustments, drug concentration measurements improve medical outcomes.[8] However, many therapeutic d measurements are made without an appropriate therapeutic question in m are drawn at inappropriate times. An essential requirement for interpreta drug concentrations is that the relationship between drug concentrations drug effects be known. Such knowledge is available for routinely monitore drugs and is often encapsulated in published ranges of therapeutic concentrations and toxic concentrations. Concentrations designated as â€œtoxicâ€• are usually higher than the upper end of the therapeutic ra and typically represent concentrations at which toxicity is acute and pote serious.

The relationships between toxic concentrations and effects cannot be systematically studied in humans and consequently are often incompletely defined. These relationships are largely inferred from data provided in ov case reports and case series. The measurement of drug concentrations in overdose cases where concentrationâ€“effect relationships are not well d

may contribute more to the management of future overdosed patients tha the management of the patient in whom the measurements were made.

For the toxicologist, drug concentrations are especially useful in two ways drugs whose toxicity is delayed or is clinically inapparent during the early phases of an overdose, drug concentrations may have substantial progno value. These concentrations

may be used to make decisions regarding the employment of antidotes or interventions to hasten drug elimination, such as hemodialysis or hemoperfusion. Specific concentrations can provide prognostic informatio facilitating anticipatory management.

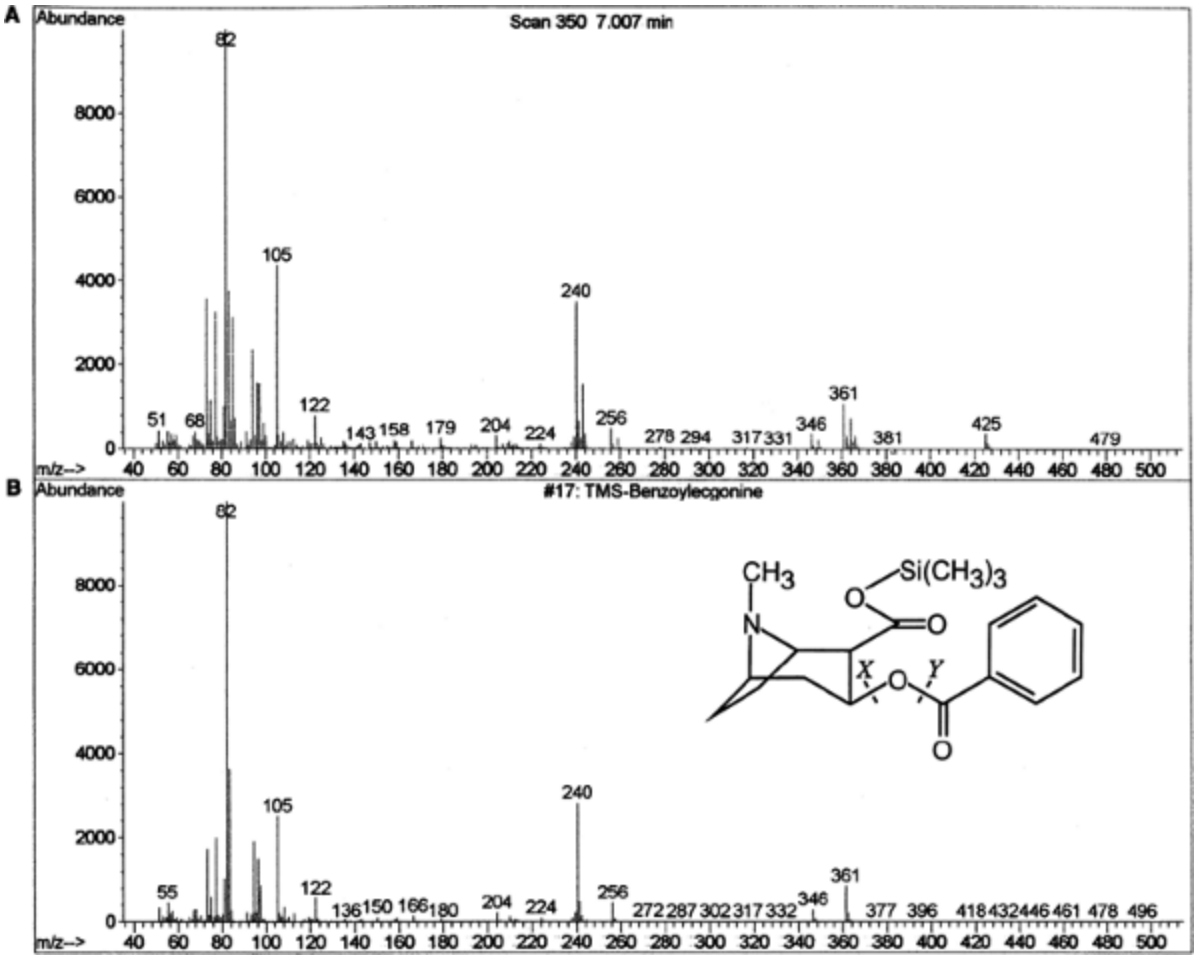

Figure 7-7. Mass spectrum of the trimethylsilyl derivative of benzoylecg (TMS-BZE). A. Mass spectrum of effluent from a GC column at the retent

time of TMS-BZE. The unfragmented parent ion of TMS-BZE is at *m/z* 361 two fragment peaks at *m/z* 243 and 259 result from fracture of the bonds and *Y* , respectively, in structure of TMS-BZE (inset in B). Additional pea *m/z* 243, 259 and 364 are derived from trideuterated TMS-BZE (d_3 -TMS- added as an internal standard. The mass spectrometer can identify and c TMS-BZE and d_3 -TMS-BZE independently of one another by measuring th heights of the peaks unique for each compound. The peak at *m/z* 425 is f coeluting contaminant. B. Mass spectrum of pure TMS-BZE.

Quantitative drug measurements are subject to various interferences, but are less problematic than in qualitative assays. Signals generated by cros reacting substances are weaker than those from the target analyte, and a relatively unlikely to lead to a false diagnosis of toxicity, particularly if th target analyte is absent. Such cross-reactivity can be exploited in some instances to provide confirmatory evidence of a poison for which no spec assay is immediately available. For example, the immunoassay finding of apparent subtoxic levels of tricyclic antidepressants can help confirm a diphenhydramine overdose, and the finding of a measurable digoxin concentration in an unexposed patient may suggest poisoning with other cardioactive steroids of plant or animal origin. Negative interferences are less frequent. Table 7-3 summarizes some of the more common interfere quantitative assays for drugs and poisons. Extensive information on interferences with laboratory tests, including toxicology tests, may be fou online at http://www.fxol.org .

Interferences in chromatographic methods usually result from the presenc other compounds with migration rates similar to the target analyte. Beca the migration rates are rarely exactly the same, the laboratory can usual recognize the presence of the interference as an overlapping peak when compounds are present. In such instances, the interference may impair accurate measurement of the drug concentration. When there is no target present, misidentification of the interfering peak as the target becomes r more likely, because a single peak is seen at

approximately the expected position. Because interferences in chromatog

methods are generally unique to a specific method, information about the interferences should be obtained by asking the laboratory.

Acetaminophen
Spectrochemical
Bilirubin, phenacetin, renal failure, salicylates

Immunoassay
Phenacetin
Carboxyhemoglobin
Spectrochemical
Fetal hemoglobin
Digoxin
Immunoassay
Other cardioactive steroids (found in oleander, red squill, Chan Su), endogenous digoxin-like substances (found in hepatic and renal failure, neonates, pregnancy), digoxin metabolites in renal failure; digoxin immun may increase or decrease results
Iron
Spectrochemical
Deferoxamine and EDTA decrease iron, with variable effect on iron-bindir capacity
Lithium
Electrochemical
Lithium, heparin anticoagulant, abnormal serum sodium
Methemoglobin
Spectrochemical
Hyperlipidemia, methylene blue, sulfhemoglobin
Salicylate
Spectrochemical
Bilirubin, diflunisal, ketosis, salicylamide, salicylsalicylate
Immunoassay
Diflunisal
Theophylline
Immunoassay

Caffeine

Analyte Technique Interference

TABLE 7-3. Interferences in Quantitative Assays for Xenobiotics

Drug measurements are unlike most other laboratory measurements in th concentrations are highly dependent on the timing of the measurement. Knowledge of a drug's pharmacokinetics can substantially enhance the ab draw meaningful conclusions from a measured concentration. Some drugs their pharmacokinetic behavior at very high concentrations. These change pharmacokinetics may be predictable from the mechanisms of drug clearа and the extent of binding to plasma proteins and to tissues (Chap. 9).

Knowledge of the relationship between drug concentrations and drug effe pharmacodynamics, is also important. Drug effects depend on local concentrations at the site of action, typically at cell membranes or intrac locations. Serum or plasma concentrations can be correlated with effects when these concentrations are in equilibrium with concentrations at the s action. Table 7-4 lists several circumstances that may alter the normal ra drug concentrations measured in serum or plasma to concentrations found the site of action, thereby altering the usual concentrationâ€“effect relationships. During the absorption and distribution phases, the concent ratio will be higher than its equilibrium value, yet often the only drug concentration measured after an acute overdose is one obtained while absorption and distribution are still ongoing. This effect may explain som observations of apparent poor correlation between measured concentrati and toxic effects.

Measurement during absorption phase
Underestimation of eventual effects
Sustained-release preparations; large ingestions of poorly soluble drugs salicylates); drugs that slow gastric emptying (eg, tricyclic antidepressar
Measurement during distribution phase
Overestimation of effects

Lithium, digoxin, tricyclic antidepressants	Decreased binding to proteins	Underestimation of effects
Phenytoin	Saturation of binding proteins	Underestimation of effects
Salicylate, valproic acid	Binding by antidote	Variable
Digoxin/digoxin immune Fab		

Factor Effect Examples

TABLE 7-4. Factors that May Alter Concentrationâ€”Effect Relationships

For drugs that bind significantly to plasma proteins, it is the concentration drug that is not bound to proteins (the free-drug concentration) that is in equilibrium with concentrations at the site of action. For most drugs at therapeutic levels, the free-drug concentration is an approximately const percentage of the total drug concentration. The total concentration is wha usually measured in the laboratory. Under these conditions, the ratio of concentration to active site concentration is approximately constant, and reasonable correlation between total concentration and drug effects can b expected.

Increasing the percentage of drug in free form results in stronger effects would be predicted from the total drug concentration. The free fraction of phenytoin may increase from its usual value of 10% when the number of albumin binding sites are decreased, either by hypoalbuminemia or by occupancy of the sites by other drugs, such as valproic acid, or by pheny metabolites when the latter accumulate in patients with renal failure. Whe protein binding sites become filled, as occurs with higher concentrations salicylate or valproate, any additional drug beyond the saturating concer will be 100% in free form, thereby increasing the average percentage of

free form.

A major change in the free fraction occurs after treatment of digoxin toxi with digoxin immune Fab, when the free digoxin concentration falls from approximately 75% of the total concentration to less than 1% as a conse of digoxin binding by the antidigoxin antibody fragments. At the same tin there is extensive redistribution of digoxin from tissues to plasma, leading substantial increases in total digoxin concentration. This situation may be further complicated by complex digoxin immune Fab interference in many digoxin immunoassays.

Measurement of free-drug concentrations can clarify such situations.[18] As for free phenytoin are available in many laboratories. Assays for other fr drug concentrations may require special arrangements. Availability and expected turnaround time can be provided by the laboratory. For patients treated with digoxin immune Fab, newer immunoassays that use antibodi attached to microparticles or glass fibers give results that can be used to upper bound on free-digoxin concentrations and thereby verify adequacy treatment.[27]

Toxicology Screening

A test unique to the toxicology laboratory is the toxicology screen, or â€ screen.â€• Depending on the laboratory, this term may refer to a single testing methodology with the ability to detect multiple drugs, such as a t layer or gas chromatography; or it may refer to a panel of individual test as a drug-abuse screen; or it may be a combination of broad-spectrum an individual tests. The widespread use of the term â€œtox screenâ€• is unfortunate, because this wrongly implies for many physicians the availa of a test that can exclude poisoning as a diagnosis. Unfortunately, no suc exists.

There are more toxic substances in the world than there are named disea However, a relatively limited number of substances account for most seri poisonings. As a result, in one study a comprehensive toxicology screenin

protocol using multiple detection methods applied to both serum and urin specimens was able to identify more than 98% of implicated substances.[1] suggests that a comprehensive â€œtox screenâ€• can exclude poisoning substantial degree of reliability. However, this study was done some time when the rate of introduction of new drugs was much slower than is curr the case. Many newer therapeutic drugs may not be identified even by â€œcomprehensiveâ€• screens currently in use.[34] Moreover, comprehen toxicology screens typically do not detect elemental ions, including brom lithium, iron, lead, and other heavy metals. Nor do they necessarily detec substances that are toxic at extremely low concentrations, such as digoxi fentanyl. Table 7-5 lists a number of substances encountered in emergen toxicology that may not be detected by routine toxicology screening.

It should be apparent that a negative toxicology screen cannot exclude poisoning. It is equally true that a positive finding does not necessarily c a diagnosis of poisoning. For assays that detect only the presence of a dr is not possible to distinguish benign or therapeutic levels from toxic ones Quantitative tests may falsely suggest toxicity when drug concentrations measured during the drug's distribution phase, which may extend for sev hours with drugs such as digoxin and lithium. Moreover, the phenomenon tolerance may allow chronic drug users to be relatively unaffected by concentrations that would be quite toxic to a nonusing individual. Becaus comprehensive drug screens may differ widely between institutions, and patterns of exposure also show substantial regional variation, there is lin ability to draw meaningful conclusions from any study of the sensitivity a specificity of such screens for detecting or excluding poisoning.

Antidysrhythmics
Î³-Hydroxybutyrate
Anticholinergics
Hypoglycemics
Anticoagulants
Iron
Anticonvulsants, newer
Isopropanol

Antipsychotics
Ketamine
Î²-Adrenergic agonists and antagonists
Lithium
Calcium channel blockers
LSD
Carbon monoxide
MDA/MDMA
Clonidine
Metals
Cyanide
Methanol
â€œDesigner drugsâ€•
Methemoglobin
Digoxin
Solvents
Diphenhydramine
Serotonin reuptake inhibitors
Ethylene glycol
Strychnine
Fentanyl
Xenobiotics (plant or animal)

TABLE 7-5. Substances of Concern that are Often Not Detected Toxicology Screens

The predictive power of the result of a toxicology screen will depend on a number of factors, including the likelihood of poisoning prior to receiving test results (the prior probability or the prevalence), the range of substa effectively detected, and the frequency of false-positive results. It should noted that false-positive and false-negative results may be either analytic clinical in origin. A clinical false positive occurs when a drug is detected t not contributing to the medical problem; for example, a therapeutic amou acetaminophen. A clinical false negative may occur when the wrong test i

ordered; for example, a screen for drugs of abuse for a patient with acetaminophen poisoning.

Table 7-6 explores the positive and negative predictive values of two hypothetical toxicology screens. The sensitivity of 98% and specificity of in one scenario reflect the sensitivity of a broadly comprehensive toxicol screen[13] and an achievable false-positive rate of 2%. The second scenari a sensitivity of only 80% and a specificity of 95% and represents plausibl mediocre performance. Three sets of prior probabilities are considered: 1 50%, and 95%. A prior probability of 10% might be seen if screening we indiscriminately applied to all patients in an emergency department, or in scenario where drugs were being excluded as a secondary cause of lethar an older patient who fell and struck his head. Both screens do well at ex drugs when their presence is already unlikely. However, a positive findin either does not yield a fully convincing diagnosis of drug presence. A pric probability of 50% falls into the range of prevalence actually observed in patients for whom toxicology screens were ordered (see below). In this scenario of maximum uncertainty, both screens do a good job of diagnos poisoning, but drug exclusion by the mediocre screen will be incorrect in 1 instances.

A prior probability of 95% represents testing where the clinical presentat strongly suggests poisoning, as in the investigation of lethargy in a know regular drug user. While positive findings in either screen raise the proba to almost complete certainty, negative findings from the excellent screen incorrect 1 time out of 4, whereas negative results from the mediocre sc are wrong 4 times out of 5. Overall, toxicology screens have better positi predictive value than negative predictive value. This observation

should give pause to those who primarily order toxicology screens â€œto out poisoning.â€•

98/98 (excellent)
84%/99.8%
98%/98%
99.9%/72%

80/95 (mediocre)
64%/98%
94%/83%
99.7%/20%

Sensitivity/Specificity (%/%)	Prior Probability 10%	50%	95%

TABLE 7-6. Positive and Negative Predictive Values of Toxicolo Screens

Although only approximately 3% of laboratories offer comprehensive tox screening,[4] most laboratories will offer some sort of testing in response t request for a toxicology screen. This may consist of a panel of immunoas for drugs of abuse or a urine TLC screen, or it may result in a compreher screening test performed at a reference laboratory. Other laboratories ma offer a focused, rather than a comprehensive, screening panel. Larger laboratories may have several types of â€œtox screensâ€• available for different situations. Among laboratories that do not limit their tests exclu to commercially available methods, it is likely that no two will have exact same menu of drugs that can be reliably detected. A survey of emergency physicians found that more than 75% were not fully aware of the range o drugs detected, and not detected, by their laboratory's toxicology screen. majority believed that the screen was more comprehensive than it actual was.[9]

Comprehensive toxicology screens typically require several hours of fairly intense labor, particularly if confirmatory testing is included. Given the t toward increasing automation and decreasing personnel in clinical labora it is relevant to ask what benefits may be derived from such testing. Stu show that comprehensive toxicologic screening has the potential to provi significant information, with utility varying with the indication for testing. prevalence of positive results has ranged from 34â€“86% of specimens submitted for testing. When drug exposure, as predicted from the history

physical, was compared with screening results, clinically unsuspected substances were found in 7â€“48% of the cases and clinically suspected substances were not found in 9â€“25%.[12,13,17,25,26] However, limit utility is suggested by studies showing that the results of comprehensive screening affect management in less than 15% of cases,[25] and in many instances, in less than 5% of cases.[12,17,23,26,32]

One reason for a limited effect on management is the substantial time de before results of comprehensive screening are available. Generally, more 3 hours are required for the report of a negative result and an even long is required for a positive finding. By this time, most consequential manag decisions have been implemented. Another possible explanation for scree limited utility is that comprehensive screening is largely available only in medical centers, where consultation from a medical toxicologist is more l to be available. Such experts may be more able to make correct diagnose initiate appropriate management relying on clinical findings alone.

Some laboratories address the issue of providing useful information in a fashion through the use of focused, rather than comprehensive, screening protocols.[33] These screens include drugs locally prevalent in overdose ca and/or drugs for which there are specific interventions. The goal is typica provide results within 1 hour, including quantitation of those substances management decisions require concentration data. A combination of serur urine tests is used. Table 7-7 suggests the possible composition of a focu screen. Such a screen should be supplemented with additional specific te when indicated.

Several recently introduced point-of-care devices are capable of rapidly screening urine for the presence of drugs of abuse, as well as tricyclic antidepressants. Results are typically available in 20â€“30 minutes. In a study of one such device, diagnosis was believed to have been aided in 8 cases and clinical management was changed in 25%.[2] Additional studies needed to ascertain the utility of point-of-care drug screening in emerge toxicology.

Acetaminophen

Cocaine metabolite
Ethanol
Opiates
Salicylates
Tricyclic antidepressants[a]
Tricyclic antidepressants (semiquantitative immunoassay)

Consider including:
Barbiturates
Amphetamines
Cooximetry[b]
Barbiturates[a]
Iron
Benzodiazepines
Lithium
Methadone
Theophylline
Phencyclidine
Valproic acid
Propoxyphene
Volatile alcohols[c]

Other locally prevalent drugs

[a] If not included in serum tests
[b] Requires whole-blood specimen
[c] Methanol, isopropanol (+ acetone)

Serum Tests Urine Tests

TABLE 7-7. Components of a Focused Toxicology Screen

A useful alternative to the toxicology screen is the *toxicology hold* . This set of serum and urine specimens drawn at the time of presentation, whe

concentrations are likely to be near maximum levels, and initially held refrigerated or frozen without testing. A maxim for management of the poisoned patient is that an evaluation is not complete until it has been re over time. In many instances, observation will clarify the diagnosis, allow toxicology screening to be dispensed with or replaced by a specific assay. the other hand, the specimens remain available for subsequent testing if diagnosis remains unclear, or if there are unexplained findings. Most laboratories will hold such specimens for several days, if necessary.

Bedside Toxicology Tests

Testing at the bedside is attractive for emergency toxicology. When a sp diagnosis is being considered, a bedside test can provide confirmation or exclusion quickly, and often inexpensively,[21] enabling appropriate manag to be initiated. This benefit must be balanced against the generally poore sensitivity and specificity of bedside tests in comparison with testing in th clinical laboratory, the lack of quantitative information for most tests, the to perform testing in accord with regulatory requirements (see below), an erosion of the time advantage when multiple bedside tests are done on th same patient.

Table 7-8 lists some tests that can be conveniently performed at the bed Spot tests can also be done at the bedside, although many spot tests em hazardous reagents that may not be suitable for use in many bedside se A major problem with bedside tests that are not done with commercial de is that these are considered â€œhighly complexâ€• tests under federal regulations, although they may be very simple to perform. This classifica results from the fact that they are not subject to the validation processes required for FDA-approved commercial devices. Meeting the regulations requires significant initial and ongoing investment of time. The Meixner t (for amatoxins in mushrooms) and breath analysis (for ethanol or carbon monoxide) are exempted

from these regulations, because they do not involve human specimens (s Regulatory Issues Affecting Toxicology Testing below).

Alcohol dehydrogenase
Saliva
Ethanol
Other alcohols may interfere. Some tests only give concentration ranges.
Breath analysis
Breath
Carbon monoxide
Ethanol may interfere.
Breath analysis
Breath
Ethanol
Good cooperation required. Ethanol in oral cavity interferes. Calibrated to whole-blood rather than serum concentration.
Ferric chloride
Urine
Salicylate
Acetaminophen and phenothiazines interfere.
Meixner
Mushroom
Amatoxins
Paper must contain lignin (use filter paper, which is lignin-free, as negati control). Requires strong acid. Some false positives and false negatives.
Microparticle agglutination
Urine
Drugs of abuse
KIMS variant with visual endpoint. Separate test for each drug.
Microparticle capture
Urine
Drugs of abuse
Single device detects one or more of the drugs listed in Table 7-10 , in a variety of menus available from multiple manufacturers. Some multitest include tricyclic antidepressants. Higher false-positive and false-negative than for clinical laboratory testing.
Oxalate crystals

Urine			
Ethylene glycol			
Metabolic end-product. Not detected during early stages. Nonspecific.			

Test	Substrate	Drug or Poison	Comments

TABLE 7-8. Bedside Toxicology Tests

Two studies compared results obtained with point-of-care drug screening devices to a gold standard of gas chromatography-mass spectrometry (G using cutoff values recommended for federal workplace testing. Both stu had disproportionately large proportions of specimens (one-half to two-t with concentrations close to the cutoff value. In these samples, false-pos and false-negative rates ranged from 0â€“50%, depending on both the d and the drug.[3,15] In actual testing practice, specimens with concentrati near the cutoff concentration should be much less frequent, with many specimens having drug concentrations that are either quite high or zero. extensive study using a more representative range of urine drug concent observed higher rates of correct results, but performance remained inferi that of immunoassays conducted with laboratory instrumentation[10].

A clinical and methodologic issue with bedside drug-screening assays is v positive results will subsequently be subjected to confirmatory testing. Th extra investment of labor needed to submit a specimen tends to discoura laboratory confirmation. The argument for confirmation is that this is an accepted standard of practice for screening assays that have lower false-positive rates than the point-of-care devices (see Special Considerations Drug Abuse Screening Tests below). The counterargument is that if testin limited to populations with a high prior probability of drug exposure, the predictive value of a positive test is high. The NACB guidelines recommer against routine confirmation of positive results of drug-screening immun done solely for medical reasons, but suggest that all such unconfirmed p results be reported as being â€œpresumptive.â€•[35]

Regulatory Issues Affecting Toxicology

Testing

Since 1992, medical laboratory testing has been governed by federal regulations (42 CFR part 405 et seq) issued under the authority of the C Laboratory Improvement Amendments of 1988 (often referred to as CLIA- simply CLIA). These regulations apply to all laboratory testing of human specimens for medical purposes, regardless of site. They include the univ requirement for possession of an appropriate certificate to perform even simplest of tests. The remaining requirements depend on the complexity test. These regulations become important to the emergency toxicologist whenever testing is done at the bedside, whether using spot tests, or commercial point-of-care devices such as dipsticks, glucose meters, or u drug-screening devices.

The regulations divide testing into three categories: waived, moderate complexity, and high complexity. Waived tests include a number of speci designated simple tests, including urine dipsticks, urine pregnancy tests, drug-screening immunoassay devices, and blood glucose measurements w hand-held monitor. The only legal requirement for performing waived tes are the possession of an appropriate CLIA certificate (certificate of waiver higher) and performance of the test in accordance with the manufacturer instructions.

There are substantial additional requirements for both moderate and high complex testing, most of which simply represent good laboratory practice 7-9 lists the most significant of these requirements. Most assays perform with commercial kits or devices are classified as belonging to the modera complex category. All tests not specifically classified as waived or moder complex are considered highly complex. This includes essentially all noncommercial tests, including spot tests, because the testing materials not been subject to review and approval by the Food and Drug Administr

These regulations have had a substantial impact in all areas of laboratory testing. Some of the most significant effects have been on bedside testin including spot tests and point-of-care devices. While clinical laboratories been following most required practices prior to the implementation of the

regulations, this was usually not the case for testing done at other sites. institutions have now established point-of-care testing programs to facili compliance with the regulations, as well as with additional requirements accrediting agencies, such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Any

toxicologic or other testing done at the point-of-care should be set up in consultation with the institutional program. Often, all point-of-care testing done under a CLIA certificate held by the program. There is frequently a of-care testing coordinator who may make recommendations or personall assist in efficiently addressing the assorted requirements.

Waived Tests
- Certificate of Waiver
- Follow manufacturer's instructions exactly

Moderate-Complexity Tests
- CLIA certificate
- Record keeping
- Test method verification
- Written procedures
- Qualified lab director
- Personnel educational requirements
- Documented training of all testing personnel
- Annual competency testing of all personnel
- Two levels of controls daily
- Participate in proficiency testing every 4 months
- Verify calibration and reportable range at least every 6 months
- Quality assessment program
- Biennial inspection and certification

High-Complexity Tests
- All moderate-complexity requirements *plus*
- Qualified on-site supervisor *or*
- Daily review of all results by qualified supervisor

This table lists only the most significant requirements of the regulations implementing the Clinical Laboratory Improvement Amendments of 1988

(CLIA). These regulations continue to evolve. Regulatory agencies such as Joint Commission on Accreditation of Healthcare Organizations (JCAHO) r have additional requirements. Consultation with the clinical laboratory or an institutional point-of-care coordinator is recommended prior to impler any testing.

TABLE 7-9. Major CLIA Requirements for Laboratory Testing

Breath tests for ethanol and carbon monoxide and the Meixner test[1] for amatoxins in mushrooms are not regulated by CLIA, because no human specimen is involved. However, such testing may be covered by state law by institutional or accrediting agency policies. The NACB guidelines recor that breath testing be overseen by the clinical laboratory and meet the s standards as other point-of-care testing.[35]

Personnel unaccustomed to quality control and assessment practices may the CLIA requirements initially burdensome. Nonetheless, compliance is important. Following these practices may lead to a 3-fold reduction in in results,[31] improving the quality of care provided to the patient. Moreover noncompliant testing is illegal under federal law and also may be illegal u state law. Any untoward outcome associated with illegal testing creates a risk management liability for both the institution and the individual. Additionally, billing for any testing that is not CLIA-compliant may be considered fraudulent.

Another area where the CLIA regulations have impacted toxicology testing the provision of infrequently requested tests. Meeting regulatory require involves a substantial labor investment even when few patient specimens being tested. Mounting pressures to reduce laboratory costs make it less that laboratories will continue to maintain such assays.

Another important regulation, although not part of CLIA regulations, requ that the medical reason for ordering a test be provided with the order. F regulations require that the ordering physician provide the diagnosis that establishes the medical necessity for the test, either by name or by diagn code (CPT code). Laboratories may not use a â€œbest guessâ€• to assig

codes to undocumented test requests.

Special Considerations for Drug-Abuse Screening Tests

Testing for drugs of abuse is a significant component of medical toxicolog testing. Initial testing is usually done with a screening immunoassay. Pos results may be confirmed by retesting using a nonimmunologic test, but t frequently not done. (Drug-abuse testing for nonmedical reasons is gene considered to be forensic testing, and confirmation is considered mandatc such circumstances.) Drug-screening immunoassays were initially develop use in workplace drug-screening programs and are not always optimal for medical purposes, but their wide availability in inexpensive, easy-to-use formats led to their nearly universal adoption in clinical laboratories. Grov the market for medical drug screening has led to the development of poi care tests specifically for medical use, but these devices largely retain th deficiencies of their predecessors.

The most commonly tested-for drugs are amphetamines, cannabinoids, c opiates, and phencyclidine. These are often referred to as the NIDA 5, be they are the five drugs that were recommended in 1988 by the National Institute on Drug Abuse (NIDA) for drug screening of federal employees. (Responsibility for recommendations for federal drug testing now lies with Substance Abuse and Mental Health Services Administration, or SAMHSA.) Drug-screening immunoassays are also frequently done for barbiturates a benzodiazepines, and less frequently for methadone and propoxyphene. I screening devices intended primarily for medical use may also include a t tricyclic antidepressants. Table 7-10 lists some of the general characteris these tests. There are also commercial urine immunoassays for lysergic a diethylamide (LSD), methaqualone, methylenedioxymethamphetamine (â€œecstasyâ€•), and oxycodone. Drug-screening immunoassays are av in a number of formats, which may differ in performance. All are designec used with urine specimens, because these can be obtained noninvasively generally have higher concentrations than serum, enhancing the sensitivit the test.

The drug-screening tests for cannabinoids and cocaine are directed towar inactive drug metabolites rather than the active parent compound. The p drugs, cocaine and tetrahydrocannabinol, are both short-lived and persist more than a few hours after use. The metabolites remain present substa longer. Detection of the metabolites increases the ability to detect any re drug use. However, this limits the utility of the assays for determining w a patient is currently under the influence of the drug. Because the metab are rapidly formed, a negative test generally excludes intoxication, but a positive test indicates only past use, not current intoxication.

To increase sensitivity for detection of less-recent drug use, substrates o than urine have been employed for drug screening, including hair and meconium. The latter is used to document intrauterine drug exposure (Ch). SAMHSA is developing regulations governing the use of hair, saliva, an sweat specimens for federal workplace testing. This can be expected to h the side

effect of increasing the availability of clinical testing using these substrat However, testing performed on hair and sweat are unlikely to offer adva over testing of serum and urine for the management of toxicologic emergencies.

Amphetamines
1000 ng/mL
500 ng/mL
1â€“2 d (2â€“4 d)
Decongestants and ephedrine may give false positives; MDA and MDMA a variably detected. Confirmation of methamphetamine requires detection o >500 ng/mL with >200 ng/mL of metabolite, amphetamine.
Barbiturates
200 ng/mL secobarbital

2â€“4 d
Phenobarbital may be detected for up to 4 weeks.
Benzodiazepines

100â€“300 ng/mL

1â€“30 d
Benzodiazepines vary in reactivity and potency. Hydrolysis of glucuronide increases sensitivity. False positives with oxaprozin.
Cannabinoids
50 ng/mL;
20 ng/mL;
25 ng/mL;
100 ng/mL THCA
15 ng/mL THCA
1â€“3 d (>1 mo)
Screening assays detect inactive and active cannabinoids; confirmatory a detects inactive metabolite tetrahydrocannabinoic acid (THCA). Duration positivity highly dependent on screening assay detection limits.
Cocaine
300 ng/mL BZE
150 ng/mL BZE
2 d (1 wk)
Screening and confirmatory assays detect inactive metabolite benzoylecg (BZE). False positives unlikely.
Opiates
2000 ng/mL;
300 ng/mL
2000 ng/mL;
morphine or codeine
1â€“2 d;
2â€“4 d (<1 wk)
>10 ng/mL of heroin metabolite 6-monoacetyl morphine is also confirma Semisynthetic opiates derived from morphine show variable cross-reactiv Fully synthetic opioids (eg, fentanyl, meperidine, methadone, propoxyphe tramadol) have minimal cross-reactivity.
Methadone
300 ng/mL

1â€“4 d
Doxylamine may cross-react.
Phencyclidine
25 ng/mL
25 ng/mL
4â€“7 d (>1 mo)
Dextromethorphan and ketamine diphenhydramine may cross-react.
Propoxyphene
300 ng/mL

3â€“10 d
Duration of positivity depends on cross-reactivity of metabolite norpropoxyphene.

[a] Performance characteristics vary with manufacturer and may change ov time. For most accurate information, consult the package insert of the cu lot or contact the manufacturer.

[b] SAMHSA recommendations[7] are shown as first value for amphetamines, cannabinoids, cocaine, opiates, and phencyclidine immunoassays, and as values for confirmatory assays. Other commercial immunoassay cutoffs ar listed. Other GC/MS cutoffs are set by the laboratory.

[c] Values are after typical use; values in parentheses are after heavy or prolonged use.

Drug/Class	Detection Limits[b]	Confirmation Limits[b]	Detection Interval[c]	Comr

TABLE 7-10. Performance Characteristics of Common Drug-Abu Screening Immunoassays [a]

The stigma attached to a positive test for an abused drug requires that s care be exercised in performing and reporting the tests. To protect citize rights, many states have legislated specific requirements for workplace d screening. In some states, the requirements apply only to screening in th

workplace, exempting testing for medical purposes. Laws in other states apply to all drug screening. Although they are not always legally required workplace drug-screening practices have been widely applied to all drug screening.

The use of specific cutoff concentrations is nearly universal. Test results considered positive only when the concentration of drugs in the specimen exceeds a predetermined threshold. This threshold should be set sufficien high that false-positive results as a consequence of analytic variability or because cross-reactivity are extremely infrequent. They should also be lo enough to consistently give a positive result in persons who are using dr Cutoff concentrations used vary with the drug or drug class under invest In some drug-screening immunoassays, the laboratory has the option of selecting from several cutoff values.

The use of cutoff values sometimes creates confusion when a patient who known to have recently used a drug has a negative result reported on a screen. In such instances, the drug is usually present, but at a concentra below the cutoff value. Another potential problem occurs when a patient's screening test is positive after previously having become negative. This i usually interpreted as indicating renewed drug use, but it may be an arti Urine drug concentrations are directly proportional to the serum drug concentrations, but inversely proportional to the rate of urine production. rate of the urine flow may vary up to 100-fold, with a resulting possible fold change in the urine drug concentration. This effect is often exploited individuals who drink large quantities of water prior to taking a urine dru in order to increase urine flow and decrease urine drug concentrations. In contrast, a decrease in the rate of urine production can result in a positiv following a negative one, despite no new drug exposure. A similar effect be produced by changes in urine pH. Drugs containing a basic nitrogen m demonstrate ionic trapping, with increasing concentrations as urine pH decreases. Similarly, excretion of the phenobarbital anion may increase w increasing pH. (This phenomenon is medically exploited by alkalinizing th to increase phenobarbital excretion.)

Another widely used practice is the confirmation of positive screening res using an analytical methodology different from that used in the screen, su an immunoassay screen followed by chromatographic confirmation. The possibility of simultaneous false-positive results by two distinct methods quite low. Clinical laboratories may differ in their policies with regard to confirmatory testing. Some may confirm all positive results from screenir immunoassays, whereas others may not provide any confirmatory testing unless it is explicitly requested.

The most common confirmatory method is GC/MS. The high specificity af by the combination of the retention time and the mass spectrum makes f positive results extremely unlikely. GC/MS also has greater sensitivity tha screening immunoassays, minimizing failed confirmations because of drug concentrations below the sensitivity of the confirmatory assay. Some sta require GC/MS confirmation for workplace drug screening and it may be required for all drug screening.

If confirmation by GC/MS is not required, a common practice is to confirm screening immunoassays by TLC and vice versa. Positive findings by both methods provide a high degree of specificity. A disadvantage of the appro the low sensitivity of TLC relative to immunoassays. True positive immunoassays may fail to be confirmed, leading to false-negative final r Some laboratories accept this, because false negatives are unlikely in the presence of serious overdoses. Other laboratories may retest TLC-negativ specimens with a more sensitive method, such as GC/MS. Sometimes, confirmatory testing may be done on positive results for illicit drugs, but legal drugs such as barbiturates, benzodiazepines, and ethanol.

Immunoassay results can generally be obtained within 1 hour. Confirmat testing usually requires at least several hours. This can create a problem confirmation of initial immunoassay results is considered mandatory. Mos laboratories will provide a verbal report of a presumptive positive result t facilitate medical management, but may not enter the result into a perma record, such as the laboratory computer, until after confirmation has bee completed.

The importance of confirmatory testing in workplace drug screening follov

from the relatively low prevalence of positive results. A screening test wi sensitivity and specificity of 98% will produce 2 false-positive results per subjects tested. A workforce with a 2% prevalence of illicit drug use will true-positive results per 100 subjects. The predictive value of a positive will only be 50% (2 of 4). This is an unacceptable level of certainty for r that might be used to terminate employment. While the prevalence of re drug use in the workforce is low, rates of positivity of 34â€“86% have be reported for selective drug screening of emergency department populatio Given a 50% prevalence of recent drug use, the positive predictive value same screening test rises to 98% (see Table 7-6).

A high prior probability of drug positivity for patients tested in medical s results in a very high posterior probability after a positive test. Confirma testing is much less critical in such a setting, particularly because a posit finding infrequently has consequences that extend beyond the medical management of the patient. An exception may occur where results of tes performed on motor vehicle crash victims can be subsequently subpoenae evidence in legal proceedings.

One workplace drug screening practice that is not widely followed in med toxicology is maintenance of a chain of custody. Employers generally insis chain of custody for workplace testing because actions taken in response positive result may be contested in court. A chain of custody provides re that are readily defended in court. Laboratories providing testing for med purposes rarely keep a chain of custody because it is quite expensive and not benefit the patient. Additionally, the medical personnel responsible fo obtaining the specimens are rarely trained in collection requirements for chain of custody.

The lack of chain of custody can create problems when persons with no r complaints present at an emergency department or other medical facility requesting the performance of a drug-screening test. Unless the facility is prepared to initiate the chain of custody at the time of specimen collectio the laboratory is prepared to maintain it, such persons should be redirect a site maintained by a commercial laboratory that routinely performs wo drug testing and has appropriate procedures in place. Many laboratories

had the experience of unwittingly performing drug-abuse testing for non purposes, because the reason for the testing is not always included on th requisition. To avoid liability issues, the laboratory may choose to include disclaimer with every drug-screening report indicating that the results are purposes of medical management only.

Another practice common in workplace testing but rare in medical labora is testing for specimen validity. It is common for individuals to try to â€œbeatâ€• a workplace drug test through a variety of means, including diluting the specimen (either physiologically by water ingestion or by dire addition of water to the specimen), substituting â€œcleanâ€• urine obta from another individual, or adding various substances that will either des drugs in the specimen or will inactivate the enzymes and/or antibodies us the screening immunoassays. Such substances include acids, bases, oxid agents (bleach, nitrite, peroxide, peroxidase, iodine, chromate), glutaraldehyde, pyridine, detergents, and soap. SAMHSA requires validity testing for all specimens in federal workplace testing, including measurem urinary pH, specific gravity, and creatinine concentration, as well as tests the presence of adulterants.[7] Dipsticks are available that detect the most common adulterants. However, manipulation or adulteration is rarely a p in medical specimens, and clinical laboratories infrequently provide validi testing.

Performance Characteristics of Common Dr Screening Assays

Medical toxicologists, toxicology laboratory directors, and practicing phys may frequently get questions about the significance of drug-screening as particularly about the causes of false-positive results. Often these questi come from an individual who recently had a positive test. Table 7-10 summarizes drug-screening test performance characteristics, which are discussed in more detail below.

Immunoassays for opiates are directed toward morphine but have good c reactivity with many (but not all) structurally similar natural and semisyr

opiates. The extent of cross-reactivity may vary between manufacturers. example, oxycodone exhibits approximately 30% cross-reactivity relative morphine in a fluorescence polarization immunoassay, but less than 5% reactivity in a number of other screening assays.[19] A failure to appreciate poor detection of oxycodone can create problems when opiate-screening immunoassays are used to confirm that patients receiving prescription oxycodone for chronic pain are indeed

taking it, rather than diverting it for illicit sale. If a low cross-reactivity a used, a patient taking oxycodone as prescribed might have a negative re whereas another patient who was selling the oxycodone and using the pr to buy heroin would have a positive result. To address this problem, a ne assay specific for oxycodone has been introduced. This assay is sensitive therapeutic amounts of oxycodone, but relatively insensitive to other opi

Synthetic opioids such as dextromethorphan, fentanyl, meperidine, meth propoxyphene, and tramadol show little or no cross-reactivity in opiate immunoassays. Urine immunoassays specific for methadone and propoxy are available. Given the increasing importance of buprenorphine in maint therapy for opiate dependency, it is worth noting that the combination of potency and low cross-reactivity means that buprenorphine will generally detected by opiate immunoassays.

A positive immunoassay result may reflect multiple contributions from va opiates and opiate metabolites. Concentrations of morphine glucuronide ir urine may be up to 10-fold higher than the concentrations of unchanged morphine and can contribute substantially to positive results. A positive result following use of heroin (diacetylmorphine) is primarily a result of t morphine and morphine glucuronide that result from heroin metabolism. Distinguishing heroin from other opiates requires detection of 6-monoacetylmorphine, the heroin-specific metabolite. Small amounts of th metabolite may be detected by GC/MS for up to 24 hours after use. A ha of 5 minutes means that unchanged heroin can only be found in the urine sampling is done immediately after use.

The duration of positivity of an opiate immunoassay after last use depend

the identity and amount of the opiate used, the specific immunoassay, th cutoff value, and the pharmacokinetics of the individual. Currently, SAMH recommends a cutoff equivalent to 2000 ng/mL of morphine for workplac screening, because poppy seeds can rarely produce transient positive res with the previously recommended cutoff of 300 ng/mL. Most toxicology laboratories continue to use a 300 ng/mL cutoff.

Drug-screening assays for â€œcocaineâ€• are actually assays for the in cocaine metabolite benzoylecgonine, which is eliminated more slowly tha cocaine. This extends the duration of positivity after last use from a few to 2 days, and sometimes to a week or longer after prolonged heavy use. Because the assay is directed toward an inactive metabolite, positive resu not equate with intoxication but merely indicate recent exposure. The ass highly specific for benzoylecgonine, and false-positive results are extrem uncommon.

Immunoassays for cannabinoids are also directed toward an inactive metabolite, in this case tetrahydrocannabinoic acid. These immunoassays exhibit cross-reactivity with other cannabinoids, but little else. Because cannabinoids are structurally unique and occur only in plants of the genus *Cannabis* , false positives are quite uncommon. It is unusual, although p to become exposed to sufficient â€œsecond-handâ€• or sidestream mar smoke to develop a positive urine test.[5] Legal hemp products include fibe and seedcake derived from *Cannabis* varieties with low levels of cannabi Although hemp food products contain insufficient amounts of tetrahydrocannabinol to produce psychoactive effects, their ingestion may urinary cannabinoid concentrations above screening thresholds.[6]

Interpretation of a positive result for cannabinoids can be problematic. U may be positive for up to 3 days after occasional recreational use. Howev with heavy or prolonged use, there may be significant accumulation of cannabinoids in adipose tissue. These stored cannabinoids are slowly rele into the bloodstream and can produce positive findings for a month or mo Consequently, little can be concluded from a positive finding in terms of intoxication. Because positive results in the absence of intoxication are v common, and because tetrahydrocannabinol rarely is responsible for seri

acute toxicity, NACB guidelines recommend against its routine inclusion in screening for patients with acute symptoms.[35]

Amphetamine-screening tests have the greatest problems with false-positi results. A number of structurally related compounds may have significant reactivity, including nonprescription decongestants such as pseudoephedri well as L-ephedrine, which is found in a variety of herbal preparations. Th cross-reactivity is beneficial from the point of view of the medical toxicol because all of these compounds may produce serious stimulant toxicity. B is problematic in drug-abuse screening because of the widespread legitim use of cold medications. Assays with greater selectivity for amphetamine methamphetamine have been developed. Although these assays produce false-positive results caused by decongestant cross-reactivity, they are a less sensitive for the detection of other abused amphetamine-like compo including methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA, Ecstasy), and phentermine. C reactivity patterns vary from assay to assay.[19] Manufacturer's literature be consulted for specific details.

Testing for benzodiazepines is complicated by the wide array of benzodiazepines that differ substantially in their potency, cross-reactivity, half-lives. There are also substantial differences in the detection patterns various immunoassays.[19] This heterogeneity complicates the interpretatio benzodiazepine-screening assays. Screening results may be positive in p using low therapeutic doses of diazepam, but negative after an overdose highly potent benzodiazepine such as clonazepam. To improve breadth of detection, some assays employ antibodies to oxazepam, which is a metal of a number of different benzodiazepines. These assays may have poor sensitivity to benzodiazepines that are not metabolized to oxazepam. Fals negative results may occur for benzodiazepines that are excreted in the almost entirely as glucuronides that have poor cross-reactivity with antib directed toward an unmodified benzodiazepine. This is one reason for the detectability of lorazepam in some screening assays. The latter situation led to the recommendation that specimens be treated with Î²-glucuronida prior to analysis.[22] Some assays now include Î²-glucuronidase in the reag mixture, or employ antibodies directed toward glucuronidated metabolites

frequency of false negative results, as well as the fact that benzodiazepin relatively benign in overdose, have led the NACB guidelines to withhold recommendation for routine screening of urine for benzodiazepines until problems with the immunoassays are addressed.[35]

Barbiturates are comparable to benzodiazepines in heterogeneity of pote cross-reactivity, and half-lives, although the differences are less substan Specific assays for serum phenobarbital can often help to clarify the significance of a positive barbiturate screen.

Some phencyclidine (PCP) screening assays may give positive results with dextromethorphan, ketamine or diphenhydramine, but only when these a used in amounts well above usual therapeutic quantities. A positive result serve as a clue to a possible overdose with either of these substances.

Measurement of Ethanol Concentrations

Measuring ethanol may have ramifications beyond guiding medical management, particularly when performed on crash victims. Although tes for ethanol in urine is common in workplace drug screening, most testing clinical laboratories is done using serum or plasma. Concentrations are m commonly measured enzymatically using alcohol dehydrogenase. In large toxicology laboratories, ethanol measurements are often done using a GC that can also distinguish and measure isopropanol and methanol, as well isopropanol metabolite acetone. Alcohols with lower volatility, including ethylene and propylene glycol, are usually not detected by this assay. Be both enzymatic and chromatographic assays have substantial specificity f ethanol, confirmatory testing with a second method is uncommon.

Breath alcohol analyzers may also be employed in assessing ethanol intoxication, as may point-of-care devices that measure salivary ethanol. measurements are less precise than laboratory assays[16, 30] and more su to interference by other alcohols and other organic solvents. Breath-alcol analyzers require good cooperation from the patient to obtain an appropr breath sample and are typically calibrated to give results approximating

blood alcohol concentrations. For the above reasons, confirmation of pos findings with a laboratory measurement may sometimes be desirable.

Blood alcohol concentrations used legally to define driving under the influ have no particular clinical significance, but may have risk management implications for patient discharge. Legal standards are written in terms of whole-blood alcohol concentrations, whereas clinical laboratories usually measure alcohol in serum or plasma. Serum and plasma alcohol concentr are essentially identical, but both will be higher than the alcohol concent measured in a whole-blood specimen obtained at the same time. This is a of the lower concentration of alcohol in the red blood cells. The ratio of s alcohol to whole-blood alcohol varies from individual to individual, with a median value of 1.15.[28] It is more likely than not that an individual with serum alcohol concentration of less than 115 mg/dL will have a whole-blo alcohol concentration of less than 100 mg/dL (<0.10%, w/v).

For More Information

For additional information about clinical toxicology laboratories, including not covered in this chapter, a recommended reference is *The Clinical Tox Laboratory: Contemporary Practice of Poisoning Evaluation* .[29]

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Chapter 8

Techniques Used to Prevent Gastrointestinal Absorption

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Gastrointestinal decontamination is the most controversial issue in medical toxicology. It plays a central role in the initial management of the orally poisoned patient, and frequently is the only treatment available other than routine supportive care. Unfortunately, as is true in most areas of medical toxicology, valid studies that demonstrate the effects of gastrointestinal decontamination on clinically meaningful end points are difficult to find. The heterogeneity of poisoned patients demands that very large randomized studies be performed because most patients who present to an emergency department (ED) generally have an unreliable history and a low-risk exposure. These factors, as well as other significant sources of bias, are often hidden in inclusion and exclusion criteria. These consequential determinants contribute to the difficulties in designing and completing studies that provide sound evidence for or against a particular therapeutic

option. Incontrovertible end points, such as a change in xenobiotic or complication specific mortality, also demand exceptionally large studies, because the overall mortality of poisoned patients is generally quite low. Whereas other end points, such as the length of stay in the hospital or intensive care unit, rate of secondary complications, and need for specific treatments such as expensive antidotes, must be considered, these surrogate markers are not adequately rigorous and are less than ideal. In the science of gastrointestinal decontamination, we are also faced with the dilemma that randomizing half of a group of potentially ill patients to no decontamination is a significant ethical concernâ€”we rarely omit decontamination unless a minimally toxic exposure has occurred or an effective, safe, readily available, and inexpensive antidote exists. Because acetaminophen poisoning fits this description, it has been used both as the xenobiotic of choice in volunteer overdose studies[26 , 47 , 138] and in a recent Australian evaluation of actually poisoned patients.[34] However, despite its widespread use as a model, the applicability of the management approach for acetaminophen poisoning to other ingestions is limited.

As might be suspected, no available study provides adequate guidance for the management of a patient who definitely has taken an unknown xenobiotic at an unknown time. Fortunately, in most cases there is some component of the history or clinical presentation, such as vital signs, physical examination, and routine diagnostic studies (such as ECG and anion gap), that offers insight into the nature of the ingested xenobiotic (Chap. 3).

For many, the ongoing controversy or debate on gastrointestinal decontamination culminated in 1997, with the publication of the position statements on activated charcoal, orogastric lavage, syrup-of-ipecac-induced emesis, and whole-bowel irrigation from the American Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT).[27 , 69 , 106 , 107 , 121 , 130 , 131 and 132] Contrary to

initial beliefs, these excellent reviews failed to end the debate; they simply highlighted many shortcomings and ambiguities within this field. A 2000 study concluded that despite having the evidence reviewed and consensus recommendations made, poison information specialists at North American poison control centers still offered a wide variety of recommendations for GI decontamination.[63] The study evaluated decontamination options for a theoretical patient with a difficult scenario of an overdose of enteric-coated aspirin. The recommendations made were often inconsistent with the published position statements, and in some cases, were frankly dangerous. Even toxicologists who made substantial contributions to the development of these consensus statements disagreed on certain aspects of the treatment, although to a lesser extent. These differences in recommendations suggest that there is inadequate evidence available to produce a proper evidence-based answer for many of the decisions in question. In most of the clinical studies that provide evidence to form the basis for these consensus statements, either there were very few patients with ingestions of enteric-coated aspirin or, if such patients existed, they were excluded from the study. Similarly, there are no studies for most drugs with modified release kinetics, or for new drugs. Thus the clinician must often make decisions based on a philosophic approach and an understanding of specific principles rather than evidence.

This chapter does not discuss details with regard to the evaluation of the amount and type of xenobiotic ingested, or other strategies for managing a patient with an unknown overdose; these issues are discussed in Chap. 4 . Rather, the focus is on determining which decontamination technique or combination of techniques is preferred once an indication for gastrointestinal

decontamination is established. The literature published since the previously mentioned position statements is emphasized, existing evidence is summarized, and those areas necessitating further

investigation are identified. Detailed discussions of emesis, catharsis, and activated charcoal can be found in the corresponding Antidotes in Depth sections, â€œSyrup of Ipecac ,â€• â€œWhole-Bowel Irrigation and Other Intestinal Evacuants ,â€• and â€œActivated Charcoal .â€• In addition, when the ingested xenobiotic is known, readers should refer to the decontamination sections found in Chaps. 34 ,35 ,36 ,37 ,38 ,39 ,40 ,41 ,42 ,43 ,44 ,45 ,46 ,47 ,48 ,49 ,50 ,51 ,52 ,53 ,54 ,55 ,56 ,57 ,58 ,59 ,60 ,61 ,62 ,63 ,64 ,65 ,66 ,67 ,68 ,69 ,70 ,71 ,72 ,73 ,74 ,75 ,76 ,77 ,78 ,79 ,80 ,81 ,82 ,83 ,84 ,85 ,86 ,87 ,88 ,89 ,90 ,91 ,92 ,93 ,94 ,95 ,96 ,97 ,98 ,99 ,100 ,101 ,102 ,103 ,104 ,105 ,106 ,107 ,108 ,109 ,110 ,111 ,112 ,113 ,114 ,115 ,116 ,117 ,118 ,119 ,120 ,121 ,122 ,123 ,124 ,125 ,126 ,127 and 128 , as they will offer insight into xenobiotic-specific issues that may alter decontamination strategies.

The xenobiotic has limited toxicity at any dose
Although the xenobiotic ingested is potentially toxic, the dose ingested is less than that expected to produce significant illness
The ingested xenobiotic is well adsorbed by activated charcoal, and the amount ingested is not expected to exceed the adsorptive capacity of activated charcoal
Significant spontaneous emesis has occurred
The patient presents many hours postingestion and has minimal signs or symptoms of poisoning
The ingested xenobiotic has a highly efficient antidote (such as acetaminophen)
There is reason to believe that, given the time of ingestion, a significant amount of the ingested xenobiotic is still present in the stomach
The ingested xenobiotic is known to produce serious toxicity *or* the patient has obvious signs or symptoms of life-threatening toxicity
The ingested xenobiotic is not adsorbed by activated charcoal
Although the ingested xenobiotic is adsorbed by activated charcoal, the amount ingested exceeds the activated charcoal-to-

xenobiotic ratio of 10:1 even with a double-standard dose of activated charcoal
The patient has not had spontaneous emesis
No highly effective specific antidote exists or alternative therapies (such as hemodialysis) pose a significant risk to the patient
[a] Patients who fulfill these criteria can be decontaminated safely with activated charcoal alone or may require no decontamination at all.
[b] Patients who fulfill these criteria should be considered candidates for gastric emptying *if* there are no contraindications. For individuals who meet some of these criteria but who are judged not to be candidates for gastric emptying, single or multiple-dose activated charcoal and/or whole-bowel irrigation should be considered.

Gastric Emptying Is Usually Not Indicated If[a]	Gastric Emptying May Be Indicated If[b]

TABLE 8-1. Risk Assessment: When to Consider Gastric Emptying

Gastric Emptying

The principle theory governing gastric emptying is very simple: If a portion of xenobiotic can be removed prior to absorption, its potentially toxic effect should either be prevented or minimized. From 1982 to 1995 several important clinical trials attempted to define the role of gastrointestinal decontamination in poisoned patients.[3,19,29,60,70,86,105,129] Although all of these studies were flawed because of the inclusion of a large number of low-risk patients, numerous restrictive exclusion criteria, and a variety of other biases, they clearly demonstrated that many patients can be successfully managed without aggressive gastric emptying. The clinical parameters listed in Table 8-1 help to

identify those individuals for whom gastric emptying is usually not indicated based on a risk-to-benefit analysis. In contrast, for a small subset of patients (Table 8-1) gastric emptying may be indicated. A thorough understanding of this risk analysis is essential when deciding whether or not gastric emptying is appropriate for a patient who ingests a xenobiotic.

Time is an important consideration, in that for gastric emptying to be beneficial, a consequential amount of xenobiotic must still be present in the stomach. Demographic studies have found that very few poisoned patients arrive at the ED within 1â€“2 hours after an ingestion. In most studies, the average time from ingestion to presentation was approximately 3â€“4 hours with significant variations.[64 , 70 , 105 , 123] This delay diminishes the likelihood of recovering a large percentage of the xenobiotic from the stomach, unless the patient has ingested a xenobiotic that slows gastric-emptying rates.

As is discussed in the â€œOrogastric Lavage â€• section below, many authors advise against interventions beyond 1-hour after ingestion. Recent data highlight the arbitrary nature of this limitation. One human volunteer study evaluated the pharmacokinetic effects of diphenhydramine and oxycodone in a simulated acetaminophen overdose.[51] This model is relevant because of the rapid absorption of acetaminophen and the presence of many such combination products in the marketplace. Whereas diphenhydramine did not delay gastric emptying significantly, oxycodone delayed the time to peak acetaminophen concentration by approximately 1 hour. Although gastrointestinal decontamination was not part of the study protocol, it can be implied that acetaminophen was available for gastrointestinal decontamination for a longer time than the 1-hour guideline suggests.

In fact, markedly prolonged gastric-emptying half-lives and gastric hypomotility were demonstrated using gastric scintigraphy in a

prospective study on 85 actually poisoned patients.[1] Remarkably, these findings occurred with ingestions such as acetaminophen, which are not typically expected to prolong gastric emptying. Patients who underwent orogastric lavage did not have significantly different gastric-emptying half-lives, which suggests that this procedure was not the cause of the gastroparesis. There was also no evidence that activated charcoal affected gastric-emptying rates. The authors speculate that stress in the overdosed patient might be part of the etiology of the hypomotility observed, and that the management of patients should not be based on the assumption that gastrointestinal motility is normal.

Assessment of whether or not gastric emptying is appropriate for a patient continues with an evaluation for potential contraindications (Table 8-2). Regardless of the severity of the ingestion and other contributing factors, such as time, there must be no contraindication to gastric-emptying procedures. Because the demonstrable benefit of emptying is marginal at best, even relative contraindications usually dictate that the procedure should not be attempted.

Once the decision to perform gastric emptying is made, the clinician must choose between the two available methods. Either emesis can be induced with the administration of syrup of ipecac or orogastric lavage can be performed by cautious aspiration of gastric contents using a large-bore tube and small amounts of water. While the numerical benefit of either method of gastric emptying has, in

several studies, rarely averaged more than a 50% reduction in the absorption of a xenobiotic when performed under optimal research conditions,[69 , 132] this clinical benefit can be sizable if the ingested dose places the patient on the steep portion of the doseâ€“response curve (Chap. 9). Under those circumstances a small reduction in dose might translate into a significant reduction in toxicity.

The patient meets criteria for gastric emptying (Table 8-1).
The benefits of gastric emptying outweigh the risks.
The patient does not meet criteria for gastric emptying (Table 8-1).
The patient has lost or will likely lose his/her airway protective reflexes and has not been intubated. (Once intubated, orogastric lavage can be performed if otherwise indicated.)
Ingestion of an alkaline caustic.
Ingestion of a foreign body (such as a drug packet).
Ingestion of a xenobiotic with a high aspiration potential (such as a hydrocarbon) in the absence of endotracheal intubation.
The patient is at risk of hemorrhage or gastrointestinal perforation because of underlying pathology, recent surgery, or other medical condition that could be further compromised by the use of orogastric lavage.
Ingestion of a xenobiotic in a form known to be too large to fit into the lumen of the lavage tube (such as many modified-release preparations).

Indications Contraindications

TABLE 8-2. Indications and Contraindications to Orogastric Lavage

Orogastric Lavage

Many authors have adopted the consensus approach that orogastric lavage should not be considered unless a patient has ingested a potentially life-threatening amount of a xenobiotic and the procedure can be undertaken within 60 minutes of ingestion.[70, 132] Since the publication of the clinical studies cited above[3, 19, 29, 60, 70, 86, 105, 129] studies of orogastric lavage have been scarce. One crossover study used 4 g of an acetaminophen

solution as a marker and randomized the subjects to either control or orogastric lavage performed at 30 minutes postingestion. Although the study found a mean 20% reduction in the AUC (area under the [plasma drug concentration versus time] curve) of acetaminophen with orogastric lavage compared to control, the confidence interval of Â±28% suggests a rather modest and very unreliable effect.[49]

Two other prospective, randomized, crossover studies in volunteers measured the effect of activated charcoal versus orogastric lavage, with interventions at either 5 or 30 minutes postingestion.[73 , 74] Both studies used therapeutic doses of moclobemide, temazepam, and verapamil. Interestingly, when orogastric lavage was performed 5 minutes after ingestion there was no significant pharmacokinetic effect for any of the drugs ingested. However, the AUC of moclobemide was reduced by 44%, compared to control, when orogastric lavage was performed 30 minutes after ingestion; there were no effects on the pharmacokinetic profiles of the other two drugs. These results most likely illustrate the very varied and unreliable effect of orogastric lavage, even when performed by the same experienced professionals under controlled experimental conditions. Another study evaluated the effect of activated charcoal compared to activated charcoal followed by orogastric lavage at 30 minutes postingestion.[73] Therapeutic doses of temazepam, ibuprofen, and citalopram were studied. In this model, the combination of activated charcoal and orogastric lavage was not superior to activated charcoal alone.

It is important to highlight the differences between volunteer studies using therapeutic doses of drugs and actual patients with clinically significant overdose. The most important aspect of this comparison is a bias toward a benefit of activated charcoal. The drugs used in these volunteer studies are all well-adsorbed by activated charcoal and the doses of activated charcoal are significantly in excess of the binding capacity for the drug. An

additional bias is introduced against gastric emptying because the small amounts of drugs used are unlikely to alter gastric motility and thus they may pass through the pylorus before gastric emptying can occur.

A synthesis of available data can be used to develop indications for orogastric lavage (Table 8-2). When deciding whether or not to actually perform orogastric lavage on a poisoned patient, these indications, contraindications, and potential adverse effects must be considered. Table 8-3 summarizes the technique of orogastric lavage.

Reported adverse effects of orogastric lavage include injury to the airway, esophagus,[21] and stomach,[36] as well as severe hypernatremia.[87] The case of hypernatremia resulted from a lavage that was performed using 12 L of hypertonic saline.[87] These cases, as

well as other well-known complications such as aspiration pneumonitis,[131 , 132] demonstrate that orogastric lavage is not risk free and should only be considered based on the rigorous indications for gastric emptying listed in Table 8-1 .

Select the correct tube size
Adults/adolescents: 36â€“40 French
Children: 22â€“28 French
Procedure

1. If there is potential airway compromise, endotracheal or nasotracheal intubation should precede orogastric lavage.
2. The patient should be kept in the left-lateral decubitus position. Because the pylorus points upward in this orientation, this positioning theoretically helps prevent the xenobiotic from passing through the pylorus during the procedure.
3. Prior to insertion, the proper length of tubing to be passed should be measured and marked on the tube. The length

should allow the most proximal tube opening to be passed beyond the lower esophageal sphincter.

4. After the tube is inserted, it is essential to confirm that the distal end of the tube is in the stomach.
5. Withdraw any material present in the stomach and consider the immediate instillation of activated charcoal for large ingestions of xenobiotics known to be adsorbed by activated charcoal.
6. Via a funnel (or lavage syringe) instill in an adult 250 mL aliquots of a room-temperature saline lavage solution. In children, aliquots should be 10â€“15 mL/kg to a maximum of 250 mL.
7. Orogastric lavage should continue for at least several liters in an adult and for at least 0.5â€“1 L in a child *or* until no particulate matter returns and the effluent lavage solution is clear.
8. Following orogastric lavage, the same tube should be used to instill activated charcoal if indicated.

TABLE 8-3. The Technique of Performing Orogastric Lavage

Syrup of Ipecac

A comprehensive summary of the pharmacology and the evidence for induced emesis is available in the Antidotes in Depth: Syrup of Ipecac . Since 1997 very little original work has been published other than reviews, and the position statement recommendations.[69] Additionally, a revision of the position paper found no new evidence to support any modification in recommendations.[106]

Although many animal and human studies show a reduction in drug concentrations with induced emesis, no clinical benefit for this

technique has been proved. Furthermore, as the benefits of activated charcoal are recognized and the time to its administration evaluated, it has become evident that the administration of syrup of ipecac delays the administration of activated charcoal, as well as any other oral treatment (symptomatic or specific antidotes).

Syrup of ipecac is absolutely contraindicated when the patient has ingested a caustic or a xenobiotic with a high aspiration potential, such as a hydrocarbon. Because vomiting in the setting of altered consciousness increases the likelihood for pulmonary aspiration, syrup of ipecac can only be used when the patient has a normal mental status *and* can be predicted to have a normal mental status at 30â€“60 minutes following administration, when emesis will occur. In the clinical setting, patients are rarely identified with consequential ingestions who present early enough to require gastric emptying, and who are expected to retain their airway protective reflexes for a minimum of 30â€“60 minutes. Therefore, most consensus statements correctly conclude that, given the lack of evidence demonstrating a clinically meaningful benefit of induced emesis *and* the significant contraindications, the routine administration of syrup of ipecac in the ED should be abandoned.[68, 106] Although other emetics, and methods to induce emesis exist, data are insufficient to support their routine use.

Gastric decontamination of children in the home has always been an attractive concept because both the xenobiotic and time of ingestion are known and there is a high likelihood that the xenobiotic is still in the stomach. A recent prospective observational study evaluated 75 cases of probably poisoned children (out of 14,603 human exposures) where home administration of syrup of ipecac had been recommended by a poison information specialist.[46] Cases where syrup of ipecac was indicated but not available in the home were included in this group if the parents stated that syrup of ipecac could be obtained within 15 minutes. The administration of syrup of ipecac occurred in less

than 30 minutes in only 20% of cases, and the overall mean time to emesis was 58 minutes. Initial emesis occurred in less than 60 minutes in only 36% of cases. Numerous studies illustrate that the time to performing gastrointestinal decontamination is critical. Clearly, the problem with syrup of ipecac is the time delay from administration to onset of emesis. Additionally, the uncertainty of the effect of the administered dose serves as a further delaying factor. A study in 12 adult volunteers showed that with a 20 mL dose, 2 of 6 volunteers had not vomited within 4 hours, whereas all volunteers (6 of 6) had vomited within 60 minutes after receiving a 30 mL dose.[136] A four-limb randomized study using 10 healthy volunteers, studied the effect of 30 mL of syrup of ipecac administered at 5, 30, and 60 minutes after the ingestion of 3.9 g of acetaminophen. The fourth limb served as control. Only the 5-minute intervention was significantly different from control and showed a decrease in bioavailability of approximately 67%.[113] This study also noted that sedation was a significant adverse effect of syrup of ipecac, which makes this therapy difficult to recommend in patients who have ingested any potentially sedating xenobiotic.

The patient meets criteria for gastric emptying (Table 8-1).
The patient does not meet criteria for gastric emptying (Table 8-1).
Orogastric lavage cannot be performed or is contraindicated because of the size of the xenobiotic formulation.
Either activated charcoal or another oral agent is expected to be necessary in the next few hours.
The history and/or physical examination suggest that there is likely to be a clinically significant amount of xenobiotic remaining in the stomach.
Airway protective reflexes might be lost within the next 30â€“60 minutes.
Ingestion of a caustic.
The benefits of gastric emptying outweigh the risks from the contraindications.

Ingestion of a foreign body such as a drug packet or sharp item.

Ingestion of a xenobiotic with a high aspirationpotential such as a hydrocarbon.
The patient is younger than 6 months of age, elderly, or debilitated.
The patient has a premorbid condition that wouldbe compromised by vomiting.

Indications Contraindications

TABLE 8-4. Indications and Contraindications for Syrup of Ipecac

A study using the 2003 Toxic Exposure Surveillance System (TESS) database (Chap. 130) evaluated the effect of home use of syrup of ipecac on the rate of referral to EDs across the United States. The study found that there was no reduction in ED use nor any improvement in patient outcome from home administration of syrup of ipecac.[18] Based on these findings and other data, the American Academy of Pediatrics published its policy statement on poison treatment in the home, concluding that syrup of ipecac should no longer be used as a standard home treatment in cases of poisoning.[6] Despite this, some authors still believe that there is a limited role for ipecac-induced emesis.[82] Table 8-4 summarizes the indications and contraindications for administration of syrup

of ipecac. The only reasonable conclusion is that induction of emesis has an extremely limited role in the contemporary management of poisoned patients.

Prevention of Xenobiotic Absorption

Activated Charcoal

Activated charcoal has long been recognized as an effective method for reducing the systemic absorption of many xenobiotics. For certain xenobiotics it also enhances elimination through interruption of either the enterohepatic or enteroenteric cycle.[17, 30, 65] Its superb adsorptive properties theoretically make it the single most useful agent in the management of a broad variety of patients with acute oral overdoses.[7, 8 and 9, 18, 26, 31, 59, 102, 103] But overall, as is true for the other methods of gastrointestinal decontamination, there is a lack of sound evidence of its benefits as defined by clinically meaningful end points. This opinion is reflected both in the consensus statements and in the overall trend toward no decontamination as shown in TESS data (Chap. 130).[27, 85, 86] The consensus opinion concluded that a single dose of activated charcoal should not be administered routinely in the management of poisoned patients and, based on volunteer studies, the effectiveness of activated charcoal decreased with time, providing the greatest benefit within 1 hour of ingestion. There was no evidence that the administration of a single dose of activated charcoal improved clinical outcome. Additionally, it is generally accepted that unless either airway protective reflexes are intact (and expected to remain so) or the patient's airway has been protected, the administration of activated charcoal is contraindicated.[27]

There are very few studies that used valid clinical end points in an attempt to demonstrate a benefit of gastrointestinal decontamination. One recent 2-year study concluded that activated charcoal was associated with a higher incidence of vomiting, a more prolonged emergency department stay, and a failure to improve clinical outcome when compared to supportive care.[85] However, in spite of randomizing 1479 patients to either activated charcoal on even days of no decontamination on odd days, only 399 patients were placed in the activated charcoal group and 1080 patients were placed in the control group. These very unevenly distributed numbers suggest a selection bias that is

inadequately described in the study. The authors concluded that there appeared to be no benefit to decontamination procedures, although they admitted that length of stay (one of their end points) for the most part was dependent on the wait for psychiatric evaluation and the availability of a mental health bed for patient transfer. The inclusion of a significant number of low-risk patients in this study introduced a clear bias against determining any benefit of decontamination. Furthermore, the validity of the study is questionable because patients with significant acetaminophen overdoses were excluded, given that there are sound data to support improved clinical outcomes in acetaminophen-poisoned patients treated with activated charcoal.[20]

Theoretically, the early administration of activated charcoal to patients presenting with a significant oral overdose of a potentially toxic xenobiotic would lower systemic exposure to that xenobiotic, and thus be of benefit to the patient. Surprisingly, this intuitive result has been difficult to demonstrate using clinically relevant end points selected in groups of poisoned patients.

Dosing

The optimal dose of oral activated charcoal has never been fully established. Since the beginning of its clinical use as a gastrointestinal decontaminant, various factors have been recommended for determining the optimal dose of activated charcoal. Two factors commonly discussed are the patient's weight, and the quantity of the xenobiotic ingested. The problem in using the quantity of the xenobiotic as a basis for activated charcoal dosing is that the amount is usually unknown, and there is an implication that nothing else in the gastrointestinal tract will occupy binding sites on activated charcoal. Additionally, the xenobiotic is often unknown and xenobiotics vary enormously in their toxicities, rate of absorption, and the clinical effects they produce (eg, respiratory depression, convulsions, effect on gastric

emptying rate). Some xenobiotics are very well adsorbed to activated charcoal, whereas others are not.[30] Because of variables such as the physical properties of the formulation ingested (liquid, solid, or sustained-release pill), the volume and pH of gastric and intestinal fluids, and the presence of other xenobiotics adsorbed by activated charcoal,[9 , 13 , 53 , 54 , 91 , 93 , 94] the optimal dose cannot be known with certainty in any given patient.

Information concerning the maximum adsorptive capacity of activated charcoal for the particular xenobiotic ingested permits a theoretical calculation of an adequate dose,[4 , 7 , 12 , 14 , 23 , 31 , 90 , 91 , 94 , 95 , 109 , 110 , 112 , 117 , 125 , 128] assuming that the amount of xenobiotic ingested is known. However, clinicians must remain cognizant of the risk of approaching or exceeding the adsorptive capacity of the standard dose of approximately 1 g/kg of activated charcoal. This possibility has been investigated in only a few studies.[4 , 14 , 23 , 112]

Thus, the idea that a fixed activated charcoal-to-xenobiotic ratio is appropriate for all xenobiotics is clearly imperfect. It is possible however, to develop a logical approach to dosing based on available data. The optimal activated charcoal dose is theoretically the minimum dose that completely adsorbs the ingested xenobiotic and, if relevant, that maximizes enhanced elimination. The results of in vitro studies show that the ideal activated charcoal-to-xenobiotic ratio varies widely, but a common recommendation is to deliver an activated charcoal-to-xenobiotic ratio of 10:1 or 50â€“100 g of activated charcoal to adult patients, whichever is greater. This amount from a theoretical perspective will adsorb 5â€“10 g of a xenobiotic, which should be adequate for most typical poisonings.[7 , 8 , 27 , 30 , 75 , 95] Based on available data from in vivo and in vitro studies, the actual recommended dosing regimen for activated charcoal is 25â€“100 g in adults (1 g/kg of body weight) and 0.5â€“2 g/kg of body weight in children.[27 , 30] These recommendations are generally based more on activated charcoal tolerance then on efficacy. When calculation of a 10:1

ratio exceeds these recommendations, either gastric emptying or multiple-dose activated charcoal (MDAC) therapy should be considered.

For example, consider a patient intentionally overdosing by ingesting thirty 0.25-mg digoxin pills (total dose of 7.5 mg). Achieving a 10:1 ratio is quite easy, and a standard dose of 1 g/kg might exceed a 10,000:1 ratio. In comparison, consider a patient who intentionally ingests thirty 325-mg aspirin pills (total dose of 9.75 g). In this case, obtaining a 10:1 activated charcoal-to-xenobiotic ratio is quite difficult, and is even less likely if a patient ingests 60 or 100 of the aspirin pills. Poisoning with a combination of xenobiotics may also approach or exceed the maximum adsorption capacity for the standard dose of activated charcoal.

Time Factor

Many authors state that administration of a single dose of activated charcoal should be considered if a patient has

ingested a potentially toxic amount of a xenobiotic (that is known to be adsorbed to activated charcoal) within the previous hour. This position was chosen as there are insufficient data to support or exclude the use of single-dose activated charcoal therapy more than 1 hour beyond the ingestion.[27] The efficacy of activated charcoal administered more than 1 hour after xenobiotic ingestion is continuously debated, and has been evaluated in several studies.

In volunteers, the effect of activated charcoal administered 2 and 4 hours after ingestion of acetaminophen demonstrated no significant difference in plasma acetaminophen concentration when compared to control. In contrast, when administered 1 hour after a simulated acetaminophen ingestion, activated charcoal reduced plasma acetaminophen concentrations significantly.[138] Likewise, when the effectiveness of activated charcoal administered 1, 2,

and 3 hours after xenobiotic ingestion was determined, only the 1-hour group had a different pharmacokinetic profile from the control group.[47] Although these data do not support the administration of activated charcoal as a gastrointestinal decontamination strategy more than 1 hour after an overdose, the applicability of these results to actual overdoses is questionable. The method in this volunteer study was an 8-hour fast, followed by a small meal 1 hour before the administration of 3â€“4 g acetaminophen.[47 , 138] Considering the rapid absorption of acetaminophen, and the small 3â€“4-g doses employed, it is highly probable that little or no acetaminophen would be left in the gastrointestinal tract to be adsorbed by activated charcoal, limiting the potential time to benefit from activated charcoal to approximately 1 hour.

In contrast, activated charcoal given 3 hours after a xenobiotic overdose was investigated in vivo, again using acetaminophen and a larger-than-standard dose (75 g) of activated charcoal. The results demonstrated some benefit in administering activated charcoal 3 hours after an overdose as there were significantly lower acetaminophen plasma concentrations in the activated charcoal group than in the control group.[115] In a similar study, activated charcoal was effective in reducing the systemic absorption of a xenobiotic (acetaminophen) when administered 1 and 2 hours after ingestion, although the effect of the 2-hour intervention was substantially less than at 1 hour, reemphasizing the importance of early intervention.[26]

It should be clear that the use of a 1-hour time frame is meant more as a guideline than an absolute cutoff. It is only logical that if an intervention is effective at 59 minutes, it will also be beneficial at 61 minutes. Although it is logical that efficacy decreases as time from ingestion increases, in certain cases some benefit may be derived many hours postingestion. As discussed above, there are good data from patients with actual ingestions to demonstrate that a significant amount of xenobiotic can be found

in the stomach beyond this arbitrary 1-hour time frame.[1]

The recommendation that activated charcoal should be administered within 1 hour of ingestion limits the potential to treat most poisoned patients. A study identifying 63 patients who had taken potentially serious overdoses over a 6-month period demonstrated a median time of arrival to healthcare of 136 minutes after the overdose. Only 15 patients presented within 1 hour and only 4 of 10 patients who qualified, received activated charcoal within 1 hour. The results demonstrate the implications for adherence to the recommended guidelines, unless activated charcoal can be safely administered to appropriate patients prior to hospitalization.[64]

Prehospital use of activated charcoal has not gained wide acceptance because of the concern that it would not be administered properly by the untrained lay public and that many children would refuse to drink the charcoal slurry. An 18-month consecutive case series demonstrated that activated charcoal can be administered successfully in the home by the lay public. Home use of activated charcoal significantly reduced the time to activated charcoal administration after xenobiotic ingestion from a mean of 73 Â± 18.1 minutes for ED treatment to a mean of 38 Â± 18.3 minutes for home treatment.[119] However, many still consider this evidence insufficient to recommend that activated charcoal be stored in the home. A prospective followup study from Finland looked at the adherence to a new protocol of administering activated charcoal in the prehospital setting. The protocol was implemented by either the first-response unit or paramedics. Activated charcoal was indicated in 722 of 2047 patients. Of these patients, 555 actually received activated charcoal at a mean of 88 minutes after ingestion. There were no adverse effects noted, although 72 patients refused to drink the charcoal. This study shows that it is feasible to administer activated charcoal in the prehospital setting, but its clinical implications are unknown.[2]

In reality, many factors, such as food, sustained-release formulations, and co-ingestion with anticholinergic or opioid properties, can slow the rate of absorption of a xenobiotic, which slows gastric emptying. These factors increase the time frame for possible adsorption to activated charcoal. An increased effect of activated charcoal was shown in a randomized crossover study where volunteers were administered acetaminophen in either the presence or absence of the anticholinergic drug atropine, and subsequently given a single dose of activated charcoal 1 hour after administration of the acetaminophen. Activated charcoal was more effective in reducing acetaminophen bioavailability in the presence of an anticholinergic agent.[48]

Methods to Increase the Palatability of Activated Charcoal

The problems surrounding the use of an activated charcoal slurry are clear to anyone who has tried to administer it to a patient. Activated charcoal has a pronounced gritty texture and it immediately sticks in the throat because it adheres to the mucosal surfaces and begins to cake.[30] In addition, the black appearance of activated charcoal makes it less attractive.

There have been numerous attempts at making activated charcoal more appealing by providing flavors, including jam,[38] chocolate syrup,[83, 89] cherry extract/syrup,[99, 137] juice,[99] sorbitol,[32, 35, 84] saccharin,[33] strawberry flavor,[98] orange or peppermint oil,[30] melted milk chocolate,[40, 41] chocolate milk,[99] soda,[99, 108] and ice cream.[24, 76, 122] Because activated charcoal adsorbs the flavoring agents, the palatable taste often disappears within minutes after mixing.[30, 32, 33, 38] But in cases where the activated charcoal does not completely adsorb the flavoring agents, they provided a pleasant taste without significantly reducing the adsorptive properties of the activated charcoal.[30, 32, 33]

Convincing children to drink the activated charcoal slurry is even more problematic than in adults.[10, 41, 50, 71, 76, 92] Providing a tasty vehicle for children could make the activated charcoal more acceptable than the recommended water slurry. Many additives have been tried to increase children's acceptance of activated charcoal.[32, 33, 108] Several investigations suggest mixtures of activated charcoal with, for example, ice cream,[24, 54, 71, 76, 92, 122] milk,[35, 71] yogurt,[71] milk chocolate,[41] or other palatability-increasing agents.[24, 30] The general recommendation, however, remains that activated charcoal should only be mixed with water.[62]

Contraindications/Complications

Vomiting frequently complicates the administration of activated charcoal. A prospective cohort study estimating the incidence of vomiting subsequent to the

therapeutic administration of activated charcoal to poisoned children younger than 18 years of age showed that 1 of 5 children and adolescents vomited. Children with previous vomiting or nasogastric tube administration were at highest risk.[100] This incidence of vomiting appears to be greater when activated charcoal is administered with sorbitol.[130] Also, although rare, inadvertent direct instillation of activated charcoal into the lungs has resulted from a misplaced nasogastric tube, leading to severe pulmonary complications and death. Administration of activated charcoal to already intubated patients is associated with a low incidence of aspiration pneumonia.[88] Another study found that pulmonary complications associated with activated charcoal aspiration might be primarily related to the aspiration of acidic gastric content and not directly related to aspiration of activated charcoal.[111] A retrospective study found that only 1.6% of unselected overdose patients aspirated, and that administration of activated charcoal was not found to be an associated risk factor.[61] Pulmonary aspiration in overdose patients who have received

activated charcoal is more easily documented, because the activated charcoal is a very identifiable marker.

The patient does not meet criteria for gastric emptying (Table 8-1) or gastric emptying is likely to be harmful.
Activated charcoal is known not to adsorb a clinically meaningful amount of the ingested xenobiotic.
Ingestion of a toxic amount of a xenobiotic that is known to be adsorbed by activated charcoal.
Airway protective reflexes are absent or expected to be lost and the patient is not intubated.
Gastrointestinal perforation is likely as in cases of caustic ingestions.
The ingestion has occurred within a time frame amenable to adsorption by activated charcoal or clinical factors are present that suggest that not all of the xenobiotic has already been systemically absorbed.
Therapy may increase the risk and severity of aspiration, such as in the presence of hydrocarbons with a high aspiration potential.
Endoscopy will be an essential diagnostic modality(acid or alkaline caustics).

Indications Contraindications

TABLE 8-5. Indications and Contraindications for Single-Dose Activated Charcoal Therapy Without Gastric Emptying

Although relatively few reports of clinically significant emesis and pulmonary aspiration resulting from the administration of activated charcoal exist, the severity of these complications is clear.
Consequently, it is important to evaluate, particularly in those patients determined to be at limited risk from their exposures, whether single-dose activated charcoal therapy is likely to be beneficial based on the indications and contraindications in Table

8-5 .

Multiple-Dose Activated Charcoal

Multiple-dose activated charcoal (MDAC) is typically defined as more than 2 sequential doses of activated charcoal.[130] In many cases, the actual number of doses administered is substantially greater. This technique serves two purposes: (a) to prevent ongoing absorption of a xenobiotic that persists in the gastrointestinal tract (usually in the form of a modified-release preparation), and (b) to enhance elimination by either disrupting enterohepatic recirculation or by â€œgut-dialysisâ€• (enteroenteric recirculation). The 1999 position statement of the AACT and the EAPCCT concluded that:

> Based on clinical studies, multiple-dose activated charcoal should be considered only if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. With all of these drugs there are data to confirm enhanced elimination, though no controlled studies have demonstrated clinical benefit. Although volunteer studies have demonstrated that multiple-dose activated charcoal increases the elimination of amitriptyline, dextropropoxyphene, digitoxin, digoxin, disopyramide, nadolol, phenylbutazone, phenytoin, piroxicam, and sotalol, there are insufficient clinical data to support or exclude the use of this therapy.[130]

Although technically correct, the preceding statements suffer from a lack of evidence. Because the clinical studies used to formulate this opinion all lack sufficient numbers of significantly poisoned

patients, they induce a bias against any benefit of MDAC. Additionally, none of the studies included a detailed analysis of sustained- or extended-release formulations, which are very popular.

A more recent single-blind, randomized, placebo-controlled trial was designed to assess the efficacy of MDAC in the treatment of patients with yellow oleander poisoning. This clinical study demonstrated that MDAC (defined as 50 g of activated charcoal every 6 hours for 3 days) effectively reduced life-threatening cardiac dysrhythmias, deaths, and the need for ICU admission.[37] In this dataset, to save 1 life only 18 patients needed to receive MDAC. This study demonstrates that consequential benefits of gastrointestinal decontamination may become evident when investigations are performed in significantly poisoned patients. It further highlights that general recommendations only apply to patients in general and that severely ill patients deserve individualized care.

Like single-dose activated charcoal, MDAC can produce emesis, with subsequent pulmonary aspiration of gastric contents containing activated charcoal. It is intuitive that these risks are greater with multiple-than with single-dose therapy. One retrospective study attempted to determine the frequency of complications associated with the use of MDAC.[39] The authors identified nearly 900 patients who had received MDAC and found that only

0.6% of patients had clinically significant pulmonary aspiration. Although no patients developed gastrointestinal obstruction, 9% had hypernatremia or hypermagnesemia without any clinical consequences noted. The authors did not specify whether the multiple-dose regimens administered included the use of cathartics, but the profile of the adverse reactions listed above suggests that this is probably the case. In spite of the obvious limitations, this study demonstrates a reasonably low rate of

complications associated with MDAC.

Ingestion of a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline
Any contraindication to single-dose activated charcoal
Ingestion of a life-threatening amount of another xenobiotic that undergoes enterohepatic or enteroenteric recirculation that is adsorbed to
The presence of an ileus or other causes of diminished peristalsis activated charcoal
Ingestion of a significant amount of any slowly released xenobiotic, or of a xenobiotic known to form concretions or bezoars

Indications Contraindications

TABLE 8-6. Indications and Contraindications for Multiple-Dose Activated Charcoal Therapy

Table 8-6 summarizes the indications and contraindications for MDAC therapy. Because the optimal doses and intervals for repeated doses of activated charcoal have not been established, recommendations are based more on amounts that can be tolerated, than on amounts that might be considered pharmacologically appropriate. Table 8-7 lists typical dosing regimens. Larger doses and shorter intervals should be used for patients with more severe toxicity. It is reasonable to base end points either on the patient's clinical condition or on xenobiotic concentrations when they are easily measured.

Further clinical studies concerning MDAC are needed in order to establish an optimal dosing regimen and to confirm an effect on relevant end points. The reader is referred to Antidotes in Depth: Activated Charcoal for a more detailed discussion of single- and

multiple-dose activated charcoal therapy.

Initial dose orally or via orogastric or nasogastric tube

Adults and children: 1 g/kg of body weight or a 10:1 ratio of activated charcoal-to-xenobiotic, whichever is greater. Following massive ingestions, 2 g/kg of body weight might be indicated, if such a large dose can be easily administered and tolerated.

Repeat doses orally or via orogastric or nasogastric tube

Adults and children: 0.25â€“0.5 g/kg of body weight every 1â€“6 hours, in accordance with the dose and dosage form of xenobiotic ingested (larger doses or shorter dosing intervals may occasionally be indicated).

Procedure

1. Add 8 parts of water to the selected amount of powdered form. All formulations, including prepacked slurries, should be shaken well for at least 1 minute to form a transiently stable suspension prior to drinking or instillation via orogastric or nasogastric tube.
2. Activated charcoal can be administered with a cathartic, *for the first dose only* , when indicated, but cathartics should never be administered routinely and never be repeated with subsequent doses of activated charcoal.
3. If the patient vomits the dose of activated charcoal, it should be repeated. Smaller, more frequent doses or continuous nasogastric administration may be better tolerated. An antiemetic may be needed.
4. If a nasogastric or orogastric tube is used for MDAC administration, time should be allowed for the last dose to pass through the stomach before removing the tube. Suctioning the tube itself prior to removal may prevent subsequent charcoal aspiration.

TABLE 8-7. Technique of Administering Multiple-Dose Activated Charcoal Therapy

Whole-Bowel Irrigation

Whole-bowel irrigation (WBI) represents a method of flushing the gastrointestinal tract in an attempt to prevent further absorption of xenobiotics. This is achieved through the oral or nasogastric administration of large amounts of an osmotically balanced polyethylene glycol electrolyte lavage solution (PEG-ELS). This decontamination technique was subjected to a thorough literature review, which was published as a position statement in 1997 and revised in 2004.[107, 121] The position statement was unable to establish a clear set of evidence-based indications for the use of WBI because no clinical outcome studies have been performed. When experimental, theoretical, and anecdotal human experience is considered, the use of WBI with PEG-ELS can be supported for patients with potentially toxic ingestions of sustained-release pharmaceuticals. Other theoretical indications include the ingestion of large amounts of a xenobiotic where morbidity is expected to be high, the ingested xenobiotic is not adsorbed by activated charcoal, and when

other methods of gastrointestinal decontamination are unlikely to be either safe or beneficial. The removal of packets of illicit drugs (eg, from body-packers) can be considered a unique indication for WBI.

The contraindications for WBI are more clearly defined. This technique cannot be applied safely if the gastrointestinal tract is not intact, there are signs of ileus or obstruction, or there is significant gastrointestinal hemorrhage, or in patients with inadequate airway protection, uncontrolled vomiting, or consequential hemodynamic instability that compromises

gastrointestinal function or integrity. Additionally, the combination of WBI and activated charcoal results in an in vitro decrease in the adsorption of xenobiotics by activated charcoal, especially when the WBI solution is premixed with activated charcoal. Activated charcoal seems to be most efficacious if administered before initiating WBI.[11,56,68,81] Since the publication of the position statement, only three studies of varying degrees of evidence and some case reports have been published, as discussed below.

The effect of WBI on the pharmacokinetics of a modified-release formulation of acetaminophen and the progression of radiopaque markers through the gastrointestinal tract was studied using a prospective randomized crossover design.[80] Ten volunteers ingested the acetaminophen in supratherapeutic doses of 75 mg/kg together with a capsule containing 24 small markers. One study day with no intervention served as control. On the intervention day, the volunteers were subjected to WBI beginning 30 minutes after ingestion and continued until rectal effluent was determined clear. The average duration of WBI was 6 hours. No tablets or markers were recovered in the effluent. Only 2 of 10 patients had adverse effects such as nausea and abdominal cramping, and 1 volunteer vomited. The authors found a nonsignificant 11.5% reduction in the AUC of acetaminophen. The study had an 80% power to detect a 25% difference in AUC, which was arbitrarily set because there is no clinically established minimal relevant difference for a reduction in the AUC of a xenobiotic. The significance of this reduction would also vary in relation to the toxic properties of a xenobiotic (small vs. large therapeutic index, availability of an effective antidote, etc). In theory, for some xenobiotics, an 11% reduction in absorption might mean the difference between serious and life-threatening toxicity. The authors also found that in 8 of 10 subjects the radiopaque markers were all located in the cecum after WBI, whereas the markers were scattered throughout the small intestine in the control group. This observation indicates that WBI

has the capability to move objects in the gastrointestinal tract, at least to some degree. Whereas the authors stated that they would discontinue WBI when the rectal effluent was clear, this did not occur, and they chose an end point where the final effluent was straw-colored to yellowish-brown, which might have been too short a time. Nevertheless, during the 6-hour mean duration of therapy they managed to move the markers out of the small intestine more rapidly with WBI. Of note, the entire model has limited applicability, as WBI would never be considered for an acetaminophen overdose.

A randomized 3-phase crossover study using 9 volunteers, studied the use of activated charcoal alone compared to activated charcoal followed by WBI, in preventing the absorption of 3 different sustained-release drugs (carbamazepine, theophylline, and verapamil), all of which were administered in therapeutic doses. This study also found that WBI seemed to decrease the efficacy of activated charcoal, but that the pharmacokinetic profile was still better than no intervention, although these results were probably largely an effect of activated charcoal.[72] As mentioned above, study designs using activated charcoal and small doses of xenobiotics tend to bias the study toward a benefit of activated charcoal. In an overdose scenario, when activated charcoal may become saturated, it is intuitive that the benefits of other modalities would be more evident.

The third study evaluating the combined use of activated charcoal and WBI found that there were significant decreases in the adsorption of fluoxetine to activated charcoal and an increase in the desorption of the xenobiotic from activated charcoal.[12] These data support the findings of the studies previously cited in the position statement, but may have limited applicability as WBI would rarely, if ever, be indicated for fluoxetine overdose.

A small retrospective descriptive case series of 16 body-packers treated with WBI support the safety of this method. Although the

complication rate was reported as 12.5% (2 of 16), these complications were not serious. One case of mild cocaine toxicity resulted from leakage and one heroin body-packer had to undergo surgery because of retained packages. There was no correlation between the dose of PEG-ELS, drug type, or packet quantity and length of hospital stay. As there was no control group, it is not possible to evaluate whether WBI influenced any clinical outcome.[43]

A randomized crossover study using 9 volunteers compared fluid volumes used in WBI in a simulated ibuprofen overdose. The study found that a total of 3 L of PEG-ELS seemed to be as effective as a volume of 8 L when the end point was the AUC of ibuprofen. The problem with this study was the lack of a control group. Ibuprofen was administered in doses of 75 mg/kg, and as there was no control AUC without intervention, it is impossible to determine if the WBI in either volume had any effect at all.[97]

Whole-bowel irrigation has also been used to treat xenobiotic overdoses in pregnant women and children. One such case involved an iron overdose in a woman during the third trimester of pregnancy; she was treated successfully and without complications.[133] A pediatric case report describes combined WBI with succimer therapy and eventually colonoscopic removal of ingested lead pellets. Abdominal radiographs showed 2 small lead pellets, which WBI failed to remove, therefore requiring endoscopic removal.[28] Several reports support the use of WBI in children: an intentional ingestion of mercury,[114] 2 pediatric body-packers,[127] and a 16-month-old boy who had ingested a significant amount of iron.[134] In the latter case, despite WBI, the iron bezoar was not removed and eventually treatment was stopped and the bezoar was expelled after a normal diet was resumed.[134]

Thus there is no new convincing evidence of the clinical efficacy of WBI. Additional case reports and series demonstrate the overall safety of this procedure as well as some beneficial effect on

secondary end points, but the benefits remain in general, theoretical. There is some evidence against the simultaneous administration of activated charcoal with WBI is increasing and there is little doubt that PEG-ELS reduce the adsorptive capacity of activated charcoal in vitro.

The indications for WBI must, at the present time, remain theoretical, as the only support for the efficacy of this procedure comes from surrogate markers and anecdotal experience. Table 8-8 summarizes the indications and the contraindications for WBI.

Cathartics

At present there is no indication for the routine use of cathartics as a method of either limiting absorption or enhancing elimination.

A single dose can be given as an adjunct to activated charcoal therapy when there are no contraindications and constipation or an increased gastrointestinal transit time is expected. (See Antidotes in Depth: Whole-Bowel Irrigation and Other Intestinal Evacuants for more information on cathartics and WBI.)

Potentially toxic ingestions of sustained-release drugs
Ingestion of a toxic amount of a xenobiotic that is not adsorbed to activated charcoal when other methods of gastrointestinal decontamination are not possible or not efficacious
Removal of packets of illicit drugs (eg, from body-packers)
Airway protective reflexes are absent or expected to become so in a patient who has not been intubated
Gastrointestinal tract is not intact
Signs of ileus obstruction, significant gastrointestinal hemorrhage, or hemodynamic instability that might compromise gastrointestinal motility
Persistent vomiting
Signs of leakage from illicit cocaine packets (indication for surgical

removal)

Indications Contraindications

TABLE 8-8. Indications and Contraindications for Whole-Bowel Irrigation

Surgery and Endoscopy

Surgery and endoscopy are occasionally indicated for decontamination of poisoned patients. As might be expected, there are no controlled studies, and potential indications are based largely on case reports and case series. A prospective uncontrolled series of 50 patients with cocaine packet ingestion was collected more than 20 years ago.[22] The patients were conservatively managed and only underwent surgery if there were signs of leakage or mechanical bowel obstruction. Bowel obstruction occurred in 3 patients who promptly underwent successful emergency laparotomy, whereas another 6 patients chose elective surgery. The authors concluded that body-packers should be treated conservatively and only operated on for xenobiotic leakage or bowel obstruction.[22] Similarly, another study performed a 16-year retrospective analysis of all body-packers treated in a single center.[116] Of the 2880 body-packers who were identified, 2.2% developed symptoms of severe cocaine toxicity following rupture of a package; 43 of the symptomatic patients (68%) died before surgery could be initiated and 20 (32%) underwent emergency laparotomy to remove the drug packets and survived. A recent report described 2 cases of body-packers who successfully underwent surgery to remove drug packets. In one case the indications were rupture and signs of cocaine toxicity. In the other cases, the indication for surgery was bowel obstruction.[96] Because most packages do not spontaneously rupture, mechanical obstruction is probably the most common reason for surgery on a

body-packer.[126] Leakage from heroin-containing packages can usually be managed by naloxone infusion, but the lack of antidote when cocaine packages rupture necessitates surgery (Chaps. 38 and 74).[126]

Over the years, a few case reports have presented mixed results for the endoscopic removal of drug packets from the stomach.[25 , 118 , 120 , 126] At present, this method is not generally recommended because of concerns about packet rupture. However, under exceptional circumstances, there is certainly a precedent for attempting this procedure in a highly controlled setting such as an ICU or operating room.

In rare cases of massive iron overdoses where emesis, orogastric lavage, and gastroscopy failed, gastrotomy was performed. The significant clinical improvement and postoperative recovery indicated that surgery in these particular cases was the correct approach.[44 , 101]

Other Adjunctive Methods used for Gastrointestinal Decontamination

Other agents, such as cholecystokinin, have been considered as adjuncts to standard measures for gastrointestinal decontamination.[42 , 55] Pharmaceuticals that either speed up gastrointestinal passage or slow down gastric emptying have been administered in an attempt to minimize the absorption of a xenobiotic. In all cases the results have been negligible, and the potential risks of administering additional pharmacologically active agents to an already poisoned patient seem to outweigh any benefit.[5 , 135] Agents other than activated charcoal that reduce the absorption of xenobiotics from the gastrointestinal tract have also been studied, including sodium polystyrene for lithium,[16 , 77 , 78 and 79 , 124] or thallium overdose.[57] There have also been case reports of the use of the lipid-lowering resins cholestyramine and

colestipol to interrupt the enterohepatic circulation of digoxin, digitoxin, and chlordane in order to increase elimination.[15 , 45 , 67 , 104] With the increased use of activated charcoal and availability of digoxin-specific Fab fragments, indications for lipid-lowering resins for cardioactive steroid ingestions seem obsolete.

Combination Treatments

The combination of several different methods of gastrointestinal decontamination has been studied and, more importantly, is extensively practiced clinically. The combination of gastric emptying (mainly orogastric lavage) followed by activated charcoal is the subject of many investigations, both in volunteers[26] and in 2 often-discussed central clinical studies.[70 , 105] Only the small subset of significantly ill patients who received the combination of orogastric lavage and activated charcoal, seemed to benefit from combined therapy. On closer examination, this group was comprised of only 3 patients, compared to 17 patients who received activated charcoal alone.[70] This comparison of small, uneven, and unpaired numbers,

together with a retrospective stratification, poses consequential statistical problems and limits the potential for generalization of the authors' results.

A volunteer study, although also small in numbers (n = 12), used a controlled, randomized, paired design.[26] The subjects received approximately 4 g of acetaminophen (as 30â€“40 tablets of 125 mg strength) 1 hour after a standardized breakfast meal. The interventions (orogastric lavage plus activated charcoal vs. activated charcoal alone) were carried out 1 hour after drug ingestion. There were no significant differences in the AUC of acetaminophen between the 2 arms (power of 80% to detect a minimum relevant difference of 15%), but there was a 50% reduction for both arms compared to control. It must be

emphasized, however, that the end point measured was the size of the AUC of the drug and not a clinical end point (because of the nature of the study).

Similarly, a clinical study of 981 consecutive acetaminophen poisonings over a 10-year period, found that those patients who had ingested >10 g of acetaminophen by history and had received activated charcoal were significantly less likely to have a concentration of acetaminophen requiring antidotal therapy when compared to patients who received no decontamination. However, orogastric lavage in addition to activated charcoal did not further decrease that risk.[20] Thus, the combination of orogastric lavage followed by activated charcoal only seems appropriate in cases where orogastric lavage is indicated and the xenobiotic is adsorbed to activated charcoal. In cases where activated charcoal alone is usually beneficial, there is little rationale to expose the patient to the additional risks of orogastric lavage. Although acetaminophen is a reasonable drug to study, the universal availability of a benign and inexpensive antidote contraindicates aggressive gastric emptying in acetaminophen overdose *even* if some benefit could be demonstrated.

The combination of activated charcoal and whole-bowel irrigation would seem to make sense in that it might speed up gastrointestinal passage and at the same time have the protective adsorptive effect of activated charcoal. However, based on the studies cited previously, it seems that if activated charcoal is administered with WBI, the adsorptive capacity of activated charcoal is reduced, and the recommendation is to administer the activated charcoal prior to the administration of PEG-ELS. There is concern about the practice of treating asymptomatic cocaine body-packers with WBI combined with activated charcoal because severe peritonitis can result if activated charcoal spills into the peritoneum following surgical intervention. The administration of activated charcoal is not expected to prevent routine surgery and because the use of activated charcoal may increase the risk of

surgical complications, activated charcoal should not be used under these circumstances.

General Aspects

Only a few gastrointestinal decontamination studies provide guidance based on meaningful clinical end points. One of the few studies addressing meaningful clinical parameters was a retrospective analysis reviewing the management of all patients presenting to an emergency department with a diagnosis of deliberate self-poisoning.[52] The study evaluated 561 patients who were treated in 1999, comparing them with patients treated in 1989, 1992, and 1996.[52] The authors found that despite dramatically changing trends of gastrointestinal decontamination, there were no significant changes in the proportion of patients admitted to the hospital, although there was a reduction in the rate of admission to the ICU. The patient populations did not change significantly over the years with regard to the female-to-male ratio, the age distribution, and the types of xenobiotics ingested. The authors mention that there might be unmeasured differences between the populations and unrecognized differences in practice that might have been influential. However, in 1989 most of the patients were treated with orogastric lavage, almost no patients received activated charcoal, and approximately 33% did not receive any gastric decontamination at all. In comparison, in 1996, more than 50% of patients received activated charcoal alone and less than 25% had no gastrointestinal decontamination at all. In 1999, only 13% of patients received activated charcoal, 0.7% a combination of orogastric lavage followed by activated charcoal, 0.5% were given WBI, and nearly 86% received no decontamination at all. There were no changes in overall mortality from poisonings over the years, although the mortality was generally very low. Thus, although the trends in gastrointestinal decontamination dramatically shifted toward less intervention over the years studied, there was no measurable worsening in outcome

when large groups of patients were studied. It must be emphasized that this was a retrospective analysis with fairly nonspecific outcome measures, and possible improvements in other aspects of clinical treatment of poisoned patients were not considered.

The trends in practice noted in the study above are reflective of the overall combined philosophy of the position statements, which are applicable to the vast majority of poisoned patients. They highlight the benign nature of many exposures and the benefits of good supportive care. In contrast, the previously mentioned survey of recommendations for a theoretical patient with a serious enteric-coated aspirin overdose reveal less consensus in that 36 different courses of action were proposed for the same case. Most of the poison centers and toxicologists did, however, recommend at least one dose of activated charcoal.[63] This distinction serves as a reminder that the existing studies and consensus statements cannot be applied to all cases, and that a lack of data produce significant uncertainty in choices for gastrointestinal decontamination in either atypical or severely poisoned patients.[58]

It is essential to note that only one study has ever demonstrated a survival advantage for any form of gastrointestinal decontamination of poisoned patients.[37] Its unique design, involving a cohort of patients with life-threatening toxicity, forces a reassessment of all previous literature and confirms that the principles of decontamination are sound. It also suggests that the failure of most studies to demonstrate a benefit results not from a failure of the techniques employed, but from applying decontamination techniques to subsets of patients who were likely to have good outcomes regardless of intervention.

Summary

The approach to gastrointestinal decontamination needs to be more individualized than previously thought. No decontamination

method is completely free of risks. The indications for when and when not to perform gastrointestinal decontamination must be well defined for each patient and the method of choice must depend

largely on what was ingested, how much was ingested, and when it was ingested. The absolute time frame for when decontamination is indicated is dependent on many factors, such as rate of gastric emptying, rate of xenobiotic absorption, and the possibility of enterohepatic cycling. The commonly stated short time frame of up to 1 hour postingestion for intervention is most likely an underestimation of the time frame during which a benefit is likely to be realized, although this has not yet been adequately investigated.

Judging from the evidence available today, activated charcoal must be the first choice, only accompanied by orogastric lavage when the desirable ratio of activated charcoal-to-xenobiotic cannot be achieved, and the xenobiotic is still thought to be accessible in the stomach. Orogastric lavage as a single intervention is reserved for those cases where the ingested xenobiotic is not adsorbed by activated charcoal and there is reason to believe that the ingested xenobiotic is both life-threatening *and* still in the stomach. Syrup of ipecac-induced emesis has a very small therapeutic role, but might be reserved for those situations where there is an absolute need for gastrointestinal decontamination, activated charcoal is not expected to be effective, and orogastric lavage and whole bowel irrigation are, for practical purposes, impossible. Multiple-dose activated charcoal and whole-bowel irrigation have defined indications, which may broaden in the future as more studies focus on subsets of significantly poisoned patients.

The advancement of medical toxicology is dependent on well-designed clinical studies that concentrate on measuring the effect of gastrointestinal decontamination using sound and relevant clinical end points. For each approach it must be determined if the benefits of decontamination outweigh the potential risks. If proven

beneficial, we need to set firm criteria for the future selection of patients for whom these treatments are beneficial and therefore indicated. One goal must be to reduce complications by identifying those patients who can be safely managed without decontamination. At the same time, we must be ever vigilant for patients with ingestions of unstudied highly lethal xenobiotics and massive amounts of studied xenobiotics, as well as those who present early in their clinical course with life-threatening signs and symptoms. This uncommon subset is most likely to benefit from more aggressive gastrointestinal decontamination. Thus it is recommended that some form of gastrointestinal decontamination be considered in *every* patient with potentially life-threatening toxicity regardless of the time since ingestion, as long as no absolute contraindications exist.

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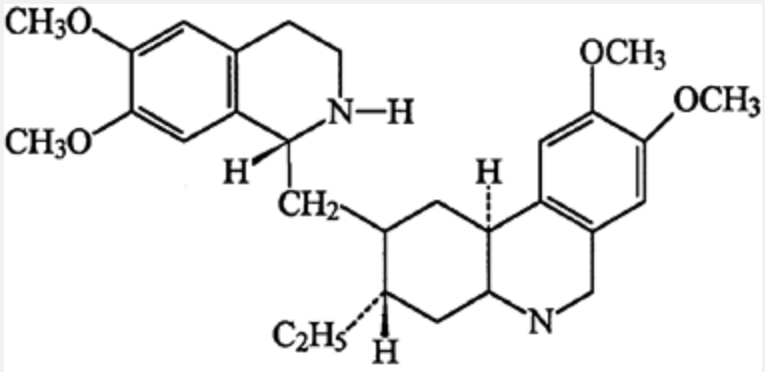
Title: *Goldfrank's Toxicologic Emergencies, 8th Edition*

Antidotes in Depth

Syrup of Ipecac

Mary Ann Howland



Emetine

The role of syrup of ipecac has changed dramatically in the last decade. Once the mainstay of poison management for children and adults, a critical evaluation of animal, volunteer, and a limited number of clinical studies suggests that ipecac administration

should be reserved for a few selected circumstances rather than administered on a routine basis.[3] The rationale for this change is based on the facts that (a) most poisonings in children are benign; (b) many adults overdose with xenobiotics that rapidly cause an altered mental status which constitutes a contraindication to the administration of ipecac; (c) ipecac-induced vomiting may be delayed and/or persistent, thereby resulting in a delay in the administration of activated charcoal.

Syrup of ipecac is an emetic that has been used for the management of poisonings since the 1950s and has been available without prescription since the late 1960s. Pediatricians were encouraged to advise parents to keep syrup of ipecac in their homes. Many pediatricians currently believe that there is no role for syrup of ipecac in the prehospital or hospital setting and that the abuse of syrup of ipecac by patients with bulimia outweighs any benefit originating from keeping syrup of ipecac as a nonprescription drug. The FDA is reviewing whether to make syrup of ipecac available only by prescription. Advocates for maintaining the nonprescription status of syrup of ipecac support home stocking of ipecac for use in remote areas and limiting use in healthcare facilities to those rare instances when activated charcoal, orogastric lavage, or whole-bowel irrigation with polyethylene glycol lavage solution may be inappropriate or inadequate. Changing the availability of syrup of ipecac to prescription status only, could result in the complete disappearance of syrup of ipecac from the pharmaceutical market if the FDA required a new drug application. Under these circumstances it might not be profitable for any drug company to invest in a new drug application.

Composition

Ipecac is derived from the dried rhizome and roots of plants found in Brazil belonging to the family Rubiaceae, such as *Cephaelis*

acuminata or *Cephaelis ipecacuanha*.[51] Ipecacuanha originates from the plant's Portuguese name â€œipecaaguenâ€• which translates to â€œsmaller roadside sick-making plant.â€•[52] Cephaeline and emetine are the two alkaloids largely responsible for the production of nausea and vomiting, with cephaeline being the more potent.[28] Each 15-mL dose of syrup of ipecac contains 16â€“21 mg of cephaeline and 6.4â€“21 mg of emetine, resulting in variable cephaeline-to-emetine ratios. Syrup of ipecac also contains a small amount of psychotrine, which does not contribute to emesis but is currently under investigation for its potential anti-HIV effects.

Pharmacokinetics of Ipecac Alkaloids

After human volunteers were administered 20 or 30 mL of syrup of ipecac, plasma, vomitus and urine concentrations of emetine and cephaeline were determined by the use of high-performance liquid chromatography (HPLC).[56] Peak plasma levels of the alkaloids were reached by 1 hour and were undetectable at 6 hours. Only 2% of the total amount of alkaloids in the ipecac were excreted in the urine within 48 hours, and remained detectable in the urine for 2 weeks in all 12 volunteers and for 12 weeks in 1 of 2 subjects who were tested subsequently.

Mechanism of Action

Syrup of ipecac induces vomiting by local activation of peripheral emetic sensory receptors in the proximal small intestine, and by central stimulation of the chemoreceptor trigger zone that serves as a sensory area resulting in subsequent activation of the central vomiting center.[47] $5HT_3$ receptors mediate the nausea and vomiting produced by syrup of ipecac by both mechanisms. This was demonstrated in 40 volunteers by administering a specific $5HT_3$ antagonist 30 minutes prior to administration of the syrup of ipecac; the $5HT_3$ antagonist prevented or attenuated the nausea

and vomiting in a dose-dependent fashion.[18] In fact, syrup of ipecac is used to assess the efficacy of new $5HT_3$ antagonists and other antiemetics.[13,45]

Time to onset of Vomiting and Number of Vomiting Episodes

In one of the earliest studies evaluating the delay in onset to vomiting after syrup of ipecac administration, 88% of 214 children who were given 20 mL of syrup of ipecac and copious amounts of water vomited within 30 minutes (mean of 18.7 minutes).[40] Adverse events secondary to syrup of ipecac were not noted. Subsequent studies demonstrate similar findings.[6,12,14,16,20,27,29,49,50]

The onset of emesis following syrup of ipecac administration does not appear to be affected by fluid administration before or after syrup of ipecac, by the temperature of the fluids, or by gentle patient motion or walking.[16,17,20,46] Consequently, it is inadvisable to force fluids and safer to maintain the patient in an

appropriate stationary setting (chair or stretcher). Milk should not be given with the syrup of ipecac, as the onset of emesis may be delayed, although the success of inducing vomiting does not appear to be affected.[17] This delay is consistent with the ability of milk to delay gastric emptying and thereby retard ipecac's contact with the peripheral emetic sensory receptors.[53] Because when followed by water, syrup of ipecac is absorbed so quickly, vomiting still occurred in the majority of overdose patients who were also given activated charcoal 10 minutes after the syrup of ipecac.[19]

The average number of episodes of vomiting following syrup of ipecac administration is 3, with a range of 1 to 8.[27] The duration of syrup of ipecac-induced vomiting averaged 23â€“60 minutes.[27,39] Although some investigators suggested durations

lasting up to 3â€“4 hours,[35] it is probably reasonable to assume that vomiting that persists for more than 2 hours is unrelated to syrup of ipecac and another cause should be sought. This warning is of particular importance when syrup of ipecac is used in the home.

Volunteer Studies

Many studies have assessed the effectiveness of syrup of ipecac-induced emesis in decreasing absorption of a xenobiotic, and then compared the results to other methods of gastric decontamination, such as gastric lavage or activated charcoal.[35,37,43] These same studies support the concept that the sooner syrup of ipecac is administered after ingestion, the greater the amount of the ingested xenobiotic that will be recovered. The decrease in the amount of xenobiotic absorbed varies from study to study as a result of differences in study design, including time to initiation of the various techniques and the particular xenobiotic used to assess efficacy. Volunteer studies using small lavage tubes were further limited because of the quantity of xenobiotic that was administered and the limited potential of the tube to recover xenobiotic. In a small, well-quantified study, when 6 adult volunteers were given 20 mL of syrup of ipecac at 5 or 30 minutes after acetaminophen ingestion, absorption was inhibited by 65% and 0%, respectively.[37] In this same volunteer model, absorption was inhibited by 80% and 40% when 50 g of activated charcoal was given at 5 and 30 minutes postingestion.[36]

A subsequent investigation demonstrated that the reduction in the area under the plasma drug concentration versus time curve was equivalent for patients treated with syrup of ipecac-induced emesis and patients treated with activated charcoal plus a cathartic. Comparison of orogastric lavage, syrup of ipecac-induced emesis, and activated charcoal, all given at 60 minutes after ingestion of ampicillin by adult volunteers, showed reductions

of 32%, 38%, and 57%, respectively.[50] Adult volunteers given syrup of ipecac 5 minutes after 30 capsules containing a radionucleotide marker demonstrated a mean 54% removal (range, 21â€“89%) as compared to a mean removal of 35.5% (range, 1â€“71%) with orogastric lavage.[57] Other researchers demonstrated recoveries from 0% to 85%.[6,14,15,49] Children given a magnesium hydroxide marker before administration of syrup of ipecac demonstrated a mean recovery of 28%, although the range was 0â€“78%.[14]

Overdosed Patients

In a study of self-poisoned adults randomized to receive either syrup of ipecac or orogastric lavage with a 33-French lavage tube, all patients had subsequent gastric endoscopy.[42] Thirteen patients were given syrup of ipecac and vomited within 23 minutes (range, 11â€“25 minutes). Two of these patients had tablets in the vomitus. On endoscopy, only those 2 patients had residual tablets in the stomach. Ten of 17 patients who were lavaged had tablets in the lavage fluid. All of these patients had tablets in the stomach at the time of endoscopy. Two additional patients also had residual tablets in the stomach. This study suggests that the presence of tablets in the vomitus or lavage fluid supports the presence of additional tablets in the stomach.[42]

This same group of investigators subsequently used barium-marked 3 mm^3 pellets to evaluate the effectiveness of gastric emptying.[43] Forty self-poisoned patients were given 20 pellets on admission and randomized immediately to therapy with either orogastric lavage or syrup of ipecac-induced emesis. Approximately 45% of the pellets were removed in both the orogastric lavage and the syrup of ipecac groups. Two patients in the lavage group and 1 in the syrup of ipecac group had 100% removal of pellets, and 2 patients in the lavage group had no removal.[43]

Outcome Studies

A large emergency department (ED) study addressed whether gastric emptying with either syrup of ipecac followed by activated charcoal or orogastric lavage followed by activated charcoal was more effective than activated charcoal alone in overdosed patients.[25] Syrup of ipecac did not affect the outcome in treated patients.

Three subsequent studies (2 adult and 1 pediatric) failed to show a benefit of gastric emptying before activated charcoal administration[2,34] compared with the administration of activated charcoal alone.[23] Furthermore, aspiration was more common in patients who had the combined regimen.[2,34]

A study using the Toxic Exposure Surveillance System (TESS) database determined that home use of syrup of ipecac did not reduce the rate of ED referrals.[11] That this study did not identify an improvement in patient outcome was not unexpected. Most children have no clinical sequelae from exposure and group statistics cannot identify a potentially beneficial effect that occurs rarely.

Contraindications

Syrup of ipecac should not be administered to patients who have ingested acids or alkalis, are younger than 6 months of age, are expected to deteriorate rapidly, have a depressed mental status, have a compromised gag reflex, have ingested objects such as batteries or sharps, or have a need for rapid gastrointestinal evacuation to prevent absorption. Syrup of ipecac should not be administered to those for whom the hazards of vomiting and aspiration of the ingested substance outweigh the risks associated with systemic absorption (eg, hydrocarbons), those who have significant prior vomiting, or those for whom vomiting will delay administration of an oral antidote, or to those with a hemorrhagic

diathesis, or a nontoxic ingestion, or when toxin is no longer expected to be in the stomach.

Adverse Effects

Considering the number of times it has been administered without incident in this country, syrup of ipecac should be considered a

relatively safe drug when given in therapeutic doses to patients for whom there are no contraindications. Uncommon problems that have occurred after therapeutic doses of syrup of ipecac include a Mallory-Weiss esophageal tear in an adult given 30 mL of syrup of ipecac for a multidrug overdose;[48] herniation of the stomach into the left chest in a child who had a previously unrecognized underlying congenital defect of the diaphragm;[41] intracerebral hemorrhage;[22] and pneumomediastinum.[54] Additional problems associated with syrup of ipecac administration include pulmonary aspiration of stomach contents, volatile hydrocarbons or foreign bodies, and the associated time delay before it is possible to perform a necessary therapeutic intervention such as administration of activated charcoal or an oral antidote. Another reported problem is the emesis-induced vagal response of bradycardia.[33]

The surreptitious self-administration of frequent doses of syrup of ipecac by patients with bulimia and other related eating disorders results in substantial morbidity such as extreme muscle weakness and congestive cardiomyopathy, and mortality.[1,8,28,30,38,44,55] Myofibril analysis of ipecac abusing patients reveals degeneration, a â€œmoth-eatenâ€• appearance, and electron microscopy reveals Z-band streaming and disorganization.[26] When emetine was routinely used for the treatment of amebiasis in the early 1900s, cardiovascular and neuromuscular toxicity occurred. Similarly, inadvertent administration of the fluid extract of ipecac, which is 14 times more potent than syrup of ipecac, produces

violent and protracted vomiting; diarrhea; seizures; cardiac toxicity including PR interval prolongation, T-wave abnormalities, QRS complex abnormalities, atrial dysrhythmias, premature ventricular beats, and ventricular fibrillation; neuromuscular toxicity, including weakness and neuropathy; shock; and death.[28] Surreptitious chronic intentional ipecac poisoning of children, a form of Munchausen syndrome by proxy, is reported.[9,31] The findings in these children included vomiting, diarrhea, lethargy, irritability, hypothermia, and hypotonia. The children described were brought to healthcare providers by their parents for atypical patterns of vomiting and had multiple unsuccessful clinical evaluations. When surreptitious use of syrup of ipecac is suspected as the cause of chronic vomiting, screening the urine, plasma, and vomitus for emetine (thin-layer chromatography screenâ€"Toxi-Lab or HPLC) may be useful.[5,31,56]

Current Role of Syrup of Ipecac in Poison Management

Most authorities agree with the American Academy of Pediatrics' statement that syrup of ipecac should no longer be used routinely.[3,4] Instead of promoting the concept of the maintenance of syrup of ipecac in the home, the Academy of Pediatrics currently states that â€œthe first action for a caregiver of a child who may have ingested a toxic substance is to consult with the local poison control center.â€•[4] Logically, the sooner that syrup of ipecac is administered after ingestion, the more effective it may be in reducing absorption of the agent. For this reason, rather than completely abandoning syrup of ipecac, perhaps a targeted approach should be developed. This would mean continuing to promote the stocking of syrup of ipecac in the home setting in remote areas. Although the Academy of Pediatrics believes that it is premature to recommend the routine home stocking of activated charcoal, home stocking of activated charcoal in remote areas

seems logical.

Only a few groups of patients are considered appropriate candidates for the use of syrup of ipecac. Patients who are candidates for syrup of ipecac are those who (a) overdose on xenobiotics that do not cause a rapid change in mental status, such as acetaminophen or salicylates; (b) consume massive amounts of a toxin that may exceed the binding capacity of activated charcoal, such as salicylates; or (c) ingest a toxin not bound to activated charcoal, such as lithium. Under these circumstances, if the presence of unabsorbed drug in the stomach remains a potential problem, then the use of syrup of ipecac may be appropriate in rare instances when weighed against the utility of activated charcoal or whole-bowel irrigation with polyethylene glycol electrolyte lavage solution. The time frame for this decision is usually within 1 to 2 hours following ingestion.

Administration

The dose of syrup of ipecac is 15 mL in children 1â€“12 years old and 30 mL in older children and adults. If vomiting does not ensue after the first dose, the same dose may be repeated once 20â€“30 minutes after administration of the first dose. For children 6â€“12 months of age, ipecac use should be limited to a maximum single dose of 10 mL.[10,24] Water can be offered, but is not essential for success. Vomiting will occur in most patients. Home users should be warned that persistent vomiting for more than 2 hours may indicate toxicity from the primary xenobiotics ingested and not the antidote, and necessitates medical evaluation.

Conclusion

There are very few cases in which syrup of ipecac is indicated in the home setting because typically either most ingestions are nontoxic or, conversely, are of such consequence that an imminent

deterioration in mental status may occur that would make syrup of ipecac administration dangerous. Parents in areas with poor access to a healthcare facility should still be encouraged to keep syrup of ipecac and activated charcoal at home as potential first aid measures, but caregivers should be cautioned to use them only on the advice of a regional poison center or physician.

In the ED, the role of syrup of ipecac is extremely limited. One of the only possible candidates for syrup of ipecac in the overdose setting is a child or adult who arrives in the ED shortly after the ingestion of a large number of poorly soluble tablets of a size unlikely to be removed by lavage and also unlikely to cause a rapid change in mental status. One other candidate is the child or adult who has taken such a large amount of a highly toxic substance that a favorable activated charcoal-to-drug ratio cannot be attained with certainty. Whole-bowel irrigation should be considered as a suitable alternative in either case.

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Antidotes in Depth

Activated Charcoal

Mary Ann Howland

History

Activated charcoal (AC), a fine, black, odorless powder, has been recognized for almost 2 centuries as an effective adsorbent of many substances. In 1930, the French pharmacist Touery dramatically demonstrated his belief in the powerful adsorbent qualities of AC by ingesting several times the lethal dose of strychnine mixed with 15 g of AC in front of colleagues; he suffered no ill effects.[6] An American physician, Holt, first used AC to save a patient from mercury bichloride poisoning in 1934.[6] However, it was not until the 1940s that Anderson began to systematically investigate the adsorbency of AC and unquestionably demonstrated that AC is an excellent broad-spectrum gastrointestinal adsorbent.[6,7 and 8] The current debate regarding the role of AC in poison management centers on reconciling evidence-based studies in volunteers and small numbers of heterogeneous overdosed patients with clinical experience.[4] AC should be considered for administration to a poisoned or overdosed patient following a risk-to-benefit

assessment for the substance presumably ingested and ideally also for the circumstances of the exposure for a particular patient. The benefits include inactivating a potentially toxic xenobiotic, whereas the risks include vomiting and subsequent aspiration. The merits of AC as a decontamination strategy are discussed in detail in Chap. 8.

Adsorption: Mechanisms and Considerations

AC is produced in a two-step process, beginning with the pyrolysis of various carbonaceous materials such as wood, coconut, petroleum, or peat. This processing is followed by treatment at high temperatures with a variety of oxidizing (activating) agents such as steam or carbon dioxide to increase the adsorptive capacity of the agent through the formation of an internal maze of pores with a huge surface area.[29,53,104,129] The rate of adsorption depends on external surface area, while the adsorptive capacity is dependent on the far larger internal surface area.[29,97,103] The adsorptive capacity can be modified by altering the size of the pores. Current AC products have pore sizes that range from 10 to 1000 angstroms (Ã…) with most of the internal surface area created by the summation of 10â€“20-Ã…-sized pores.[25,27,29] Most xenobiotics are of moderate molecular weight (100â€“800 daltons) and adsorb well to pores in the range of 10â€“20 Ã…. Mesoporous charcoals with a pore size of 20â€“200 Ã… have a greater capacity to adsorb larger xenobiotics as well as those in their larger hydrated forms.[77]

The relationship between AC surface area and adsorptive capacity was studied in vitro and in vivo in animals and in humans. When surface area is large, adsorptive capacity is increased, but affinity is decreased because van der Waals forces and hydrophobic forces are diminished.[131] In 1996, a superactivated charcoal with a surface area approximately double the current AC formulations

was marketed. Both in vitro and in vivo studies of this preparation indicated a greater maximum adsorptive capacity.[30,116]

The actual adsorption of a xenobiotic by activated charcoal is believed to rely on hydrogen bonding, ion-ion, dipole, and van der Waals forces, suggesting that most xenobiotics are best adsorbed by activated charcoal in their dissolved, nonionized form.[29] Thus, according to the Henderson-Hasselbalch equation, weak bases are best adsorbed at basic pHs and weak acids are best adsorbed at acid pHs. For example, cocaine, a weak base, binds to AC with a maximum adsorptive capacity of 273 mg of cocaine per gram of AC at pH 7.0; this capacity is reduced to 212 mg of cocaine per gram of AC at pH 1.2.[76] Strongly ionized and dissociated salts like sodium chloride or potassium chloride are not adsorbed, whereas nonionized or weakly dissociated salts like iodine and mercuric chloride, respectively, are adsorbed. The adsorption to AC of a weakly dissociated metallic salt like mercuric chloride ($HgCl_2$) decreases with decreasing pH because the number of complex ions of the type $HgCl_3$ and $HgCl_4$ increases and the number of electroneutral molecules ($HgCl_2$) is reduced.[7] Nonpolar, poorly water soluble organic substances are more likely to be adsorbed from an aqueous solution than polar, water-soluble substances.[29] Among the organic molecules, aromatics are better adsorbed than aliphatics, molecules with branched chains are better adsorbed than those with straight chains, and molecules containing nitro groups are better adsorbed than those containing hydroxyl, amino, or sulfonic groups.[29] In vitro studies demonstrate that adsorption begins within about 1 minute of administration of AC, but may not reach equilibrium for 10â€“25 minutes.[30,92]

Accordingly, desorption (drug dissociation from activated charcoal) may occur, especially for weak acids, as the activated charcoal-drug complex passes from the stomach through the intestine and as the pH changes from acidic to basic.[12,42,98,103,128] Desorption may lead to systemic absorption of larger total amounts of xenobiotic over several days; in this case, the elimination half-life

of the xenobiotic appears to increase, but peak levels remain unaffected.[98] The clinical effects of desorption can be minimized by giving a sufficiently large dose of AC to overcome the decreased affinity of the xenobiotic secondary to pH change such as by using multiple-dose activated charcoal. Either whole-bowel irrigation or cathartic may reduce gastrointestinal transit time and possibly increase xenobiotic elimination. However, in spite of numerous human volunteer studies,[62,85,96,107,121] increased xenobiotic elimination has been demonstrated for cathartics only in a single study.[62]

Although ethanol and other solvents such as polyethylene glycol are minimally adsorbed by AC, they nonetheless may decrease the adsorptive capacity of AC for a coingested xenobiotic by competing for AC binding with that xenobiotic.[13,98,101]

AC decreases the systemic absorption of most xenobiotics, including aspirin, acetaminophen, barbiturates, glutethimide, phenytoin, theophylline, cyclic antidepressants, and most inorganic and organic materials.[41,92,106] Notable xenobiotics not amenable to AC are the alcohols, acids and alkalis, and iron,[45] potassium, magnesium, sodium, and lithium salts. Although the binding of AC to

cyanide is less than 4%, the toxic dose is small and 50 g of AC would theoretically be able to bind more than 10 lethal doses of potassium cyanide.

Efficacy of AC is directly related to the amount of AC administered. The effect of the AC-to-drug ratio on adsorption was demonstrated both in vitro and in vivo with *para*-aminosalicylate (PAS): In vitro, the fraction of unadsorbed PAS decreased from 55% to 3% as the AC-to-PAS ratio increased from 1:1 to 10:1 at pH 1.2.[102] This study most likely provides the best scientific basis for the 10:1 AC-to-drug ratio dose recommendation. In human volunteers, as the AC-to-PAS ratio increased from 2.5:1 to 50:1, the total 48-

hour urinary excretion decreased from 37% to 4%.[103] Presumably this occurred because more of the PAS was adsorbed by AC in the lumen of the gastrointestinal tract rather than being absorbed systemically. These same studies demonstrate AC saturation at low ratios of AC to drug and argue for a 10:1 ratio of AC to xenobiotic.

The clinical efficacy of administered AC is also inversely related to the time elapsed following ingestion of the substance to be adsorbed and depends largely on the rate of absorption of the drug. For example, early administration is much more important with rapidly absorbed drugs. In this situation, AC functions to prevent the absorption of drug into the body by achieving rapid adsorption in the GI tract. Once a drug is systemically absorbed or parenterally administered AC may still enhance elimination through a mechanism referred to as gastrointestinal dialysis. This is accomplished with multiple doses of AC.

Palatability

The black and gritty nature of AC has led to many formulations to increase palatability and patient acceptance. Bentonite, carboxymethyl cellulose, and starch[49,91,119] are used as thickening agents; cherry syrup, chocolate syrup, sorbitol, sucrose, saccharin, ice cream, and sherbet [30,71,78,135] are used as flavoring agents. Most of these additives do not decrease adsorptive capacity; however, improvement in palatability and acceptance is minimal or nonexistent with all of these formulations.[28] Although a milk chocolate formulation of AC evaluated by a group of children was rated superior in palatability to standard AC preparations,[38] it was never marketed. A marketed AC product with cherry flavoring was rated by adult human volunteers as preferable over plain AC and a statistically significant larger quantity of the flavored AC was ingested.[24] However, in adult overdosed patients, this was not the case, as

most patients consumed the entire bottle of AC with or without cherry flavoring. Many of the subjects did not like the taste and surprisingly preferred the plain AC.[58] Two studies in adult overdosed patients compared different brands of AC without additives or flavoring to determine the quantity of activated charcoal typically ingested.[17,43] In one study, approximately half of the 50 g of activated charcoal offered was ingested and 7% of the patients vomited.[17] In the other study, 60 g of AC as Liqui-Char or CharcoAid G was offered and approximately 95% of each formulation was consumed in 20 minutes. There was no difference in the amount consumed even though the palatability of the granular form of AC (CharcoAid G) was rated higher.[43]

Recently cold cola was used to enhance palatability in volunteer children and adults. Children preferred regular cola as compared to diet cola. The adults rated the cola charcoal combination preferable to the plain charcoal.[113,118]

Adverse Effects

The use of AC is relatively safe, although vomiting (which especially occurs after rapid administration), constipation, and diarrhea frequently occur following AC administration.[97] Constipation and diarrhea are more likely to result from the ingestion itself than from the AC. However, black (heme-negative) stools, tongues, and mucous membranes are frequently observed. Serious adverse effects of AC include the complications that may result from the pulmonary aspiration of AC with or without gastric contents,[9,39,47,50,51,59,86,92,108,120] peritonitis from spillage of AC into the peritoneum from gastrointestinal perforation caused by orogastric lavage,[79] and intestinal obstruction and pseudo-obstruction, especially following repeated doses of AC in the presence of either dehydration[18,73,88,114,132] or prior bowel adhesions.[48]

Although a significant number of patients aspirate gastric contents

prior to endotracheal intubation and administration of AC,[90,117] the incidence of AC aspiration following endotracheal intubation varies from 4% to 25%, depending on the nature of the study. A more recent retrospective investigation demonstrated a 1.6% incidence of aspiration pneumonitis in unselected overdosed patients. Altered mental status, spontaneous emesis, and tricyclic antidepressant overdose were associated risk factors, whereas AC was not.[57]

Home and Prehospital Administration

Prehospital administration of AC by emergency medical technicians and paramedics may offer a significant advantage in facilitating the administration of AC more rapidly following the time of overdose.[2,133] However, the cost of implementation of such a program would have to be weighed against the small number of patients who would actually benefit.[56]

In a study intended to simulate home administration of AC the acceptance of a dose of AC given as a water slurry in a paper cup was studied in 50 young children.[20] The children were told to drink the contents, that the substance did not taste bad, and that it would make them feel better and not feel ill. Eighty-six percent of the children readily drank the AC slurry, and 76% of them consumed 95â€“100% of the total dose. Of 7 children in a simulated home environment administered AC in regular cola, 3 drank 1 g/kg, 2 drank very little, and the other 2 drank about half a therapeutic dose.[118] A prospective poison center case series demonstrated successful administration of AC in the home. In this series the median age of the patients was 3 years and the median dose ingested was 12 g.[124] However, other attempts at getting children to ingest AC were not as successful; in one study difficulty was noted in 70% of attempts to administer a standard dose of AC to children in the home setting.[35]

Administration and Dosing

AC should not be administered routinely to all overdosed patients. Single-dose AC should be administered when xenobiotic is still expected to be available for adsorption in the GI tract and the benefit outweighs the risk. The optimal dose of AC is unknown.[4] However, most authorities recommend a dose of AC of 1 g/kg of body weight when the amount of xenobiotic exposure is unknown or when

known in a 10:1 ratio of AC to xenobiotic, up to an amount that is tolerated by the patient and safely administered. AC that is not premixed is best administered as a slurry in a 1:8 ratio of AC to suitable liquid, such as water or cola. Using cold cola may offer improved palatability.[113,118] Administering the mixture to children from an opaque, covered cup decorated with stickers and through a straw may be helpful.[134] Contraindications to AC include presumed GI perforation and the need for endoscopic visualization, as may be the case with caustic ingestion. To prevent aspiration pneumonitis from oral AC administration it is imperative that the patient's airway be assessed. When the potential for airway compromise is substantial, oral AC should be withheld until a decision about airway protection is made. A risk-to-benefit assessment with regard to the need for airway protection and the need for AC should be made. Other considerations that must be made prior to the administration of AC are the determination of normal gastrointestinal motility, normal bowel sounds, and a normal abdominal examination without distension or signs of an acute abdomen. If bowel function is compromised, the stomach should be decompressed to decrease the risk of subsequent vomiting and aspiration prior to administration of AC.

The use of Activated Charcoal, Cathartics, and Whole-Bowel Irrigation

with Polyethylene Glycol Electrolyte Lavage Solution

Cathartics are often used with AC, however the evidence suggests that AC alone is comparably effective to AC plus a single dose of cathartic (sorbitol or magnesium citrate).[3,62,80,81,85,91,97,105] If a cathartic is used, it should be used only once as repeated doses of magnesium-containing cathartics are associated with hypermagnesemia[89,123] and repeated doses of any cathartic can be associated with severe fluid and electrolyte problems. A child died following repeated doses of AC-sorbitol mixtures.[40]

Whole-bowel irrigation with polyethylene glycol electrolyte lavage solution may significantly decrease the in vitro and in vivo adsorptive capacity of AC[52] depending on the individual xenobiotic and the drug's formulation.[10,68] The most likely explanation is competition with the activated charcoal's surface for solute adsorption.

Multiple-Dose Activated Charcoal

Multiple-dose activated charcoal (MDAC) functions in two ways: (a) to prevent the absorption of xenobiotics that are slowly absorbed from the GI tract, and (b) to enhance the elimination of suitable xenobiotics that have already been absorbed.

MDAC decreases xenobiotic absorption when large amounts of xenobiotics are ingested and dissolution is delayed (eg, masses, bezoars), when xenobiotic formulations exhibit a delayed or prolonged release phase (eg, enteric coated, sustained release), or when reabsorption can be prevented (eg, enterohepatic circulation of either active drug, active metabolites, or conjugated xenobiotic hydrolyzed by gut bacteria to active xenobiotic).

The ability of MDAC to enhance elimination once absorption had already occurred was first reported in 1982.[14] This report

concluded that orally administered MDAC enhanced the total body clearance (nonrenal clearance) of 6 healthy volunteers given 2.85 mg/kg of body weight of intravenous (IV) phenobarbital.[14] The serum half-life of phenobarbital decreased from 110 Â± 8 to 45 Â± 6 hours. An accompanying editorial suggested that MDAC enhanced the diffusion of phenobarbital from the blood into the gastrointestinal tract and trapped it there, to be excreted later in the stool. In this manner, AC was said to perform as an â€œinfinite sinkâ€• allowing for â€œgastrointestinal dialysisâ€• to take place.[70] These findings were subsequently confirmed by studies in dogs and rats using intravenous aminophylline.[34,83] Using an isolated perfused rat small intestine the concept of gastrointestinal dialysis[83] was elegantly demonstrated, as AC dramatically affected the pharmacokinetics of theophylline and produced a constant intestinal clearance that was approximately equivalent to intestinal blood flow.[83] Although MDAC increases the elimination of digitoxin;[109] phenobarbital;[111] carbamazepine;[16] phenylbutazone;[93] dapsone;[94] nadolol;[37] theophylline;[15,75,127] salicylate;[112] quinine;[5] cyclosporine;[54] propoxyphene;[60] nortriptyline; and amitriptyline, its clinical utility remains to be defined.[5,61,125] The adsorptive capacities for these and other agents are well documented.[5,21,22,29,84]

Volunteer and Experimental Studies

An analysis of 28 volunteer studies involving 17 xenobiotics was unable to correlate the physiochemical properties of a particular xenobiotic with the ability of MDAC to decrease the plasma half-life of that xenobiotic.[21] Although the half-life was not thought to be the best marker of enhanced elimination, it was the only parameter consistently mentioned in all of the studies that otherwise substantially differed from one another with regard to study design. The xenobiotics with the longest intrinsic plasma half-lives seemed to demonstrate the largest percent reduction in plasma half-life when MDAC was used. A subsequent animal model

with therapeutic doses of four simultaneously administered intravenous xenobiotics (acetaminophen, digoxin, theophylline, and valproic acid) clarified the role of pharmacokinetics on the effectiveness of AC.[23] Theophylline, acetaminophen, and valproic acid all have small volumes of distribution. However, of the three, only valproic acid is highly protein-bound at the doses employed, which probably accounted for the inability of AC to increase its clearance. An increased clearance was demonstrated for the three other xenobiotics with MDAC. The most rapid and dramatic effect of MDAC was demonstrated on the clearance of theophylline. Large volumes of distribution alone may not exclude benefit from MDAC. Although digoxin has a large volume of distribution, it requires several hours to distribute from the blood to the tissues. MDAC is beneficial before distribution is complete, and the digoxin still remains accessible in the blood compartment.

The benefits of MDAC undoubtedly depend on a number of patient variables and xenobiotic exposure characteristics. Most important to remember, however, is that volunteer studies do not accurately reflect the overdose situation[84] in which saturation of plasma protein binding, saturation of first-pass metabolism, and acidâ€“base disturbances may make more free xenobiotics available for an enteroenteric effect and therefore more amenable to MDAC use.

Overdose Studies

As noted, MDAC appears to enhance gastrointestinal elimination of many xenobiotics by interfering with enteroenteric circulation, interrupting enterohepatic circulation, and/or minimizing desorption. Shortening the half-life of a xenobiotic in overdose would

logically benefit the patient clinically by limiting the time of associated central nervous system depression, risk of aspiration,

intensive care, nursing hours, and hospitalization, although the actual clinical evidence for these benefits is limited. In a randomized clinical study designed to determine whether these potential benefits could be achieved, some patients who overdosed with phenobarbital were given a single dose of AC, while others were given multiple doses.[111] Although the half-life of phenobarbital was significantly decreased in the MDAC group (36 vs. 93 hours), the length of intubation time required by each group did not differ from one another. This study has been criticized as being too small, having unevenly matched groups, and focusing on a single end point (extubation) that may be dependent on factors other than patient condition (such as the time of day) to determine potential clinical benefit. The most compelling demonstration of the benefits of MDAC in the overdose setting to date comes from a study done in Sri Lanka of patients with severe cardiac toxicity caused by intentional overdose with yellow oleander seeds.[33] An initial dose of 50 g of AC was administered to all patients who were then randomized to 50 g of AC every 6 hours for 3 days or placebo. There were statistically fewer deaths and fewer life-threatening cardiac dysrhythmias in the MDAC group.

Administration of MDAC

An initial loading dose of AC should be administered to adults and children in an AC-to-xenobiotic ratio of 10:1 or 1 g/kg of body weight (if drug exposure amount is unknown). The correct dose and interval of AC for multiple dosing, when it is indicated, is best tailored to the amount and dosage form of the xenobiotic ingested, the severity of the overdose, the potential lethality of the xenobiotic, and the patient's ability to tolerate AC. Benefit should always be weighed against risk. Doses of AC for multiple dosing have varied considerably in the past, ranging from 0.25 to 0.5 g/kg of body weight every 1â€“6 hours, to 20â€“60 g for adults every 1, 2, 4, or 6 hours. There is some evidence that the total dose administered may be more important than the frequency of

administration.[55,130] In some cases, continuous nasogastric administration of AC can be employed, especially when vomiting is a problem.[42,100,130] The editors of this text consider a dose of 0.5 g/kg of body weight every 2 to 4 hours for up to 12 hours to be an appropriate regimen in most circumstances.

Adverse Effects

The adverse effects of MDAC include diarrhea (only when sorbitol-containing charcoal preparations are used), constipation, vomiting with a subsequent risk of aspiration, intestinal obstruction, and reduction of serum concentrations of therapeutically employed xenobiotics.[36,88,92,108] Obviously any complication observed with single-dose AC is a possibility with MDAC.

Summary

When administration is timely, AC is a very effective nonspecific adsorbent. AC should be of benefit to a patient with a potentially life-threatening ingestion involving a xenobiotic still expected to be accessible in the GI tract, adsorbable by AC, and for whom there are no contraindications. MDAC is useful to prevent systemic absorption of a xenobiotic with a prolonged absorptive phase such as a sustained-release formulation. In the postabsorptive phase of managing an exposure, MDAC can decrease the elimination half-lives of a variety of xenobiotics through diverse mechanisms, including gastrointestinal dialysis, thereby providing treatment even to some nonoral xenobiotic overdoses and exposures. For this postabsorptive effect to be of clinical importance the xenobiotic or active metabolite must first be characterized by a lengthy elimination phase, as MDAC is given every 2â€“6 hours. In addition, those xenobiotics with a small volume of distribution or that fit a two-compartment model with a prolonged initial distribution phase, and low or saturable plasma protein binding are theoretically most accessible to MDAC. In both the use of AC and

MDAC care must be taken to avoid pulmonary aspiration and intestinal obstruction. With respect to the use of AC prior to the patient's arrival at the hospital, home availability of AC should be encouraged especially in remote locations where organized healthcare is not immediately available. As more palatable forms of AC are developed, children may accept this agent more readily, but even without such forms, the problems may not be as significant as some believe them to be.[67,69]

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Antidotes in Depth

Whole-Bowel Irrigation and Other Intestinal Evacuants

Mary Ann Howland

Drugs that promote intestinal evacuation are referred to as *laxatives, cathartics*, *purgatives, promotility agents*, and *evacuants*. Using different doses, the same drug may often accomplish any or all of these tasks, but with different side-effect profiles. Laxatives promote a soft-formed or semifluid stool within 6 hours to 3 days, depending on the agent and the dose employed. Cathartics promote a rapid watery evacuation within 1â€“3 hours.[30] Purgatives relate to the force associated with bowel evacuation. Promotility agents stimulate gastrointestinal motor function via the enteric nervous system by affecting acetylcholine, serotonin, or motilin. Evacuants are commonly used to cleanse the bowel prior to a procedure, with an onset of action of as little as 30 to 60 minutes, but typically requiring 4 hours for a more complete effect. The most effective process of evacuating the intestinal tract in poisoned patients is referred to as whole-bowel irrigation (WBI). WBI is typically accomplished using polyethylene

glycol 3350 (PEG) and an added electrolyte lavage solution (PEG-ELS).

The traditional classification of laxatives into the categories of bulk-forming, softener or emollient, lubricant, stimulant or irritant, saline, hyperosmotic, and evacuant is largely empirical. Bulk-forming agents include high-fiber products like methylcellulose, polycarbophil, and psyllium; softeners or emollients include docusate calcium. Mineral oil is the sole lubricant. None of these three classes of agents is employed therapeutically in medical toxicology because their onsets of action are often delayed several days. In addition, softeners cause an increase in intestinal permeability for a few hours and may therefore increase the absorption of some xenobiotics.[69] Mineral oil may enhance the absorption of lipid soluble drugs and aspiration could result in a lipoid pneumonia.[92]

Stimulant or irritant laxatives include anthraquinones (sennosides, aloe, and casanthranol), diphenylmethane (bisacodyl), and castor oil. Abdominal discomfort, cramping, and tenesmus often occur acutely. Long-term use produces bowel habituation and damage to intestinal tissue. Thus, stimulant and irritant laxatives are rarely used today in medical toxicology because of their significant gastrointestinal side effects.

Saline cathartics, which include magnesium citrate, magnesium hydroxide, magnesium sulfate, sodium phosphate, and sodium sulfate, are used cautiously in medical toxicology. Hyperosmotic agents, including sorbitol and lactulose, are also considered in poisoned patients.

When different cathartics were compared with respect to time to first stool and number of stools,[31,38,59,60,80] sorbitol produced 10â€“15 watery stools and the most abdominal cramping before catharsis. Additionally, its taste was rated second to that of magnesium citrate because of its nauseating sweetness. Sorbitol produced stools in the shortest amount of time but with the

highest incidence of nausea and vomiting. In comparison, the first bowel movement should occur about 1 hour after the start of WBI with PEG-ELS. In other studies, sorbitol resulted in nausea, vomiting, generated gas, abdominal cramping, and increased flatus.[34,35,62]

Potential adverse effects associated with cathartics and promotility agents include dehydration, absorption of magnesium or other absorbable electrolytes, hypokalemia and metabolic alkalosis from dehydration, activation of the reninâ€“angiotensinâ€“aldosterone system, and colonic fermentation of digestible sugars. Cathartic-induced rectal prolapse occurred in 2 geriatric patients.[37] The use of repetitive doses of cathartics, either by design or unintentionally, has led to further exaggeration of the serious sequelae such as hypermagnesemia and death. [33,61,76]

Following the use of hypertonic phosphate enemas and oral sodium phosphate, hypocalcemia, hyperphosphatemia, and hypokalemia were reported.[19,25,27,44,49,70,78] In many of these cases, the recommended dose of the therapeutic agent was used.[19] Frail elderly patients, children, and those with decreased renal function may be most susceptible to adverse effects.[9,11]

Multiple-dose activated charcoal regimens containing 70% sorbitol used to enhance elimination resulted in severe cathartic-related adverse effects in 4 case reports.[1,24,43,53] The potential for sorbitol related adverse events from the unintentional use of repetitive activated charcoal (AC) dosing was emphasized by a survey revealing that 16% of hospitals surveyed only stocked AC premixed with sorbitol.[93] The retention of sorbitol after repetitive doses in an aperistaltic gut may lead to significant morbidity due to the gas formation and abdominal distension as a result of the digestive action of gut bacteria.[43]

Mechanism of Action

The effects of saline cathartics are largely attributed to their relatively nonabsorbable ions that establish an osmotic gradient and draw water into the gut. The increased water leads to increased intestinal pressure and a subsequent increase in intestinal motility.[17] Magnesium ion also releases cholecystokinin from the duodenal mucosa, which stimulates intestinal motor activity and alters fluid movement, contributing to its effect.[12,79] The hyperosmotic laxatives, including sorbitol, lactulose, and glycerin, also draw water into the gut and produce diarrhea.

Polyethylene glycol is a nonabsorbable, isoosmotic indigestible agent that remains in the colon and together with the water diluent is evacuated, resulting in WBI without producing flatus and cramps. Electrolytes are added to limit the ensuing electrolyte and fluid shifts. Many studies of WBI using PEG-ELS demonstrate patient acceptance, effectiveness, and safety when used for bowel preparation.[3,10,18,20,22,68,84,87]

Promotility agents such as metoclopramide and erythromycin stimulate gut motor function. Metoclopramide does this through gastrointestinal $5HT_4$ receptor agonist and D_2 receptor antagonist activity that together increase acetylcholine release and gastrointestinal motility. Erythromycin also stimulates gut motor function but via direct stimulation of gastrointestinal motilin receptors.[66]

Gastrointestinal Evacuation and Poison Management

Although recommended for basic poison management for many years, cathartics should not be used routinely in the management of overdosed patients.[5] Intuitively, the advantages of cathartics appear to result from their ability to decrease the potential for constipation or obstruction from AC and hasten the delivery of AC

to the small intestine. However, these theoretical advantages have never been demonstrated clinically.

Studies demonstrate that when administered alone, cathartics such as sorbitol or sodium sulfate may decrease peak and/or total absorption of some drugs, but no study has achieved results comparable to that of AC alone.[2,16,52,67,91] When comparing the efficacy of a single dose of AC alone with that of AC plus a single dose of cathartic, studies suggest the combination to be equal to,[2,56,65,67,75] slightly better than,[16,34] or slightly worse than AC alone.[52,91]

WBI with PEG-ELS is currently advocated to hasten the elimination of poorly absorbed xenobiotics or sustained-release medications before they can be absorbed. This approach is theoretically sound, and does not produce the fluid and electrolyte complications associated with cathartics. Unfortunately, evidence of efficacy is limited to anecdotal case reports and volunteer studies.

Although animal models suggest WBI may enhance systemic clearance via gastrointestinal dialysis, much like multiple-dose activated charcoal (MDAC),[42] low flow rates, the typical delay in administering WBI in actual clinical situations, and the inconvenience of this procedure make it highly unlikely that enhanced systemic clearance can be achieved in humans.

In human volunteer studies, WBI was more effective than single-dose AC or MDAC for acetylsalicylic acid (ASA),[35] decreased peak lithium (Li) and Li AUC (area under the [plasma drug concentration versus time] curve) compared to control,[77] decreased the bioavailability of two sustained-release medications,[15,40] and propelled radiopaque markers through the gut more efficiently than control.[46]

Not unexpectedly, WBI was inferior to AC with regard to prevention of absorption when administered following 650 mg of immediate-release aspirin.[73] Additionally, once aspirin was

absorbed, WBI was unable to enhance systemic clearance.[51]

There are reports of successful use of WBI in the management of overdoses of iron,[23,48,82,83] sustained-release theophylline,[32] sustained-release verapamil,[13] zinc sulfate,[14] lead,[55,57,63,72] mercuric oxide powder,[45] arsenic-containing herbicide,[41] delayed-release fenfluramine,[58] and for body packers.[29,85,89] Although some clinicians express enthusiasm for the use of WBI for a variety of ingestions, others question its efficacy.[14,74,81] Whole-bowel irrigation for 5 hours following ingestion of 10 fluorescent coffee beans by each of 7 volunteers removed an average of only 4 beans (range, 1â€“8).[74] Similar failures were reported with jequirity beans[81] and button batteries.[82] It can be argued that because of their physical characteristics (density, solubility, size), these agents might not be representative of substances amenable to whole-bowel irrigation. Additionally, the experience of the editors of this text in caring for body packers demonstrates that whole-bowel irrigation may not always evacuate all of the drug packets because of inadequate dosing, partial obstruction, or the nature of the procedure. As a result of these failures, promotility agents were successfully added to WBI to enhance bowel evacuation in two body packers suspected of having ingested well-constructed drug packets.[86]

Adverse Effects of WBI

Adverse effects resulting from the use of WBI with PEG-ELS include vomiting, particularly following rapid administration, abdominal bloating, fullness, cramping, flatulence, and pruritus ani. Typically, the patient will need to remain on a commode for 4â€“6 hours to complete the procedure. Slow or low-volume administration of PEG-ELS results in sodium absorption. If a total of 500 mL of PEG-ELS were used instead of multiple liters, potentially 1.5 g of sodium may be absorbed.[21] This adverse effect may have resulted in the exacerbation of congestive heart failure

in an unstable patient with cardiac and renal dysfunction.[26]

An unusual complication of WBI is colonic perforation, which occurred in a patient with severe diverticulitis.[39] Other adverse effects noted by the manufacturer include isolated reports of upper GI bleeding from a Mallory-Weiss tear, esophageal perforation, aspiration pneumonitis after vomiting, and acute lung injury.

Unfortunately, administration of PEG-ELS by other than the enteral route has occurred. A 4-year-old child inadvertently received 390 mL of PEG-ELS intravenously with no obvious adverse result.[71] In contrast, acute lung injury developed in an 11-year-old child administered PEG-ELS through a nasogastric tube inadvertently inserted in the trachea.[64]

Interaction of AC and WBI

Several in vitro studies demonstrate that the addition of PEG-ELS to AC significantly decreases the adsorptive capacity of AC.[8,28,47] Some interactions were affected by pH and magnified by high ratios of PEG-ELS to AC.[7,36,47] The most likely explanation is competition with the AC surface for solute adsorption. Additionally, in an animal model, whole-bowel irrigation appeared to have an adverse effect by washing the AC away from the sustained-release theophylline.[15]

Contraindications

Contraindications to whole-bowel irrigation include prior, current or anticipated diarrhea; volume depletion; significant gastrointestinal pathology or dysfunction such as ileus, perforation, colitis, toxic megacolon, hemorrhage, and obstruction; an unprotected or compromised airway; and hemodynamic instability.[4,82]

Dosing

The recommended dose of WBI with PEG-ELS solutions is 0.5 L/h or 25 mL/kg/h for small children and 1.5â€“2 L/h or 20â€“30 mL/min for adolescents and adults. WBI solution may be administered orally or through a nasogastric tube for 4â€“6 hours or until the rectal effluent becomes clear. If the xenobiotic being removed is radiopaque, a diagnostic imaging technique demonstrating the xenobiotic's absence may serve as a reasonable clinical end point. An antiemetic such as metoclopramide or a serotonin antagonist may be required for the treatment of nausea or vomiting. Whole-bowel irrigation

with large volumes of fluid was used successfully in 2 pregnant women at 38 and 26 weeks of gestation.[88,90]

Available Forms of PEG-ELS for WBI

The original WBI solution was GoLYTELY from Braintree. This solution contained PEG with electrolytes and sodium sulfate as an added laxative. Colyte is manufactured by Schwartz Pharma and is very similar to GoLYTELY. Braintree later introduced NuLYTELY, a PEG formulation with 52% less total salt than GoLYTELY and no added sodium sulfate. These changes in formulation decreased the salty taste and the chances for fluid or electrolyte abnormalities.[54] NuLYTELY is available in flavors. The following lists the composition of the 3 available PEG-ELS products. All are prepared by filling the container to the 4-L mark with water and shaking vigorously several times to ensure dissolution. Lukewarm water facilitates dissolution but chilling afterward improves palatability. Chilled solutions, however, are not recommended for infants because of the risk of hypothermia. The product is stable with refrigeration for 48 hours after reconstitution.

GoLYTELY contains 236 g (17.6 mmol/L) polyethylene glycol 3350, 22.74 g sodium sulfate (anhydrous) (sulfate 40 mmol/L), 6.74 g sodium bicarbonate (bicarbonate 20 mmol/L), 5.86 g sodium

chloride (total sodium 125 mmol/L), and 2.97 g potassium chloride (potassium 10 mmol/L and total chloride 35 mmol/L). Colyte contains 240 g (18 mmol/L) polyethylene glycol 3350, 22.72g sodium sulfate (anhydrous) (40 mmol/L sulfate), 6.72 g sodium bicarbonate (20 mmol/L bicarbonate), 5.84 g sodium chloride (total sodium 125 mmol/L), and 2.98 g potassium chloride (potassium 10 mmol/L and total chloride 35 mmol/L). NuLYTELY contains 420 g polyethylene glycol 3350, 5.72 g sodium bicarbonate, 11.2 g sodium chloride, and 1.48 g potassium chloride.

MiraLax by Braintree (prescription only) contains PEG 3350 powder meant for oral administration after dissolution in water, juice, or soda. It is indicated for occasional constipation, with a recommended dose of 1 heaping teaspoon (17 g) in 240 mL liquid per day. For MiraLax to be useful in WBI, it would need to be administered at a dose of 2 L/h (8 heaping teaspoons in 2 L of water/h) in adults. This is not recommended for WBI because it does not contain any added electrolytes and may result in an electrolyte imbalance.

Summary

Cathartics should never be considered part of routine management of poisoning and overdose in either children or adults. Cathartics should never be used as an AC substitute when xenobiotics known to be adsorbed to AC are involved. Moreover, when total xenobiotic absorption is evaluated, a single dose of a cathartic given with AC appears to be only about as efficacious as AC given alone.

Although investigators have also studied the rapidity of stools resulting from the use of various cathartics, promotility agents, and WBI, administering a cathartic just to produce a faster onset of charcoal stools has never been shown to produce a better clinical outcome. In adults, when large amounts of xenobiotics

have been ingested or when desorption from charcoal may be an important consideration (such as with aspirin), a single dose of a cathartic, preferably magnesium citrate or sorbitol, may be given with the AC. When MDAC is being administered, if a cathartic is used at all, it should only be given with the first dose. Sufficient oral fluids should always be administered with a cathartic to avoid inspissation and dehydration. Unless contraindicated, WBI is preferable to repetitive dose cathartics for evacuation of sustained-release or poorly soluble xenobiotics not adsorbed to AC.

The precise role of WBI and the interactions between AC and PEG-ELS in the overdosed patient remain to be defined. There have been no controlled clinical studies assessing outcome, although theoretically, ingestions of sustained-release xenobiotics (theophylline, glyburide XL, verapamil), xenobiotics not adsorbed by charcoal (iron, lead, lithium), and drug packets (in body packers) may be amenable to the use of WBI. An added advantage of using PEG-ELS WBI is that should the patient require endoscopy, diagnostic imaging, or surgery, the gastrointestinal tract may be more easily visualized, facilitating the intervention or procedure. Activated charcoal should be given to those patients for whom it is indicated, and if WBI is being performed in conjunction, a comparable dose of AC should be given following the WBI to prevent or overcome the potential xenobiotic desorption and possible further systemic absorption of the xenobiotic.

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Chapter 9

Pharmacokinetic and Toxicokinetic Principles

Mary Ann Howland

Xenobiotics are foreign to the body and include natural or synthetic chemicals, drugs, pesticides, environmental agents, and industrial agents.[43] *Pharmacokinetics* is the study of the absorption, distribution, metabolism, and excretion of xenobiotics. Mathematical models and equations are used to describe and to predict this behavior. *Pharmacodynamics* is the term used to describe an investigation of the relationship of xenobiotic concentration to clinical effect. *Toxicokinetics*, which is analogous to pharmacokinetics, is the study of the absorption, distribution, metabolism, and excretion of a xenobiotic under circumstances that produce toxicity or excessive exposure. *Toxicodynamics*, which is analogous to pharmacodynamics, is the study of the relationship of toxic concentrations of xenobiotics to clinical effect.

Humans with overdoses provide many challenges to the mathematical precision of toxicokinetics and toxicodynamics because many of the variables (eg, dose, time of ingestion, presence of vomiting) that

affect the result are often unknown. In contrast to the therapeutic setting, atypical solubility characteristics are noted and saturation of enzymatic processes occurs. Alterations in enzymatic saturation and protein binding may lead to enhanced absorption (decreased first-pass effect), more free drug available in the serum because of saturation of plasma protein binding, or prolonged elimination because of saturation of hepatic enzymes or active renal tubular secretion. In addition, age, obesity, gender, genetics, chronopharmacokinetics (diurnal variations), and the effects of critical illness and compromised organ perfusion all further inhibit attempts to achieve precise analyses.[3,15,35,40,61,65] In addition, various treatments may alter one or more kinetic parameters. There are numerous approaches to recognizing these variables, such as obtaining historical information from the patient's family and friends, performing pill counts, procuring sequential serum concentrations during the phases of toxicity, and occasionally repeating a pharmacokinetic evaluation during therapeutic dosing of that same agent to obtain comparative data.

Despite all of the confounding and individual variability, toxicokinetic principles can, nonetheless, be applied to facilitate our understanding and to make certain predictions. These principles can be used to help evaluate whether a certain antidote or extracorporeal removal method is appropriate for use, when the serum concentration might be expected to drop into the therapeutic range (if one exists), what ingested dose might be considered potentially toxic, what the onset and duration of toxicity might be, and what the importance is of a serum concentration. While considering all of these factors, the clinical status of the patient is paramount, and mathematical formulas and equations can never substitute for evaluating the patient. This chapter explains the principles, presents the mathematics in a â€œuser-friendlyâ€• fashion,[72] and demonstrates the application of these principles and mathematical approaches by example and case illustration.

Absorption

Absorption is the process by which a xenobiotic enters the body. For an agent to cause a systemic effect, it must reach the bloodstream and then be distributed to the site or sites of action. Both the rate (k_a) and extent of absorption (F) are measurable and important determinants of toxicity. The rate of absorption often predicts the onset of action and relies on dosage form, while the extent of absorption (*bioavailability*) often predicts the intensity of the effect and depends in part on first-pass effects.[32,33] Figure 9-1 depicts how changes in the rate of absorption may affect toxicity when the bioavailability is held constant versus how toxicity may be affected by changes in bioavailability when the rate of absorption is held constant.

The route by which the xenobiotic enters the body significantly affects both the rate and extent of absorption. As an approximation, the rate of absorption proceeds in the following order from fastest to slowest: intravenous, inhalation > intramuscular, subcutaneous, intranasal, oral > cutaneous, rectal. Following the oral intake of 200 mg of cocaine hydrochloride, the onset of action is 20 minutes, with an average peak concentration of 200 ng/mL.[64] In marked contrast, smoking 200 mg of cocaine freebase results in an onset of action of 8 seconds and a peak level of 640 ng/mL, or when administered intravenously as 200 mg cocaine hydrochloride, which then has an onset of action of 30 seconds and a peak level of 1000 ng/mL.[64]

A xenobiotic must diffuse through a number of membranes before it can reach its site of action. Figure 9-2 shows the number of membranes through which a xenobiotic typically diffuses. Membranes are predominantly composed of phospholipids and cholesterol in addition to other lipid compounds.[48] A phospholipid is composed of a polar head and a fatty acid tail, which are arranged

in membranes so that the fatty acid tails are inside and the polar heads face outward in a mirror image.[52] Proteins (in a 1:5 ratio with

lipids) are found on both sides of the membranes and may traverse the membrane.[48] These proteins may function as receptors and channels. Pores are found throughout the membranes. The principles relating to diffusion apply to absorption, distribution, certain aspects of elimination, and to each instance when a xenobiotic is transported through a membrane.

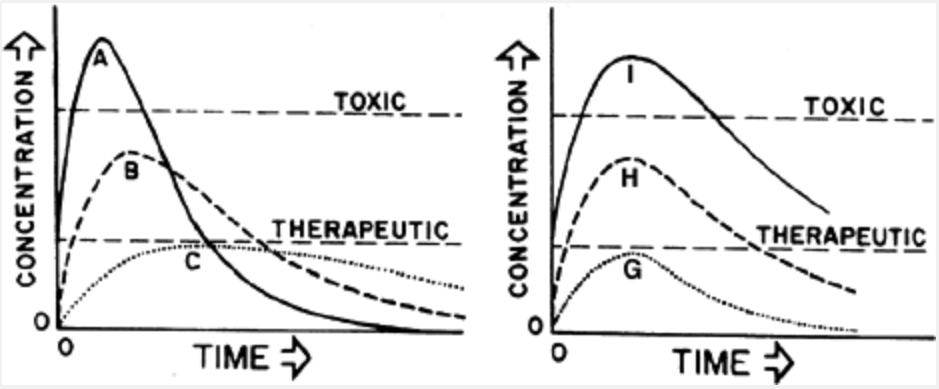


Figure 9-1. Effects of changes in k_a (rate of absorption) and F (bioavailability) on the blood concentration time graph and achieving a toxic threshold. In curves A, B, and C, F is constant as k_a is decreased. In curves G, H, and I, k_a is constant as F is increased. *(Reprinted, with permission, from Riviere JE: Absorption and distribution. In: Hodgson E, Levi P, eds: Introduction to Biochemical Toxicology. Norwalk, CT, Appleton & Lange, 1994, p. 22.)*

Transport through membranes occurs via passive diffusion through the membrane, filtration (bulk flow is the major mechanism of transport which occurs with water directly through water pores [aquapores] for small molecules with a molecular weight [MW] < 100), carrier-mediated active or facilitated transport, and, rarely, endocytosis (Fig. 9-3). Most xenobiotics traverse membranes via

simple passive diffusion. The rate of diffusion is determined by the Fick Law of Diffusion (Eq. 9-1).

$$\text{Rate of diffusion} = \frac{dQ}{dt} = \frac{DAK(C_1 - C_2)}{h}$$

D = diffusion constant
A = surface area of the membrane
h = membrane thickness
K = partition coefficient
$C_1 - C_2$ = difference in concentrations of the xenobiotic at each side of the membrane

(Eq. 9–1)

The driving force for passive diffusion is the difference in concentration of the xenobiotic on both sides of the membrane. D is a constant for each xenobiotic and is derived when the difference in concentrations between the two sides of the membrane is 1. The larger the surface area A, the higher the rate of diffusion. Most ingested xenobiotics are absorbed more rapidly in the small intestine than in the stomach because of the tremendous increase in surface area created by the presence of microvilli. The partition coefficient K represents the lipid-to-water partitioning of the xenobiotic. To a substantial degree, the more lipid soluble a xenobiotic is, the more easily it crosses membranes. Membrane thickness (h) is inversely proportional to the rate at which a xenobiotic diffuses through the membrane. Xenobiotics that are uncharged, nonpolar, of low molecular weight, and of the appropriate lipid solubility have the highest rates of diffusion.

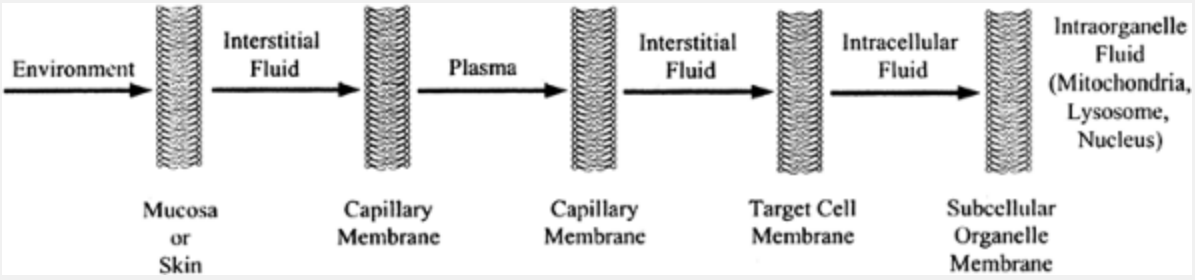


Figure 9-2. Illustration of the number of membranes encountered by a xenobiotic in the processes of absorption and distribution. *(Adapted from Riviere JE: Absorption and distribution. In: Hodgson E, Levi P, eds: Introduction to Biochemical Toxicology. Norwalk, CT, Appleton & Lange, 1994, p. 12.)*

The extent of ionization of weak electrolytes (weak acids and weak bases) affects their rate of passive diffusion. Nonpolar and uncharged molecules penetrate faster. The Henderson-Hasselbalch relationship is used to determine the degree of ionization. An acid (HA), by definition, gives up a hydrogen ion and a base (B), accepts a hydrogen ion. RCOOH (HA) (ie, aspirin, phenobarbital) and RNH_3^+ (BH^+) are acids and $RCOO^-$ (A^-) and RNH_2(B) (amphetamines, tricyclic antidepressants [TCAs]) are bases. The equilibrium dissociation constant K_a can then be described by Equations 9-2A and 9-2B.

$$\text{For weak acids: } HA = H^+ + A^- \qquad K_a = \frac{[H^+][A^-]}{[HA]} \qquad \text{(Eq. 9–2A)}$$

$$\text{For weak bases: } BH^+ = B + H^+ \qquad K_a = \frac{[H^+][B]}{[BH^+]} \qquad \text{(Eq. 9–2B)}$$

To work with these numbers in a more comfortable fashion, the negative log of both sides is determined and results in Equations 9-3A and 9-3B.

$$\text{For weak acids: } -\log K_a = -\log [H^+] - \log \frac{[A^-]}{[HA]} \qquad \text{(Eq. 9–3A)}$$

$$\text{For weak bases: } -\log K_a = -\log [H^+] - \log \frac{[B]}{[BH^+]} \qquad \text{(Eq. 9–3B)}$$

Type of Transport	Example
Diffusion	Nonelectrolytes (ethanol) and unionized forms of weak acids (salicylic acid) and bases (phenobarbital)
Filtration and bulk flow	Molecules of varying sizes
Endocytosis	Sabin polio virus vaccine
Facilitated	5-Fluorouracil Lead Methyldopa Thallium
Active	Thiamine Pyridoxine

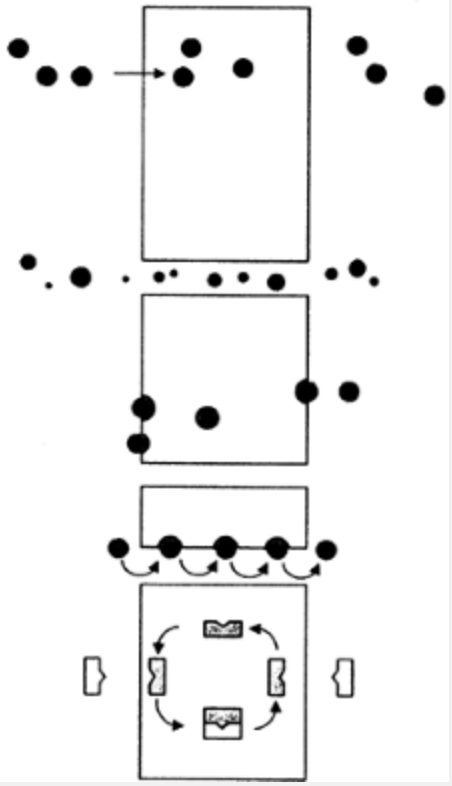


Figure 9-3. Illustration of transport mechanisms involved in the

passage of xenobiotics across membranes. *(Adapted from Gram TE: Drug absorption and distribution. In: Craig CR, Stitzel RE, eds: Modern Pharmacology with Clinical Applications. Boston, Little, Brown, 1997, p. 17.)*

By definition, the negative log of $[H^+]$ is expressed as pH and the negative log of K_a is pK_a. Rearranging the equations gives the familiar forms of the Henderson-Hasselbalch equations as shown in Equations 9-4A, 9-4B, and 9-4C.

$$pH = pK_a + \log \frac{\text{unprotonated species}}{\text{protonated species}} \qquad \text{(Eq. 9–4A)}$$

$$\text{For weak acids: } pH = pK_a + \log \frac{[A^-]}{[HA]} \qquad \text{(Eq. 9–4B)}$$

$$\text{For weak bases: } pH = pK_a + \log \frac{[B]}{[BH^+]} \qquad \text{(Eq. 9–4C)}$$

Because noncharged molecules traverse membranes more rapidly, it is understood that weak acids cross membranes more rapidly in an acidic environment and weak bases move more rapidly in a basic environment. When the pH equals the pK_a, half of the xenobiotic is charged and half is noncharged. An acid with a low pK_a is a strong acid while a base with a low pK_a is a weak base. For an acid, a pH less than the pK_a favors the protonated or noncharged species facilitating membrane diffusion, whereas for a base, a pH greater than the pK_a achieves the same result. Table 9-1 lists the pH of selected body fluids and Figure 9-4 illustrates the extent of charged versus noncharged xenobiotic at different pH and pK_a values.

Lipid solubility and ionization each have a distinct influence on absorption. Figure 9-5 demonstrates these characteristics for three different xenobiotics. Although the three xenobiotics have similar pK_a values, their different partition coefficients result in different degrees of absorption from the stomach.

Specialized transport mechanisms either require energy (adenosine triphosphate [ATP] dependent) to transport xenobiotics against a concentration gradient (active transport), or they can be energy independent (ATP independent) and lack the ability to transport against a concentration gradient (facilitated transport). These transport mechanisms are of importance in numerous parts of the body including the intestines, liver, lungs, kidneys, and the biliary systems. These same principles apply to a small number of lipid-insoluble molecules that resemble essential endogenous agents.[24,57] For example, 5-fluorouracil resembles pyrimidine and is transported by the same system, whereas thallium and lead are actively absorbed by the endogenous transport mechanisms that absorb and transport potassium and calcium, respectively.

TABLE 9-1. pH of Selected Body Fluids

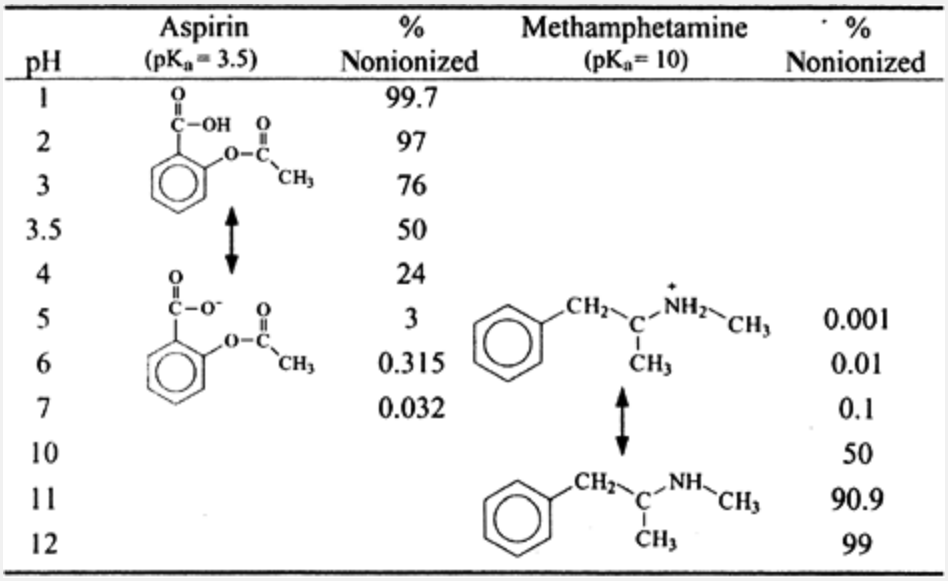
Fluids	pH
Cerebrospinal	7.3
Eye	7â€“8
Gastric secretions	1â€“3
Large intestinal secretions	8
Plasma	7.4
Rectal fluid: infants and children	7.2â€“12

Saliva	6.4â€“7.2
Small intestinal secretions: duodenum	5â€“6
Small intestinal secretions: ileum	8
Urine	4â€“8
Vaginal secretions	3.8â€“4.5

Adapted from Brody TM: Absorption, distribution, metabolism and elimination. In: Brody TM, Larner J, Minneman KP, Neu HC, eds: Human Pharmacology: Molecular to Clinical, 2nd ed. St. Louis, Mosby, 1994, p. 51.

P-glycoprotein is a transmembrane protein that is an example of a carrier used for carrier-mediated, active (ATP-dependent) transport. P-glycoprotein is being extensively investigated because of its role in controlling xenobiotic entry into the body and because of its contribution to drug interactions.[18,28,66] The discovery of P-glycoprotein resulted from an investigation into why certain tumors exhibit multidrug resistance to many cancer chemotherapy agents. P-glycoprotein is an efflux transporter located in the intestines, renal proximal tubule, hepatic bile canaliculi, and bloodâ€“brain barrier that is responsible for transporting compounds from inside to outside the cell.[14] First-generation transport inhibitors such as amiodarone, ketoconazole, quinidine, and verapamil are responsible for increasing body levels of P-glycoprotein substrates such as digoxin, the protease inhibitors, vinca alkaloids, and paclitaxel. St. John's wort is a transport inducer, and lowers serum concentrations of these same

agents. Second- and third-generation agents that will affect transport with a higher affinity and specificity are in development.[58] Many of the same agents that affect cytochrome P450 (CYP) 3A4 also affect P-glycoprotein.



pH	Aspirin (pK_a = 3.5)	% Nonionized	Methamphetamine (pK_a = 10)	% Nonionized
1		99.7		
2		97		
3		76		
3.5		50		
4		24		
5		3		0.001
6		0.315		0.01
7		0.032		0.1
10				50
11				90.9
12				99

Figure 9-4. Effect of pH on the ionization of aspirin (pK_a = 3.5) and methamphetamine (pK_a = 10).

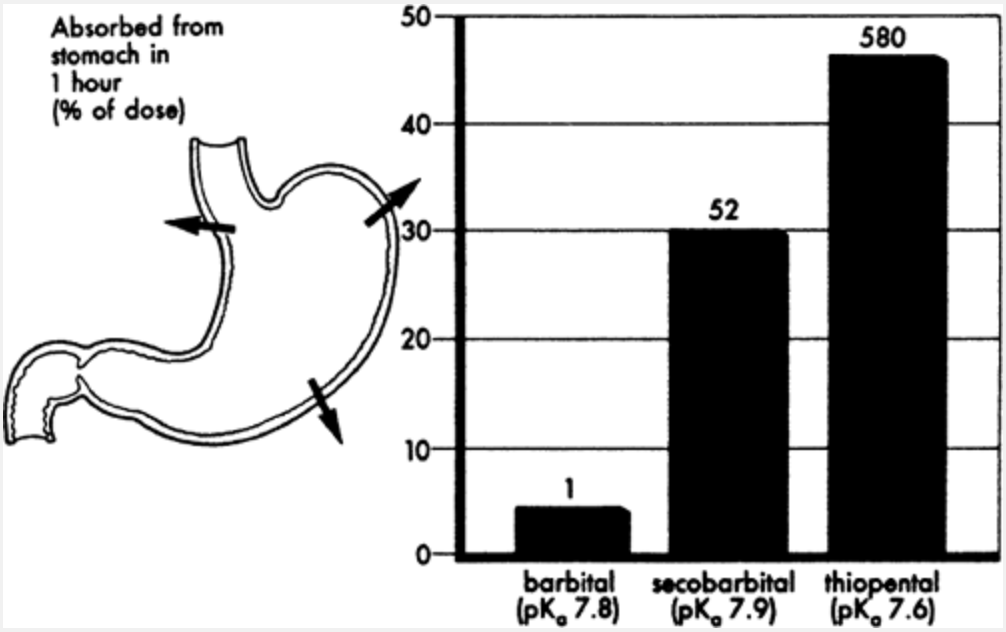


Figure 9-5. Influence of increasing lipid solubility on the amount of xenobiotic absorbed from the stomach for three xenobiotics with similar pK_a values. The number above each column is the oil/water equilibrium partition coefficient. *(Reprinted, with permission, from Brody T: Absorption, distribution, metabolism and elimination. In: Brody TM, Larner J, Minneman KP, Neu HP, eds: Human Pharmacology: Molecular to Clinical, 2nd ed. St. Louis, Mosby, 1994, p. 50.)*

Filtration is generally considered to be of limited importance in the absorption of most xenobiotics, but is substantially more important with regard to elimination. Endocytosis, which describes the encircling of a xenobiotic by a cellular membrane, is responsible for the absorption of large macromolecules such as the oral Sabin polio vaccine.[57]

Gastrointestinal absorption is affected by xenobiotic-related characteristics such as dosage form, degree of ionization, partition

coefficient, and patient factors such as gastrointestinal blood flow, gastrointestinal motility, and the presence or absence of food, ethanol, or other interfering substances (Fig. 9-6).

The formulation of a xenobiotic is extremely important in predicting GI absorption. Disintegration and dissolution must precede absorption. Controlled-release, extended-release, and sustained-release formulations are designed to release the xenobiotic over a prolonged period of time in order to simulate the blood concentrations achieved with the use of a constant intravenous infusion. These formulations minimize blood level fluctuations, reduce peak-related side effects, reduce dosing frequency, and improve patient compliance. A variety of products employ different pharmaceutical strategies, including dissolution control (encapsulation or matrix; Feosol), diffusion control (membrane or matrix; Slow K, Plendil ER), erosion (Sinemet CR), osmotic pump systems (Procardia XL, Glucotrol XL), and ion exchange resins (MS Contin suspension). Overdoses with controlled-release formulations result in a prolonged absorption phase, a delay to peak concentrations, and a prolonged duration of effect.[7] Enteric-coated (acetylsalicylic acid [ASA], divalproex sodium) formulations resist disintegration and delay the time to onset of effect.[6] Dissolution is affected by ionization, solubility, and the partition coefficient, as noted earlier. In the overdose setting, the formation of poorly soluble or adherent masses such as concretions (meprobamate) and bezoars (bromide) significantly delays the time to onset of toxicity (Table 9-2).[4,9,25,26]

Most ingested xenobiotics are primarily absorbed in the small intestine as a result of the large surface area and extensive blood flow of the small intestines.[53] Critically ill patients who are hypotensive, have a reduced cardiac output, or are receiving vasoconstrictors such

as norepinephrine, have a decreased perfusion of vital organs, including the GI tract, kidneys, and liver.[3] Not only is absorption

delayed, but elimination is also diminished.[51] Extremely short gastrointestinal transit times reduce absorption. This change in transit time is the unproven rationale for our prior substantial use of cathartics and current use of whole-bowel irrigation. Delays in emptying of the stomach impair absorption as a result of the delay in delivery to the small intestine. Delays in gastric emptying occur as a result of the presence of food, especially fatty meals; agents with anticholinergic, opioid, or antiserotonergic properties; ethanol; and any agent that results in pylorospasm (salicylates, iron).

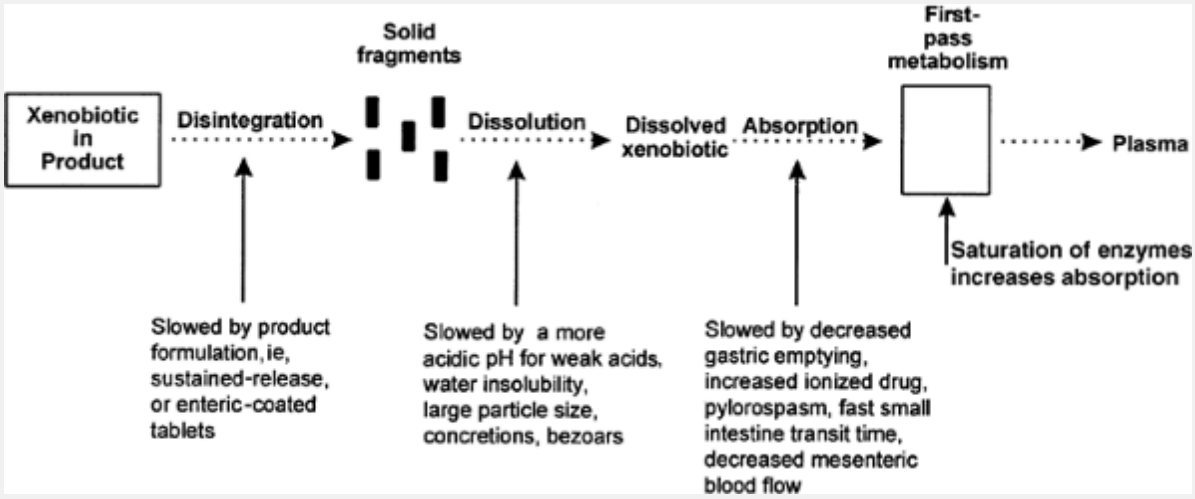


Figure 9-6. Determinants of absorption.

Bioavailability is a measure of the amount of xenobiotic that reaches the systemic circulation unchanged (Eq. 9-5).[34] The fractional absorption (F) of a xenobiotic is defined by the area under the plasma drug concentration versus time curve (AUC) of the designated route of absorption as compared to the AUC of the intravenous route. The AUC for each route represents the amount absorbed.

$$F = \frac{(AUC)_{\text{route under study}}}{(AUC)_{IV}} \qquad \text{(Eq. 9–5)}$$

Gastric emptying and activated charcoal are used to decrease the bioavailability of ingested xenobiotics. The oral administration of certain chelators (deferoxamine, D-penicillamine) actually enhances the bioavailability of the complexed xenobiotic. The net effect of some chelators, such as succimer, is a reduction in body burden via enhanced urinary elimination even though absorption is enhanced.[27] Historically, the enteral administration of sodium bicarbonate was used to theoretically reduce the solubility of iron salts; unfortunately, this approach was ineffective.[13]

Presystemic metabolism may decrease or increase the bioavailability of a xenobiotic or a metabolite.[47] The GI tract contains microbial organisms that can metabolize or degrade xenobiotics such as digoxin and oral contraceptives, and enzymes such as peptidases that metabolize insulin.[48] However, in rare cases, gastrointestinal hydrolysis can convert a xenobiotic into a toxic metabolite, as occurs when amygdalin is enzymatically hydrolyzed to produce cyanide, a metabolic step that is not produced following intravenous amygdalin administration.[23] Xenobiotic metabolizing enzymes and P-glycoprotein can also affect bioavailability. Xenobiotic metabolizing enzymes are found in the lumen of the small intestine and can substantially decrease the absorption of a xenobiotic.[39,66] Some of the xenobiotic that enters the cell can then be removed by the P-glycoprotein transporter out of the cell and back into the lumen to be exposed again to the metabolizing enzymes.[39,66] Venous drainage from the stomach and intestine delivers orally (and intraperitoneally) administered xenobiotics to the liver via the portal vein and avoids direct delivery to the systemic circulation. This venous drainage allows hepatic metabolism to occur before the xenobiotic reaches the blood and is referred to as the *first-pass effect*.[2,69] The hepatic extraction ratio is the percentage of xenobiotic metabolized in one pass of blood through the liver.[42] Drugs that undergo significant first-pass metabolism (eg, propranolol, verapamil) are used at much lower IV doses than oral doses. Some drugs are not administered by the oral route at all because of significant first-pass effect (eg,

lidocaine, nitroglycerin).[4] Instead, sublingual or rectal administration of agents such as nitroglycerin is used to bypass the portal circulation and avoid first-pass metabolism. In the overdose setting, presystemic metabolism may be saturated, leading to an increased bioavailability of xenobiotics such as cyclic antidepressants, phenothiazines, opioids, and many Î²-adrenergic antagonists.[50] Hepatic metabolism usually transforms the xenobiotic into a less-active metabolite, but occasionally results in the formation of a more toxic agent such as occurs with the transformation of parathion to paraoxon.[45] Biliary excretion into the small intestine usually occurs for these transformed xenobiotics of molecular weights >350 daltons and may result in a xenobiotic appearing in the feces, even though it had not been administered orally.[30,48,60] Hepatic conjugated metabolites such as glucuronides may be hydrolyzed in the intestines to the parent form or to another active metabolite that can be reabsorbed by the enterohepatic circulation.[36,43,46,48] The enterohepatic circulation may be responsible for what is termed a double-peak phenomenon following the administration of certain xenobiotics.[57] The double-peak phenomenon is characterized as a serum concentration which falls and then rises again as xenobiotic is reabsorbed from the GI tract.

Other causes include variability in stomach emptying, presence of food, or failure of a tablet dosage form.[57]

TABLE 9-2. Xenobiotics that Form Concretions or Bezoars, Delay Gastric Emptying, and/or Result in Pylorospasm

Anticholinergics	Meprobamate
Barbiturates	Methaqualone
Bromides	Opioids
Enteric-coated tablets	Phenytoin
Glutethimide	Salicylates
Iron	Verapamil

Distribution

After the xenobiotic reaches the systemic circulation or central compartment, it is available for transport to peripheral tissue compartments. Both the rate and extent of distribution depend on many of the same principles discussed with regard to diffusion. Additional factors include affinity of the xenobiotic for plasma and tissue proteins, acidâ€“base status of the patient (which affects ionization), and physiologic barriers to distribution (bloodâ€“brain barrier, placental transfer, bloodâ€“testis barrier).[20,31,52] Blood flow accounts for the initial phase of distribution, whereas xenobiotic affinities determine the final distribution pattern. Hypoperfusion of the various organs in the critically ill affects absorption, distribution, and elimination.[67]

Plasma and serum concentrations are terms often used

interchangeably by medical personnel. When a reference or calculation is made with regard to a concentration in the body, it is actually a plasma concentration. When concentrations are measured in the laboratory, a serum concentration (clotted and centrifuged blood) is often determined. In reality, the laboratory measurements of most xenobiotics in serum or plasma are nearly equivalent. Frequently, this is not the case for whole-blood determination if the xenobiotic distributes into the erythrocyte, such as lead and most other heavy metals.

Volume of distribution (Vd) is the proportionality term used to relate the dose of the xenobiotic that the individual receives and the resultant plasma concentration. Vd is an apparent or theoretic volume into which a xenobiotic distributes. It is a measure of how much xenobiotic is located inside and outside of the plasma compartment, because only the plasma compartment is routinely assayed. In a 70-kg adult male, the total body fluid (TBF) is 60% of total body weight or 42 L, with two-thirds (28 L) of the fluid accounted for by intracellular fluid. Of the 14 L of extracellular fluid, 8 L are considered interstitial or between the cells; 3 L, or 0.04 L/kg, is plasma; and 6 L, or 0.08 L/kg, is blood. If 42 g of a xenobiotic is administered and remains in the plasma compartment (Vd = 0.04 L/kg), the concentration would be 15 g/L. If the distribution of the 42 g of xenobiotic approximated TBF (methanol; 0.6 L/kg), the concentration would be 100 mg/dL. These calculations can be performed by using Equation 9-6, where S equals the percent pure drug if a salt form is used.

$$V_d = \frac{S \times F \times \text{dose (mg)}}{C_0} \qquad \text{(Eq. 9–6)}$$

Experimental determination of a Vd involves administering an IV dose of the xenobiotic and extrapolating the plasma concentration time curve back to time zero (C_0). If the determination takes place after steady state has been achieved, the volume of distribution is then referred to as the Vdss. For many xenobiotics the Vd is known and

readily available in the literature (Table 9-3). When the Vd and the dose ingested are known, a maximum predicted plasma concentration can be calculated, after assuming all of the xenobiotic is absorbed and no elimination occurred. This assumption usually overestimates the plasma concentration. Distribution is complex, and differential affinities for various storage sites (plasma proteins, liver, kidney, fat, and bone) in the body determine where a xenobiotic ultimately resides.

For the purposes of determining the utility of extracorporeal removal of a xenobiotic, a low Vd is often considered to be <1 L/kg. For some xenobiotics, as digoxin (Vd = 5 L/kg) or the cyclic antidepressants (Vd =10â€“15 L/kg), the Vd is much larger than the actual volume of the body. A large Vd indicates that the xenobiotic resides outside of the plasma compartment, but, again, it does not describe the site of distribution.

The site of accumulation of a xenobiotic may or may not be a site of action or toxicity. If the site of accumulation is not a site of toxicity, then the storage depot may be relatively inactive and the accumulation at that site may be theoretically protective to the animal/person.[52] Selective accumulation of xenobiotics occurs in certain areas of the body because of affinity for certain tissue-binding proteins. For example, the kidney contains metallothionein, which has a high affinity for metals such as cadmium, lead, and mercury.[20] The retina contains the pigment melanin, which binds and accumulates chlorpromazine, thioridazine, and chloroquine.[20] Other examples of xenobiotics accumulating at primary sites of toxicity are carbon monoxide binding to hemoglobin and myoglobin and paraquat distributing to type II alveolar cells in the lungs.[49] Dichlorodiphenyltrichloroethane (DDT), chlordane, and polychlorinated biphenyls are stored in fat, which can be mobilized following starvation.[70] Lead sequestered in bone[29] is not immediately toxic, but mobilization of bone through an increase in osteoclastic activity[52] (hyperparathyroidism, possibly pregnancy) may free lead for distribution to sites of toxicity (CNS, blood).

Several plasma proteins bind xenobiotics and act as carriers and storage depots. The percentage of protein binding varies among xenobiotics, as do their affinities and potential for reversibility. Once bound to plasma protein, a xenobiotic with high binding affinity will remain largely confined to the plasma until elimination occurs. However, dissociation and reassociation may occur if another carrier is available with a higher binding affinity. Most plasma measurements of xenobiotic concentration reflect total drug (bound plus unbound). Only the unbound drug is free to diffuse through membranes for distribution or for elimination. Albumin (a protein of MW 67,000 daltons) binds primarily to weakly acidic, poorly water-soluble xenobiotics, which include salicylates, phenytoin, and warfarin, as well as endogenous substances like free fatty acids, cortisone, aldosterone, thyroxine, and bilirubin.[55] Î±$_1$-Acid glycoprotein (a globulin of MW 44,000 daltons) usually binds basic xenobiotics including lidocaine, imipramine, and propranolol.[55] Transferrin, a Î²$_1$-globulin, transports iron, and ceruloplasmin carries copper.

Phenytoin is an example of a xenobiotic whose effects are significantly influenced by changes in concentration of plasma albumin. When albumin concentrations are in the normal range, approximately 90% of phenytoin is bound to albumin. As the albumin concentration decreases, however, more xenobiotic is free for distribution and a greater clinical response to the same serum phenytoin concentration is often observed. It is this free form of phenytoin that is active. The free plasma phenytoin concentration can be calculated based on the albumin concentration. This achieves an appropriate interpretation of total phenytoin within the conventional therapeutic range of 10â€“20 mg/L of free plus bound phenytoin (Eq. 9-7).

$$\text{Adjusted phenytoin concentration} = \frac{\text{actual phenytoin concentration}}{(0.25 \times [\text{albumin}]) + 0.1} \quad \text{(Eq. 9–7)}$$

The clinical implications are that a malnourished patient with an

albumin of 2 g/dL receiving phenytoin can manifest toxicity with a plasma phenytoin concentration of 14 mg/L. This measurement is total phenytoin (bound + unbound). Because the patient has a reduced albumin concentration, this actually represents a substantially higher proportion and absolute amount of active unbound phenytoin. Substitution into the above equation of 14 mg/L for actual

plasma phenytoin concentration and 2 g/dL for albumin gives an adjusted plasma phenytoin concentration of 23.33 mg/L (therapeutic range, 10â€“20 mg/L).

	Vd L/kg	Protein Binding %	Renal Elimination % Unchanged	Hepatic Metabolism (CYP)	Active Metabolite	Enterohepatic
Analgesics						
Acetaminophen	0.8–1	5–20	2	95% (2E1)	*N*-acetyl-*p*-benzoquinoneimine	27–42% excreted in bile
Aspirin	0.15–0.2	50–80 (salicylic acid) saturable	10 (pH dependent)	Majority	Salicylic acid	None
Methadone	3.59	71–87	5–10	Majority (3A4, 2D6)	None?	Yes
Morphine	3–4	35	<10	*n*-Demethylation	15% Morphine 6-glucuronide, 55% morphine 3-glucuronide	Yes
Propoxyphene	12–26	80	<10	>90% (3A4, 2D6)	Norpropoxyphene	Yes?
Antidepressants						
Amitriptyline	8.3 ± 2	96	5	Yes (2C9)	Nortriptyline (2D6)	Yes
Bupropion	18.6	84	0	Yes (2B6)	Hydroxybupropion	No
Citalopram	12	80	0	Yes (3A4, 2C19)	Desmethylcitalopram	Yes
Desipramine	33–42	92	0.3–2.6	Yes (2D6)	None	Yes
Doxepin	20 ± 8	—	0	Yes	Desmethyldoxepin	Yes
Imipramine	15 ± 6	85	0–1.7	Yes (2D6)	Desipramine	Yes
Lithium	0.79	None	89–98	None	None	None
Cardiovascular Drugs						
Digoxin	5.1–7.4	20–25	57–80 in 6–12 h		Minor amount	Yes
Diltiazem	5.3	70–80	1–3	90% (3A)	Yes, many	No
Nifedipine	0.8–1.4	92–98	?	98% (3A4)	No	No
Propranolol	3.6	93	<0.5	>95% (2C19, 2D6)	No	No
Verapamil	4.7	83–92	3–4%	97% (3A4, 1A2, 2C9)	Norverapamil	No
Stimulants and Drugs of Abuse						
Amphetamine	6.11 (in drug dependent;) 3.5–4.6 (in naive)	16	45 (pH dependent)	50%	*p*-Hydroxynorephedrine 0.3%; *p*-hydroxyamphetamine 2–4%	No
Cocaine	1.96–2.7	8.7	9.5–20 (pH dependent)	5–10% (3A4)	Norcocaine; (?) others	No
Heroin	25	40	Minor		Acetylmorphine 1.3%; morphine 4.2%	No

Methamphetamine	9.2–9.7	pH dependent			Amphetamine 4–7%; *p*-hydroxynetham-phetamine 15%	No
Sedative/Hypnotics						
Alprazolam	1–2	80	100%	None	None	No
Chloral hydrate	0.75	70–80	Minor	Alcohol dehydrogenase	Trichloroethanol	No
Phenobarbital	0.88	40–50	20–50 (pH dependent)	Yes (2C9, 2C19)	None	No
Quetiapine	10	83	0	Yes (3A4)	None	Yes
Alcohols						
Ethanol	0.5–0.6	None	Very little	95% Alcohol dehydrogenase	Acetaldehyde	No
Ethylene glycol	0.6–0.8	None	20		Oxalic acid	No
Methanol	0.6–0.7	None	3–5	95% Alcohol dehydrogenase	Formic acid	No
Miscellaneous						
Cyanide	0.4	60	0		None	None
Theophylline	0.5	50–60	7	90% (1A2, 2 E1 >3A4)	1,3-Dimethyluric acid; caffeine (in neonates)	
Organic Phosphorus Compounds						
Malathion	?	None		Metabolized by microsomal enzymes	Malaoxon	No
Chlorpyrifos	?	None		Yes	3,5,6-Trichloro-2-pyridonol	No
Rodenticides						
Brodifacoum	0.985 (rats)	None		Yes		No
Strychnine	13	None	10–20 in 24 h	Yes		

TABLE 9-3. Pharmacokinetic Characteristics of Xenobiotics Associated with the Largest Number of Toxicologic Deaths

Although drug interactions are often attributed to the displacement of xenobiotics, usually concurrent metabolic interactions are more consequential. Displacement transiently increases the amount of unbound, active drug. This may result in an immediate increase in drug effect. This is followed by enhanced distribution and elimination of unbound drug. Gradually the unbound plasma concentration returns to predisplacement concentrations.[53]

Saturation of plasma proteins may occur in the therapeutic range for a drug such as valproic acid. Acute saturation of plasma protein binding following an overdose often leads to consequential adverse effects. Saturation of plasma protein binding with salicylates and iron after overdose increases distribution to the CNS (salicylates) or to the liver, heart, and other tissues (iron), producing increased

toxicity.

Specific therapeutic maneuvers in the overdose setting are designed to alter xenobiotic distribution by inactivating and/or enhancing elimination to limit toxicity. These therapeutic maneuvers include (a) manipulation of serum or urine pH (salicylates); (b) use of chelators (lead); and (c) the use of antibodies or antibody fragments (digoxin).

The Vd permits predictions about plasma concentrations and also assists in defining whether an extracorporeal method of removal is beneficial for a particular toxin. If the Vd is large (>1 L/kg), it is unlikely that hemodialysis, hemoperfusion, or exchange transfusion would be effective because most of the xenobiotic is outside of the plasma compartment. Plasma protein binding also influences this decision. If the xenobiotic is more tightly bound to plasma proteins than to activated charcoal, then hemoperfusion is unlikely to be beneficial even if the Vd of the xenobiotic is small. In addition, high plasma protein binding limits the effectiveness of hemodialysis, because only unbound xenobiotic will freely cross the dialysis membrane. Exchange transfusion can be effective for a xenobiotic with a small Vd and substantial plasma protein binding, because both bound and free xenobiotic are removed simultaneously.

Elimination

Removal of a parent compound from the body (*elimination*) begins as soon as the xenobiotic is delivered to clearance organs such as the liver, kidneys, and lungs. Elimination begins immediately, but may not be the predominant kinetic process until absorption and distribution are substantially completed. As expected, the functional integrity of the major organ systems (cardiovascular, lungs, renal, hepatic) are major determinants of the efficiency of xenobiotic removal and of therapeutically administered antidotes. The xenobiotics themselves may cause renal or hepatic failure (acetaminophen), subsequently compromising their own elimination. Other factors influencing elimination include age (enzyme

maturation), competition or inhibition of elimination processes by interacting xenobiotics, saturation of enzymatic processes, gender, genetics, and the physicochemical properties of the xenobiotic.[41]

Elimination can be accomplished by biotransformation to one or more metabolites, or by *excretion* from the body of unchanged xenobiotic. Excretion can occur via the kidneys, lungs, GI tract, and body secretions (sweat, tears, milk). Hydrophilic (polar) or charged xenobiotics and their metabolites, because of their water solubility, are generally excreted via the kidney. The majority of xenobiotic metabolism occurs in the liver but it also commonly occurs in the blood, skin, GI tract, placenta, or kidneys. Lipophilic (noncharged or nonpolar) xenobiotics are usually metabolized in the liver to hydrophilic metabolites, which are then excreted by the kidneys.[21,45] These metabolites are generally inactive, but if active, may contribute to toxicity. Examples include the metabolism of amitriptyline to nortriptyline, procainamide to *N*-acetylprocainamide, and meperidine to normeperidine (Table 9-4).

Metabolic reactions catalyzed by enzymes (categorized as either phase I or phase II) generally result in pharmacologically active

metabolites; frequently, the latter have different toxicities than the parent compounds. *Phase I*, or preparative metabolism, which may or may not precede phase II, is responsible for introducing polar groups onto nonpolar xenobiotics by oxidation, reduction, and hydrolysis or dealkylation. The result of phase I metabolism is commonly to add or expose polar groups.[19,43] *Phase II*, or synthetic reactions, conjugate the polar group with a glucuronide, sulfate or acetate (often a less-polar metabolite, which is reabsorbed), methyl groups, glutathione (mercapturic acid synthesis), and amino acids (glycine, taurine, and glutamic acid).[12,19,43]

TABLE 9-4. Examples of Xenobiotics Activated by Human P450

CYP1A1	Benzene
Benzo[*a*]pyrene and other polycyclic aromatic hydrocarbons	Carbon tetrachloride Chloroform
CYP1A2	Dichloromethane
Acetaminophen	Ethylene dibromide
NNK	Ethylene dichloride
CYP2A6	Ethyl carbamate
NNK	*N*-Nitrosodimethylamine
CYP2B6	Trichloroethylene
CYP2C 8,9,18,19	Vinyl chloride
None known	CYP3A4
CYP2D6	Acetaminophen
NNK	Aflatoxin B and G

CYP2E1	Cyclophosphamide
Acetaminophen	Ifosphamide
Acrylonitrile	

NNK: 4-(methylnitrosamino)-1-(3-pyridyl)-/-butanone, a tobacco-specific nitrosamine.
Adapted from Guengerich, FP: Reactions and significance of cytochrome P450 enzymes. J Biol Chem 1991;266:10019â€“10022.
Adapted, with permission, from Parkinson A: Biotransformation of xenobiotics. In: Klaassen C, ed: Casarett & Doull's Toxicology: The Basic Science of Poisons, 5th ed. New York. McGraw-Hill, 1996, p. 154.

Comparatively, phase II reactions produce a much larger increase in hydrophilicity than phase I reactions. The enzymes involved in these reactions have low substrate specificity, and those in the liver are usually localized to either the endoplasmic reticulum (microsomes) or the soluble fraction of the cytoplasm (cytosol).[43] The location of the enzymes becomes important if they form reactive metabolites which then concentrate at the site of metabolism and cause toxicity (Table 9-5). For example, acetaminophen causes centrilobular necrosis because the cytochrome P450 2E1 isoenzymes, which form *N*-acetyl-*p*-benzoquinoneimine (NAPQI), the toxic metabolite, are located in their highest concentration in that zone of the liver.

The enzymes that metabolize the largest variety of xenobiotics are heme-containing proteins referred to as *CYP monooxygenase enzymes*.[24,43] This group of enzymes, formerly called the mixed function oxidase system, is found in abundance in the microsomal

endoplasmic reticulum of the liver. These enzymes primarily catalyze the oxidation of xenobiotics. However, cytochrome P450 in a reduced state (Fe^{2+}) binds carbon monoxide. Its discovery and initial name resulted from spectral identification of the CO-bound cytochrome P450, which absorbs light maximally at 450 nm. The cytochrome P450 system is composed of many enzymes grouped into gene families and subfamilies, of which approximately 57 of these functional human genes have been sequenced. Members of a gene family have >40% similarity of their amino acid sequencing and subfamilies have >55% similarity. Toxicity may result from induction or inhibition of cytochrome P450 isoenzymes by another xenobiotic, resulting in a consequential drug interaction (Table 9-6). Many of these interactions are predictable based on the known xenobiotic affinities and their capability to induce or inhibit the P450 system.[10,37,43,44,59] However, *polymorphism* (individual genetic expression of isoenzymes),[1] stereoisomer variability[68] (enantiomers with different potencies and isoenzyme affinities), and the capability to metabolize a xenobiotic by alternate pathways, contribute to unexpected metabolic outcomes. The pharmaceutical industry is now exploiting the concept of chiral switching (marketing a single enantiomer instead of the racemic mixture) to alter efficacy or side-effect profiles. Enantiomers are named either according to the direction in which they rotate polarized light (*l* or â€“ for levorotatory, and *d* or + for dextrorotatory), or according to the absolute spatial orientation of the groups at the chiral center (S or R). Chiral means â€œhandâ€• in Greek, and the latter designations refer to either sinister (left-handed) or rectus (right-handed). There is no direct correlation between levorotatory or dextrorotatory and S and R.[63]

TABLE 9-5. General Pathways of Xenobiotic Biotransformation and Their Major Subcellular Location

Reaction	Enzyme	Localization
Phase 1		
Hydrolysis	Carboxylesterase	Microsomes, cytosol
	Peptidase	Blood, lysosomes
	Epoxide hydrolase	Microsomes, cytosol
Reduction	Azo- and nitro-reduction	Microflora, microsomes, cytosol
	Carbonyl reduction	Cytosol
	Disulfide reduction	Cytosol
	Sulfoxide reduction	Cytosol
	Quinone reduction	Cytosol, microsomes
	Reductive dehalogenation	Microsomes
Oxidation	Alcohol dehydrogenase	Cytosol
	Aldehyde dehydrogenase	Mitochondria, cytosol

	Aldehyde oxidase	Cytosol
	Xanthine oxidase	Cytosol
	Monoamine oxidase	Mitochondria
	Diamine oxidase	Cytosol
	Prostaglandin H synthase	Microsomes
	Flavin-monooxygenases	Microsomes
	Cytochrome P450	Microsomes
Phase II		
	Glucuronide conjugation	Microsomes
	Sulfate conjugation	Cytosol
	Glutathione conjugation	Cytosol, microsomes
	Amino acid conjugation	Mitochondria, microsomes

	Acylation	Mitochondria, cytosol
	Methylation	Cytosol

Reprinted, with permission, from Parkinson A: Biotransformation of xenobiotics. In: Klaassen CD, ed: Casarett & Doull's Toxicology: The Basic Science of Poisons, 5th ed. New York, McGraw-Hill, 1996, p. 114.

Excretion is primarily accomplished by the kidneys, although, as mentioned earlier, biliary, pulmonary, and body fluid secretions contribute to lesser degrees. Urinary excretion occurs through glomerular filtration, tubular secretion, and passive tubular reabsorption. The glomerulus filters unbound xenobiotics of a particular size and shape in a manner that is not saturable, subject to renal blood flow and perfusion. Passive tubular reabsorption accounts for the reabsorption of noncharged, lipid-soluble xenobiotics, and is therefore influenced by the pH of the urine and the pK_a of the xenobiotic. The principles of diffusion discussed earlier permit, for example, the ion trapping of salicylate (pK_a = 3.5) in the urine through urinary alkalinization. Tubular secretion is an active process subject to saturation and drug interactions (Table 9-7). Tubular secretion is often less developed in the neonate.

Classical Versus Physiologic Compartment Toxicokinetics

Models exist to study and describe the movement of xenobiotics in the body with mathematical equations. Traditional *compartmental* models (one or two compartments) are data-based and assume that changes in plasma concentrations represent tissue concentrations

(Fig. 9-7).[42] Advances in computer technology facilitate the use of the classic concepts developed in the late 1930s.[62] Physiologic models consider the movement of xenobiotics based on known or theorized biologic processes and are unique for each xenobiotic. This allows the prediction of tissue concentrations, while incorporating the effects of changing physiologic parameters, and affording better extrapolation from laboratory animals.[72] Unfortunately, physiologic modeling is still in its infancy and the mathematical modeling it entails is often very complex.[16] Regardless, the most commonly used mathematical equations are based on traditional compartmental modeling.

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The *one-compartment model* is the simplest for analytic purposes and is applied to xenobiotics that rapidly enter and distribute throughout the body. This model assumes that changes in plasma concentrations will result in, and reflect proportional changes in tissue concentrations. Many xenobiotics, such as digoxin, lithium, and lidocaine, do not instantaneously equilibrate with the tissues and are better described by a two-compartment model. In the *two-compartment model*, a xenobiotic is distributed instantaneously to highly perfused tissues (central compartment) and then is secondarily, and more slowly, distributed to a peripheral compartment. Elimination is assumed to take place from the central compartment.

TABLE 9-6. Cytochrome P450 isozymes and P-glycoprotein: Selected inducers, Inhibitors, and Substrates[a]

TABLE 9-7. Xenobiotics Secreted by Renal Tubules

Organic Anion Transport	Organic Cation Transport
Acetazolamide	Acetylcholine
Bile salts	Amiodarone
Cephalosporins	Atropine
Indomethacin	Cimetidine
Hydrochlorothiazide	Digoxin
Furosemide	Diltiazem
Methotrexate	Dopamine
Penicillin G	Epinephrine
Probenecid	Morphine
Prostaglandins	Neostigmine
Salicylate	Procainamide
	Quinidine

	Quinine
	Triamterene
	Trimethoprim
	Verapamil

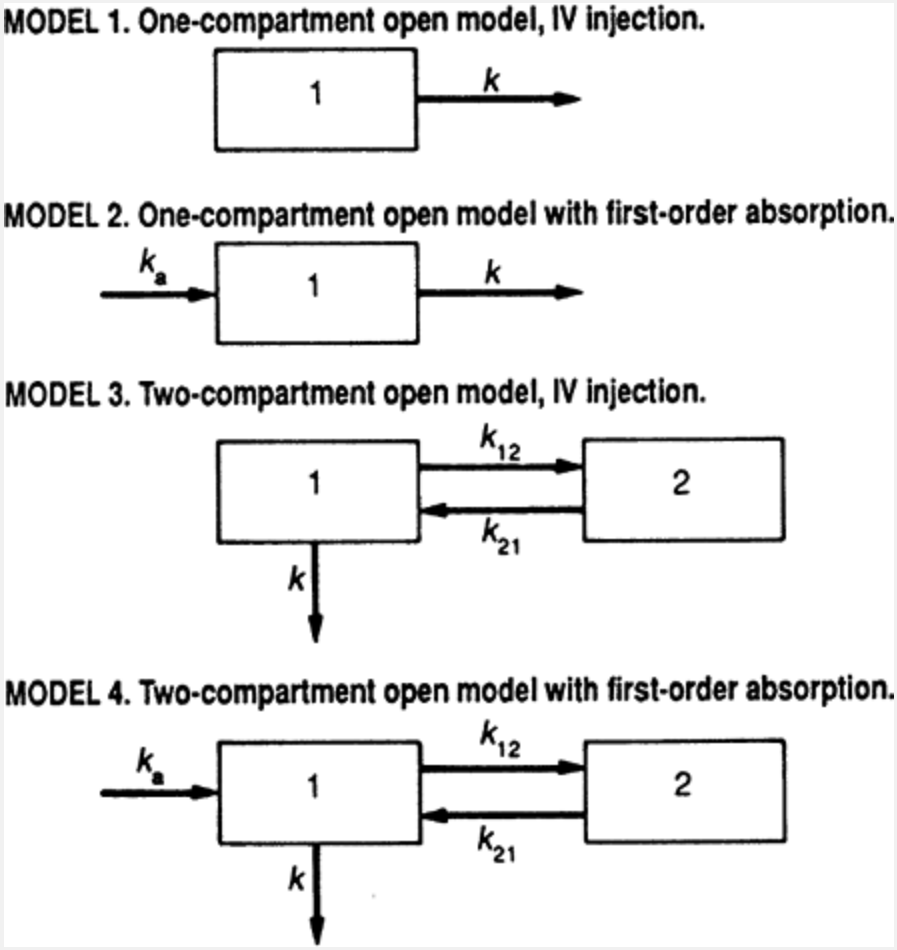

Figure 9-7. Various classical compartmental models. k =

pharmacokinetic rate constants; 1 = plasma or central compartment; 2 = tissue compartment; k_{12} = rate constant into tissue from plasma; k_{21} = rate constant into plasma from tissue; k_a = absorption rate constant. *(Reprinted, with permission, from Shargel L, Yu A: Introduction to Pharmacokinetics: Applied Biopharmaceutics and Pharmacokinetics, 3rd ed. Norwalk, CT, Appleton & Lange, 1993, p. 40.)*

If the rate of a reaction is directly proportional to the concentration of xenobiotic, it is termed *first order or linear*. Processes that are capacity limited or saturable are termed *nonlinear* (not proportional to the concentration of xenobiotic) and are described by the *Michaelis-Menten* equation, which is derived from enzyme kinetics. Calculus is used to derive the first-order equation, as done by Yang and Andersen.[72] Rate is directly proportional to concentration of xenobiotic as in Equation 9-8.

$$\text{Rate} \propto \text{concentration (C)} \qquad \text{(Eq. 9–8)}$$

An infinitesimal change in concentration of a xenobiotic (dC) with respect to an infinitesimal change in time (dt) is directly proportional to the concentration (C) of the xenobiotic as in Equation 9-9.

$$\frac{dC}{dt} \propto C \qquad \text{(Eq. 9–9)}$$

The proportionality constant k is added to the right side of the expression to mathematically allow the introduction of an equal sign. The constant k represents all of the bodily factors, such as metabolism and excretion, that contribute to the determination of concentration (Eq. 9-10).

$$\frac{dC}{dt} = kC \qquad \text{(Eq. 9–10)}$$

Introducing a negative sign to the left-hand side of the equation

describes the â€œdecayâ€• or decreasing xenobiotic concentration (Eq. 9-11).

$$-\frac{dC}{dt} = kC \qquad \text{(Eq. 9–11)}$$

This equation is impractical because of the difficulty of measuring infinitesimal changes in C or t. Therefore, the use of calculus allows the integration or summing of all of the changes from one concentration to another beginning at time zero and terminating at time *t*. This relationship is mathematically represented by the integration sign (âˆ«). âˆ« means to integrate the term from concentration at time zero (C_0) to concentration at a given time *t* (C_t). âˆ« means the same with respect to time, where t_0 = zero. Prior to this application, the previous equation is first rearranged (Eq. 9-12).

$$-\frac{dC}{C} = kdt$$

$$\int_{C_0}^{C_t} -\frac{dC}{C} = k\int_{t_0}^{t} dt \qquad \text{(Eq. 9–12)}$$

The integration of d*C* divided by *C* is the natural logarithm of *C* (ln *C*) and the integration of dt is *t* (Eq. 9-13).

$$-\ln C \Big|_{C_0}^{C_t} = kt \Big|_{t_0}^{t} \qquad \text{(Eq. 9–13)}$$

The vertical straight lines proscribe the evaluation of the terms between those two limits. The following series of manipulations are then performed (Eq. 9-14A-D).

$$-(\ln C_t - \ln C_0) = k(t - 0) \qquad \text{(Eq. 9–14A)}$$

$$-\ln C_t + \ln C_0 = kt \qquad \text{(Eq. 9–14B)}$$

$$-\ln C_t = -\ln C_0 + kt \qquad \text{(Eq. 9–14C)}$$

$$\underset{\substack{\text{Can be}\\\text{measured}}}{\ln C_t} = \underset{\text{Constant}}{\ln C_0} - \underset{\substack{\text{Can be}\\\text{selected}}}{kt} \qquad \text{(Eq. 9–14D)}$$

Equation 9-14D can be recognized as taking the form of an equation of a straight line (Eq. 9-15), where the slope is equal to the rate constant *k* and the intercept is C_0.

$$y = b + mx \qquad \text{(Eq. 9–15)}$$

Instead of working with natural logarithms, an exponential form (the antilog) of Equation 9-14D may be used (Eq. 9-16).

$$C_t = C_0 e^{-kt} \qquad \text{(Eq. 9–16)}$$

Graphing the ln (natural logarithm) of the concentration of the xenobiotic at various times for a first-order reaction is a straight line. Equation 9-16 describes the events when only one first-order process occurs. This is appropriate for a one-compartment model (Fig. 9-8).

In this model, regardless of the concentration of the xenobiotic, the rate (percentage) of decline is constant. The absolute amount of xenobiotic eliminated changes continuously while the percent eliminated remains constant. k is reported in h^{-1}. A k of 0.10 h^{-1} means that the xenobiotic is being processed (eliminated) at a rate of 10% per hour. k is often designated as k_e and referred to as the elimination rate constant. The time necessary for the xenobiotic concentration to be reduced by 50% is called the *half-life*. The half-life is determined by a rearrangement of Equation 9-14D whereby C_2 becomes C at time t_2 and C_1 becomes C at t_1, and by rearrangement giving Equation 9-17.

$$(t_1 - t_2) = \frac{(\ln C_1 - \ln C_2)}{k_e} \qquad \text{(Eq. 9–17)}$$

Substitution of 2 for C_1 and 1 for C_2 or 100 for C_1 and 50 for C_2 gives Equations 9-18A and 9-18B.

$$t_{1/2} = \frac{(\ln 2 - \ln 1)}{k_e} \qquad \text{(Eq. 9–18A)}$$

$$t_{1/2} = \frac{0.693}{k_e} \qquad \text{(Eq. 9–18B)}$$

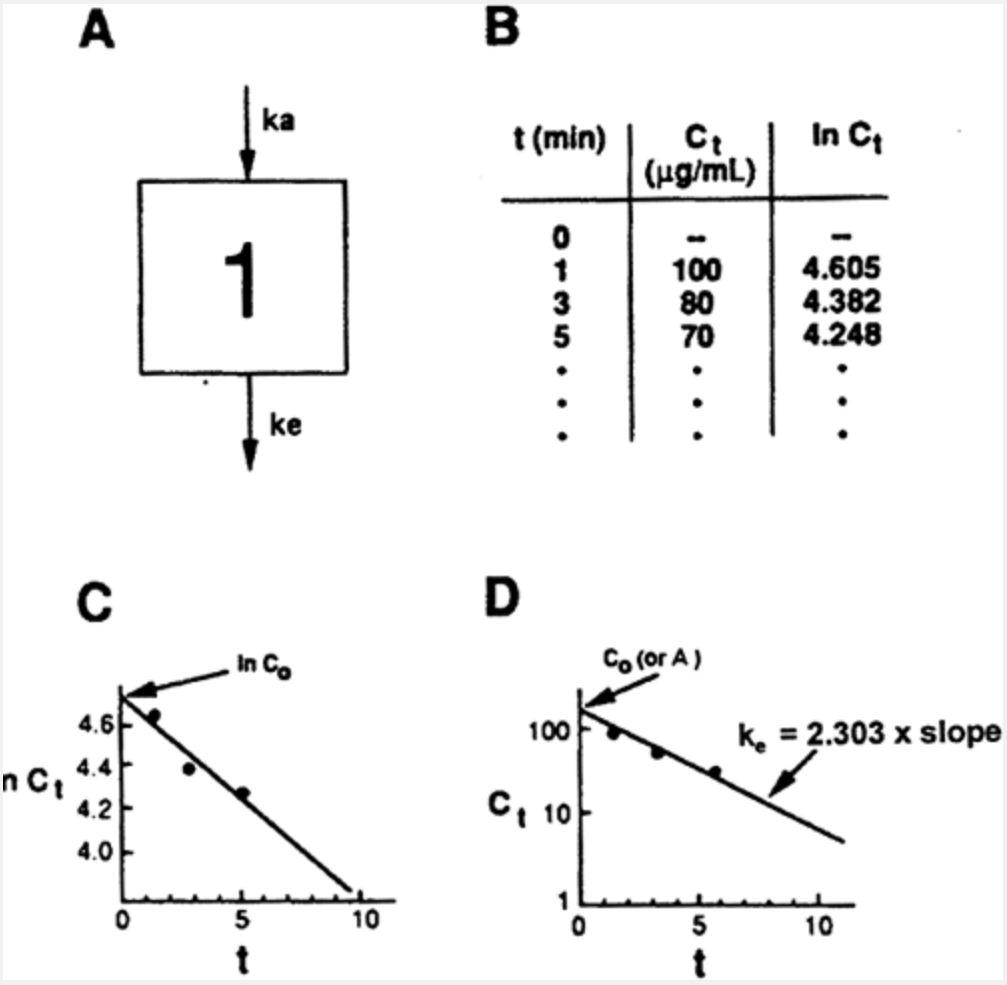

Figure 9-8. A one-compartment pharmacokinetic model

demonstrating (A) graphical illustration; (B) hypothetical dataset; (C) linear plot; and (D) semilogarithmic plot. *(Modified and reprinted, with permission, from Yang R, Andersen M: Pharmacokinetics. In: Hodgson E, Levi P, eds: Introduction to Biochemical Toxicology. Norwalk, CT, Appleton & Lange, 1994, p. 54.)*

The use of semilog paper facilitates graphing the first-order equation. However, because semilog paper plots log (not ln) versus time, to retain appropriate mathematical relationships the rate constant or slope (k) must be divided by 2.303 (see Fig. 9-8).

The mathematical modeling becomes more complex when more than one first-order process contributes to the overall elimination process. The equation that incorporates two first-order rates is used for a two-compartment model and is Equation 9-19.

$$C_t = Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(Eq. 9–19)}$$

Figure 9-9 demonstrates a two-compartment model where Î± often represents the distribution phase and Î² is the elimination phase.

The rate of reaction of a saturable process is not linear (not proportional to the concentration of xenobiotic) when saturation occurs (Fig. 9-10). This model is best described by the Michaelis-Menten equation used in enzyme kinetics (Eq. 9-20) in which *v* is the velocity or rate of the enzymatic reaction; *C* is the concentration of the xenobiotic; V_{max} is the maximum velocity of the reaction between the enzyme and the xenobiotic; and K_m is the affinity constant between the enzyme and the xenobiotic.[72]

$$v = \frac{V_{max} \times C}{K_m + C} \qquad \text{(Eq. 9–20)}$$

Application of this equation to toxicokinetics requires *v* to become the infinitesimal change in concentration of a xenobiotic (dC) with respect to an infinitesimal change in time (dt) as previously

discussed (see Eq. 9-10). V_{max} and K_m both reflect the influences of diverse biologic processes. The Michaelis-Menten equation then becomes Equation 9-21, in which the negative sign again represents decay.

$$\frac{dC}{dt} = \frac{V_{max} \times C}{K_m + C} \qquad \text{(Eq. 9–21)}$$

When the concentration of the xenobiotic is very low ($C<<<K_m$), it can be dropped from the bottom right of the equation because its contribution becomes negligible and the resultant equation is described as a first-order process. (Eq. 9-22A and 9-22B). Conceptually, this is understandable, because at a very low xenobiotic concentration the process is not saturated.

$$-\frac{dC}{dt} = \frac{V_{max} \times C}{K_m} \qquad \text{(Eq. 9–22A)}$$

Because V_{max} divided by K_m is a constant, K, then:

$$-\frac{dC}{dt} = kC \qquad \text{(Eq. 9–22B)}$$

However, when the concentrations of the xenobiotic are extremely high and exceed the capacity of the system ($C>>>K_m$), the rate becomes fixed at a constant maximal rate regardless of the exact concentration of the xenobiotic, termed a zero-order reaction. Tables 9-8A and 9-8B compare a first-order reaction to a zero-order reaction. In this particular example, zero order is faster, but if the fraction of xenobiotic eliminated in the first-order example were

0.4, then the amount of xenobiotic in the body would fall below 100 before the xenobiotic in the zero-order example. It is inappropriate to perform half-life calculations on a xenobiotic displaying zero-order behavior because the metabolic rates are continuously changing. Following overdoses, enzyme saturation is a common occurrence as the capacity of enzyme systems are overwhelmed.

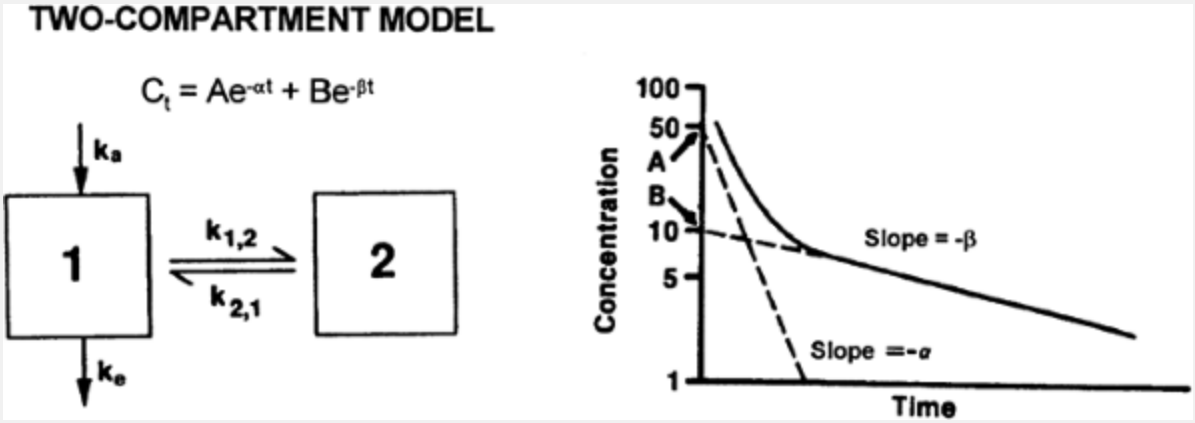

Figure 9-9. Mathematical and graphical forms of a two-compartment classical pharmacokinetic model. k_a represents the absorption rate constant, k_e represents the elimination rate constant, Î± represents the distribution phase, and Î² the elimination phase. *(Reprinted, with permission, from Yang R, Andersen M: Pharmacokinetics. In: Hodgson E, Levi P, eds: Introduction to Biochemical Toxicology. Norwalk, CT, Appleton & Lange, 1994, p. 55.)*

Clearance

Clearance (Cl) is the relationship between the rate of transfer or elimination of a xenobiotic from a reference fluid (usually plasma) to the plasma concentration of the xenobiotic and is expressed in units of volume per unit time (ie, mL/min) (Eq. 9-23).[22,42,54]

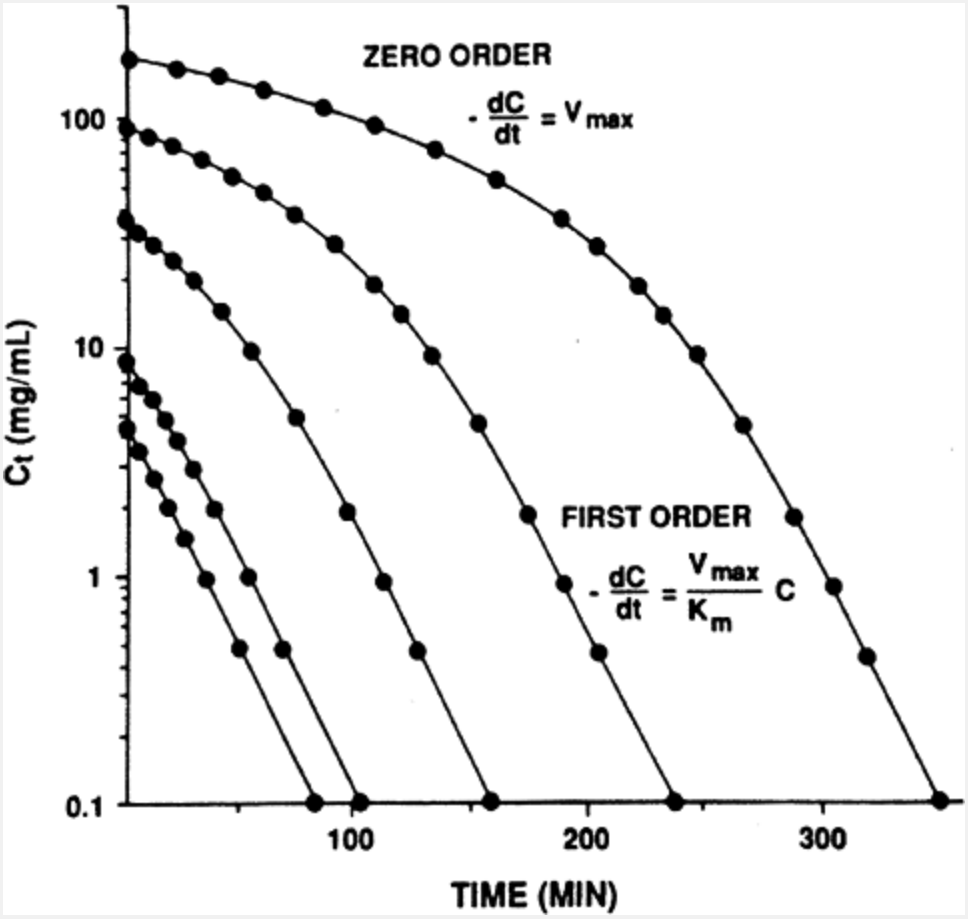

Figure 9-10. Concentration versus time curve for a xenobiotic showing nonlinear pharmacokinetics concentrations <10 mg/mL represent first order elimination. *(Reprinted, with permission, from Yang R, Andersen M: Pharmacokinetics. In: Hodgson E, Levi P, eds: Introduction to Biochemical Toxicology. Norwalk, CT, Appleton & Lange, 1994, p. 57.)*

$$Cl = \frac{\text{Rate of elimination}}{C} \qquad \text{(Eq. 9–23)}$$

The determination of creatinine clearance is a well-known example of the concept of clearance. Creatinine clearance ($Cl_{creatinine}$) is

determined by Equation 9-24,

$$Cl_{creatinine} = \frac{U \times V}{C} \qquad \text{(Eq. 9–24)}$$

in which *U* is the concentration of creatinine in urine (mg/mL); *V* is the volume flow of urine (mL/min); *C* is the plasma concentration of creatinine (mg/mL); and the units for clearance are mL/min. A creatinine clearance of 100 mL/min means that 100 mL of plasma is completely cleared of creatinine each minute. Clearance for a particular eliminating organ or for extracorporeal elimination is calculated with Equation 9-25.

$$Cl = Q \times (ER) = Q \times \frac{(C_{in} - C_{out})}{C_{in}}$$

Cl = clearance for the eliminating organ or extracorporeal device
Q = blood flow to the organ or device
ER = extraction ratio
C_{in} = xenobiotic concentration in fluid (blood or serum) entering the organ or device
C_{out} = xenobiotic concentration in fluid (blood or serum) leaving the organ or device

(Eq. 9–25)

TABLE 9-8A. Illustration of 1000 mg of Xenobiotic in Body Following First-Order Elimination

Time After Drug Administration (h)	Amount of Drug in Body (mg)	Amount of Drug Eliminated Over Preceding Hour (mg)	Fraction of Drug Eliminated Over Preceding Hour
0	1000	â€”	â€”
1	850	150	0.15
2	723	127	0.15
3	614	109	0.15
4	522	92	0.15
5	444	78	0.15
6	377	67	0.15

TABLE 9-8B. Illustration of 1000 mg of Xenobiotic in Body Following Zero-Order Elimination

Time After Drug Administration (h)	Amount of Drug in Body (mg)	Amount of Drug Eliminated Over Preceding Hour (mg)	Fraction of Drug Eliminated Over Preceding Hour
0	1000	â€”	â€”
1	850	150	0.15
2	700	150	0.18
3	550	150	0.21
4	400	150	0.27
5	250	150	0.38
6	100	150	0.60

Clearance can be applied to any elimination process independent of the precise mechanisms (ie, first-order, Michaelis-Menten), and will represent the sum total of all of the rate constants for xenobiotic elimination. Total body clearance ($Cl_{totalbody}$) is the sum of the clearances of all of the individual eliminating processes, as seen in

Equation 9-26.

$$Cl_{\text{total body}} = Cl_{\text{renal}} + Cl_{\text{hepatic}} + Cl_{\text{intestinal}} + Cl_{\text{chelation}} + \cdots \quad \text{(Eq. 9–26)}$$

For a first-order process (one-compartment model), clearance is given by Equation 9-27.

$$Cl = k_e Vd \quad \text{(Eq. 9–27)}$$

Experimentally, the clearance can be derived by examining the intravenous dose of xenobiotic in relation to the AUC from time zero to time *t* (Eq. 9-28). The AUC is calculated using the trapezoidal rule or through integral calculus (units: eg, mg/mL) (Figs. 9-11 and 9-12).

$$Cl = \frac{\text{dose}_{IV}}{AUC_{0-t}} \quad \text{(Eq. 9–28)}$$

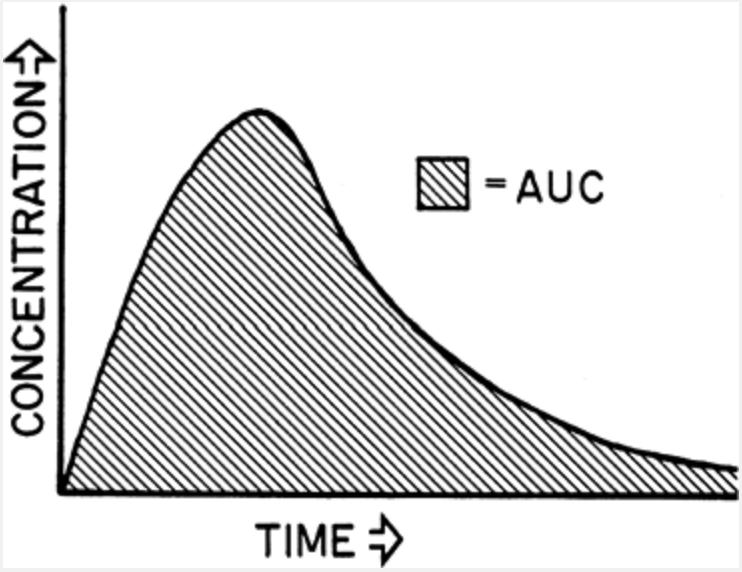

Figure 9-11. The AUC profile obtained after extravascular administration of a xenobiotic. *(Reprinted, with permission, from Riviere JE: Absorption and distribution. In: Hodgson E, Levi P, eds: Introduction to Biochemical Toxicology. Norwalk, CT,*

Appleton & Lange, 1994, p. 21.)

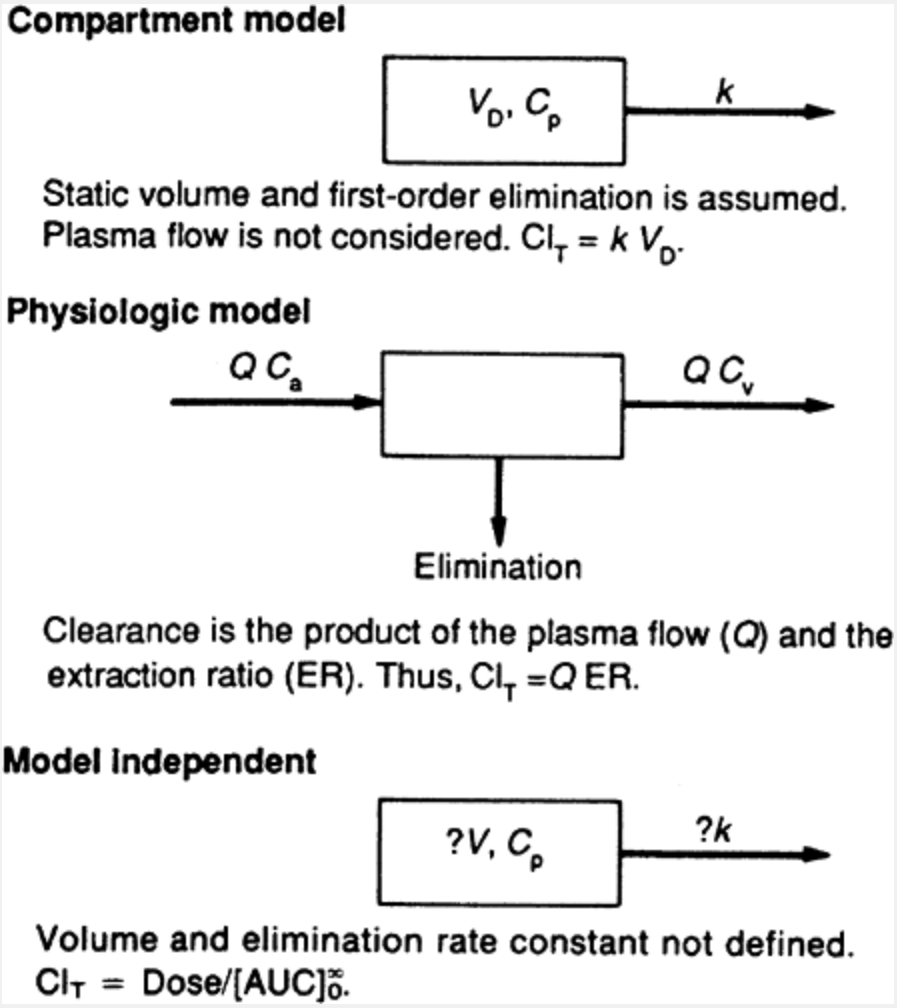

Figure 9-12. General approaches to clearance. *(Reprinted, with permission, from Shargel L, Yu A: Introduction to pharmacokinetics. In: Applied Biopharmaceutics and Pharmacokinetics, 3rd ed. Norwalk, CT, Appleton & Lange, 1993, p. 280.)*

Steady State

When exposure to a xenobiotic occurs at a fixed rate, the plasma concentration of the xenobiotic gradually achieves a plateau level at a concentration at which the rate of absorption equals the rate of elimination and is termed *steady state*. The time to achieve 95% of steady-state concentration for a first-order process is dependent on the half-life and usually necessitates 5 half-lives. The concentration achieved at steady state depends on the Vd, the rate of exposure, and the half-life.

Iatrogenic toxicity can occur in the therapeutic setting when dosing decisions are based on plasma concentrations determined prior to achieving a steady state. This adverse event is particularly common when using drugs with long half-lives such as digoxin[71] and phenytoin.

Peak Plasma Concentrations

Peak plasma concentrations (C_{max}) of a xenobiotic occur at the time of peak absorption. At this point in time, the absorption rate is at least equal to the elimination rate. Thereafter, the elimination rate predominates and plasma concentrations begin to decline. Whereas the C_{max} depends on the dose, the *rate of absorption* (k_a), and *the rate of elimination* (k_e), the *time to peak* (t_{max}) is independent of dose and only depends on the k_a and k_e. For the same dose of xenobiotic, if the k_e remains constant and the rate of absorption decreases, then the t_{max} will occur later and the C_{max} will be slightly lower. Controlled-release dosage forms and xenobiotics that form concretions and have a decreased rate of absorption may

not achieve peak concentrations until many hours after an immediate-release preparation with rapid absorption. The AUC will remain the same. However if the k_a remains constant and the k_e is increased, then the t_{max} occurs sooner, the C_{max} decreases, and the

AUC decreases (Table 9-9).[46]

TABLE 9-9. Pharmacokinetic Effects of the Absorption Rate Constant and Elimination Rate Constant[a]

Absorption Rate Constant k_a (h^{-1})	Elimination Rate Constant k_e (h^{-1})	t_{max} (h)	C_{max} (Âµg/mL)	AUC (ÂµgÂ·h/mL
0.1	0.2	6.93	2.50	50
0.2	0.1	6.93	5.00	100
0.3	0.1	5.49	5.77	100
0.4	0.1	4.62	6.26	100
0.5	0.1	4.02	6.69	100
0.6	0.1	3.58	6.69	100
0.3	0.1	5.49	5.77	100
0.3	0.2	4.05	4.44	50
0.3	0.3	3.33	3.68	33.3
0.3	0.4	2.88	3.16	25

0.3	0.5	2.55	2.79	20

t_{max} = time to peak plasma concentration; C_{max} = peak xenobiotic concentration; AUC = area under the (plasma drug concentration versus time) curve.
Values are based on a single oral dose (100 mg) that is 100% bioavailable (F = 1) and has an apparent Vd of 10 L. The drug follows a one-compartment open model. The AUC is calculated by the trapezoidal rule from 0 to 24 h.
Reprinted, with permission, from Shargel L, Yu A: Pharmacokinetics of drug absorption. In: Applied Biopharmaceutics and Pharmacokinetics, 3rd ed. Norwalk, CT: Appleton & Lange, 1993, p. 183.

In the overdose setting, gastric emptying, single-dose activated charcoal, and whole-bowel irrigation decrease k_a. Multiple-dose activated charcoal, manipulation of pH to promote ion trapping to facilitate elimination, and certain chelators (ie, succimer, deferoxamine) increase k_e and are likely to decrease C_{max}, t_{max}, and AUC.

Interpretation of Plasma Concentrations

For plasma concentrations to have significance, there must be an established relationship between effect and plasma concentration. For many medications, such as phenytoin, digoxin, carbamazepine, and theophylline, there is an established therapeutic range. However, there are also many drugs for which there is no established therapeutic range (diazepam, propranolol, verapamil). Some xenobiotics exhibit *hysteresis* in which the effect increases as the plasma concentration decreases (eg, physostigmine). For many xenobiotics, there is very little information on toxicodynamics. Sequential plasma concentrations often are collected for

retrospective analysis in an attempt to correlate plasma concentrations and toxicity. Tolerance to drugs, such as ethanol, also influences the interpretation of plasma concentrations. *Tolerance* is an example of a pharmacodynamic or toxicodynamic effect as a result of cellular adaptation, and it occurs when larger doses of a xenobiotic are necessary to achieve the same clinical or pharmacologic result.

Other factors that influence the interpretation of plasma concentrations include chronicity of dosing (a single dose vs. multiple doses); whether absorption is still ongoing and therefore concentrations are still rising; whether distribution is still ongoing and therefore concentrations are uninterpretable (Figure 9-13); or whether the value is a peak, trough, or steady-state concentration. Clinical examples where interpretation is dependent on the dosing pattern of a single dose versus multiple doses include theophylline, digoxin, lithium, and acetaminophen. Controlled-release preparations and those xenobiotics that delay gastric emptying or form concretions are expected to have prolonged absorptive phases and require serial plasma concentrations to obtain a meaningful analysis of plasma concentrations (Chap. 7). A combination of trough, peak and minimum inhibitory concentrations are often consequential for monitoring antibiotics such as gentamicin.[8,38]

Pitfalls in interpretation arise when the units for a particular plasma concentration are not obtained or are unfamiliar (eg, mmol/L) to the clinician. In the overdose setting, the type of analysis used is not generally applied to such large concentrations, and the laboratory may make errors in dilution, or errors can be inherent in the assay (Chap. 7). In those cases, the director of the laboratory should be consulted for advice with regard to the need for a reference laboratory. The type of collection tube (eg, plasma or serum instead of whole-blood for certain metals), or receptacle, or the conditions during delivery of the sample may give rise to inaccurate or inadequate information. When in doubt, the laboratory should be called prior to sample collection. The laboratory usually measures

total xenobiotic (free plus bound), and for agents that are highly plasma protein bound, reductions in albumin increase free

concentrations and alter the interpretation of the reported value (see Eq. 9-7). Active metabolites may contribute to toxicity and may not be measured.[33] Collection of accurate data for analysis requires at least 4 data points during 1 elimination half-life. During extracorporeal methods of elimination, ideal criteria for determining the amount removed require assay of the dialysate or charcoal cartridge or multiple simultaneous serum concentrations going into and out of the device and not random serum concentrations. Clearance calculations for drugs such as lithium that partition significantly into the red cell are more accurate when measurements are taken on whole blood.[11,17] Patient weight and height and, when indicated, hemoglobin, creatinine, albumin, and other parameters to assess elimination pathways, may be helpful.

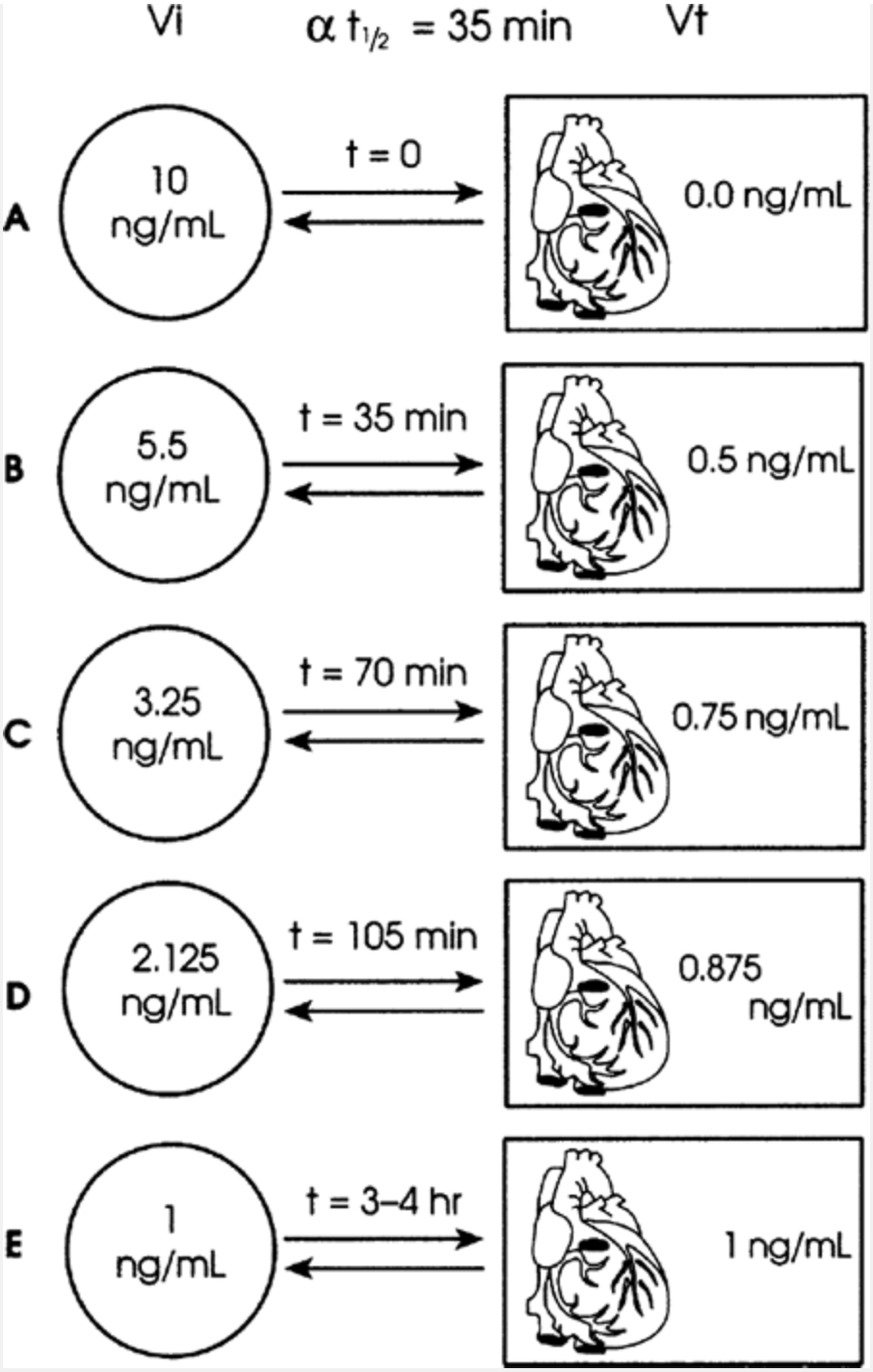

Figure 9-13. A theoretical two-compartment model for digoxin. *(Reprinted, with permission, from Winter ME: Digoxin. In: Koda-Kimble MA, Young LY, eds: Basic Clinical Pharmacokinetics, 3rd*

ed. Vancouver, WA, Applied Therapeutics, 1994, pp. 198â€“235.)

Case Illustrations

The following cases are designed to illustrate a number of pharmacokinetic and toxicokinetic principles. The cases demonstrate the applications of many of the mathematical models explained above.

Case 1

A 23-year-old, 90-kg female is seen in the emergency department 2 hours after the ingestion of 50 of her brother's Theo-Dur (300 mg) tablets. She is alert and oriented. Her vital signs are a blood pressure of 130/75 mm Hg; a heart rate of 110 beats/min; a respiratory rate of 20 breaths/min; and a temperature of 99.7Â°F (37.6Â°C) rectally. Her initial theophylline serum concentration is 40 mg/L.

- Estimate a peak serum concentration knowing that theophylline has a Vd of 0.5 L/kg, an *S* = 1 (not a salt form), and an *F* = 1 (100% bioavailable). Rearrange Equation 9-6.

$$C_0 = \frac{S \times F \times \text{dose (mg)}}{Vd}$$

$$C_0 = \frac{1 \times 1 \times 50 \times 300\ \text{mg}}{0.5\ \text{L/kg} \times 90\ \text{kg}} = 333\ \text{mg/L}$$

- If the history were correct what would prevent the patient from achieving this serum concentration?

  Increasing the number of tablets of sustained-release dosage forms may alter release characteristics, delay absorption, and

reduce k_a (absorption rate constant). Elimination (k_e) occurs during the absorptive phase, so C_{max} and AUC are reduced. Vomiting typically occurs following theophylline ingestion and will decrease bioavailability.

- How would treatment strategies affect the toxicokinetics of theophylline?

  Activated charcoal and whole-bowel irrigation decrease bioavailability. Multiple-dose activated charcoal, charcoal hemoperfusion, and hemodialysis enhance elimination.

- Can the patient be considered medically clear at this time?

  No. Serum concentrations may continue to rise and may not achieve peak levels for 12â€“24 hours. Therefore, sequential serum concentrations should be analyzed frequently until concentrations start to fall, and then less frequent determinations are necessary as the concentration approaches the therapeutic range (Chap. 63).

Case 2

A 63-year-old, 60-kg female is brought to the emergency department by her family 30 minutes after ingesting twenty-five 0.25-mg digoxin tablets. The patient complains of nausea, but is otherwise asymptomatic. Her physical examination is normal. Her vital signs are a blood pressure of 130/85 mm Hg; a heart rate of 76 beats/min and irregular; a respiratory rate of 17 breaths/min; and a temperature of 98Â°F (36.6Â°C) rectally. The ECG shows controlled atrial fibrillation at a rate of 76.

- Estimate this patient's plasma digoxin concentration. Assume Vd = 5 L/kg, S = 1, and F = 0.7 (70%).

$$C_0 = \frac{S \times F \times dose}{Vd}$$

$$C_0 = \frac{1 \times 0.7 \times 25 \times 0.25\ mg \times 1{,}000{,}000\ ng/1\ mg}{5\ L/kg \times 1000\ mL/L \times 60\ kg} = 14.6\ ng/mL$$

- Her serum digoxin concentration is reported to be 15 ng/mL (therapeutic = 0.8â€“2 ng/mL). Why doesn't this patient show more severe signs of digoxin toxicity?

  This patient does not show serious signs and symptoms of toxicity from digoxin because digoxin fits a two-compartment model with a long distribution half-life. Toxicity is related to the concentration in the peripheral (heart) compartment. However, in several hours she may demonstrate severe signs of toxicity (see Fig. 9-13).

- How do digoxin-specific antibody fragments (DSFab) alter the toxicokinetics of digoxin?

  Digoxin-specific antibody fragments reduce the Vd of digoxin by binding digoxin in the plasma, thereby establishing a concentration gradient to remove digoxin from reversible myocardial binding sites. All digoxin bound to digoxin-specific antibody fragments is inactive. The digoxin-specific antibody fragmentsâ€“digoxin complex is eliminated slightly faster than digoxin alone because of a reduced Vd.

- How would you calculate the appropriate dose of Digoxin-specific antibody fragments?

  If the ingested dose is known:

$$\text{Total body load (TBL)} = S \times F \times \text{dose}$$
$$= 1 \times 0.7 \times 25 \times 0.25 \text{ mg} = 4.375$$
1 vial of DSFab binds 0.5 mg of digoxin

$$\text{No. vials DSFab} = \frac{\text{TBL (4.375 mg)}}{\text{0.5 mg digoxin/vial DSFab}}$$
$$= 8.75 \text{ (Round up to 9 vials) vials}$$

If serum concentration is known:

$$\text{TBL (mg)} = C \text{ (ng/mL)} \times (1 \text{ mg}/1{,}000{,}000 \text{ ng}) \times V_d \text{ (L/kg)}(1000 \text{ mL/L}) \times \text{weight of patient (kg)}$$

$$= \frac{15 \text{ ng/mL} \times 5 \text{ L/kg} \times 60 \text{ kg}}{1000} = 4.5 \text{ mg}$$

$$\text{No. vials DSFab} = \frac{\text{TBL(4.5 mg) of digoxin}}{\text{0.5 mg digoxin/vial DSFab}}$$
$$= 9 \text{ vials DSFab}$$

OR a simplified version:

$$\text{No. vials DSFab} = \frac{C\text{(ng/mL)} \times \text{weight per patient (kg)}}{100}$$
$$= 9 \text{ vials DSFab}$$

The numbers of vials of digoxin-specific antibody fragments calculated either by using the history of the amount ingested or based on the serum concentration are usually different because each formula has independent inherent errors.

Case 3

A patient receives a continuous infusion of pentobarbital for 3 days. The infusion is terminated, but the patient has not awakened after 6 hours. The reported duration of hypnotic action after a single IV dose

is 1â€“4 hours. Is there a toxicokinetic explanation for the persistent somnolence?

Yes. The short duration of action after a single dose of IV pentobarbital is attributed to redistribution. With chronic dosing, accumulation occurs and the elimination half-life becomes 15â€“48 hours. This patient may require several days to awaken.

Case 4

A 70-kg man with no history of alcoholism ingests methanol and is found to have a serum concentration of 100 mg/dL (1 g/L). The following information is available:

- Methanol: molecular weight 32 daltons; water soluble
- Specific gravity (sp gr) of absolute ethanol and methanol: 0.8 g/mL
- Vd of ethanol and methanol = 0.6 L/kg
- Protein binding of ethanol and methanol = negligible
- Bioavailability for ethanol and methanol = 100%
- Hemodialysis clearance of ethanol and methanol = 150 mL/min; assume hemodialysis is a first-order process
- Hemodialysis extraction ratio of ethanol and methanol = 100%
- V_{max} = 0.13 g/kg/h for ethanol for a naive person
- How much methanol did the patient drink if he drank gas-line antifreeze which is 95% methanol?

$$C_0 = \frac{S \times F \times \text{dose}}{V_d} \quad \text{Rearranging: } S \times F \times \text{dose} = C_0 \times V_d$$

$$1 \times 1 \times \text{dose} = 1\text{g/L} \times 0.6\ \text{L/kg} \times 70\ \text{kg}$$
$$= 42\ \text{g of 100\% concentration}$$
$$(S = 1; \text{there is no salt form of an alcohol})$$
$$42\ \text{g} \times 1\ \text{mL}/0.95\ \text{g (95\% conc)} \times 1\ \text{mL}/0.8\ \text{g (sp gr)}$$
$$= 55\ \text{mL of 95\% methanol}$$

- How much ethanol as vodka (80 proof = 40%) should be given to the patient as a loading dose to achieve a serum ethanol concentration of 100 mg% (100 mg/dL or 1 g/L)?

$$C_0 = \frac{S \times F \times \text{dose}}{Vd} \quad \text{Rearranging: } S \times F \times \text{dose} = C_0 \times Vd$$

$$1 \times 1 \times \text{dose} = 1\text{g/L} \times 0.6\ \text{L/kg} \times 70\ \text{kg} = 42\ \text{g}$$
$$42\ \text{g} \times 1\ \text{mL}/0.4\ \text{g (40\% conc)} \times 1\ \text{mL}/0.8\ \text{g (sp gr)}$$
$$= 131\ \text{mL of 40\% ethanol}$$

- What maintenance dose of ethanol should be given to the patient to maintain an ethanol serum concentration of 100 mg/dL (1 g/L)?

  The V_{max} of 0.13 g/kg/h is the maximum rate of elimination for a patient not tolerant to ethanol. The maintenance dose is designed to replace the amount of ethanol eliminated. Therefore:

  0.13 g/kg/h Ã— 70 kg = 9.1 g/h Ã— 1 mL/0.1(10%) Ã— 1 mL /0.8 (sp gr) = 113.75 mL/h of 10% ethanol (can be given P0 or IV)

- How many hours of hemodialysis are necessary to reduce the methanol serum concentration to 10 mg/dL (0.1 g/L)?

  k_e = Cl/Vd; $Cl_{\text{total body}} = Cl_{HD} + Cl_{\text{endogenous}}$

  $= Cl_{HD} + 0$ (minimal endogenous clearance when methanol metabolism is blocked with ethanol)

$$\frac{150\ \text{mL/min} \times 60\ \text{min/h} \times 1\ \text{L}/1000\ \text{mL}}{0.6\ \text{L/kg} \times 70\ \text{kg}}$$

$$= 0.214\ \text{h}^{-1} = 21.4\%\ \text{per hour eliminated}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.214\ \text{h}^{-1} = 3.22\ \text{h}$$

$$t_1 - t_2 = \frac{\ln C_1 - \ln C_2}{k_e} = \frac{\ln 100 - \ln 10}{0.214\ \text{h}^{-1}}$$

$$= 10.74\ \text{hours to go from 100 mg/dL to 10 mg/dL}$$

Case 5

A 70-kg male is brought to the hospital with a serum phenytoin concentration of 80 Âµg/mL (mg/L). Assume the ingestion occurred 2 days earlier and there is no ongoing absorption. Estimate how long it might take this patient to reach 20 Âµg/mL. The following information is available:

$$Vd = 0.7\ \text{L/kg}$$

V_m (maximum metabolic capacity) $= 7$ mg/kg/d

K_m (serum concentration at which the metabolic rate is at one-half the maximum metabolic rate) $= 4$ mg/L

$$v = \frac{V_{max} \times C}{K_m + C} = \frac{7\ \text{mg/kg/d} \times 70\ \text{kg} \times 80\ \text{mg/L}}{4\ \text{mg/L} + 80\ \text{mg/L}}$$

$$= 466.6\ \text{mg/day eliminated at zero order}$$

Estimate the initial amount of phenytoin in body:

Dose = C Ã— Vd 80 mg/L Ã— 0.7 L/kg Ã— 70 kg = 3920 mg

Estimate the amount of phenytoin in body at 20 mg/L:

Dose = C Ã— Vd = 20 mg/L Ã— 0.7 L/kg Ã— 70 kg = 980 mg

3920 mg - 980 mg = 2940 mg as the amount that needs to be eliminated

At an elimination rate of 466.6 mg/d, it takes about 6.3 days for the

serum phenytoin concentration of 80 mg/dL to fall to 20 mg/dL assuming neither ongoing absorption nor enhanced elimination from repeat dose activated charcoal occurs.

A similar result is found using the following formula:

$$t = \frac{[(K_m)(\ln Cp_1/\ln Cp_2)] + (C_1 - C_2)}{V_m/Vd}$$

$$= \frac{(4\ \text{mg/L}) \times (4.38 - 3) + (80 - 20)}{(7\ \text{mg/kg/d} \times 70\ \text{kg})/(0.7\ \text{L/kg} \times 70\ \text{kg})}$$

$$= 6.55\ \text{days}$$

Case 6

Compare the utility of exchange transfusion, peritoneal dialysis, hemodialysis, and hemoperfusion for the ingestion of 2 g of either amitriptyline or theophylline in a 15-kg child.

The following information is available:

Vd of amitriptyline = 30 L/kg; protein binding = high

Vd of theophylline = 0.5 L/kg; protein binding = moderate

Blood volume = 85 mL/kg: a double volume exchange

= 85 mL/kg Ã— 2

Estimate that 300 mL of peritoneal fluid is administered over 10 min, that the equilibration time is 20 min, and that 300 mL is removed over 30 min for a total time of 60 min.

Assume HP clearance of 200 mL/min for theophylline.

- Would exchange transfusion be reasonable for amitriptyline or theophylline removal?

Double volume exchange = 85 mL/kg Ã— 2

In this child = 85 mL/kg Ã— 15 kg Ã— 2 = 2550 mL = 2.55L

Vd for amitriptyline in this child = 30 L/kg Ã— 15 kg = 450 L

450 L/ 2.55 L = 176 double-exchange transfusions, an unrealistic number!

Vd for theophylline in this child = 0.5 L/kg Ã— 15 kg = 7.5 mL

7.5 L/2.55 L = about 3 double-exchanges, a reasonable number!

- Would peritoneal dialysis be reasonable for amitriptyline or theophylline removal? (For peritoneal dialysis, assume a 300-mL/h exchange which equals 7.2 L/d.)

  No for both amitriptyline and theophylline.

  For amitriptyline, 450 L/7.2 L/d = 62.5 days

  for theophylline, 7.5 L/7.2 L/d = 25 hours

  which is too long in a life-threatening situation.

- Would hemodialysis be reasonable for amitriptyline or theophylline removal?

  No, for amitriptyline; yes, for theophylline.

  For hemodialysis, there is unlikely to be any benefit for amitriptyline removal because of the high protein binding and large Vd. Moderate protein binding of theophylline would be a limiting factor but a small Vd would be advantageous. The result would be acceptable for theophylline.

- Would activated charcoal hemoperfusion be reasonable for amitriptyline or theophylline removal?

  No, for amitriptyline; yes, for theophylline.

  For hemoperfusion, protein binding may be of less importance if binding to activated charcoal is more substantial than protein binding.

k_e = Cl/Vd

Assume HP Cl = 200 mL/min Ã— 60 min/h = 12 L/h and the endogenous clearance is minimal.

For amitriptyline:

12 L/h/30 L/kg Ã— 15 kg = 0.0266 h^{-1}

$t_{Â½}$ = 0.693/k_e = 0.693/0.0266 = 26 hours, which is clinically unreasonable.

For theophylline:

12 L/h/0.5 L/kg Ã— 15 kg = 1.6 h^{-1}

$t_{Â½}$ = 0.693/k_e = 0.693/1.6 = 0.433 hours, which is clinically reasonable.

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Chapter 10

Principles and Techniques Applied to Elimination

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Daniel Matalon

Enhancement of the elimination of a xenobiotic from a poisoned patient is techniques to inhibit absorption such as orogastric lavage, multiple-dose whole-bowel irrigation are initiated. Table 10-1 lists methods that might elimination. Some of these techniques are described in more detail in cha specific xenobiotics. In this chapter, hemodialysis, hemoperfusion, and h considered *extracorporeal therapies* because xenobiotic removal occurs in the body. These methods are used infrequently because current methods care keep the overall mortality rate low in poisoned patients who reach t these elimination techniques are not without adverse effects and complica in only a relatively small proportion of patients. Although undoubtedly an use, enhancement of elimination was used relatively infrequently in a coh patients reported by the American Association of Poison Control Centers Surveillance System (TESS) in 2004 (Chap. 130). Alkalinization of the u 8654 times; multiple-dose activated charcoal 5031 times; hemodialysis 1 29 times; and â€œother extracorporeal proceduresâ€• (most likely cont

hemofiltration [CVVH]) 33 times. Recent annual reports from the AAPCC c regarding the specific poisonings treated with the various modalities of e the past, when these data were reported, there were many instances of t therapies that would today be considered inappropriate, such as in the tr antidepressant overdose.

In comparing these most recent data to past reports, and recognizing tha is imperfect (Table 10-2), there is a continued increase in the reported paralleling a decline in reports of charcoal hemoperfusion (Chap. 130). T this decline are described in the â€œCharcoal Hemoperfusionâ€• section, and other sorbents once used for hemoperfusion are not currently availab Peritoneal dialysis (PD), a slower modality that should have little or no ro longer separately reported (Chap. 130). â€œOther extracorporeal proced reports may include some cases in which PD was used. In the later data, includes fewer reports of PD use and more reports of the more recently venovenous hemo(dia)filtration,â€• or CVVH(D). There are very few pro controlled clinical trials to determine which groups of patients actually be elimination of various xenobiotics, and which modalities are most efficaci it is unlikely that such studies will ever be performed, given the relative cases of sufficient severity and because of the many variables that would comparisons. Thus, anecdotal evidence predominates. We must still rely o principles of these methods to identify the individual patients for whom e indicated. Isolated case reports in which the kinetics are studied before, enhanced elimination are also very useful in establishing the efficacy of a

Indications for Enhanced Elimination

Enhanced elimination may be indicated in several types of patients:

- *Patients who fail to respond adequately to full supportive care.* Such intractable hypotension, heart failure, seizures, metabolic acidosis, o Hemodialysis or hemoperfusion are much better tolerated than in the potentially life-saving opportunities for patients with life-threatening t theophylline, lithium, salicylates, or toxic alcohols.
- *Patients in whom the normal route of elimination of the xenobiotic is*

may have renal or hepatic dysfunction, either preexisting or caused b example, a patient with chronic renal insufficiency associated with lon more likely to develop lithium toxicity and to require hemodialysis as

- *Patients in whom the amount of xenobiotic absorbed or its high conce indicates that serious morbidity or mortality is likely.* Such patients m on presentation. Xenobiotics in this group may include ethylene glyco paraquat, salicylate, and theophylline.

- *Patients with concurrent disease or in an age group (very young or o increased risk of morbidity or mortality from the overdose.* Such pati prolonged coma, immobility, and hemodynamic instability. An example severe underlying respiratory disease and chronic theophylline poison
- *Patients with concomitant electrolyte disorders that could be addresse* example is the lactic acidosis associated with metformin toxicity discu â€œHemodialysis â€• section of this chapter.

Cerebrospinal fluid drainage and replacement
Chelation
Cholestyramine
Colestipol
Continuous hemo(dia)filtration
Diuresis
Exchange transfusion
Hemodialysis
Kayexalate
Manipulation of urinary pH
Multiple doses of activated charcoal
Nasogastric suction
Peritoneal dialysis
Plasmapheresis
Sorbent hemoperfusion (charcoal, others)
Xenobiotic-specific antibody fragments
Whole bowel irrigation

TABLE 10-1. Potential Methods of Enhancing Elimination of Xenol

Ideally, these techniques will be applied to poisonings for which studies s outcome in treated patients as compared to patients not treated with ex previously mentioned, these data are rarely available.

The need for extracorporeal elimination is less clear for patients who are that are known to be removed by the various modalities of treatment, bu morbidity if supportive care is provided. Relatively high rates of endogen make extracorporeal elimination redundant. Examples of such xenobiotics barbiturates. Both are subject to substantial rates of hepatic metabolism, expected to lead to significant morbidity after the affected patient has b intubated and is mechanically ventilated. There may be instances of sever substances in which enhanced elimination will reduce the length of ICU st nosocomial risks; extracorporeal elimination may then be a reasonable o

Hemodialysis
297
584
1280
1400
1726
Hemoperfusion
  Charcoal
99
111
45
30
29
  Resin
23
37

Peritoneal dialysis
62
27

â€œOther extra corporeal proceduresâ€•

26
27
33
[a] Data derived from annual reports of AAPCC TESS (Chap. 130).

1986 1990 2001 2002 2004

TABLE 10-2. Changes in Use of Extracorporeal Therapies [a]

Characteristics of Xenobiotics Appropriate Extracorporeal Therapy

The appropriateness of any modality for increasing the elimination of a g
on various properties of the molecules in question. Effective removal by
procedures and other methods listed in Table 10-1 is limited by a large v
volume of distribution (Vd) relates the concentration of the xenobiotic in t
total body burden. The Vd can be envisioned as the apparent volume in w
of drug is distributed before metabolism and excretion occur:

Vd(L/kg) = dose (mg)/concentration (mg/L)

The larger the Vd, the less the xenobiotic is available to the blood compa
drug with a relatively small Vd, considered amenable to extracorporeal e
distribute in an apparent volume not much larger than total body water. T
approximately 60% of total body weight, so that a Vd equal to total body

0.6 L/kg body weight.

Ethanol is an example of a xenobiotic with a small Vd approximately equa substantial fraction of a dose of ethanol could be removed by hemodialysi insignificant fraction of digoxin, with a large volume of distribution (Vd = weight), would be removed by this therapy. Lipid-soluble xenobiotics, and protein bound, have large volumes of distribution, which can exceed total body weight. These high apparent volumes of distribution imply that the to extracorporeal removal because only a small portion would be in the b extracorporeal circuit. In addition to the alcohols, other xenobiotics with phenobarbital, lithium, salicylates, bromide and fluoride ions,[10] and theo those with a high Vd (up to 40 L/kg of body weight), which would not be hemodialysis, include many Î²-adrenergic antagonists (with the possible e diazepam, organic phosphorus compounds, phenothiazines, quinidine, and antidepressants.

Whether a xenobiotic can be removed is also determined by the pharmac compound. Kinetic parameters after an overdose may differ from those a experimental doses. For instance, carrier or enzyme-mediated elimination overwhelmed by higher levels of the xenobiotic in question, making extr potentially more useful. Similarly, plasma protein- and tissue-binding sites higher concentrations, making extracorporeal removal feasible in instances role in less significant overdoses. An example is valproic acid, which may nontoxic levels associated with high rates of protein binding. Higher, pot concentrations saturate protein-binding sites and lead to a higher proportio serum and amenable to being removed at a clinically relevant rate by he the expected endogenous rates of elimination of a xenobiotic in the settin

should be made, where possible, from knowledge of the toxicokinetics ob of toxicity, not after therapeutic doses.

When assessing the efficacy of any technique of enhanced elimination, a principle is that the intervention is worthwhile only if the total body clear increased by at least 30%.[17] This substantial increase is easier to achieve a low endogenous clearance. Examples of xenobiotics with low endogenou mL/min/kg) include the toxic alcohols (particularly when their metabolism

sotalol, lithium, paraquat, phenytoin, salicylate, and theophylline. Xenobic endogenous clearances include many Î²-adrenergic antagonists, lidocaine, tricyclic antidepressants. Enhancement of elimination is expected to contri group than to the latter.

The efficacy of any technique of elimination can be directly assessed by c plasma concentrations of the substance at the beginning and at the end c example, a xenobiotic like theophylline, with one-compartment kinetics, is extracellular space. The difference between the theophylline concentration minus the concentration at the end of the procedure, divided by the conc beginning, is the fraction of the body burden of the xenobiotic that is eli

Certain xenobiotics like lithium distribute in part to the intracellular comp equilibrium is established for the drug between the intracellular and ext The latter compartment includes the blood from which xenobiotic eliminat the elimination rate from the extracellular compartment, such as by hem equilibrium. The rate of redistribution of the xenobiotic from the intracell now-dialyzed extracellular compartment may be slower than the rate of c dialysis membrane. In that case, the plasma concentration may become r substantial intracellular burden. This low plasma concentration reduces t for diffusion from plasma to dialysate so that dialysance, the dialysis clea although plasma or blood concentrations may fall precipitously during the body burden of the xenobiotic may not be affected significantly. An examp ingests one hundred 25-mg amitriptyline tablets, a tricyclic antidepressar fully absorbed, the 2500 mg distributes in an apparent volume of 40 L/kg achieve a plasma concentration of 1000 ng/mL, a potentially toxic level. is performed with a blood flow rate of 350 mL/min (plasma flow rate of 2 hematocrit of approximately 43%), and the extraction ratio is 100% (see Hemoperfusion ,â€• below), the clearance of drug is 200 mL/min or 200 minutes) of treatment, only 48 mg (48,000 Âµg), or less than 2% of the removed, which will have no effect on toxicity.

Further evidence that a xenobiotic is in a slowly equilibrating compartmen monitoring the blood concentrations after discontinuation of the procedur rebounding serum levels. This rebound indicates postdialysis redistribution magnitude of the rebound depends on total-body stores of the xenobiotic,

there is ongoing absorption from the gastrointestinal tract.

When assessing efficacy, the evidence of enhanced elimination must be c the clinical response. In some instances, improvement is observed that w based on the kinetics of the parent compound. For example, in severe ca antidepressant poisoning, unexpected improvement during hemoperfusion because the toxicity is manifested early and ameliorates rapidly during t phase.

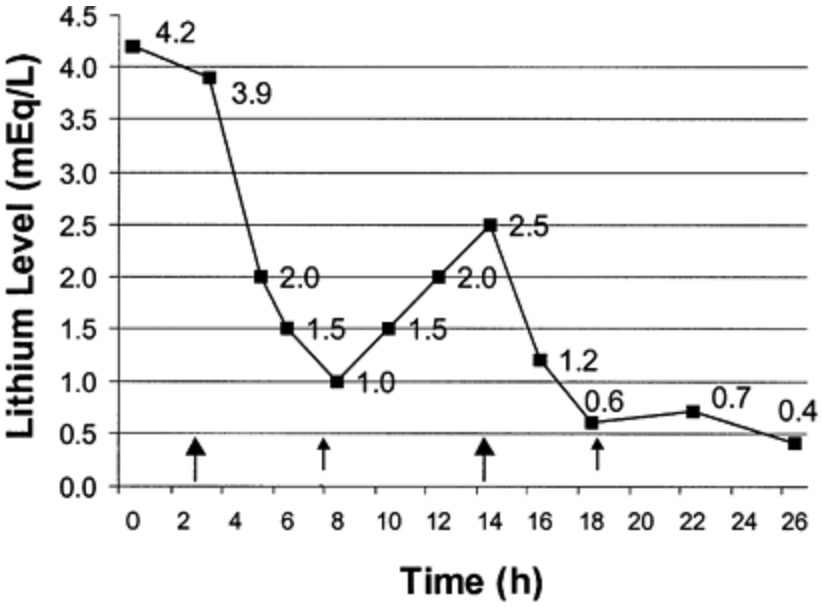


Figure 10-1. Repeated serum lithium concentrations after an acute inge beginning (large arrows) and end (small arrows) of hemodialysis. Followi treatment, a significant rebound in serum concentration occurred, with r impairment. An additional 4-hour hemodialysis treatment was then begur

Beginning a procedure during the initial distribution phase may increase t burden that can be removed. Later, after the xenobiotic has distributed in by plasma or tissue proteins, administration of extracorporeal treatment r clearance rates and benefits. Poisonings with paraquat and hepatotoxic m examples in which only early extracorporeal therapy *may* have benefit. A for unanticipated evidence of improvement is the removal of small amoun active metabolites from a shallow â€œtoxic effectâ€• compartment. This advanced to explain the response to hemodialysis of patients overdosed

chlorprothixene,[40] or with a combination of diltiazem and metoprolol.[3] Su transient improvements that are not sustained as drug redistributes from leading to early benefit but eventual recurrence of symptoms. Much of th to provide long-term followup to demonstrate prolongation of benefits af is completed and xenobiotics have redistributed.

Other examples also demonstrate that removal of a xenobiotic is a poor benefit. Enhanced elimination of phenobarbital[3,53] or carbamazepine[73] b charcoal did not affect clinical outcomes as compared to those of overdo despite a fall in their serum concentrations. In another study, no differer patients with lithium poisoning for whom hemodialysis was done and those recommended by a poison control center but not done.[8] The conclusion w should be considered appropriate only for the more severe cases. In ace efficacy of administration of *N* -acetylcysteine makes extracorporeal

removal unnecessary and not part of the recommended treatment strateg

Techniques Available to Enhance Removal

Although controversies remain about the efficacy of, or need for, removal consensus regarding the indications for a number of procedures has deve led to consistent application of several techniques of enhanced eliminatior exposures that occur relatively more frequently. The techniques to enha most commonly applied over the last decade have been alkalinization of hemodialysis for methanol, ethylene glycol, lithium, and salicylates; and theophylline.

Forced Diuresis and Manipulation of Urinary

Forced diuresis by volume expansion with isotonic sodium-containing solut or lactated Ringer solution, may increase renal clearance of some molecu theoretically be most true for xenobiotics such as lithium for which the g (GFR), the volume of plasma filtered across the glomerular basement mer important determinant of excretion. In people with normal extracellular flu had loss of sodium via renal, gastrointestinal, or other routes of excretion

expected with plasma volume expansion is variable and unpredictable and significant increases. The effect is potentially more important in patients of the extracellular fluid volume because of sodium loss. Loss of extracellu reduction of GFR partly as a result of decreased cardiac preload and card reduces renal plasma flow. This circumstance is also accompanied by acti small peptide that acts as a pressor and stimulates sodium reabsorption i Because small molecules like lithium are both filtered at the glomerulus a proximal tubule, especially when sodium depletion has occurred and angio activated, repletion of extracellular fluid volume with isotonic saline will i sodium reabsorption. The result is an increase in excretion of low-molec lithium. After the extracellular fluid volume is restored, continued infusion urine volume proportionally more than GFR, which may increase excretion such as urea, but which has marginal efficacy in the case of most poisoni not a significant determinant of excretion.

The significant risk of this therapy is extracellular fluid volume overload, and cerebral edema. This complication may be particularly likely in patie lithium use in whom chronic tubulointerstitial disease can lead to renal ir improve with fluid therapy. Other patients with acute renal failure not m fluid volume depletion are also at risk. Knowing the result of past serum may help distinguish acute from chronic renal insufficiency in such cases diuretics such as furosemide along with saline may diminish the risk of e overload, but complicate the therapy, confuse the assessment of extracel increase the risk of metabolic alkalosis and hypokalemia. The unproven e in the management of *any* overdose has led most experts to abandon its the repletion of extracellular fluid volume when it is contracted, as deterr physical examination, is, of course, appropriate.

Many xenobiotics are weak acids or bases that are ionized in aqueous solu depends on the pK_a of the compound and the pH of the solution. Knowing Henderson-Hasselbalch equation (Chap. 9) can be used to determine th the acids, bases, and buffer pairs. Cell membranes are relatively imperme molecules (such as an unprotonated salicylate anion), whereas nonionized the protonated, noncharged salicylic acid) can cross more easily. As xeno kidney, they may be filtered, secreted, and reabsorbed. If the urinary pH the formation of the ionized form in the tubular lumen, the xenobiotic is

fluid and not passively reabsorbed into the bloodstream (â€œion trapping
extent of its elimination can be increased. To make manipulation of urina
renal excretion of the compound must be a major route of elimination. A
American Academy of Clinical Toxicology (AACT) and the European Associ
and Clinical Toxicologists (EAPCCT) emphasizes that, as discussed above
therapies, enhanced removal does not necessarily translate into a clinical
outcomes.[55]

Acidification of the urine by systemic administration of HCl or NH_4 Cl to
weak bases, such as phencyclidine or the amphetamines, is not useful ar
The technique has been abandoned because it does not significantly enha
xenobiotics and is complicated by systemic metabolic acidosis.

Alkalinization of the urine to enhance elimination of weak acids has a lim
such as salicylates,[48] phenobarbital, chlorpropamide, formate, diflunisal,
and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D). These weak aci
urine pH and tubular reabsorption is thereby greatly reduced. Alkalinizatio
intravenous administration of sodium bicarbonate, 1â€“2 mEq/kg infused
goal is to increase urinary pH to 7â€“8.

This degree of alkalinization may be difficult, if not impossible, if metabo
are present, as often is the case with salicylate poisoning. In this situati
(administered as the sodium salt) is consumed by titration of plasma prot
in the urine. On the other hand, salicylate poisoning often causes respirat
that case, where PCO_2 is low, raising serum bicarbonate, equivalent to th
alkalosis, may lead to profound, life-threatening alkalemia. Finally, the ri
volume overload with sodium bicarbonate administration is the same as v
0.9% NaCl. Hypernatremia may also ensue after administration of hyper
Bicarbonaturia will also be associated with urinary potassium losses, so s
concentration should be monitored frequently and KCl given liberally as lo
impaired. A further complication of alkalemia is a decrease of ionized cal
bound by albumin as protons are titrated off serum proteins; if this occur
these complications can be identified and dealt with judiciously and safely

salicylate can increase 4-fold as urine pH increases from 6.5 to 7.5 with

Increasing urine pH by decreasing proximal tubular bicarbonate reabsorpt

carbonic anhydrase inhibitors such as acetazolamide is not recommended. xenobiotic may be increased, metabolic acidosis will ensue unless ample administered. In the case of salicylates, metabolic acidosis with acidemia distribution of drug into the central nervous system. As with $NaHCO_3$ ad bicarbonaturia is accompanied by urinary potassium losses; hypokalemia c of urinary alkalinization in the management of salicylate poisoning is disc .

Alkalinization is also used to increase the solubility of methotrexate and precipitation in tubules when patients are given high-dose folinic acid res Precipitation of sulfonamide antibiotics with renal stones or renal failure c alkalinization. Extracellular fluid volume expansion with 0.9% NaCl and N protects the kidneys from the toxic effects of myoglobinuria in patients w rhabdomyolysis. However, because patients with rhabdomyolysis may hav $NaHCO_3$ administration must be used before renal injury occurs and may volume overload if its administration continues once renal failure is estal

Peritoneal Dialysis

Theoretically, peritoneal dialysis enhances the elimination of a few wate weight, poorly protein-bound xenobiotics with a low volume of distribution lithium, salicylate, and theophylline. Clearance of xenobiotics in the aqueo dialysate flow rate, the surface area of the peritoneum, and the molecular compound. The highest clearances are achieved for molecules with MW < of peritoneal dialysis is markedly decreased when the patient is hypotens

Although peritoneal dialysis is a relatively simple method to enhance xen too slow to be clinically useful. Consequently, peritoneal dialysis is never unless hemodialysis and hemoperfusion are unavailable and transfer to a these techniques is not feasible. Besides exchange transfusion, it may be in small children if experience with extracorporeal techniques in younger a until a child can be transported to an appropriate center.

Hemodialysis

The utility of hemodialysis for the treatment of toxicity caused by lithium

salicylates, and theophylline is unquestionable and is not dealt with here these xenobiotics has its own chapter in which the toxicity and indicatior therapies are reviewed. Instead, this section describes the hemodialysis p its application to some newer situations.

Prompt consultation with a nephrologist is always indicated in the case of xenobiotic that might benefit from extracorporeal removal. The most rece that a number of deaths related to salicylate poisoning could have been had been instituted earlier (Chap. 130). The nephrologist has to call in a dialysis machine requires preparation, and the vascular access catheter ha of several hours before hemodialysis can be instituted should be anticipa modalities of treatment such as ethanol or fomepizole should be adminis to enhance elimination, such as urinary alkalinization or oral multiple-dos (MDAC), should be used where appropriate.

The technical details of the performance of hemodialysis for treatment of markedly from those used in the treatment of acute renal failure. Vascula via the femoral vein. The subclavian and internal jugular veins are also a slightly higher rates of such complications as pneumothorax and arterial after catheter removal is also more easily achieved at the femoral site. H hemoperfusion (see these sections below) are usually performed using a manufactured for dialysis that is made of silicon, polyethylene, polyuretha pumped through one lumen, passed through the machine, and returned t through the second lumen. Blood flow rates with these catheters can be a mL/min, although 350 mL/min may sometimes be the maximum rate ach

The blood lines and artificial kidney (the dialysis membrane) should be p volume of fluid to reduce or avoid hypotension when the procedure is sta efficiencyâ€• or â€œhigh-fluxâ€• artificial kidneys should be selected. H heparin is usually required. A typical adult heparin dose is 4000â€“5000 u by 400â€“500 units hourly. Alternatively, periodic flushes of the dialysis heparinized saline exposes the patient to very low doses of heparin and l anticoagulation. Regional anticoagulation of the dialysis circuit with citrate if heparin is absolutely contraindicated, although these agents complicate dialysate which contains citrate may be adequate for anticoagulation and avoided.[2]

In poisoned patients, hemodialysis is usually performed for 4â€“8 hours. patient's serum potassium concentration is normal, a standard bicarbonat potassium concentration of 3 or 4 mEq/L and a calcium concentration of 3 600â€“800 mL/min, is sufficient. If dialysis is performed in a dialysis unit, a concentrate with $NaHCO_3$ and highly purified water, usually derived by deionization. Dialysis procedures done in intensive care units should use generate the water for mixing, but in the past tap water has been period

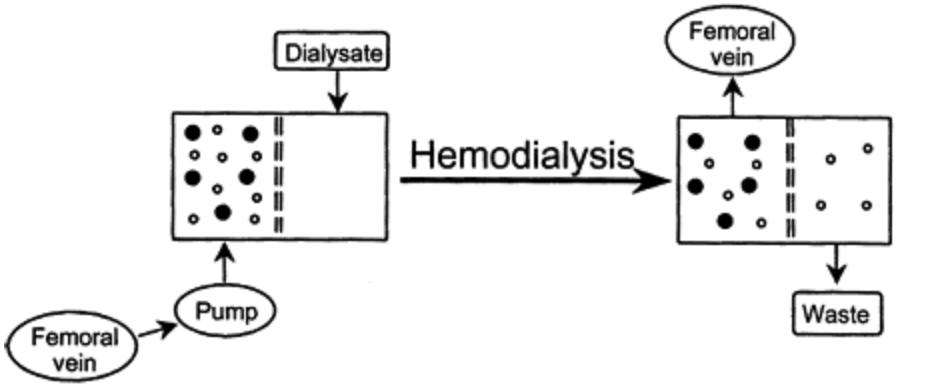
During conventional hemodialysis, blood flows through hollow fibers whic membranes. The hollow fibers are bathed by a dialysis solution, or dialy across the membrane from blood into the dialysate down their concentrat Table 10-3 lists the characteristics of xenobiotics that make them amena requirements greatly reduce the number of substances that can be expect dialysis. During hemodialysis, clearance of a xenobiotic (Cl_H) can be cal

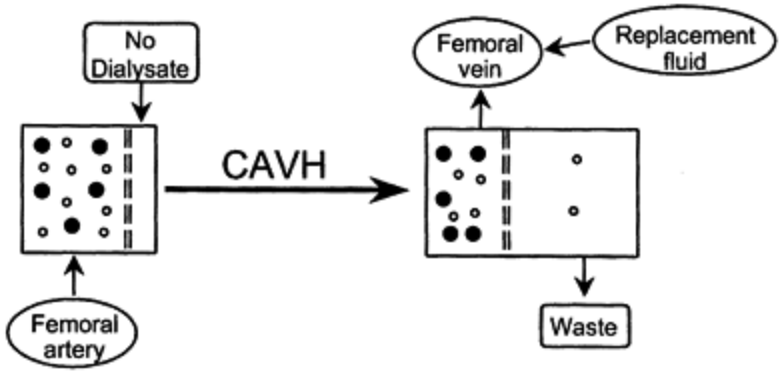
$$CI_H = [Q_{in} (C_{in} - C_{out}]/C_{in}$$

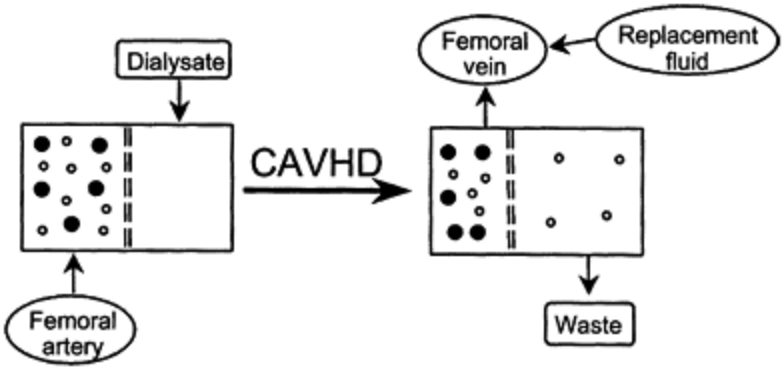
where Q_{in} is the blood flow entering the dialyzer, C_{in} is the concentration entering the system, and C_{out} is the concentration in blood leaving the s (ER) is a measure of the percentage of xenobiotic passing through

the artificial kidney, or charcoal hemoperfusion cartridge. This can be cal

$$ER = \frac{C_{in} - C_{out}}{C_{in}} \times 100$$


Dialysate
Femoral vein
Hemodialysis
Pump
Femoral vein
Waste


No Dialysate
Femoral vein
Replacement fluid
CAVH
Femoral artery
Waste


Dialysate
Femoral vein
Replacement fluid
CAVHD
Femoral artery
Waste

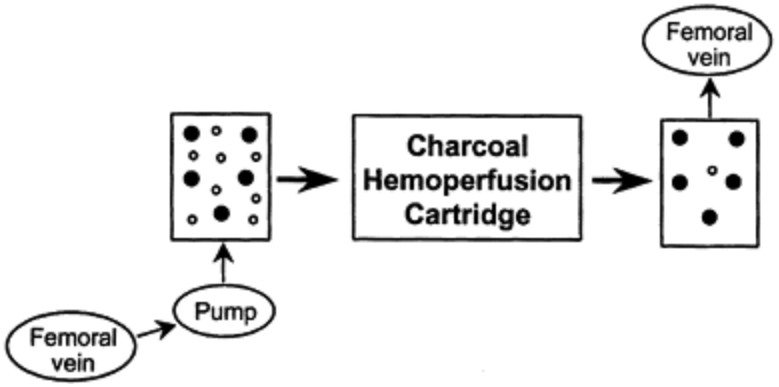

Femoral vein
Charcoal Hemoperfusion Cartridge
Pump
Femoral vein

Figure 10-2. The comparative schematic layouts of HD (hemodialysis), C arteriovenous hemofiltration), CAVHD (CAVH with dialysis), and HP (her are high-molecular-weight substances such as plasma protein; *open circl* weight diffusible solutes such as urea or methanol. In dialysis, solute mov semipermeable membrane (*dashed lines*) from a solution in which it is p concentration (blood) to one in which it is at a low concentration (dialysa plasma moves across a similar membrane in response to hydrostatic pre *venovenous* hemofiltration with dialysis, not pictured, is similar to CAVHD blood pump because it does not have arterial pressure to drive hemofiltr pumps has made arteriovenous modalities nearly obsolete. Charcoal hem movement of blood through a sorbent-containing cartridge and does not hemofiltration.

For All Three Techniques
- Low volume of distribution (<1 L/kg)
- Single-compartment kinetics
- Low endogenous clearance (<4 mL/min/kg)

For Hemodialysis
- MW <500 daltons
- Water soluble
- Not bound to plasma proteins

For Hemoperfusion
- Adsorption by activated charcoal
- Binding by plasma proteins does not preclude

For Hemofiltration
- MW <10,000 or <40,000 daltons, depending on filter used

TABLE 10-3. Characteristics of Xenobiotics That Allow Clearan Hemoperfusion, and Hemofiltration

Several technologic advances enable patients to tolerate dialysis with bet Clearance rates reported in the literature of the 1970s and 1980s may currently achievable clearance rates.[50] Patients undergoing hemodialysis

much less hemodynamic instability than in the past. For instance, the sou routinely is now $NaHCO_3$ rather than sodium acetate; the latter caused h cardiac output. Computerized machines allow fine control of ultrafiltration losses; in the past, imprecise calculations and manipulations led to freque hypotension. The sodium concentration of the dialysate can be programme course of the procedure, a technique called *sodium modeling* , which ma stability as well. Better hemodynamic stability and larger dual-lumen cath blood flows, up to 400â€“500 mL/min. As a result of such innovations, tr in more instances than was previously possible. Hypotension may still occ Saline, colloid, vasopressors, or inotropic agents may also be required in dialysis seems to offer the best chance for the patient's survival, it shoul

Dialysis membrane composition has continued to evolve. The hollow-fiber thousands of blood-filled capillary tubes held together in a bundle and ba generated dialysate. Conventional dialyzers, which are less frequently en made of cellulose-derived polymers, most commonly called cuprophane. have larger surface areas and therefore larger clearances. Hemodialysis with low-molecular-weight substances should improve with the use of lar larger clearances. The prototypical â€œmiddle molecule,â€• the clearance express a dialyzer's high-flux dialysance, is $Î²_2$ -microglobulin (MW 11,80

â€œHigh-flux,â€• synthetic dialyzers have larger pores that allow more molecules. Because these membranes also have higher water permeabili ultrafiltration control is necessary. These membranes, composed of polys polyacrylonitrile (PAN), and other polymers have better biocompatibility t derived membranes. Biocompatibility is measured by the rate of activation exposure to the membrane, of inflammatory mediators that include white complement, and cytokines. Better biocompatibility means less activation

damaging mechanisms as compared with more bioincompatible membrane biocompatibility on the outcomes of patients receiving long-term hemodia failure is still being assessed. Patients with chronic renal failure are expo materials during at least 3 treatments a week for many years. It is unlike biocompatibility will affect outcomes for dialysis of poisoned patients who treatments.

There are some instances in which high-flux dialyzers might be important larger molecules, such as vancomycin, which are not readily removed by membranes.[25] However, the indications for performing hemodialysis to en vancomycin and other xenobiotics with higher molecular weights have no Nonetheless, a sound pharmacologic basis for the efficacy of dialysis must amount of increased clearance will eliminate a xenobiotic with a large vol significant tissue binding.

With that proviso, recent experience suggests a role for high-flux hemodia certain xenobiotics that were previously thought to be effectively removed hemoperfusion. As valproic acid is increasingly prescribed for neurologic the incidence of both intentional and unintentional overdoses of this drug discussed previously, valproic acid is largely protein bound at therapeuti Toxic concentrations saturate protein binding sites leading to a higher pr in the serum and a lower apparent volume of distribution, thereby making dialyzable. Indeed, several case reports have demonstrated that the clear high flux hemodialysis is at least equivalent to, if not greater than, that hemoperfusion.[29, 34, 36, 38, 39] Although carbamazepine has a low mole volume of distribution that would allow for clearance by hemodialysis, its lack of water solubility would be expected to impede the efficacy of hem carbamazepine is also effectively cleared with high-flux hemodialysis.[61], underwent high-flux hemodialysis followed by charcoal hemoperfusion for removal rates were similar for the two modalities.[70] Unlike the case for v for these anecdotal reports for enhanced carbamazepine elimination is no pharmacokinetics of the drug are altered at toxic serum concentrations, a acid, is not known. Because of its potential efficacy and availability, and cost and adverse events, high-flux hemodialysis should probably replace as the treatment modality of choice when extracorporeal elimination of va carbamazepine is to be performed. As stated above, however, effective c a surrogate for improved outcomes.[73] The availability of more effective c reassessment of the utility of these therapies worthwhile.

In addition to removing xenobiotics, hemodialysis can correct acidâ€“base abnormalities such as metabolic acidosis or alkalosis, hyperkalemia, and overload. Consequently, hemodialysis is preferred for poisonings characte if clearance rates resulting from hemoperfusion and hemodialysis are rel

include salicylate poisoning which is often associated with metabolic acid glycol toxicity, which is often associated with lactic acidosis, especially in hepatic impairment.[52]

A more controversial question is the role of dialysis in the treatment of acidosis. Metformin may not always be primarily responsible for the lactic drug by hemodialysis would then be less likely to affect the outcome. An between serum metformin concentrations and mortality in patients with lactic acidosis.[42] This finding may indicate that many of those with lower concentrations and metformin-associated lactic acidosis have another, pri production other than metformin such as sepsis or bowel ischemia. These worse outcomes. In cases of metformin-associated lactic acidosis in patie function, extracorporeal removal is generally not indicated, as endogenou is quite high and prognosis is good without dialysis.[9]

The more important role for hemodialysis is in cases of metformin-associ involving acute renal failure without other causes of lactic acidosis such or in patients with chronic renal failure who are inappropriately treated w small molecular weight and negligible plasma protein binding of metformir drug removal despite a relatively large volume of distribution.[41] In additi correct acidosis via administration of bicarbonate. Clinical improvement w result as much or more from correction of the acidosis as from removal o

Complications of acute hemodialysis are relatively rare. Bleeding or throm vascular access, usually the femoral vein, is infrequent with normal hemo postprocedure tamponade of the catheter site. Bleeding in the gastrointe caused by systemic anticoagulation with heparin, can be avoided if low do Low-dose heparin is an appropriate choice when dialyzing patients for to are at risk for intracerebral bleeding. Nosocomial bacteremia can occur if place for prolonged periods; central lines should be removed after 5 days lines should always be removed in patients who are out of bed.

In addition, hemodialysis increases the elimination of some drugs admir such as folic acid and other water-soluble vitamins and antibiotics. Doses increased during dialysis or administered immediately afterwards. Similarly infusions used in the treatment of toxic alcohol ingestions must be increa a low molecular weight (MW 82.1) and a low volume of distribution (0.6â€

be dialyzed, but it is not significantly removed by hemofiltration.[60] If nec redosed after dialysis (see Antidotes in Depth: Ethanol and Fomepizole). limited in such cases by enriching the dialysate with ethanol to a concent Similarly, hypophosphatemia after more prolonged high-flux hemodialysis adding sodium phosphate salts, in the form of Fleet Phospho-Soda, to th administering phosphate intravenously. Angiotensin-converting enzyme inh used if dialysis is performed with PAN membranes as the combination is angioedema.[13]

Charcoal Hemoperfusion

In general, if a xenobiotic is adsorbed by activated charcoal, charcoal he exceed that of hemodialysis.

During hemoperfusion, blood is pumped through a cartridge containing a sorbent, either activated charcoal or carbon (see Fig. 10-2). The sorbent layer of polymer membrane such as cellulose acetate (Adsorba, made by hydrogel (Biocompatible Hemoperfusion Systems, made by Clark) or poly methacrylate; Hemosorba, made by Asahi). The membrane prevents direc and sorbent, improves biocompatibility, and helps to prevent charcoal em a further theoretical advantage to the heparin-hydrogel coating to dimini The adsorptive capacity of the cartridge is reduced with use because of and blood proteins, and saturation of active sites by the xenobiotic in qu residual adsorptive capacity by serial serum levels is usually not practical obtaining results. The cartridge should therefore be changed after 2 hours hemodialysis, patients must be anticoagulated with heparin, and regional cartridge is possible if full anticoagulation is undesirable. The technique ca [74] or children.[16 , 51] Hemoperfusion is usually performed for 4â€“6 hours 250â€“400 mL/min.

The characteristics of xenobiotics that make them amenable to hemoperf Table 10-3) differ from those for hemodialysis in the important respect limited by plasma protein binding. This is exemplified in a report in which hemodialysis increased the elimination of the avidly protein-bound oral h chlorpropamide.[43] Some xenobiotics are poorly adsorbed by activated ch

alcohols, lithium, and many metals (see Antidotes in Depth: Activated Ch hemoperfusion inappropriate in their management. Hemoperfusion clearanc manner similar to that for hemodialysis. Although hemoperfusion has his the preferred method to enhance the elimination of carbamazepine, phen theophylline (Table 10-4), recent improvements in hemodialysis technolo membranes, may make older comparisons of hemodialysis and hemoperfu obsolete.[50] Hemodialysis and hemoperfusion have been performed in ser thallium, theophylline, and carbamazepine overdoses, with greater appare with either procedure alone.[11 , 21 , 37] In this technique, blood circulates hemodialysis membrane, and then through the charcoal cartridge. If bloo membrane first, some of the xenobiotic is dialyzed, and the activated cha drug to adsorb.[30] The activated charcoal cartridge is exhausted more slo ratios are maintained in a patient who ingested 2 g of propranolol. A he has been inserted into an extracorporeal membrane oxygenation (ECMO) flow rate was >3 L/min.[66] The plasma concentrations of propranolol decre ECMO than after it was discontinued. The high flow rate through the cartr substantial clearance of the drug. Hemoperfusion does not correct acidâ€ disorders, another reason why the combination of the two modalities is and salicylate poisoning.

A practical problem limiting the use of charcoal hemoperfusion is the ava Many dialysis units do not routinely have them in stock. The cartridges a ($350â€“$425 as compared to the maximal cost for a high-flux dialysis m $20â€“$23). Some have expiration dates, limiting shelf life. Others, such have an indefinite shelf life but must be autoclaved before use, which ma in an emergency. Charcoal cartridges were more available in chronic hem were more frequently needed for the treatment of chronic aluminum toxic aluminum-associated dementia and osteodystrophy were once more preva hemodialysis patients, but aluminum carbonate has been supplanted as a calcium salts (carbonate and acetate) and sevelamer (Renagel), a phospl addition, the most frequent indication for acute charcoal hemoperfusion in theophylline toxicity. Theophylline is now less popular in the treatment o and asthma. Its lower rate of prescription today in asthmatic teenagers m frequently used drug for suicide attempts. In turn, the low incidence of currently contributes to poor stocking of the cartridges. All of these facto

diminished availability of charcoal cartridges and the relative infrequency is performed. In our recent survey of New York City hospital dialysis units of 34 units had cartridges (unpublished data).

The complications of hemoperfusion are similar to those of hemodialysis. develop thrombocytopenia, leukopenia, and hypocalcemia. Better membr techniques have made embolization of charcoal particles extremely rare. A hemodialysis, doses of drugs used therapeutically may need to be increase hemoperfusion.

Other Sorbents for Hemoperfusion

Other adsorptive resins have been used for hemoperfusion, such as the and XAD-4 and anion exchange resins such as Dow 1X-2. None of these approved or available for use in the United States. The literature regardir and relatively anecdotal. Though there is in vitro evidence that these resi adsorptive capacities than activated charcoal, there are few, if any, mear clinical setting.

A new concept in sorbents for poisonings is that of albumin dialysis. The available in the United States only for investigational use. The patient's b hollow-fiber hemodialyzer. The dialysate bathing the fibers contains huma serves as a sorbent to bind the xenobiotic of interest and maintain levels zero. A steep concentration gradient from blood to dialysate is established protein-bound xenobiotics can be removed from the plasma. The membra albumin which remains in the dialysate. The albumin is reprocessed by pa activated charcoal cartridge as well as an anion exchanger so that it can current proprietary version of this procedure is called Molecular Adsorber (MARS), manufactured in Germany by Teraklin. The procedure was used the mortality associated with hepatic encephalopathy and liver failure.[47] procedure includes a conventional hemodialysis treatment as well as an membrane. The mechanism of the significant benefit of the procedure is understood, although it does remove both water-soluble and protein-bound known which protein-bound molecules are being removed from the blood,

as bile salts and aromatic amino acids to account for the therapeutic adv

The MARS system increases removal of fentanyl and midazolam in an ani report suggests potential benefit in a patient treated for toxicity with phe significant protein-binding and therefore not expected to be removed by hemoperfusion.[64] Whether this relatively expensive, complicated and nor offer benefit in a handful of instances where protein-binding limits remova known. A similar device, using a powdered sorbent and called HemoClean shortly in the United States. The report of its initial use in 10 cases of t overdoses claimed benefit, although the limitations of extracorporeal ther class of drugs is discussed above.[5]

Clinically Beneficial
Bromide
35
Yes
0.7
0
0.1
HD

Ethylene glycol
62
Yes
0.6
0
2.0
HD
Isopropanol
60
Yes
0.6
0
NA
HD

Lithium
7
Yes
0.6â€“1.0
0
0.4
HD
Cl â†“ in renal failure
Methanol
32
Yes
0.6
0
0.7
HD
Salicylate
138
Yes
0.2
50
0.9
HD, HP
Cl and protein binding â†“, with â†‘ dose; HD also corrects electrolytes,
Theophylline
180
Yes
0.5
56
0.7
HP>HD
HP & HD can also be combined
Valproic acid
144
Yes

0.13â€“0.22
90
0.1
HD, HP
â†‘ Levels associated with â†“ % protein binding
Possibly Clinically Beneficial
Amatoxins
373â€“990
Yes
0.3
0
2.7â€“6.2
HP
Possibly effective if performed within the first 24 h of exposure
Aminoglycosides
>500
Yes
0.3
1.5
<10
HD/HF
Cl â†“ with renal failure
Atenolol
255
Yes
1.0
2.5
<5
HD or HP
Useful if Cl â†“ caused by renal failure
Carbamazepine
236
No
1.4

74
1.3
HP
Cl â†‘ in patients on long-term therapy
Disopyramide
340
No
0.6
1.2
90
HP
Protein binding â†“ as concentration â†‘
Fluoride
19
Yes
0.3
50
2.5
HD
Hypocalcemia can be improved by HD; may add little if endogenous rena
Meprobamate
218
Yes
0.5â€“0.8
0â€“30
Low
HP
Most drug eliminated in 24â€“36 h
Methotrexate
454
Yes
0.4â€“0.8
50
1.5

HF

Paraquat
186
Yes
1.0
6
24.0
HP
Tight tissue binding precludes efficacy, unless early in course
Phenobarbital
232
No
0.5
24
0.1
HP
Only for prolonged coma
Phenytoin
252
No
0.6
90
0.3
HP
Cl â†“, as dose â†‘ procainamide
Trichloroethanol
149
Yes
0.6
0.4
0.7
HD
Metabolite of chloral hydrate

Cl = clearance; NA = not available; HP = hemoperfusion; HD = hemodia

Xenobiotic	MW (daltons)	Water Soluble	Vd (L/kg)	Protein Binding (%)	Endogenous Clearance (mL/min/kg)

TABLE 10-4. Properties of Xenobiotics Grouped by Benefit of Ex for Elimination

Multiple-Dose Activated Charcoal: â€œGa Dialysisâ€•

Oral administration of multiple doses of activated charcoal increases elim xenobiotics present in the blood. This modality is dealt with in more detai Activated Charcoal .

Continuous Hemofiltration and Hemodiafil

Continuous, as opposed to intermittent, modalities of dialytic therapy are for the treatment of poisoning. These techniques find relatively widesprea of acute renal failure in the intensive care unit, and in this context are r modalities of *continuous renal replacement therapies* (CRRTs). The cleara xenobiotics that are achieved with these techniques are significantly lowe with hemodialysis. But as continuous modalities, what they lack in clearan in time.

There are several possible advantages of continuous modalities. One is th therapy for 24 hours each day, permitting hemofiltration to be instituted hemoperfusion to further remove a xenobiotic after it redistributes from t an attractive modality for slow, continuous removal of drugs such as lith slowly from tissue-binding sites or from the intracellular compartment (s xenobiotics with volumes of distribution that are large enough to preclude hemoperfusion might also be eliminated with longer courses.

Hemofiltration, or ultrafiltration, refers to the movement of plasma acros

membrane in response to hydrostatic pressure gradients. Table 10-3 sum
xenobiotics that make them amenable to hemofiltration. However, the rate
form of therapy may be insufficient to benefit critically ill patients. Patien
slower clearance rates may not require this enhanced elimination therapy
treatment to avoid redistribution of intracellularly

distributed lithium, for example, is preferable to repeating conventional h
clear.[45, 71] Rebound of serum levels indicates that the drug is moving ou
compartment where it is toxic, into the extracellular compartment where
removal by hemodialysis. Despite many anecdotal reports demonstrating
clearance, there are no data demonstrating that these continuous technic
mortality in treatment of xenobiotic toxicity. In most cases, hemodialysis
preferred initial mode of therapy.

The continuous modalities may be best suited for patients with hypotensi
conventional hemodialysis or hemoperfusion.[12] They may have a slight a
conventional hemodialysis membranes, but not high-flux membranes, in b
molecules such as methotrexate (MW 454.4).[26] There is growing evidence
the clearance of many molecules occurs because of adsorption of the mo
membranes.[20] Another practical advantage is that the procedure is usuall
care units by ICU nurses, and, where available in such units, might not
Familiarity of ICU staff with the procedure is critical to having it available
likely to be used effectively then, in hospitals with higher incidence rates

In pure hemofiltration, sometimes called *slow continuous ultrafiltration* (S
dialysate solution on the other side of the dialysis membrane (see Fig. 10
as urea or sodium, are transported across the membrane with plasma wa
as *convective transport* or *bulk flow* . Larger solutes, depending on perm
the membrane, are excluded. The extracellular fluid volume status of the
whether replacement of all or some of the filtered plasma with physiolog
(lactated Ringer solution or other commercially available preparations) is
technique can be done intermittently using a hemodialysis machine, it has
intensive care units as a continuous form of treatment, particularly where
fluid is indicated. The clearance of low-molecular-weight solutes such as

Solute clearance can be significantly enhanced by adding a diffusive mec

permitting a dialysate solution to bathe the blood-filled capillaries running blood flow. The combination of hemofiltration with dialysis is known as *he* of dialysis also usually suffices to treat supervening acute renal failure o failure. Hemodiafiltration, like hemodialysis, requires that blood perfuse membranes made of synthetic plastics such as polysulfone or polyamide.[2] procedures, the patient must be fully anticoagulated, but some hemofilter not require anticoagulation. Anticoagulation can be achieved either with h The hydrostatic pressure required for hemofiltration can be derived either a blood pump. In continuous arteriovenous hemofiltration (CAVH), blood i filter by the patient's arterial pressure via a single-lumen femoral artery femoral vein catheter. Arteriovenous modalities are less favored now beca at least 16-French, catheter in the femoral artery while heparin is admini CAVH because a blood pump is required to maintain adequate flow rates, large-bore catheters is avoided. However, the need for a blood pump also experienced ICU team to be continuously present for more than the 4â€“6 hemodialysis or hemoperfusion. Both the expense and the complexity of procedure are thereby increased. One large case series found hemodialysi complicated than CVVH.[65] The addition of a dialysate bathing solution to apparatus changes CAVH and CVVH to the augmented CAVHD (CAVH with (CVVH with dialysis), respectively (see Fig. 10-2).

Ultrafiltrate flows of 100â€“6000 mL/h across the membrane can be achi losses must be replaced carefully. Depending on the filter, xenobiotics wit <10,000 or <40,000 daltons, as well as water, urea, creatinine, and sodiu ultrafiltrate. Heparin, myoglobin, insulin, and vancomycin are examples o with relative efficiency.[22] CVVH seems to be quite effective in the elimin clearance rates comparable to those of charcoal hemoperfusion.[28] For pr theophylline, continuous removal of the free unbound drug from the plasm equilibrium so that some drug is always moving from plasma protein to p components and molecules larger than the pore size of the membrane ret the venous line. For instance, a hemofilter with a molecular weight cutoff remove digoxin-antibody complexes (MW 45,000â€“50,000).[56] Essential e ultrafiltrate are replaced by balanced IV fluids.

Attention must be paid to the undesirable removal of therapeutic drugs s these continuous modalities. Drug clearances with different synthetic mer

the literature; the doses necessary to maintain therapeutic drug levels ca [20, 57]

Plasmapheresis and Exchange Transfusion

Plasmapheresis and exchange transfusion are intended to eliminate xenob molecular weights that are not dialyzable. This would include xenobiotics molecules with molecular weights greater than 150,000 daltons, typified substance should also have limited endogenous metabolism to make pher worthwhile. By removing plasma proteins, both techniques offer the cons removal of protein-bound molecules such as *Amanita* toxins,[32] thyroxine, of digoxin and antidigoxin antibodies. However, there is little evidence th the clinical course and prognosis. Thyroxine or carbamazepine removal a example, is followed by significant rebound from tissue stores, so that re only transient.[27, 35]

Pheresis is particularly expensive, and both pheresis and exchange transf to the risks of infection with plasma- or blood-borne diseases. Replaceme during plasmapheresis can be accomplished with fresh frozen plasma, alb both. The former is associated with manifestations of hypersensitivity, su wheezing, and hypotension, in as many as 21% of cases.[35]

A different setting in which exchange transfusion may be an appropriate t management of small infants or neonates in whom dialysis or hemoperfus difficult or impossible. Anticoagulation and MDAC may be hazardous and in the neonatal nursery where the risk of intracerebral bleeding and nec high. In premature neonates, a single volume exchange appears to

alleviate manifestations of theophylline toxicity.[6, 49] The therapy has be treat other pediatric poisonings, including severe salicylism.[44]

Toxicology of Hemodialysis

Unlike patients who receive acute hemodialysis once or twice in the man patients with chronic renal failure are repeatedly exposed to large volume municipal reservoirs during the course of their hemodialysis treatments.

regimen consists of 3 treatments of 4 hours each week, with dialysate flo patients will be exposed to more than 400 L of water separated from them semipermeable membrane designed to allow solute passage in either dire dialysate generation therefore have the potential to be lethal to this popu to significant quantities of toxins. Two potential sites of dialysate contam municipality's reservoirs and water treatment plants and in the dialysis u used for dialysate generation is regulated in the United States by the Ass Advancement of Medical Instrumentation (AAMI).[1] This organization regul to incorporate new technology and data.

Contamination of dialysate at the municipal water supply can occur as a r chemicals into reservoirs or as a result of the municipality's addition of s inadvertently or intentionally. Chlorine and chloramine are frequently add supplies to control bacterial populations. Chlorine can combine with nitro form chloramine, which can cause nausea, vomiting, methemoglobinemia, Recently, chloramine was blamed for decreased bone marrow sensitivity Aluminum is present in some municipal water supplies, and before it was aluminum led to encephalopathy characterized by seizures, myoclonus, ar osteomalacia; and to microcytic anemia.

Water from the municipal supply entering the dialysis unit is first treated remove calcium and magnesium. It is then run through an activated charc chloramine. The potential toxicity (hemolysis and death) from this compou mandates a redundancy in the carbon beds; when the active sites in one exhausted, a second will ensure that no toxicity will occur. Most commonl then generated by reverse osmosis, a process that requires that water, ir hydrostatic pressure (and against the osmotic gradient), cross a membran impermeable to solutes, leaving them behind. Alternatively, but less comn purified using deionization, a technique that runs water over an exchang ions in exchange for charged species in the water. Deionization is inferior removal of aluminum, and may be associated with release of lethal levels exchange sites are exhausted.[4] General water chemistry testing is manda testing for chlorine and chloramine is done daily.

Current requirements are that water be highly purified, but not sterile, b cross from the dialysate into the blood. However, small quantities of end

5â€“15,000 daltons) can cross, particularly in situations that include the membranes. Endotoxin is suspected of being responsible for activation of malnutrition, fever, and other syndromes such as carpal tunnel syndrome with chronic inflammation. Recommendations for the frequency of testing maximum amounts of endotoxin are continually debated and recently hav Water distribution systems are cleaned at least monthly with bleach, pera sterilants. Care must be taken that all of these potential toxins are thoro system before dialysis is restarted. Other products of bacterial metabolism containing compounds, generated on the dialysate side of the membrane, symptoms in hemodialysis patients.[62]

Unusual microbes have also been associated with serious toxicity. Untreate Brazil demonstrated growth of Cyanobacteria (blue-green algae) and pro cyclic peptides that cause serious hepatic toxicity; patients dialyzed with had a dramatic rate of death from liver failure.[33] Water contamination sho suspected when multiple patients experience similar symptoms nearly si distribution systems are always made of PVC (polyvinyl chloride) or other than copper, which also can leach into the water and cause hemolytic an

Besides water for dialysate, another potential source of poisoning in hemo process of reusing dialysis membranes. Until recently, up to 70% of dialys States reused membranes because of cost considerations. Each dialysis m peracetic acid, formaldehyde, or glutaraldehyde. Careful quality assurance there is no significant exposure of the patients to these molecules during Nonetheless, reuse programs are associated with a variety of syndromes reactions attributed to patient exposure to germicides or endotoxin due procedures.[58] Controversial data over the years have suggested, but not rates with reuse. Occupational exposure of dialysis personnel to the relev been monitored closely.

Summary

Further discussions of some of the techniques to enhance elimination, not found in Chaps. 30 (exchange transfusion), 52 (cerebrospinal fluid draina (toxin-specific antibodies), and 91 (chelation). All of these techniques ha indications, and the effect of these interventions on the overall body burd

usually small.

Urinary alkalinization, and many of the other techniques listed in Table 1 quickly in the emergency department. In contrast, the extracorporeal me removal, including hemodialysis, sorbent hemoperfusion, and continuous consultation with a nephrologist or intensivist. Timely use of these techr of a competent team and preparation of the requisite equipment. Rapid i exposure for which these techniques are appropriate, and the presence o features, should lead to prompt notification of the appropriate consult se of these techniques can proceed in an expeditious manner.

The applicability of these techniques to new xenobiotics should be conside principles discussed here so that these and newer treatment modalities ar indiscriminately. The relative infrequency of toxicity with individual xenol

continue to hinder accumulation of useful data and limit the numbers of trials performed. The literature regarding these techniques in general, and specific exposures to xenobiotics in particular should be read critically an

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Chapter 11
Use of the Intensive Care Unit

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Over the past several decades, use of the ICU and its attendant resources has led to improved survival from many serious conditions. This is the direct result of the ability to continuously monitor physiologic parameters, pay meticulous attention to supportive care, and use the most modern medical technology and treatment. Most critically ill poisoned patients have acutely reversible conditions that will clearly benefit from intensive care intervention.[83]

Unlike many patients with diseases managed in the ICU, poisoned patients often do not have a well-recognized clinical course or predictable complications. More than almost any other disease managed in the ICU, uncertainties typify toxicologic emergencies. A patient's history is often unreliable with regard to the kind of xenobiotic ingested, time of ingestion, and amount ingested. The xenobiotic may have unknown or unpredictable toxic effects. The therapies, antidotes, and complications of acute poisoning may be unfamiliar to the ICU staff. These uncertainties challenge

healthcare providers and influence decisions about admitting patients to the ICU.

Often a patient is admitted to the ICU for observation and monitoring, not for intervention.[101] Of the 11.4 million reported xenobiotic exposures reported in the American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System (TESS) data from 1999 to 2003, only 5% were admitted to the hospital (Chap. 130). In addition, fewer than 25% of those hospitalized required specific treatments or antidotes other than GI decontamination.[11,101] Many physicians elect to observe poisoned patients in an ICU in anticipation of possible delayed, unrecognized life-threatening toxicity. The ICU provides necessary monitoring and individual nursing care that can help in the early recognition of developing toxicity. Intensive care units give healthcare providers the best opportunity to minimize morbidity and decrease mortality. However, ICU care is very expensive and has contributed significantly to the escalation of healthcare costs.

The ICU admission guidelines presented in this chapter are intended to encourage effective use of ICU resources without compromising patient care. Effective guidelines must consider the unique characteristics of a xenobiotic, the capabilities of the hospital, and all realistic alternatives for managing and observing poisoned patients without compromising care. Current medical literature allows us to develop only very general guidelines. Future clinical studies addressing the use of healthcare resources for the poisoned patient will allow refinement of these guidelines. Although it is impossible to be all-inclusive, this chapter provides a decision-making strategy for most xenobiotics discussed in this text.

Are There Nontoxicologic Criteria to Help Select Those Poisoned Patients

Needing ICU Admission?

Severity of Illness Models and ICU Admission

Overcrowded ICUs and escalating healthcare costs have been incentives to develop severity-of-illness models that predict the benefits of ICU care. The Acute Physiology and Chronic Health Evaluation (APACHE II/III), the Mortality Probability Model (MPM II), and the Pediatric Risk of Mortality (PRISM II/III) models are widely studied and generally accepted severity-of-illness models that score certain physiologic parameters and other factors in order to estimate risks and predict outcomes in critically ill individuals.[17,47â€“49,57,58] Additional acute clinical assessment tools such as the Simplified Acute Physiology Score (SAPS II) and the Glasgow Coma Score (GCS) are commonly used â€œbedsideâ€• methods of quickly assessing the severity of physiologic derangement and altered neurologic status, respectively.[54] Both the SAPS II and the GCS are included in the more comprehensive APACHE severity of illness models. These models are most effective for stratifying risks in clinical research trials and comparing quality of care among ICUs. Clinical studies to validate such scoring systems included patients with a variety of medical and surgical conditions, although few trials have validated these scoring systems in large cohorts of poisoned patients. The original APACHE II cohort of 5815 intensive care admissions from 13 hospitals included only 153 patients admitted to the ICU with a diagnosis of â€œdrug overdose.â€•[47] APACHE II is limited by its failure to distinguish between traumatic and nontraumatic causes of altered mental status, a fact of potentially vital import in cases of xenobiotic overdose. The development of APACHE III addressed this shortcoming of its predecessor. However, even this very complicated scoring system with proprietary mathematical modeling has limited value when applied to a wide range of

poisoned patients. In fact, when APACHE III was used by its authors to screen a large independent database of almost 40,000 ICU admissions including 1032 patients admitted with â€œdrug overdose,â€• predicted and actual mortality statistics

for these patients were vastly different.[102] Seven deaths (0.7%) were predicted in this cohort, although the actual number turned out to be 25 (2.4%). The difference was highly statistically significant. Additional articles addressing the usage of severity of illness scoring systems to identify high-risk overdose patients are lacking, although one review of 216 consecutive ICU admissions for intentional overdose found that admission APACHE II and GCS scores were equally strong predictors of morbidity and mortality.[37] Specifically, a GCS of â‰¤ 12 was 88% sensitive and 92% specific in identifying patients at risk of developing ICU requiring morbidity.

Given the unique characteristics of individual xenobiotics, other authors have attempted to apply severity of illness models in specific xenobiotic overdosages. APACHE II scores within 24 hours of presentation, showed promise as a predictor of mortality when studied prospectively in acetaminophen-induced acute liver failure, revealing similar power to predict a poor outcome when compared against the widely accepted King's College Criteria.[68] A second xenobiotic-specific study including 23 organic phosphorus compound poisoned adults found that an APACHE II score â‰¥ 26 was 95% sensitive and 100% specific in predicting mortality.[56] However, some clinical outcome predictors used in these scoring systems, such as neurologic outcome following cardiac arrest, are unreliable in the poisoned patient.[23,81] A patient with severe poisoning may have clinical characteristics that mimic brain death yet have a complete neurologic recovery. Case reports of poisoning from barbiturates, cyclic antidepressants, baclofen, ethylene glycol, botulism, solvents, and sedative hypnotics provide specific examples of this observation.[5,74,77,94,97,100] In addition,

many toxicologic emergencies occur in young patients who are free of underlying disease. This increases the likelihood of surviving significant insults such as prolonged hypotension or hypoxia. Indeed, one prospective trial involving 286 patients admitted to the ICU with nontraumatic coma found that 91% of the 101 xenobiotic-induced coma patients survived, a much higher rate than those patients whose cause of coma was hypoxia (33%), sepsis (28%), focal cerebral (26%), or a general cerebral insult (17%).[33] Despite negative predictors of outcome, aggressive resuscitation efforts may be justified for poisoned patients. Specifically, prolonged cardiac resuscitation should be provided for the victim of a cardiac arrest resulting from cyclic antidepressant overdoses, Î²-adrenergic antagonists, calcium channel blockers, or severe hypothermia.[25,42,66,73,86]

Few studies have evaluated the use of the ICU for poisoned patients.[11,23,35,39,41,44,52,88,90] Prospective studies have focused on mortality rates, use of resources, or types of xenobiotics ingested, whereas others, mostly retrospective, have focused on patients exposed to a specific xenobiotic. More study is needed before any severity of illness model can be considered reliable in predicting which patients are at the highest risk of developing ICU-requiring morbidity or mortality.

Other Criteria for ICU Admission

A set of criteria was established to determine whether initial clinical assessment could identify those poisoned patients who were at risk of developing serious toxicity, thus needing ICU admission.[11] The specific xenobiotic ingested was not considered in defining risks. Criteria defining high-risk patients were; need for intubation, unresponsiveness to verbal stimuli, seizures, PCO_2 >45 mm Hg, systolic blood pressure <80 mm Hg, QRS duration >0.12 seconds, or any cardiac rhythm except normal sinus rhythm, sinus tachycardia, or sinus bradycardia. Patients were classified as low

risk when none of the above criteria were present in the emergency department (ED). Retrospectively, 209 cases were analyzed using the above parameters. The most commonly ingested xenobiotics in both the high- and low-risk groups were barbiturates, benzodiazepines, cyclic antidepressants, ethanol, opioids, phenothiazines, and salicylates. None of the 151 patients who were considered low risk developed complications or required ICU interventions after admission. Of the 58 patients deemed high risk, 35 required ICU interventions such as intubation, treatment of dysrhythmias, the treatment of seizures, intravenous vasopressors, or hemodialysis/hemoperfusion. Seven patients developed high-risk complications such as hypoxia, respiratory failure, hypotension, or seizures after admission, but all had other high-risk criteria in the ED. Although the authors concluded that the clinical course of poisoned patients can be predicted during the initial 2 to 3 hours of observation, xenobiotics with delayed or prolonged toxic effects, such as sustained-release products, lithium, and oral hypoglycemic agents, were not prominent in their study population.

In this study population, 70% of the low-risk patients were admitted to the ICU for observation. Because none of these patients developed complications or required ICU intervention, the authors postulated that applying these criteria would have eliminated 50% of the ICU days without compromising care. The limitations of this study are its retrospective design, relatively small study population, and limited variety of xenobiotic exposures. However, it does suggest that with some clinical judgment, many poisoned patients will not require ICU admission.

Ideally, clinical indicators for ICU care should be established for each xenobiotic. Universal criteria cannot be applied to all poisoned patients because of the unique clinical course of some xenobiotics and the uncertainty regarding which xenobiotics were ingested. Until more specific predictors of outcome are developed for individual xenobiotics, nothing will be more useful than

experience and good clinical judgment in predicting who may benefit from ICU admission. At present, withholding ICU care from poisoned patients based solely on a nonspecific â€œscoreâ€• will not result in significant cost savings in the ICU but may increase the risk of morbidity and mortality.[14,50,91]

End-Organ Toxicity as the Basis for ICU Admission

It seems reasonable to assume that a patient's signs and symptoms can be used to decide the need for ICU admission. The presence of certain signs, symptoms, or abnormal diagnostic tests requires ICU observation or intervention, whatever the toxic exposure. This approach is most consistent with the philosophy of â€œtreating the patient and not the poisonâ€• and may prove most helpful for patients with polydrug ingestions.

CNS manifestations are common to many poisonings. Xenobiotic-induced acute delirium or coma often requires ICU admission because these findings will not resolve quickly. Many comatose or delirious patients without identifiable causes require continued investigation in the ICU. Likewise, xenobiotic-induced status epilepticus is best managed in the ICU.

Poisoned patients with signs of respiratory compromise may need ICU admission, regardless of whether the respiratory compromise is caused by CNS depression, hypoventilation, or acute lung injury. In addition, ICU admission is required when impaired

oxygen-carrying capacity or tissue hypoxia is evident from poisons such as hydrogen sulfide, cyanide, carbon monoxide, or methemoglobin inducers.

Xenobiotics can cause cardiac dysrhythmias, hypotension, hypertension, and tissue ischemia.

Gastrointestinal symptoms, particularly vomiting and diarrhea, are an early manifestation of poisoning by many xenobiotics. When symptoms are severe or persistent, significant fluid and electrolyte losses can occur. For example, a patient with a significant iron ingestion can have a GI mucosal injury, leading to vomiting, diarrhea, profound volume loss, and significant hypotension. Hepatotoxicity from poisoning or overdose usually occurs days after xenobiotic exposure, meaning there is no need for expectant admission to the ICU. If hepatotoxicity is evident at the time of admission (especially with hepatic encephalopathy), ICU management is strongly suggested.

Renal toxicity may be a direct effect of the xenobiotic or a complication of other toxic manifestations, such as hypotension or rhabdomyolysis. Severe xenobiotic-induced metabolic acidosis is best managed in an ICU. Metabolic acidosis is an important clue to the presence of xenobiotics such as ethylene glycol, methanol, and salicylates. Persistent or refractory hypoglycemia, resulting from an oral antidiabetic agent, insulin overdose, or other xenobiotics, is also best managed in an ICU. In addition, severe xenobiotic-induced alterations in temperature regulation or electrolyte disturbances merit close monitoring and intervention in the ICU.

The complications of chemical burns of the skin are similar to those of thermal burns. The injured dermis may be unable to prevent significant fluid losses, regulate core body temperature, and prevent infection. Besides these complications, systemic toxic effects may occur through dermal absorption of the xenobiotic that caused the injury.

Diagnostic tests such as routine laboratory analysis, electrocardiography, and diagnostic imaging are used as indicators of end-organ toxicity. Diagnostic tests may demonstrate definite end-organ toxicity or provide early warning signs of impending serious toxic effects. These diagnostic tests may suggest the need for aggressive management or more careful monitoring. Elevated

serum levels of some xenobiotics indicate that serious toxicity is likely. Although diagnostic tests are extremely useful for deciding about using the ICU, relatively few patients should be admitted to the ICU based on the results of a single diagnostic test.

Additional Information Influencing ICU Admission of the Poisoned Patient

End-organ toxicity is the most important reason to admit poisoned patients to the ICU. However, restricting ICU admission to those with only end-organ toxicity is inappropriate. Minimally symptomatic or asymptomatic patients may require ICU admission because other factors must be considered. In addition to end-organ toxicity, the xenobiotic, its treatment, and specific patient characteristics should influence ICU admission decisions.

Xenobiotic Characteristics as Basis for ICU Admission

Both the known and unknown characteristics of a xenobiotic will assist with ICU admission decisions. Some xenobiotics have proven their capability to cause harm or death to humans. Well-described, expected toxic effects assist in early recognition of poisoning. For other xenobiotics, the consequences after human exposure are not yet reported.

ICU admission is warranted for patients with expected serious toxic effects from an ingested xenobiotic. This is especially true for those xenobiotics known to be deadly, such as calcium channel blockers, cyanide, cyclic antidepressants, and salicylates. For example, patients with calcium channel blocker poisoning who exhibit hemodynamic compromise require close attention and aggressive treatment available only in the ICU.

Indicators of toxicity should be identified for individual xenobiotics

so that high-risk patients may be closely monitored and aggressively treated. Because cyclic antidepressants are some of the most common and potentially lethal overdoses reported, they have been studied in great detail to determine indicators of toxicity and safe disposition.[2,12,13,24,44,70,76,92] Cyclic antidepressants have accounted for up to 25% of drug overdoses admitted to adult ICUs, yet many admissions are for trivial ingestions.[19] Research efforts have focused on identifying those patients at risk for serious toxicity. These studies suggest that patients may be safely discharged if they remain asymptomatic for a 6-hour observation period after presentation.[2,13,44,75,92] Prolonged QRS duration on a 12-lead ECG is predictive of serious complications such as seizures and dysrhythmias.[6,70,98] Any patient manifesting persistent tachycardia, ECG abnormalities (including QRS â‰¤0.10 seconds), hypotension, anticholinergic signs, or neurologic signs or symptoms, requires ICU monitoring.[13,27] Unlike cyclic antidepressants, most xenobiotics do not have such an extensive literature to define high-risk patients.

Most acetaminophen poisoned patients can be safely managed outside of the ICU because they exhibit no end-organ toxicity and their hospital management entails only laboratory monitoring and antidotal therapy with *N*-acetylcysteine. However, acetaminophen poisoning can be lethal and at some point in the clinical course, manifestations of toxicity require close monitoring and treatments available only in the ICU. Predictors of poor outcome have been studied and can be useful guides for selecting patients who need ICU care. The King's College Criteria are well established indicators of impending hepatic failure and the need for transplantation. A pH <7.30 after adequate fluid resuscitation, a serum creatinine â‰¤3.3 mg/dL, a prothrombin time >100 seconds, and a grade III or higher encephalopathy are all predictive of poor outcome.[72] A serum lactate level greater than 3 mmol/L 12 hours after admission can be used in conjunction with the traditional King's College Hospital criteria to improve the

sensitivity of the criteria when attempting to identify patients who are likely to require liver transplantation.[3] Patients with abnormal clinical and laboratory data approaching these criteria are candidates for ICU admission or transfer to a specialized center with advanced ICU resources and transplantation services.

The natural history of many xenobiotics is unknown. New pharmaceutical and industrial products are introduced each year with little data on toxic exposure doses or human health effects in overdose. Sometimes animal studies provide the only known toxicologic data, and preclinical trials for new drugs may have excluded the populations at risk, such as infants, children, or the elderly. In these cases, the clinician must often make therapeutic decisions and anticipate potential toxicity with little or no reliable data. Because early recognition of serious toxicity may prevent an adverse outcome, expectant observation may be the only rational

approach. For example, intentional and unintentional ingestions followed the introduction of fluoxetine. Because, at that time, clinicians lacked experience treating overdoses of this drug and had no data regarding the natural course and toxic dose, many patients were admitted to the ICU to observe for toxic effects. Now that clinicians have experience with this drug and studies are available demonstrating few severe manifestations, ICU resources are seldom needed to treat such patients.[8]

Failure to appreciate the potential for serious, delayed toxic effects is a major pitfall in managing poisoned patients. An asymptomatic patient may be a â€œtime bombâ€• with the potential to deteriorate rapidly. Delayed or continued absorption, slow tissue distribution, interference with cellular function, production of toxic metabolites, or depletion of target organ reserve capacity are causes of delayed onset of clinical effects.[9]

Certain xenobiotics prolong gastrointestinal absorption, delaying onset of toxicity.[64] Sustained-release pharmaceutical preparations

and those with enteric coatings enhance patient compliance but, in overdose, may delay absorption and, in turn, make the onset of toxicity unpredictable.[67] Published cases of overdoses with sustained-release theophylline, verapamil, bupropion, and enteric-coated aspirin report delayed onset of toxicity (more than 16 hours), and peak serum levels were measured more than 24 hours after ingestion.[7,26,82,87,99]

Serial xenobiotic level measurements are necessary to verify peaks and ensure decreasing levels. Serial levels may, if available, warn of increasing potential for serious toxic effects. When serum levels are unobtainable, admission and observation are required for many patients with overdoses of sustained-release and enteric-coated agents, including patients smuggling (â€œbody-packingâ€•) or hiding (â€œbody-stuffingâ€•) contraband drugs in the gastrointestinal tract, which has resulted in delayed onset of serious toxicity from ruptured bags.[93]

Clinical effects may be delayed when toxicity is dependent upon alteration of enzyme functions, cellular reproduction, or metabolic function. For example, toxicity of a monoamine oxidase inhibitor (MAOI) may not be apparent for more than 12 hours after an overdose but then may progress rapidly to cardiovascular collapse.[60] Because of the delay in onset of severe toxicity, even if the patient is asymptomatic, a history of MAOI ingestion mandates ICU monitoring for 24 hours. When there is potential for serious delayed toxicity, the patient necesitates prolonged close monitoring.

Physiologic Monitoring and Specialized Treatment as Requirements for ICU Admission

The ICU setting offers the most highly skilled staff and modern technology available to manage complex medical problems. It also

provides a nurse-to-patient ratio that allows for frequent or continuous monitoring of basic physiologic parameters. Invasive monitoring is routinely used in the ICU and may be beneficial to some poisoned patients. Hemodynamic parameters are valuable for managing the patient with hypotension, intravascular volume depletion, or respiratory failure from acute lung injury (ALI). Intraarterial monitoring provides a more accurate and continuous record of actual blood pressure in a patient with cardiovascular compromise. A pulmonary artery catheter assists in the management of fluid and inotropic therapy for patients with complex hemodynamic abnormalities. Both invasive and noninvasive measurements of vital signs, neurologic status, and intake/output measurements, along with continuous cardiac monitoring, make possible early detection of toxicity, recognition of conditions needing active intervention, and prevention of complications.

Most critically ill poisoned patients have acute reversible conditions requiring supportive care measures (ie, ventilator support, vasopressor support, and close monitoring) that ICUs are most equipped to provide. Most often, supportive care measures improve the outcome of critically ill poisoned patients more than antidotes and specialized treatments. Focus on supportive care measures such as maintaining a patent airway, preventing hypoxia with the administration of oxygen, and treatment of shock decreased the mortality for patients with barbiturate overdoses from 20% in the 1930s to less than 2% in the 1950s.[15] Both adult and pediatric studies report good outcomes in most critically ill overdosed patients treated with only mechanical ventilation, vasopressor support, and careful monitoring.[23,52]

Antidotes and specific treatments should be administered in the emergency and ICU settings. Although possibly lifesaving, these treatments may have inherent risks. For example, antivenom administration for black widow spider envenomations can cause anaphylaxis, and rapid intravenous infusion of deferoxamine for

iron poisoning can cause hypotension. Because these treatments may be unfamiliar to staff and have their own inherent risks, the ICU is the most prudent environment to administer such treatments. In toxicologic emergencies, a familiar medication may be an antidotal therapy that requires doses that far exceed conventional regimens or indications that deviate from common treatment protocols. High doses of atropine (hundreds of milligrams) may be necessary for the treatment of organic phosphorus insecticide poisoning.[21,30,55] Also, intravenous calcium, which is no longer a routine part of advanced cardiac life support (ACLS) protocols, is commonly used to reverse toxicity from calcium channel blockers[79] and (by intraarterial infusion) from hydrofluoric acid burns of the extremities.[95] Sodium bicarbonate as a bolus and infusion is the treatment of choice for cyclic antidepressant and type IA antidysrhythmic agent cardiac toxicity.[75] Instead of the usual first-line vasopressor dopamine, direct vasopressors such as norepinephrine or phenylephrine may be more appropriate for the treatment of xenobiotic-induced hypotension. Some drugs are administered in unconventional doses, whereas other familiar drugs should be avoided in treating toxic emergencies. For example, type IA antidysrhythmic agents, such as procainamide, must not be used in patients with overdoses of cardiac sodium channel antagonists, such as cyclic antidepressants, phenothiazines, and propoxyphene.

A false sense of security can result when an antidote reverses toxicity but has a shorter duration of effect than the xenobiotic. An example is a patient, comatose from an opioid overdose, who responds to naloxone, awakens, and refuses further treatment. Toxicity may recur when naloxone's short duration of effect allows opioid toxicity to recur. These patients must be closely observed for the possible need to readminister the antidote. In a retrospective review of patients presenting with opioid overdosage, 31% of 84 naloxone responders experienced resedation necessitating readministration.[96] Resedation is

particularly problematic with long-acting opioids such as methadone and oxycodone controlled release preparations.[40]

Extracorporeal methods of eliminating xenobiotics, such as hemodialysis or hemoperfusion, are ideally performed in the ICU. Invasive procedures such as extracorporeal membrane oxygenation, cardiopulmonary bypass, and intraaortic balloon pump-assisted perfusion are used successfully in resuscitating critically ill poisoned

patients.[16,22,38,42,53] A bioartificial liver support system and a Molecular Adsorbents Recirculating System (MARS) using albumin dialysis, including a charcoal filter shows promise as a treatment in patients presenting with liver failure, including acetaminophen poisoning.[10,71]

Toxicologic emergencies, where the need for surgical intervention or specialized wound care is anticipated, are ideally managed in the ICU. Although transplantation becomes necessary in a minority of critically ill acetaminophen-poisoned patients, this treatment can improve survival to discharge by as much as 75%.[4] Compartment syndrome complicating crotaline envenomation is a rare but limb-threatening occurrence, sometimes resulting in the need for fasciotomy.[36] Any poisoned patient with significant rhabdomyolysis, whether localized or more widespread, is at risk for the development of compartment syndrome. If contemplating fasciotomy, monitoring and specialized postoperative care in an intensive care unit is warranted. Plasmapheresis and specialized wound care in an ICU are necessary in cases of toxic epidermal necrolysis (TEN) secondary to xenobiotics. Early referral to a specialized burn center reduces mortality in this condition.[65]

Patient Factors as Criteria for ICU Admission

Preexisting medical conditions increase a patient's risk for developing toxicity. Many patients who have chronic medical problems do not tolerate major physiologic stressors without significant compromise. For example, a patient with underlying cardiac disease could develop severe myocardial ischemia from a modest carbon monoxide exposure. An elderly or infirm patient with chronic salicylism is more likely to have major respiratory and CNS complications than a younger or healthier patient.[1] Conditions that alter drug metabolism or elimination, such as renal or hepatic disease, may prolong toxicity or produce toxicity after lesser amounts are ingested.

Patients with physical dependency on ethanol, benzodiazepines, or barbiturates may be admitted to the hospital for acute withdrawal or, during hospitalization, go through a period of abstinence that results in an acute withdrawal syndrome. Withdrawal from ethanol and sedative-hypnotics can have serious consequences and complications. ICU management is frequently indicated because large doses of medications with respiratory depressant effects may be required for treatment.

Eighty percent of recognized suicide attempts involve an overdose of medications.[69] Acute complications of poisoning make it difficult to adequately assess suicidal risks. Patients have an increased rate of suicide following discharge from an ICU for drug overdose.[88] Until suicidal risks are adequately assessed, it must be assumed that an overdosed patient needs close observation. Institutions differ on monitoring policies for suicidal patients not admitted on a psychiatric unit. The ultimate goal of treatment for any suicidal patient is to provide a secure and safe environment. In many hospitals, the ICU is the safest place, (but also the most expensive place) to observe a patient with suicidal risks until it is medically safe to transfer the patient to the psychiatric service.

Complications That Prolong ICU care

Poisoning produces both anticipated and unanticipated complications that can prolong ICU care and decrease survival. Serious complications of poisoning include pulmonary compromise, rhabdomyolysis, compartment syndrome, and anoxic brain injury. Complications such as acute renal or hepatic failure also might prolong an ICU course.

Pulmonary compromise following toxic exposures often develops after several hours or days in the ICU. Pulmonary complications following a toxic exposure include aspiration pneumonitis, ALI, and adult respiratory distress syndrome (ARDS). Aspiration of gastric contents is a common complication following poisoning, especially when a patient's mental status is altered and protective airway reflexes are lost.[31,46,85] Poisoned patients may aspirate spontaneously while lying unresponsive before being discovered, from stomach dilation secondary to bag-valve-mask ventilation, from GI decontamination procedures such as orogastric lavage, or during insertion of endotracheal or nasogastric tubes.[51] In a review of 4562 poisoning admissions, 71 clearly suffered from aspiration pneumonitis, giving a rate of 1.6%.[45] Older age, a GCS <15, spontaneous emesis, delayed presentation to the hospital, and ingestion of cyclic antidepressants were associated with aspiration pneumonitis in logistic regression analysis. Not only were the rates of ICU admission and length of stay increased in the patients with aspiration pneumonitis, but mortality was also higher, with a rate of 8.5% compared to 0.4% for those without.

Poisoning causes global cerebral anoxia from prolonged shock, respiratory failure, or direct toxic/metabolic effects. Distinguishing anoxic cerebral injury from reversible encephalopathy can be difficult in poisoned patients. Coma and loss of brainstem reflexes after prolonged, severe cerebral hypoxia indicates a poor prognosis.[59] Although poorly studied in toxicologic patients, new diagnostic technologies, including computer tomography, cerebral angiography, brain radionuclide perfusion imaging techniques, and the use of multimodality evoked potentials, may prove useful in

confirming brain death.[1,18,78] Electroencephalography can be particularly misleading in certain overdoses, such as those involving benzodiazepines or barbiturates, where the lack of brain electrical activity is a direct effect of the ingested xenobiotic. Angiographic imaging via computer tomography or direct arteriography may prove particularly useful in such cases, although such tests can reveal continued blood flow when intracranial hypertension is absent, despite severe axonal injury and brain death.[62] Further study is necessary before these modalities obtain widespread acceptance as diagnostic aids in toxicologic cases where the diagnosis of brain death is in question.[62] Because clinical predictors of outcome may be unreliable when applied to poisoned patients, the diagnosis of brain death should be made cautiously. Cerebral edema often is a secondary effect of global cerebral anoxia, although some xenobiotics have direct cellular effects. Cerebral edema can be a complication of acetaminophen-induced fulminant hepatic failure and the result of direct neuronal injury from salicylate and lead poisoning.[61,80,89] Aggressive ICU care is preferred to treat xenobiotic-induced cerebral injuries.

Criteria for Safe Disposition from the ICU

Once the acute toxic effects have resolved, most patients are safe to transfer out of the ICU. Patients with cyclic antidepressant overdoses were studied to determine when it was safe to discontinue

monitoring. Concerns arose from case reports of patients developing sudden death as late as several days following a cyclic antidepressant overdose.[12,63,84] In most cases, delayed complications developed in the setting of continued toxicity evidenced by lethargy or sinus tachycardia. More recent studies

demonstrate that dysrhythmias do not occur after signs of toxicity have resolved (ie, CNS and cardiac manifestations).[13,29,75] Current recommendations based on these studies suggest cardiac monitoring for an additional 24 hours after normalization of the ECG and resolution of other signs of continued toxicity.[12] This additional period of monitoring should occur after discontinuation of all specific forms of therapy, such as serum alkalinization.

Most xenobiotics have not received the level of attention given to cyclic antidepressants, making clinical judgments the only basis for deciding when to discharge a patient from the ICU, pending further research and experience. For example, drug-induced QTc interval prolongation may increase the risk of developing torsade de pointes.[28] Cardiac monitoring may be required until other clinical signs of toxicity resolve and the QTc interval returns to normal.

The same issues previously mentioned may be pitfalls to a patient's safe discharge from an ICU. GI decontamination should be completed before discharge from the ICU because it may cause prolonged or worsening clinical effects. Carefully consider discharge decisions about patients exposed to xenobiotics with serious delayed clinical effects, such as colchicine. Also be mindful that the duration of action of the xenobiotic may be longer than the duration of action of the specific treatment or antidote.

Finally, the patient's suicidal intent must be considered before transfer to a less closely monitored hospital unit. Transfer from the ICU should occur following assessment of suicide risk or other important psychosocial issues. Early involvement of psychiatric services, chemical dependency counseling, and social services can expedite ICU disposition. Disposition and treatment options can be considered at a time when the patient is still medically unstable by interviewing family, friends, and outpatient counselors.

Alternatives to ICU Admission

Placing patients in the ICU solely for observation often is an ineffective use of this expensive resource. Until further clinical studies are available to define those patients who are at risk for serious toxicity or life-threatening complications, many poisoned patients will be admitted to the ICU for observation. When information about the xenobiotic, the patient, and the capabilities of the medical unit are all considered, many patients can be safely observed outside the ICU. Table 11-1 presents some items to consider when making disposition decisions.

Alternatives to the ICU include a medical or pediatric floor bed, an intermediate care unit, a telemetry-monitored bed, a medical psychiatric unit, or an ED observation unit. Capabilities for managing poisoned patients may vary considerably between institutions and in different types of patient care areas. It is essential to understand the capabilities of the unit where a patient is being considered for admission. If the nursing staff is unfamiliar with the potential for rapid deterioration of the patient, or the staffing pattern does not allow for close observation, the results could be disastrous. For example, it is unrealistic to expect a nurse to manage intravenous fluids, record hourly intake and output measurements, record frequent vital signs, and check hourly urine pH measurements for a salicylate-poisoned patient while caring for 8 other patients. Emergency department observation may be an alternative for the care of select poisoned patients.[20,34,43] These units are capable of frequent monitoring of vital signs, continuous cardiac monitoring, and maintaining a safe environment for suicidal patients.[32] Patients with a low risk of serious toxicity or life-threatening complications who require only observation may be ideal candidates for ED observation units.

TABLE 11-1. Considerations for Intensive Care Unit Admission

Xenobiotic characteristics

Are there known serious sequelae (eg, cyclic antidepressant cardiotoxicity)?

Can the patient deteriorate rapidly from its toxic effects?

Is the onset of toxicity likely to be delayed (eg, sustained-release preparation, slowed GI motility, or delayed toxic effects)?

Does the xenobiotic have cardiac effects that will require cardiac monitoring?

Is the amount ingested a potentially serious or potentially lethal dose?

Is the required or planned therapy unconventional (eg, large doses of atropine for treating overdoses of organic phosphorus insecticides)?

Does the therapy have potentially serious adverse effects?

Is there insufficient literature to describe the potential human toxic effects?

Are potentially serious coingestants likely (must take into account the reliability of the history)?

Patient characteristics

Does the patient have any signs of serious end-organ toxicity?

Is there progression of the end-organ effects?

Are laboratory data suggestive of serious toxicity?

Are drug concentrations rising?

Is the patient a high risk for complications requiring ICU intervention?

Seizures

Unresponsive to verbal stimuli

Level of consciousness impaired to the point of potential airway compromise

PCO_2 >45 mm Hg

Systolic blood pressure <80 mm Hg

Cardiac dysrhythmias

Prolonged ECG complexes and intervals (QRS duration â‰¥ 0.10 seconds; QT prolongation)

Does the patient have preexisting medical conditions that could predispose to complications?

Chronic alcohol or drug dependence

Chronic liver disease

Chronic renal failure or insufficiency

Heart disease

Pregnancy

Is the patient suicidal?

Assessing the capabilities of the inpatient unit/observation unit

Does the admitting team (attending, house staff, students) appreciate the potential seriousness of a toxicologic emergency?

Is the nursing staff:

Familiar with this toxicologic emergency?

Familiar with the potential for serious complications?

Is the staffing adequate to monitor the patient?

What is the ratio of nurses to patients?

Are time-consuming nursing activities required? (eg, hourly urine pH assessments or whole-bowel irrigation)

Can a safe environment be provided for a suicidal patient?

Can a patient have suicide precautions and monitoring with a medical floor bed?

Can a one-to-one observer be present in the room with the patient?

Can the patient be restrained?

Many poisoned patients are placed in the ICU because they are suicide risks. Other than the ICU, many hospitals cannot provide an alternative for observing a high-risk suicidal patient. Less-

alternatives are available, but they must assure a safe environment for suicidal patients. An ED observation unit, an intermediate care unit, a medical psychiatric unit, or a one-on-one observer can safely monitor these patients.

Future studies must define prognostic factors for poisoning complications. Patients can then be stratified into high-risk or low-risk groups. The limitations of current studies prevent generalizing the results to individual patients or certain subgroups. Unfortunately, many current clinical guidelines now being used to ration care may be derived from poorly tested models with no scientific basis and may be motivated by financial concerns. Guidelines should be based on sound evidence so that they can provide the best care with less intensive use of health care resources.

Summary

Acute poisoning challenges medical and nursing staff because of its unpredictable clinical course and unfamiliar therapies. Poisoned patients are especially problematic because their clinical history is incomplete and the medical literature is often limited. These potential unknowns create many uncertainties in management. Because the ICU offers the highest level of skilled staff and modern technology available, most seriously poisoned patients should be admitted there. Whether this is clinically justified or is an effective use of resources for a given patient is always an issue because admission of the poisoned patient continues to be based mostly on clinical judgment and the best available information.

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Chapter 12
Chemical Principles

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Chemistry is the science of matter; it encompasses the structure, physical properties, and reactivities of atoms and their compounds. In many respects, toxicology is the science of the interactions of matter with physiologic entities. Chemistry and toxicology are intimately linked. The study of the principles of inorganic, organic, and biologic chemistry offer important insight into the mechanisms and clinical manifestations of xenobiotics and poisoning, respectively. This chapter reviews many of these tenets and provides relevance to the current practice of medical toxicology.

The Structure of Matter

Basic Structure

Matter includes the substances of which everything is made. *Elements* are the foundation of matter, and all matter is made from one or more of the known elements. An *atom* is the smallest quantity

of a given element that retains the properties of that element. Atoms consist of a nucleus, incorporating protons and neutrons, coupled with its orbiting electrons. The *atomic number* is the number of protons in the nucleus of an atom, and is a whole number that is unique for each element. Thus, elements with 6 protons are always carbon, and all forms of carbon have exactly 6 protons. However, although the vast majority of carbon nuclei have 6 neutrons in addition to the protons, accounting for an *atomic mass* (ie, protons plus neutrons) of 12 (^{12}C), a small proportion of naturally occurring carbon nuclei, called *isotopes*, have 8 neutrons and a mass number of 14 (^{14}C). This is the reason that the *atomic weight* of carbon displayed on the periodic table is 12.011, and not 12, as it actually represents the average atomic masses of all isotopes found in nature weighted by their frequency of occurrence. Moreover, ^{14}C is actually a *radioisotope*, which is an isotope with an unstable nucleus that emits radiation (particles and/or rays), presumably in an effort to attain a stable state (Chap. 128). The atomic weight, measured in grams/mole (g/mol), also indicates the molar mass of the element. That is, in 1 atomic weight (12.011 g for carbon) there is 1 mole of atoms (6.023 Ã— 1023 atoms).

Elements combine chemically to form *compounds*, which generally have physical and chemical properties that differ from those of the constituent elements. The elements in a compound can only be separated by chemical means that destroy the original compound, as occurs during the burning (ie, oxidation) of a hydrocarbon which releases the carbon as carbon dioxide. This important property differentiates compounds from *mixtures*, which are combinations of elements or compounds that can be separated by physical means. For example, this occurs during the distillation of petroleum into its hydrocarbon components or the evaporation of sea water to leave sodium chloride. With notable exceptions, such as the elemental forms of many metals or halogens (eg, Cl_2), most xenobiotics are compounds or mixtures.

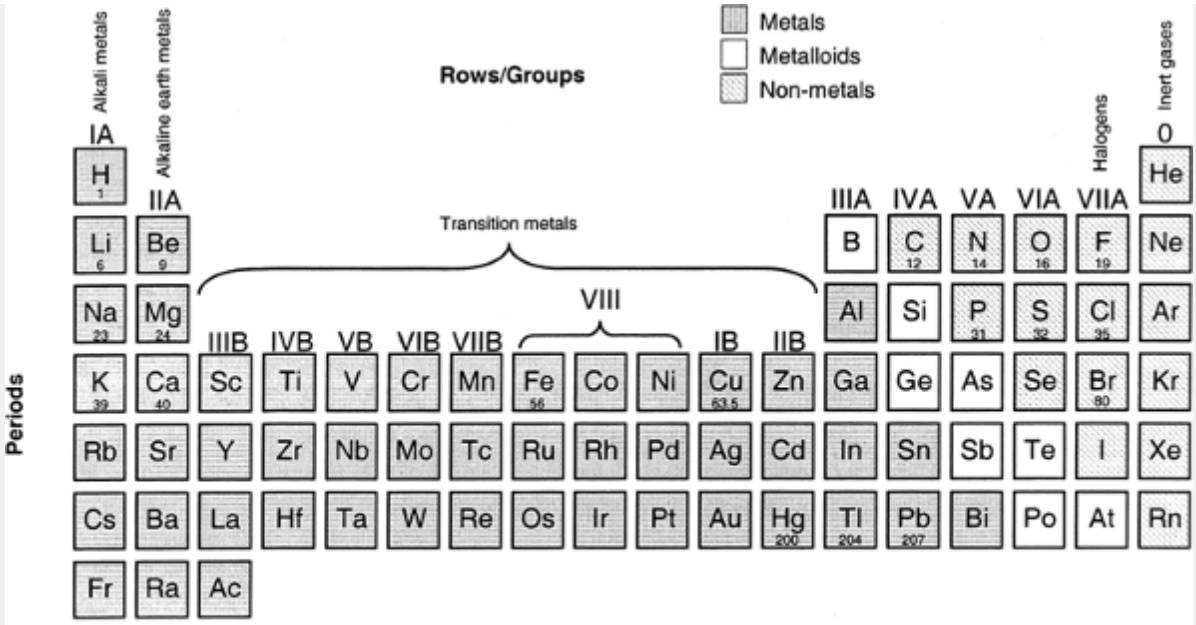
Dimitri Mendeleev, a Russian chemist in the mid-19th century,

recognized that when all of the known elements were arranged in order of atomic weight, certain patterns of reactivity became apparent. The result of his work was the Periodic Table of the Elements (Fig. 12-1), which, with some minor alterations, is still an essential tool today. All of the currently recognized elements are represented; those heavier than uranium are not known to occur in nature. Many of the symbols used to identify the elements refer to the Latin name of the element. For example, silver is Ag, for argentum, and mercury is Hg, for hydrargyrum, literally â€œsilver water.â€•

The reason for the periodicity of the table relates to the electrons that circle the nucleus in discrete orbitals. Although the details of quantum mechanics and electronic configuration are complex, it is important to review some aspects in order to predict chemical reactivity. Orbitals, or quantum shells, represent the energy levels in which electrons may exist around the nucleus. The orbitals are identified by various schemes, but the maximum number of electrons each orbital may contain is calculated as $2x^2$, where x represents the numerical rank order of the orbital. Thus, the first orbital may contain 2 electrons, the second orbital may contain 8, the third may contain 18, and so on. However, the outermost shell (designated by s, p, d nomenclature) of each orbital may only contain up to 8 electrons. This is irrelevant through element

20, calcium, because there is no need to fill the third-level or d shells. Even though the third orbital may contain 18 electrons, once 8 are present, the 4s electrons dip below the 3d electrons in energy and this shell begins to fill. This occurs at element 21, scandium, and accounts for its chemical properties and those of the other transition elements. Note that hydrogen and helium are unique in needing only 2 electrons to complete their valence shell; all other elements require 8 to be complete. Also, because the inert gas elements, which are also known as noble gases, have complete outermost

orbitals, they are unreactive under standard conditions. Transition elements are chemically defined as elements which form at least one ion with a partially filled subshell of d electrons.



Symbol	Name	Atomic Number	Atomic Weight
Ac	Actinium	89	227.0278
Al	Aluminum	13	26.9815
Am	Americium	95	243.06
Sb	Antimony	51	121.75
Ar	Argon	18	39.948
As	Arsenic	33	74.9216
At	Astatine	85	209.99
Ba	Barium	56	137.33
Bk	Berkelium	97	247.07
Be	Beryllium	4	9.0122
Bi	Bismuth	83	208.9804
Bh	Bohrium	107	262
B	Boron	5	10.81
Br	Bromine	35	79.904
Cd	Cadmium	48	112.41
Ca	Calcium	20	40.08
Cf	Californium	98	251.08
C	Carbon	6	12.011
Ce	Cerium	58	140.12
Cs	Cesium	55	132.9054
Cl	Chlorine	17	35.453
Cr	Chromium	24	51.996
Co	Cobalt	27	58.9332
Cu	Copper	29	63.546
Cm	Curium	96	247.07
Db	Dubnium	105	262
Dy	Dysprosium	66	162.5
Es	Einsteinium	99	252.08
Er	Erbium	68	167.26
Eu	Europium	63	151.96
Fm	Fermium	100	257.1
F	Fluorine	9	18.9984
Fr	Francium	87	223.02
Gd	Gadolinium	64	157.25
Ga	Gallium	31	69.72
Ge	Germanium	32	72.59
Au	Gold	79	196.9665

Symbol	Name	Atomic Number	Atomic Weight
Hf	Hafnium	72	178.49
Hs	Hassium	108	265
He	Helium	2	4.0026
Ho	Holmium	67	164.9304
H	Hydrogen	1	1.0079
In	Indium	49	114.82
I	Iodine	53	126.9045
Ir	Iridium	77	192.22
Fe	Iron	26	55.847
Kr	Krypton	36	83.8
La	Lanthanum	57	138.9055
Lr	Lawrencium	103	260.11
Pb	Lead	82	207.2
Li	Lithium	3	6.941
Lu	Lutetium	71	174.97
Mg	Magnesium	12	24.305
Mn	Manganese	25	54.938
Mt	Meitnerium	109	266
Md	Mendelevium	101	258.1
Hg	Mercury	80	200.59
Mo	Molybdenum	42	95.94
Nd	Neodymium	60	144.24
Ne	Neon	10	20.179
Np	Neptunium	93	237.0482
Ni	Nickel	28	58.7
Nb	Niobium	41	92.9064
N	Nitrogen	7	14.0067
No	Nobelium	102	259.1
Os	Osmium	76	190.2
O	Oxygen	8	15.9994
Pd	Palladium	46	106.4
P	Phosphorus	15	30.9738
Pt	Platinum	78	195.09
Pu	Plutonium	94	244.06
Po	Polonium	84	208.98
K	Potassium	19	39.0983
Pr	Praseodymium	59	140.9077

Symbol	Name	Atomic Number	Atomic Weight
Pm	Promethium	61	146.92
Pa	Protactinium	91	231.0359
Ra	Radium	88	226.0254
Rn	Radon	86	222.02
Re	Rhenium	75	186.207
Rh	Rhodium	45	102.9055
Rb	Rubidium	37	85.4678
Ru	Ruthenium	44	101.07
Rf	Rutherfordium	104	261
Sm	Samarium	62	150.4
Sc	Scandium	21	44.9559
Sg	Seaborgium	106	263
Se	Selenium	34	78.96
Si	Silicon	14	28.0855
Ag	Silver	47	107.868
Na	Sodium	11	22.98977
Sr	Strontium	38	87.62
S	Sulfur	16	32.06
Ta	Tantalum	73	180.9479
Tc	Technetium	43	98.906
Te	Tellurium	52	127.6
Tb	Terbium	65	158.9254
Tl	Thallium	81	204.37
Th	Thorium	90	232.0381
Tm	Thulium	69	168.9342
Sn	Tin	50	118.69
Ti	Titanium	22	47.9
W	Tungsten	74	183.85
U	Uranium	92	238.029
V	Vanadium	23	50.9414
Xe	Xenon	54	131.3
Yb	Ytterbium	70	173.04
Y	Yttrium	39	88.9059
Zn	Zinc	30	65.38
Zr	Zirconium	40	91.22

Figure 12-1. The periodic table of the elements.

In general, only electrons in unfilled shells, or *valence shells*, are involved in chemical reactions. This property relates to the fact that the most stable form of an element occurs when the configuration of its valence shell resembles that of the nearest noble gas, found in group 0 on the periodic table. This state can be obtained through either the gaining, losing, or sharing of electrons with other elements and is the basis for virtually all chemical reactions.

Inorganic Chemistry

The Periodic Table

Chemical Reactivity

Broadly, the periodic table is divided into metals and nonmetals. Metals, in their pure form, are typically malleable solids that conduct electricity, whereas nonmetals are usually dull, fragile, nonconductive compounds (C, N, P, O, S, Se, halogens). The metals are found on the left side of the periodic table, and account for the majority of the elements, whereas the nonmetals are on the right side. Separating the two groups are the metalloids, which fall on a jagged line starting with boron (B, Si, Ge, As, Sb, Te, At). These agents have chemical properties that are intermediate between the metals and the nonmetals. Each column of elements is termed a family or group, and each row is a period. Although conceived and organized in periods, trends in the chemical reactivity, and therefore toxicity, typically exist within the groups.

The ability of any particular element to produce toxicologic effects relates directly to one or more of its many physicochemical properties, which may, to some extent, be predicted by their location

on the periodic table. For example, the substitution of arsenate for phosphate in the mitochondrial production of adenosine triphosphate (ATP) creates adenosine diphosphate monoarsenate (Chap. 13). Because this compound is unstable and not useful as an energy source, energy production by the cell fails; in this manner arsenic â€œuncouplesâ€• oxidative phosphorylation. Similarly, the existence of an interrelationship between Ca^{2+} and either Mg^{2+} or Ba^{2+} is predictable, although the actual effects are not. That is, under most circumstances, Mg^{2+} is a Ca^{2+} antagonist, and patients with hypermagnesemia present with neuromuscular weakness caused by blockade of myocyte calcium channels. Alternatively, Ba^{2+} mimics Ca^{2+} and closes Ca^{2+}-dependent K^{+} channels in myocytes, producing life-threatening hypokalemia. Additionally, the physiologic relationship between lithium (Li^{+}), potassium (K^{+}), and sodium (Na^{+}) are consistent with their chemical similarities (all alkali metals in Group IA). However, the clinical similarity between thallium (thallous) ion (Tl^{+}) and K^{+} is not predictable. Other than their monovalent nature (ie, +1 charge), it is difficult to predict the substitution of Tl^{+} (Group IIIA, Period 6) for K^{+} (Group IA, Period 4) in membrane ion channel functions, until the similarity of their ionic radii is known (Tl^{+}, 1.47Ã…; K^{+}, 1.33Ã…).

The Alkali (Group IA: Li, Na, K, Rb, Cs, Fr) and Alkaline Earth (Group IIA: Be, Mg, Ca, Sr, Ba, Ra) Metals

Alkali metals and hydrogen (not an alkali metal on earth) have a single outer valence electron and lose this electron easily to form compounds with a valence of 1+. The alkaline earth metals (between the alkali and rare earth, Group IIIB) readily lose 2 electrons, and their cations have a 2+ charge. In their metallic form, members of both of these groups react violently with water to liberate strongly basic solutions, accounting for their group names ($2Na^{0} + 2H_2O$ â†’ $2NaOH + H_2$). The soluble ionic forms of sodium, potassium, or

calcium, which are critical to survival, also produce life-threatening symptoms following excessive intake (Chap. 17). Toxins may interfere with the physiologic role of these key electrolytes. Li^+ may mimic potassium and enter neurons through K^+ channels, following which it serves as a poor substrate for the repolarizing Na^+-K^+-ATPase. Thus, lithium interferes with cellular potassium homeostasis and alters neuronal repolarization accounting for the neuroexcitability manifesting as tremor. Similarly, as noted previously, the molecular effects of Mg^{2+} and Ba^{2+} may supplant those of calcium. More commonly though, the consequential toxicities ascribed to alkali or alkaline earth salts actually relate to the anionic component. In the case of NaOH or $Ca(OH)_2$, it is a hydroxide anion (not the hydroxyl radical), while it is a CN^- anion in patients poisoned with potassium cyanide (KCN).

The Transition Metals (Group IB to VIIIB)

Unlike the alkali and alkaline earth metals, most other metallic elements are neither soluble nor reactive. This includes the transition metals, a large group that contains several ubiquitous metals such as iron (Fe) and copper (Cu). These elements, in their metallic form, are widely used both in industrial and household applications because of their high tensile strength, density, and melting point, which is partly a result of their ability to delocalize the electrons in the d orbital throughout the metallic lattice. Transition metals also form brightly colored salts that find widespread applications including pigments for paints or fireworks. However, the ionic forms, unlike the metallic form, of these elements are typically highly reactive and toxicologically important. Transition elements are chemically defined as elements which form at least one ion with a partially filled subshell of d electrons. Because the transition metals have partially filled valence shells, they are capable of obtaining several, usually positive, oxidation states. This important mechanism explains the role of transition metals in redox reactions generally as electron acceptors (see Oxidation-Reduction below). This reactivity is used by

living organisms in various physiologic catalytic and coordination roles, such as at the active sites of enzymes and in hemoglobin, respectively. Expectedly, the substantial reactivity of these transition metal elements is highly associated with cellular injury caused by the generation of reactive oxygen species. For example, manganese ion exposure is implicated in the free radical damage of the basal ganglia causing parkinsonism.

The Heavy Metals

Heavy metal is often loosely used to describe all metals of toxicologic significance, but in reality, the term should be reserved to describe only those metals in the lower period of the periodic table, particularly those with atomic masses greater than 200. The chemical properties and toxicologic predilection of this group vary among the agents, but their unifying toxicologic mechanism is electrophilic interference with nucleophilic sulfhydryl-containing enzymes. Some of the heavy metals also participate in the generation of free radicals through Fenton chemistry (Fig. 12-2). The likely determinant of the specific toxicologic

effects produced by each metal is the tropism for various physiologic systems, enzymes, or microenvironments; thus the lipophilicity, water solubility, ionic size, and other physicochemical parameters are undoubtedly critical. Also, because the chemistry of metals varies dramatically based on the chemical form (ie, organic, inorganic, or elemental), as well as the charge on the metal ion, prediction of the clinical effects of a particular metal is often difficult.

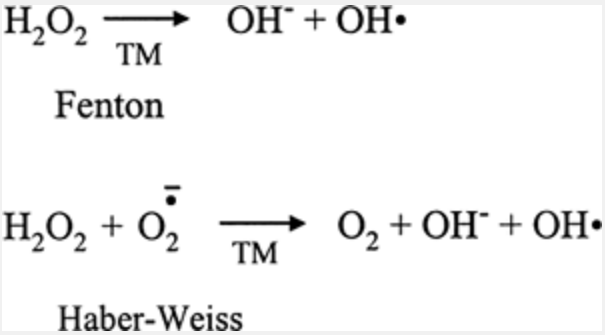


Figure 12-2. The Fenton and Haber-Weiss reactions which are the two most important mechanisms to generate hydroxyl radicals are both mediated by transition metals (TM). Iron (Fe^{2+}) and copper (Cu^{+}) are typical transition metals.

Mercury

Elemental mercury (Hg^0) is unique in that it is the only metal that exists in liquid form at room temperature, and as such is capable of creating solid solutions, or amalgams, with other metals. Although it is relatively innocuous if ingested as a liquid, it is readily volatilized (ie, high vapor pressure) transforming into a physical state that causes significant pulmonary mucosal irritation on inhalation. In addition, this change in the route of exposure raises its systemic bioavailability. Absorbed, or incorporated, Hg^0 undergoes biotransformation in the erythrocyte and brain to the mercuric (Hg^{2+}) form, which has a high affinity for sulfhydryl-containing molecules including proteins. This causes a depletion of glutathione in organs such as the kidney, and also initiates lipid peroxidation. The mercurous form (Hg^{+}) is considerably less toxic than the mercuric form, perhaps because of its reduced water solubility. Organic mercurial compounds, such as methylmercury and

dimethylmercury, are environmentally formed by anaerobic bacteria containing the methylating agent methylcobalamin, a vitamin B_{12} analog (Chap. 92).

Thallium

Another toxicologically important member of the heavy metal group is thallium. Metallic thallium is used in the production of electronic equipment and is itself minimally toxic. Thallium ions, however, have physicochemical properties that most closely mimic potassium, allowing it to participate in, and potentially alter, the various physiologic activities related to potassium. This property is clinically used during a thallium-stress test to assess for myocardial ischemia or infarction. Because ischemic myocardial cells lack adequate energy for normal Na^+-K^+-ATPase function, they cannot exchange sodium for potassium (or in this scenario radioactive thallium) producing a â€œcold spotâ€• in the ischemic areas on cardiac scintigraphy (Chap. 96).

Lead

Although lead is not very abundant in the earth's crust (only 0.002%), exposure may occur during the smelting process or from one of its diverse commercial applications. Most of the useful lead compounds are inorganic lead (II) (Pb^{2+}) salts, but lead (IV) (Pb^{4+}) compounds are also used. The Pb^{2+} compounds are typically ionizable, releasing Pb^{2+} when dissolved in a solvent, such as water. Lead (II) ions are absorbed in place of Ca^{2+} ions by the gastrointestinal tract and replace calcium in certain physiologic processes. This mechanism is implicated in the neurotoxic effect of lead ions. Lead (IV) compounds tend to be covalent compounds that do not ionize in water. However, some of the Pb^{4+} compounds are oxidants. Although elemental lead is not itself toxic, it rapidly develops a coating of toxic lead oxide or lead carbonate upon exposure to air or water (Chap. 91).

The Metalloids (B, Si, Ge, As, Sb, Te, At)

Although the metalloids share many physical properties with the metals, they are differentiated because of their propensity to form compounds with both metals and the nonmetals carbon, nitrogen, or oxygen. Thus, metalloids may be either oxidized or reduced in chemical reactions.

Arsenic

Toxicologically important inorganic arsenic compounds exist in either the pentavalent arsenite (As^{5+}) form or the trivalent arsenate (As^{3+}) form. The reduced water solubility of the arsenate compounds, such as arsenic pentoxide, accounts for its limited clinical toxicity when compared to trivalent arsenic trioxide. The trivalent form of arsenic is primarily a nucleophilic toxin, binding sulfhydryl groups and interfering with enzymatic function (Chaps. 13 and 85).

The Nonmetals (C, N, P, O, S, Se, Halogens)

The nonmetals are highly electronegative and, unlike the metals, may be toxic in either their compounded or their elemental form. The nonmetals with large electronegativity, such as O_2 or Cl_2, generally oxidize other elements in chemical reactions. Those with smaller electronegativity, such as C, behave as reducing agents.

The Halogens (F, Cl, Br, I, At)

In their highly reactive elemental form, which contains a covalent dimer of halogen atoms, the halogens carry the suffix -ine (eg, Cl_2, chlorine). Halogens require the addition of one electron to complete their valence shell; thus, halogens are strong oxidizing agents. Because they are highly electronegative, they form halides (eg, Cl^-, chloride) by abstracting electrons from less electronegative elements. Thus, the halogen ions, in their stable ionic form, generally carry a charge of â€“1. The halides, although much less reactive than

their respective elemental forms, are reducing agents. The hydrogen halides (eg, HCl, hydrogen chloride) are gases under standard conditions, but they ionize when dissolved in aqueous solution to form the hydrohalidic acids (eg, HCl, hydrochloric acid). All hydrogen halides except HF (hydrogen fluoride) ionize completely in water to release H^+ and are considered *strong acids*. Because of its small ionic radius, lack of charge dispersion, and intense electronegativity, HF ionizes poorly and is a *weak acid*. This specific property of HF has important toxicologic implications (Chap. 101).

Group 0: The Inert Gases (He, Ne, Ar, Kr, Xe, Rn)

Inert gases, also known as noble gases, maintain completed valence shells and are thus entirely unreactive except under extreme experimental conditions. However, despite their lack of chemical reactivity, the inert gases are toxicologically important as simple asphyxiants. That is, because they displace ambient oxygen from a confined space, consequential hypoxia may occur, and the expected warning

signs may be completely absent (Chap. 119). During high-concentration exposure, inert gases may produce anesthesia, and xenon is used as an anesthetic agent. Radon, although a chemically unreactive gas, is radioactive, and prolonged exposure is associated with the development of lung cancer.

Bonds

Electrons are not generally shared evenly between atoms when they form a compound. Instead, unless the bond is between the same elements, as in Cl_2, one of the elements exerts a larger attraction for the shared electrons. The degree to which an element draws the shared electron is determined by the element's *electronegativity* (Fig. 12-3). The electronegativity of each element was catalogued by Linus

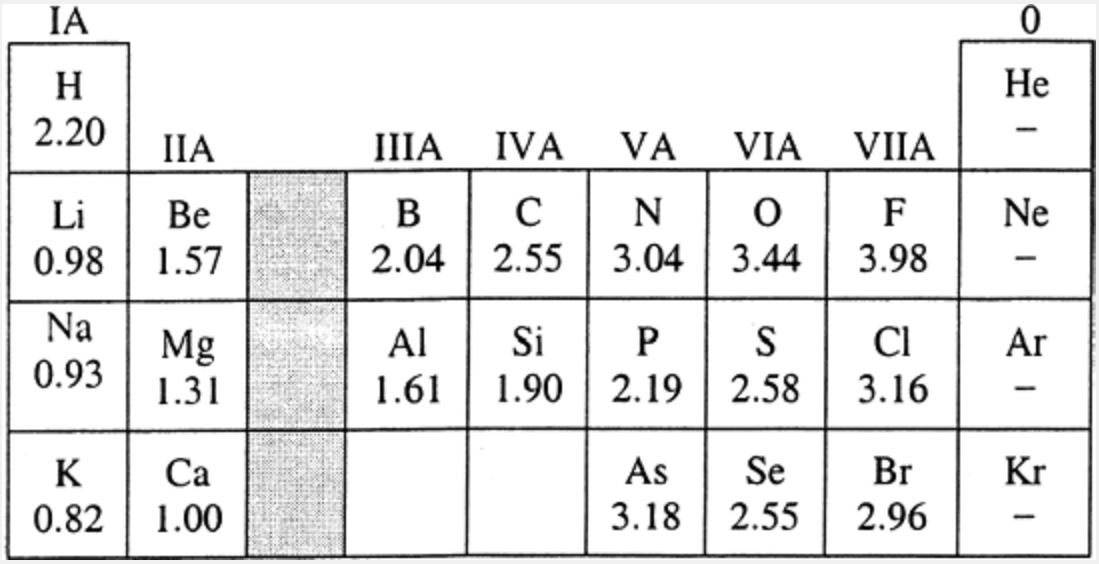
Pauling and relates to the ionic radius, or the distance between the orbiting electron and the nucleus, and the shielding effects of the inner electrons. The electronegativity rises toward the right of the periodic table, corresponding with the expected charge obtained on an element when it forms a bond. Fluoride ion has the highest electronegativity of all elements, which explains many of its serious toxicologic properties.

Several types of bonds exist between elements when they form compounds. When one element gains valence electrons and another loses them, the resulting elements are charged and attract one another in an *ionic*, or *electrovalent*, bond. An example is NaCl, or table salt, in which the electronegativity difference between the elements is 1.9, or greater than the electronegativity of the sodium (see text below and Fig. 12-3). Thus, the chloride wrests control of the electrons in this bond. In solid form, ionic compounds exist in a crystalline lattice, but when put into solution, as in the serum, the elements may separate and form charged particles, or *ions* (Na^+ and Cl_2). The ions are stable in solution, however, because their valence shells contain 8 electrons and are complete. The properties of ions differ from both the original atom from which the ion is derived and the noble gas with which it shares electronic structure.

It is important to recognize that when a mole of a salt, such as NaCl (molecular weight 58.45 g/mol), is put in aqueous solution, 2 moles of particles result. This is because NaCl essentially ionizes fully in water; that is, it produces 1 mole of Na^+ (23 g/mol) and 1 mole of Cl^- (35.45 g/mol). For salts that do not ionize completely, less than the intrinsic number of moles are released and the actual quantity liberated can be predicted based on the defined solubility of the compound, or the solubility product constant (K_{sp}). For ions that carry more than a single charge, the term *equivalent* is often used to denote number of moles of other particles to which one mole of the substance will bind. Thus, an equivalent of calcium ion will typically bind 2 moles (or equivalents) of chloride ions (which are monovalent) because calcium ions are divalent. Alternatively stated, a 10%

calcium chloride ($CaCl_2$) aqueous solution contains approximately 1.4 mEq/mL or 0.7 mmol/mL of Ca^{2+}.

Compounds formed by two elements of similar electronegativity have little ionic character because there is little impetus for separation of charge. Instead, these elements share pairs of valence electrons, a process known as *covalence*. The resultant molecule contains a *covalent bond*, which is typically very strong and generally requires a high-energy chemical reaction to disrupt it. There is wide variation in the extent to which the electrons are shared between the participants of a covalent bond, and the physicochemical and toxicologic properties of any particular molecule are in part determined by its nature. Rarely is sharing truly symmetric, as in oxygen (O_2) or chlorine (Cl_2). If sharing is asymmetric and the electrons thus exist to a greater degree around one of the component atoms, the bond is *polar*. However, the presence of a polar bond does not mean that the compound is polar. For example, methane contains a carbon atom that shares its valence electrons with 4 hydrogen atoms, in which there is a small charge separation between the elements (electronegativity [EN] difference = 0.40). Furthermore, because the molecule is configured in a tetrahedral formation, there is no notable polarity to the compound; this compound is *nonpolar*. The lack of polarity suggests that methane molecules have little affinity for other methane molecules and they are held together only by weak intermolecular bonds. This explains why methane is highly volatile under standard conditions.



IA							0
H 2.20	IIA		IIIA	IVA	VA	VIA	VIIA	He –
Li 0.98	Be 1.57		B 2.04	C 2.55	N 3.04	O 3.44	F 3.98	Ne –
Na 0.93	Mg 1.31		Al 1.61	Si 1.90	P 2.19	S 2.58	Cl 3.16	Ar –
K 0.82	Ca 1.00				As 3.18	Se 2.55	Br 2.96	Kr –

Figure 12-3. Electronegativity of the common elements. Note that the inert gases are not reactive and thus do not have electronegativity.

Because the electronegativity differences between hydrogen (EN = 2.20) and oxygen (EN = 3.44) are greater (EN difference = 1.24), the electrons in the HO bonds in water are drawn toward the oxygen atom, giving it a partial negative charge and the hydrogens a partial positive charge. Furthermore, because H_2O is angular, not linear or symmetric, water is a polar molecule. Water molecules are held together by hydrogen bonds, which are stronger than intermolecular bonds (also called van der Waals forces, see below). These hydrogen bonds have sufficient energy to open many ionic bonds and *solvate* the ions. In this process, the polar ends of the water molecule surround the charged particles of the dissolved salt. Thus, because there is little similarity between the nonpolar methane and the polar water molecules, methane is not water soluble. Similarly, salts cannot be solvated by nonpolar compounds, and thus a salt, such as sodium chloride, cannot dissolve in a nonpolar solvent, such as

carbon tetrachloride.

Alternatively, the stability and irreversibility of the bond between an organic phosphorus insecticide and the cholinesterase enzyme are a result of covalent phosphorylation of an amino acid at the active site of the enzyme. The resulting bond is essentially irreversible in the absence of another chemical reaction.

Compounds may share multiple pairs of electrons. For example, the two carbon atoms in acetylene (HC[triple bond]CH) share three pairs of double bonds between them, and each shares one pair with its own hydrogen. Carbon and nitrogen share three pairs of electrons in forming cyanide (C[triple bond]N^-) making this bond very stable and accounting for the large number of xenobiotics capable of liberating cyanide.

Complex ions are covalently bonded groups of elements that behave as a single element. For example, the hydroxide ion (OH^-) and sulfate (SO_4^{2-}) form sodium salts as if they were simply a chloride ion.

Noncovalent bonds, such as hydrogen or ionic bonds, are important in the interaction between ligands and receptors, and between ion channels and enzymes. These are low-energy bonds and easily reversible. Van der Waals forces, also known as London dispersion forces, are intermolecular forces that arise from induced dipoles as a consequence of nonuniform distribution of the molecular electron cloud. These forces become stronger as the atom (or molecule) becomes larger because of the increased polarizability of the larger, more dispersed electron clouds. This accounts for the fact that under standard temperature and pressure, fluorine and chlorine are gases, whereas bromine is a liquid, and iodine is a solid.

Oxidation-Reduction

Reduction-oxidation (*redox*) reactions involve the movement of

electrons from one atom or molecule to another, and actually comprise two dependent reactions: reduction and oxidation. *Reduction* is the gain of electrons by an atom that is thereby *reduced*. The electrons derive from a *reducing agent*, which in the process becomes *oxidized*. *Oxidation* is the loss of electrons from an agent, which is, accordingly, *oxidized*. An *oxidizing agent* accepts electrons, and in the process, is reduced. By definition, these chemical reactions involve a change in the valence of an atom. It is also important to note that acid/base and electrolyte chemical reactions involve electrical charge interactions but no change in valence of any of the involved components. The implications of redox chemistry for medical toxicology are profound. For example, the oxidation of ferrous (Fe^{2+}) to ferric (Fe^{3+}) iron within the hemoglobin molecule creates dysfunctional methemoglobin.

Also, metallic lead and elemental mercury are both intrinsically harmless metals, but when oxidized to their cationic forms both produce devastating clinical effects. Additionally, the oxidation of methanol to formic acid involves a change in the oxidation state of the molecule. In this case, an enzyme, alcohol dehydrogenase, acting as a catalyst, oxidizes (ie, removes electrons from) the C-O bond and delivers the electrons to oxidized nicotinamide adenine dinucleotide (NAD^+), reducing it to the reduced form (NADH). As in this last example, *oxidation* is occasionally used to signify the gain of oxygen by a substance. That is, when elemental iron (Fe^0) undergoes rusting to iron oxide (Fe_2O_3), it is said to oxidize. The use of this term is consistent because in the process of oxidation, oxygen derives electrons from the atom to which it is binding.

Reactive Oxygen Species

Free radicals are reactive molecules that contain one or more unpaired electrons, and are typically neutral but may be anionic or cationic. However, because certain toxicologically important reactive molecules do not contain unpaired electrons, such as hydrogen

peroxide (H_2O_2) and ozone (O_3), the term *reactive species* is preferred. The reactivity of these molecules directly relates to their desire to fill their outermost orbitals by receiving an electron; the result is *oxidative stress* on the biologic system. Molecular oxygen is actually a diradical with two unpaired electrons in the outer orbitals. However, its reactivity is less than that of the other radicals because the unpaired electrons have parallel spins, so catalysts (ie, enzymes or metals) are typically involved in the use of oxygen in biologic processes.

Reactive species are continually generated as a consequence of endogenous metabolism and there is an efficient system for their control. Under conditions of either excessive endogenous generation or exposure to exogenous reactive species, the physiologic defense against these toxic products is overwhelmed. When this occurs, reactive species induce direct cellular damage as well as initiate a cascade of oxidative reactions that perpetuate the toxic damage.

Intracellular organelles, particularly the mitochondria, may also be disrupted by various reactive oxygen species. This causes further injury to the cell as energy failure occurs. This initial damage is compounded by the activation of the host inflammatory response by chemokines that are released from cells in response to reactive oxygen species-induced damage. This inflammatory response aggravates cellular damage. The resultant membrane dysfunction or damage causes cellular apoptosis or necrosis (Chap. 13).

The most important reactive oxygen species in medical toxicology are derived from oxygen, although those derived from nitrogen are also important. Table 12-1 lists some of the important reactive oxygen and nitrogen species.

This biradical nature of oxygen explains both the physiologic and toxicologic importance of oxygen in biologic systems. Physiologically, the majority of oxygen is used by the body to serve as the ultimate electron acceptor in the mitochondrial electron transport chain (Fig. 13-3). In this situation, four electrons are added to each molecule of

oxygen to form two water molecules (O_2 + 4 H^+ + 4 e^- â†' 2 H_2O).

Superoxide is generated within neutrophil and macrophage lysosomes as part of the oxidative burst, a method of eliminating infectious agents and damaged cells. Superoxide may subsequently be enzymatically converted, or dismutated, into hydrogen peroxide by superoxide dismutase (SOD). Hydrogen peroxide may be subsequently converted into hypochlorous acid by the enzymatic addition of chloride by myeloperoxidase. Both hydrogen peroxide and hypochlorite ion are more potent reactive oxygen species than superoxide. However, this lysosomal protective system may also be responsible for tissue damage following poisoning as the innate inflammatory response attacks toxin-damaged cells. Examples include acetaminophen-induced hepatotoxicity (Chap. 34), carbon monoxide neurotoxicity (Chap. 120), and chlorine-induced

pulmonary toxicity (Chap. 119), each of which may be altered, at least in experimental systems, by the addition of scavengers of reactive oxygen species.

	Structure
Reactive Oxygen Species	
Free radicals	
Hydroxyl radical	OH·
Alcoxyl radical	RO·
Singlet oxygen (Σ)	[O] or $^1O_2$
Peroxyl radical	ROO·
Superoxide radical	O_2^- or O_2^-
Nonradicals	
Hydrogen peroxide	H_2O_2
Hypochlorous acid	HOCl
Singlet oxygen (Δ)	[O] or $^1O_2$
Ozone	O_3
Reactive Nitrogen Species	
Free radicals	
Nitric oxide	NO·
Nitrogen dioxide	NO_2·
Nonradicals	
Peroxynitrite anion	$ONOO^-$
Nitronium cation	NO_2^+

TABLE 12-1. Structure of Important Reactive Oxygen and Nitrogen Species

Although superoxide and hydrogen peroxide are reactive oxygen species, it is their conversion into the hydroxyl radical (OHÂ·) that accounts for their most consequential effects. The hydroxyl radical is generated by the Fenton reaction (Fig. 12-2), in which hydrogen peroxide is decomposed in the presence of a transition metal. This catalysis typically involves Fe^{2+}, Cu^+, Cd^{2+}, Cr^{5-}, Ni^{2+}, or Mn^{2+}. The Haber-Weiss reaction (Fig. 12-2), in which a transition metal catalyzes the combination of superoxide and hydrogen peroxide, is the other important means of generating the hydroxyl radical. Superoxide dismutase, within the erythrocyte, contains an atom of Cu^{2+} that participates in the catalytic dismutation (reduction) of superoxide to hydrogen peroxide (SOD was originally called

erythrocuprein) and the subsequent detoxification of hydrogen peroxide by glutathione peroxidase or catalase.

Transition metal cations may bind to the cellular nucleus where they locally generate reactive oxygen species, most importantly hydroxyl radical. This results in DNA strand breaks and modification, accounting for the promutagenic effects of many transition metals.[2] In addition to the important role that transition metal chemistry plays following iron or copper salt poisoning, the long-term consequences of chronic transition metal poisoning are exemplified by asbestos. The iron contained in asbestos is the origin of the Fenton-generated hydroxyl radicals that are responsible for the pulmonary fibrosis and cancers associated with long-term exposure.[2]

The most consequential toxicologic effects of reactive oxygen species occur on the cell membrane, and are caused by the initiation by hydroxyl radical of the lipid peroxidative cascade. The alteration of these lipid membranes ultimately causes membrane destruction. Identification of released oxidative products such as malondialdehyde is a common method of assessing lipid peroxidation.

Under normal conditions, there is a delicate balance between the formation and immediate endogenous detoxification of reactive oxygen species. For example, the conversion of superoxide radical to hydrogen peroxide via SOD is rapidly followed by the transformation of hydrogen peroxide to water by glutathione peroxidase or catalase. Furthermore, transition metals cannot be unattended in biologic systems and exist in â€œfreeâ€• form in only minute quantities, presumably to minimize the formation of hydroxyl radicals through Fenton reactions. Thus, cells have developed extensive systems by which transition metal ions can be sequestered and rendered harmless. Ferritin (binds iron), ceruloplasmin (binds copper), and metallothionein (binds cadmium) are specialized proteins that safely sequester transition metal ions. Certain proteins and enzymes that contain transition metals at their active sites, such as hemoglobin or SOD, harness the activity of transition metal ions in a controlled

fashion.

Detoxification of certain reactive species is difficult because of their extreme reactivity. Widespread antioxidant systems exist to trap reactive species before they can damage tissues. An example is the availability of glutathione, a reducing agent and nucleophile, to prevent both exogenous oxidants from producing hemolysis and the acetaminophen metabolite *N*-acetyl-*p*-benzoquinoneimine (NAPQI) from damaging the hepatocyte.

The key reactive nitrogen species is nitric oxide. At typical physiologic concentrations, this radical is responsible for vascular endothelial relaxation through stimulation of guanylate cyclase. However, during oxidative burst, high concentrations of nitric oxide are formed from L-arginine. At these concentrations, nitric oxide has primarily both damaging effects and reacts with superoxide radical to generate the peroxynitrite anion. This is particularly important because peroxynitrite may spontaneously degrade to form the hydroxyl radical. Peroxynitrite ion is implicated in both the delayed neurologic effects of carbon monoxide poisoning and the hepatic injury from acetaminophen.

Redox Cycling

Although transition metals are an important source of reactive species, certain xenobiotics are also capable of independently generating reactive species. Most do so through a process called *redox cycling*, in which a molecule accepts an electron from a reducing agent and subsequently transfers that electron to oxygen, generating the superoxide radical. At the same time, this second reaction regenerates the parent molecule, which itself can gain another electron and restart the process. The toxicity of paraquat is selectively localized to pulmonary endothelial cells. Its pulmonary toxicity results from redox cycling generation of reactive oxygen species (Fig. 111-1). A similar process, localized to the heart, occurs with anthracycline antineoplastic agents such as doxorubicin.

Acidâ€“Base Chemistry

Water is *amphoteric*, which implies that water can function as either an acid or a base, much the same way as the bicarbonate ion (HCO_3^-). In fact, because of the amphoteric nature of water, H^+, despite the nomenclature, does not ever actually exist in aqueous solution; rather, it is covalently bound to a molecule of water to form the hydronium ion (H_3O^+). However, the term H^+, or proton, is used for convenience.

Even in neutral solution, a tiny proportion of water is always undergoing ionization to form both H^+ and OH^+ in exactly equal amounts. It is, however, the quantity of H^+ that is of concern, and this is the basis of using the pH to characterize a solution. In a perfect system at equilibrium, the concentration of H^+ ions in water is precisely 0.0000001, or 10^{-7}, moles per liter and that of OH^- is the same. The number of H^+ ions increases when an acid is added to the solution and falls when an alkali is added. In an attempt to make this quantity more practical, the negative log of the H^+ concentration is calculated, which defines the *pH*. Thus, the negative log of 10^{-7} is 7, and the pH of a neutral aqueous solution is 7. In actuality, the pH of water is approximately 6 because of dissolution of ambient carbon dioxide to form carbonic acid ($H_2O + CO_2$ â†' H_2CO_3), which ionizes to form H^+ and bicarbonate (HCO_3^-).

There are many definitions of acid and base. The three commonly used definitions are those advanced by (a) Arrhenius, (b) BrÃ¸nsted-Lowry, and (c) Lewis. Because the focus is on physiologic systems, which are aqueous, the original definition by the Swedish chemist Arrhenius is the most practical. In this view, an acid is any xenobiotic that releases hydrogen ions, or protons (H^+), in water. Similarly, a base is a xenobiotic that produces hydroxyl ions (OH^-) in water. Thus, hydrogen chloride (HCl), a neutral gas under standard conditions, dissolves in water to liberate H^+, and is therefore an acid.

For nonaqueous solutions the BrÃ¸nsted-Lowry definition is preferable. An acid, in this schema, is a substance that donates a proton and a base is one that accepts a proton. Thus, any molecule that has a hydrogen in the 1+ oxidation state is technically an acid, and any molecule with an unbound pair of valence electrons is a base. Because most of the acids or bases of toxicologic interest

have ionizable protons or available electrons, respectively, the BrÃ¸nsted-Lowry definition is most often considered when discussing acid-base chemistry (ie, $HA + H_2O$ â†' $H_3O^+ + A^-$; $B^- + H_2O$ â†' $HB + OH^-$). However, this is not a defining property of all acids or bases. Thus, Lewis offered the least-restrictive definition of such substances. A Lewis acid is an electron acceptor and a Lewis base is an electron donor. Simplistically, acids are sour and turn litmus paper red, whereas bases are slippery and bitter and turn litmus paper blue.

Because acidity and alkalinity are determined by the number of available H^+ ions, it is useful to classify chemicals by their effect on the H^+ concentration. Strong acids ionize completely in aqueous solution and very little of the parent compound remains. Thus, 0.001 (or 10^{-3}) mole of HCl, a strong acid, added to 1 L of water produces a solution with a pH of 3. Weak acids, on the other hand, obtain an equilibrium between parent and ionized forms, and thus do not alter the pH to the same degree as a similar quantity of a strong acid. This chemical notation defines the strength or weakness of an acid and should not be confused with the concentration of the acid. Thus, the pH of a dilute strong acid solution may be substantially less than that of a concentrated weak acid (Table 12-2).

The degree of ionization of a weak acid is determined by the pK_a, or the negative log of the *ionization constant*, which represents the pH at which an acid is half dissociated in solution. The same relationship applies to the pK_b of an alkali, although by convention the pK_b is expressed as the pK_a ($pK_a = 14$ â€“ pK_b). The lower the pK_a, the stronger the acid; the converse is true for bases. Knowledge of the

pK_a does not itself denote whether a substance is an acid or an alkali. To some extent, this quality may be predicted by its chemical structure or reactivity, or obtained through direct measurement or from a reference source. The pK of a strong acid is clinically irrelevant because it is fully ionized under all but the most extreme acid conditions.

Because only uncharged compounds cross lipid membranes spontaneously, the pK_a has clinical relevance. Salicylic acid, a weak acid with a pK_a of 3, is nonionized in the stomach (pH 2) and passive absorption occurs (Fig. 9-4). Because it is predominantly in the ionized form (ie, salicylate) in blood, which has a pH of 7.4, little of the ionized bloodborne salicylate passively enters the tissues. However, because in overdose the serum salicylate rises considerably, enough enters the tissue to have devastating clinical effects. Salicylate, a conjugate base of a weak acid and thus a strong base, equilibrates within the various tissues across the outer mitochondrial membrane. In this intermembrane space (between the inner and outer mitochondrial membrane) abundant protons exist, which are transported there via the electron transport chain of this organelle (Chap. 13). Because salicylate is a strong base, it protonates easily in this environment. In this nonionized form, some of the salicylic acid may pass through the inner mitochondrial membrane, into the mitochondrial matrix, and again establish equilibrium by losing a proton. The process just described uncouples oxidative phosphorylation, by dispersing the highly concentrated protons in the intermembrane space that are normally used to generate adenosine triphosphate (Chap. 13). Uncoupling in the skeletal muscle, for example, produces a metabolic acidosis, and this shifts the blood equilibrium of salicylate toward the nonionized, protonated form, enabling salicylic acid to cross the bloodâ€“brain barrier. Presumably, once in the brain, the salicylate uncouples the metabolic activity of neurons with the subsequent development of cerebral edema. This is the rationale for serum alkalinization in patients with aspirin overdose (Chap. 35).

TABLE 12-2. pH of 0.10 M Solutions of Common Acids and Bases Represents the Strength of the Acid or Base

Acid Base	pH
HCl (hydrochloric acid)	1.1
H_2SO_4 (sulfuric acid)	1.2
H_2SO_3 (sulfurous acid)	1.5
H_3PO_4 (phosphoric acid)	1.5
HF (hydrofluoric acid)	2.1
CH_3CO_2H (acetic acid)	2.9
H_2CO_3 (carbonic acid)	3.8
H_2S (hydrogen sulfide)	4.1
NH_4Cl (ammonium chloride)	4.6
HCN (hydrocyanic acid)	5.1
$NaHCO_3$ (sodium bicarbonate)	8.3
$NaCH_3CO_2$ (sodium acetate)	8.9

Na_2HPO_4 (sodium hydrogen phosphate)	9.3
Na_2SO_3 (sodium sulfite)	9.8
NaCN (sodium cyanide)	11.0
NH_4OH (aqueous ammonia)	11.1
Na_2CO_3 (sodium carbonate)	11.6
Na_3PO_4 (sodium phosphate)	12.0
NaOH (sodium hydroxide)	13.0

In a similar manner, alkalinization of the patient's urine prevents reabsorption by ionization of the urinary salicylate. Conversely, because tricyclic antidepressants are organic bases, alkalinization of the urine reduces their ionization and actually decreases the drug's urinary elimination. However, in the management of cyclic antidepressant poisoning, because the other beneficial effects of sodium bicarbonate on the sodium channel outweigh the negative effect on drug elimination, serum alkalinization is recommended.

Organic Chemistry

The study of carbon-based chemistry and the interaction of inorganic molecules with carbon-containing compounds is called *organic chemistry*, because the chemistry of living organisms is carbon based. *Biochemistry* (Chap. 13) is a subdivision of organic chemistry; it is the study of organic chemistry within biologic systems. This section reviews many of the salient points of organic chemistry,

focusing on those with the most applicability to medicine and the study of toxicology: nomenclature, bonding, nucleophiles and electrophiles, stereochemistry, and functional groups.

Chemical Properties of Carbon

Carbon, atomic number 6, has a molecular weight of 12.011 g/mol. With few exceptions (notably cyanide ion and carbon monoxide), carbon forms 4 bonds in stable organic molecules. In organic compounds, carbon is commonly bonded to other carbon atoms, as well as to hydrogen, oxygen, nitrogen, or halide (ie, fluorine, bromine, or iodine) atoms. Under certain circumstances, carbon can be bonded to metals, as is the case with methylmercury.

Nomenclature

The most rigorous method to name organic compounds is in accordance with standards adopted by the International Union of

Pure and Applied Chemistry (IUPAC); these names are infrequently used, especially for larger molecules, and *alternative chemical names* are common. Alternative chemical names are those based on the structure of a molecule, but which do not adhere completely to IUPAC rules. The complete details of the IUPAC naming system are beyond the scope of this text and can be reviewed elsewhere (http://www.iupac.org), but a brief description of the fundamentals of this system is included here.

The carbon backbone serves as the basis of the chemical name. Once the carbon backbone has been identified and named, *substituents* (atoms or groups of atoms that substitute for hydrogen atoms) are identified, named, and numbered. The number refers to the carbon to which the substituent is attached. Some of the common substituents in organic chemistry are â€“OH (hydroxy), â€“NH_2 (amino), â€“Br (bromo), â€“Cl (chloro), and â€“F (fluoro). Substituents are then

alphabetized and placed as prefixes to the carbon chain.

As an example, consider the molecule 2-bromo-2-chloro-1,1,1-trifluoroethane. The molecule has a 2-carbon backbone (ethane), 3 fluoride atoms on the first carbon, a bromine atom on the second carbon, and a chlorine atom on the second carbon (Fig. 12-4A). A basic understanding of a few simple rules of nomenclature thus allows one to quickly generate the molecular structure of a familiar compound, halothane, from what initially appeared to be an intimidating name.

Although the above-mentioned rules suffice to name simple structures, they are inadequate to describe many others, such as molecules with complex branching or ring structures. The IUPAC rules for naming compounds such as [1R-(exo,exo)]-3-(benzoyloxy)-8-methyl-8-azabicyclo[3,2,1]octane-2-carboxylic acid methyl ester, for example, are too complex to include here. Fortunately, many compounds with complex chemical names have simpler names for day-to-day use; as an example, this molecule is commonly referred to as cocaine (Fig. 12-4B).

Cocaine is an example of a *common* or *trivial* name, that is, one without a rigorous scientific basis, but which is generally accepted as an alternative to frequently unwieldy proper chemical names. Common names may refer to the origin of the substance; for example, cocaine is derived from the coca leaf, and wood alcohol (methanol) can be prepared from wood. Alternatively, a common name may refer to the way in which a compound is used; â€œrubbing alcoholâ€• is a common name for isopropanol. Common names are often imprecise and may generate some confusion, however, as evidenced by the fact that â€œrubbing alcohol,â€• when commercially marketed, may be ethanol or isopropanol.

An even less precise system of nomenclature is the use of *street* names. A street name is a slang term for a drug of abuse, such as â€œblowâ€• (cocaine), â€œweedâ€• (marijuana), or â€œsmackâ€• (heroin). The street name *ecstasy* refers to the stimulant 3,4-

methylenedioxymethamphetamine (MDMA), which is most frequently consumed in pill form. It would stand to reason that *liquid ecstasy* might refer to a solution of MDMA, but street names are not necessarily logical. Instead, liquid ecstasy refers to the drug Î³-hydroxybutyrate (GHB), a sedative-hypnotic agent with a completely different pharmacologic and toxicologic profile. Furthermore, there are no standards for the content of ecstasy and many street pills contain other chemicals or no chemicals at all.

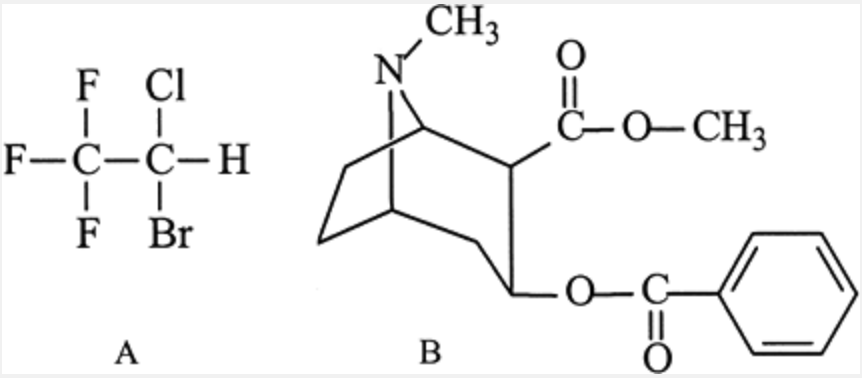


Figure 12-4. Nomenclature. A. 2-Bromo-2-chloro-1,1,1-trifluoroethane, or halothane. B. [1R-(exo,exo)]-3-(Benzoyloxy)-8-methyl-8-azabicyclo-[3,2,1]-octane-2-carboxylic acid methyl ester, or cocaine.

A final consideration must be given to *product names.* Product names are â€œtrade namesâ€• under which a given compound might be marketed, and are frequently different from both the chemical name and common name. Thus, the inhalational anesthetic in Figure 12-4A with the chemical name *2-bromo-2-chloro-1,1,1-trifluoroethane* has the common name *halothane* and the trade name *Fluothane*.

Bonding in Organic Chemistry

Whereas much of the bonding in inorganic chemistry is ionic or electrovalent, the vast majority of bonding in organic molecules is *covalent*. Whereas electrons in ionic bonds are described as â€œbelongingâ€• to one atom or another, electrons in covalent bonds are shared between two atoms; this type of bonding occurs when the difference in electronegativity between two atoms is insufficient for one atom to wrest control of an electron from another. Single bonds are represented by 1, double bonds by 2, and triple bonds by 3 lines between the atoms.

Nucleophiles and Electrophiles

Many organic reactions of toxicologic importance can be described as the reactions of *nucleophiles* with *electrophiles*. *Nucleophiles* (literally, nucleus-loving) are species with increased electron density, frequently in the form of a lone pair of electrons (as in the cases of cyanide ion and carbon monoxide). Nucleophiles, by virtue of this increased electron density, have an affinity for atoms or molecules which are electron deficient; such moieties are called *electrophiles* (literally, electron-loving). The electron deficiency of electrophiles can be described as absolute or relative. Absolute electron deficiency occurs when an electrophile is charged, as is the case with cations such as Pb^{2+} and Hg^{2+}. Relative electron deficiency occurs when one atom or group of atoms shifts electrons away from a second atom, making the second atom relatively electron deficient. This is the case for the neurotoxin 2,5-hexanedione (Fig. 12-5); the electronegative oxygen of the carbon-oxygen double bond pulls electron density away from the second and fifth carbon atoms of this molecule, making these carbon atoms electrophilic.

The reaction of a nucleophile with an electrophile involves the movement of electrons, by forming and/or breaking bonds. This movement of electrons is frequently denoted by the use of curved arrows, which better demonstrates how the nucleophile and electrophile

interact. The interaction of acetylcholinesterase with acetylcholine, organic phosphorus pesticides, and pralidoxime hydrochloride provides an excellent example of the way in which nucleophiles and electrophiles interact, and of how the use of curved arrow notation can lead to better understanding of the reactions involved.

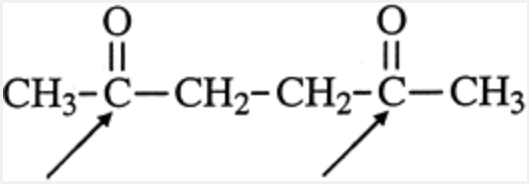


Figure 12-5. Chemical properties of 2,5-hexanedione. *Arrows* designate the electrophilic carbon atoms.

Under normal circumstances, the action of acetylcholine is terminated when the serine residue in the active site of acetylcholinesterase attacks this neurotransmitter, forming a transient serineâ€“acetyl complex and liberating choline; this serineâ€“acetyl complex is then rapidly hydrolyzed, producing an acetic acid molecule and regenerating the serine residue for another round of the reaction (Fig. 12-6A). In the presence of an organic phosphorus agent, however, this serine residue attacks the electrophilic phosphate atom, forming a stable serineâ€“phosphate bond, which is not hydrolyzed (Fig. 12-6B). The enzyme, thus inactivated, can no longer break down acetylcholine, leading to an increase of this neurotransmitter in the synapse, and possibly to a

cholinergic crisis.

The enzyme can be reactivated, however, by the use of another nucleophile. Pralidoxime hydrochloride (2-PAM) is referred to as a *site-directed nucleophile.* Because part of its chemical structure (the charged nitrogen atom) is similar to the choline portion of acetylcholine, this antidote is directed to the active site of acetylcholinesterase. Once in position, the nucleophilic oxime moiety (â€“NOH) of 2-PAM attacks the electrophilic phosphate atom; this displaces the serine residue, regenerating the enzyme (Fig. 12-6C). For a further discussion of organic phosphorus compound toxicity and the use of 2-PAM, see Chap. 109 and Antidotes in Depth: Pralidoxime.

A second toxicologically important electrophile is NAPQI (Fig. 12-7). NAPQI is formed when the endogenous detoxification pathways of acetaminophen metabolism (glucuronidation and sulfation) are overwhelmed (Chap. 34). As a result of the electron configuration of NAPQI, the carbon atoms adjacent to the *carbonyl carbon* (a carbonyl carbon is one that is double-bonded to an oxygen) are very electrophilic; the sulfur groups of cysteine residues of hepatocyte proteins react with NAPQI to form a characteristic *adduct*, 3-(cystein-*S*-yl)acetaminophen in a multistep process (an adduct is formed when one compound is added to another). These adducts are released as hepatocytes die, and can be found in the blood of patients with acetaminophen-related liver toxicity. Figure 12-7 diagrams the mechanism of the proteinâ€“NAPQI reaction (Chap. 34).

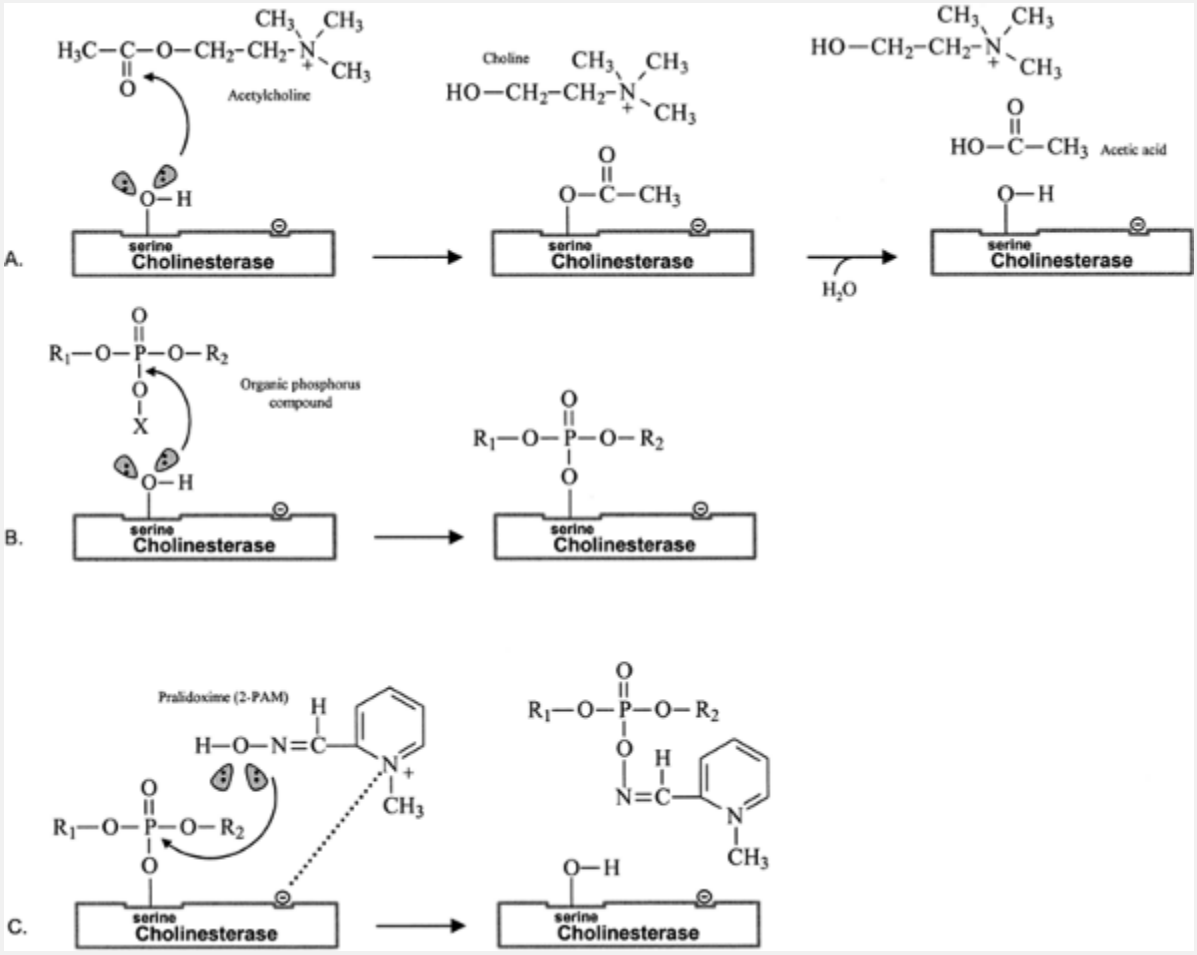


Figure 12-6. The reactions of acetylcholinesterase (AChE), organic phosphorus compounds, and pralidoxime hydrochloride (2-PAM). Curved arrows represent the movement of electrons as bonds are formed or broken. A. Normal hydrolysis of acetylcholine by acetylcholinesterase. B. Inactivation (phosphorylation) of acetylcholinesterase by organic phosphorus compound. C. Reactivation by 2-PAM of functional acetylcholinesterase.

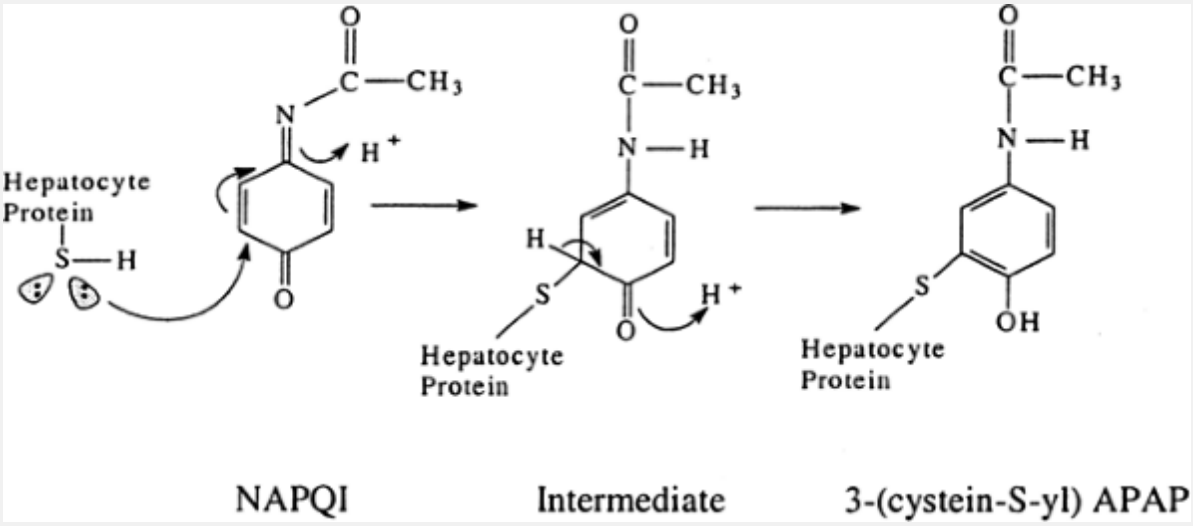


Figure 12-7. The reaction of cysteine residues on hepatocyte proteins with NAPQI to form the characteristic adducts 3-(cystein-S-yl) APAP.

Nucleophiles can be described by their strength; strength is related to the rate at which they react with a reference electrophile CH_3I. Of more use in pharmacology and toxicology, however, are the descriptive terms â€œhardâ€• and â€œsoft.â€• Although imprecise, the designations â€œhardâ€• and â€œsoftâ€• help to predict, on a qualitative level, how nucleophiles and electrophiles interact with one another.

â€œHardâ€• species have a charge (or partial charge) that is highly localized; that is, their charge to radius ratio is high. Hard nucleophiles are molecules in which the electron density or lone pair is tightly held; fluoride, a small atom that cannot spread its electron density over a large area, is an example. Similarly, hard electrophiles are species in which the positive charge cannot be spread over a large area; ionized calcium, a small ion, is a hard electrophile.

â€œSoftâ€• nucleophiles and electrophiles, on the other hand, are capable of delocalizing their charge over a larger area. In this case the charge to mass ratio is low, either because the atom is large or because the charge can be spread over a number of atoms within a given molecule. Sulfur is the prototypical example of a soft nucleophile and the lead ion, Pb^{2+}, is a typical soft electrophile.

The utility of this classification lies in the observation that hard nucleophiles tend to react with hard electrophiles, and soft nucleophiles with soft electrophiles. For example, a principal toxicity of fluoride ion poisoning (Chap. 101) is hypocalcemia; this is because the fluoride ions (hard nucleophiles) readily react with calcium ions (hard electrophiles). On the other hand, the soft nucleophile lead is effectively chelated by soft electrophiles such as the sulfur atoms in the chelating agents dimercaprol (Antidotes in Depth: Dimercaprol [British Anti-Lewisite or BAL]) and succimer (Antidotes in depth: Succimer [2,3-Dimercaptosuccinic Acid]).

Isomerism

Isomerism describes the different ways in which molecules with the same chemical formula (ie, the same number and types of atoms) can be arranged to form different compounds. These different compounds are called *isomers.* Isomers always have the same chemical formula, but differ either in the way that atoms are bonded to each other (*constitutional isomers*) or in the spatial arrangement of these atoms (*geometric isomers* or *stereoisomers*).

Figure 12-8. Two molecules with chemical formula C_2H_6O. A. Dimethylether. B. Ethanol (ethyl alcohol).

Constitutional isomers are conceptually the easiest to understand, because a quick glance shows them to be very different molecules. The chemical formula C_2H_6O, for example, can refer to either dimethyl ether or ethanol (Fig. 12-8). These molecules have very different physical and chemical characteristics, and have little in common other than the number and type of their atomic constituents.

Stereoisomerism, also referred to as *geometric isomerism*, refers to the different ways in which atoms of a given molecule, with the same number and types of bonds, might be arranged. The most important type of stereoisomerism in pharmacology and toxicology is the stereochemistry around a *chiral carbon*, a carbon atom to which four different substituents are bonded.

Consider the two representations of halothane shown in Figure 12-9. In this figure the straight solid lines and the atoms to which they are bonded exist in the plane of the paper, the solid triangle and the atom to which it is bonded are coming out of the paper, and the dashed triangle and the atom to which it is bonded are receding into

the paper. It is clear that, for the molecules in Figure 12-9A and B, no amount of rotation or manipulation will make these molecules superimposable. They are, therefore, different compounds.

The molecules in Figure 12-9A and B are *enantiomers* or *optical isomers.* They differ only in the way in which their atoms are bonded to the chiral carbon. It is important to define the stereochemical configuration of these two molecules, which can be done in one of two ways. In the first classificationâ€”the D(+)/L(â€“) systemâ€”molecules are named empirically based on the direction in which they rotate plane-polarized light. Each enantiomer will rotate plane-polarized light in one direction; the enantiomer that rotates light clockwise (to the right) is referred to as D(+), or

dextrorotatory; the L(â€“), or *levorotatory* enantiomer rotates plane-polarized light in a counterclockwise fashion (to the left).

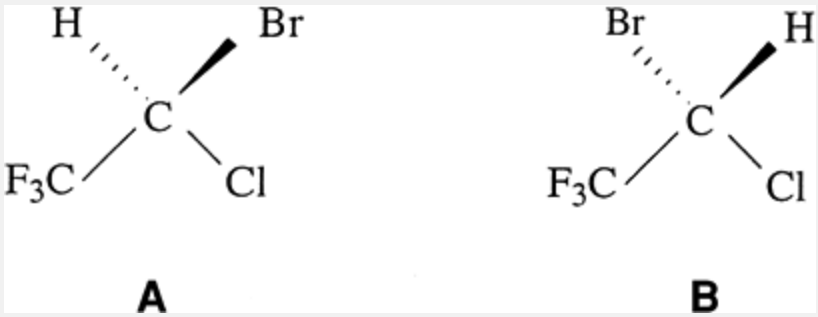


Figure 12-9. The graphic representation of the enantiomers of halothane.

Alternatively, enantiomers can be named using an elaborate and formal set of rules known as *Cahn-Ingold-Prelog.* These rules establish priority for substituents, based primarily upon molecular

weight, and then use the arrangement of substituents to assign a configuration. To correctly assign configuration in this system, the molecule is rotated into a projection in which the chiral carbon is in the plane of the page, the lowest priority substituent is directly behind the chiral carbon (and therefore behind the plane of the page), and the other three substituents are arranged around the chiral carbon. Figure 12-10 assigns Cahn-Ingold-Prelog priority to the halothane enantiomers of Figure 12-9, and rearranges the molecules in the appropriate projections.

If the priority of the substituents increases as one moves clockwise (to the right), the enantiomer is named *R* (Latin, *rectus* = right); if it increases as one moves counterclockwise, the enantiomer is named *S* (Latin, *sinister* = left). Thus, Figure 12-10A is the *R* enantiomer of halothane and Figure 12-10B is the *S* enantiomer.

Enantiomers have identical physical properties, such as boiling point, melting point, and solubility in different solvents; they differ from each other in only two significant ways. The first, as mentioned above, is that enantiomers rotate plane-polarized light in opposite directions; this point has no practical toxicologic importance. The second is that enantiomers may interact in very different ways with other three-dimensional structures (such as proteins and other cell receptors), which is of both pharmacologic and toxicologic significance.

Perhaps the best analogy to explain the toxicologic and pharmacologic importance of stereochemistry is that of the way a hand (analogous to a molecule of drug or toxin) fits into a glove (analogous to the biologic site of activity). Consider the left hand as the *S* enantiomer and the right hand as the *R* enantiomer. There are, qualitatively, three different ways in which the hand can fit into (interact with) a glove.

First, if the glove is very pliable (such as a disposable latex glove), it can accept either the left hand or the right hand without difficulty; this is the case for halothane, whose *R* and *S* enantiomers possess

equal activity. Second, if a glove is constructed with greater (but imperfect) specificity, one hand will fit well and the other poorly; this is the case for many substances, such as epinephrine and norepinephrine, whose naturally occurring levorotatory enantiomers are 10-fold more potent than the synthetic dextrorotatory enantiomers. Finally, a glove can be made with exquisite precision, such that one hand fits perfectly, while the other hand does not fit at all. This is the case for physostigmine, in which the (â€“) enantiomer is biologically active, whereas the (+) enantiomer is inactive.

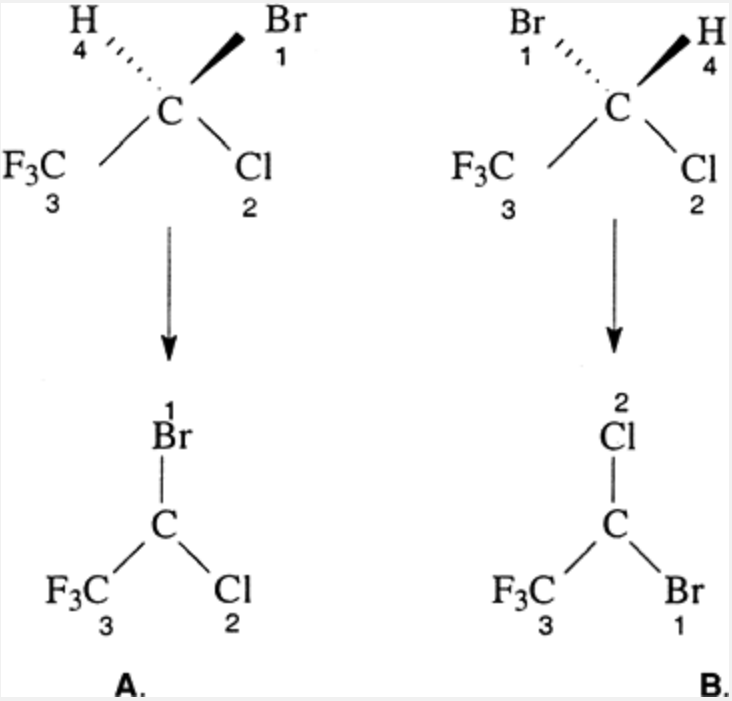


Figure 12-10. R and S enantiomers of halothane. A. The substituents increase in a clockwise fashion, so the configuration is R. B. The substituents increase in a counterclockwise fashion, so the configuration is S. In this projection, hydrogen atoms are directly behind the carbon atoms.

The above analogy is oversimplified, however, as one enantiomer of

a drug can be an agonist, while the other enantiomer is an antagonist. Dobutamine, for example, has one chiral carbon and thus two enantiomers. At the Î±$_1$ receptor, *l*-dobutamine is a potent agonist and *d*-dobutamine is a potent antagonist. Because dobutamine is marketed as a *racemic mixture* (a racemic mixture is a 1:1 mixture of enantiomers), however, these effects cancel each other out. Interestingly, at the Î²$_1$ receptor, *d*- and *l*-dobutamine have unequal agonist effects, with *d*-dobutamine approximately 10 times more potent than *l*-dobutamine.

Functional Groups

There is perhaps no concept in organic chemistry as powerful as that of the *functional group*. Functional groups are atoms or groups of atoms that confer similar reactivity on a molecule; of less importance is the molecule to which it is attached. Some representative functional groups in organic chemistry and toxicology are the *hydrocarbons* (*alkanes* and *alkenes*), *alcohols*, *carboxylic acids*, and *thiols.* These groups are discussed here because they illustrate important principles, not because this represents an exhaustive list of important functional groups in toxicology.

Hydrocarbons, as their name implies, consist of only carbon and hydrogen. *Alkanes* are hydrocarbons that contain no multiple bonds; they may be straight chain, usually designated by the prefix *n*- (Fig. 12-11A), or branched (isobutane, Fig. 12-11B). *Alkenes* contain carbon-carbon double bonds. *Alkynes*, which contain carbon-carbon triple bonds, are of limited toxicologic importance. Butane (lighter fluid) is an alkane, and gasoline is a mixture of alkanes.

Hydrocarbons are of toxicologic importance for two reasons: they are widely abused as inhalational drugs for their central nervous system depressant effects, and they can cause profound toxicity when aspirated. Although these effects are physiologically disparate, they are readily understood in the context of the chemical characteristics of the hydrocarbon functional group.

Hydrocarbons do not contain *polar groups*, or groups that introduce full or partial charges into the molecule; as such, they interact readily with other nonpolar substances, such as lipids or lipophilic substances. Hydrocarbons readily interact with the myelin of the CNS, disrupting normal ion channel function and

causing CNS depression. When aspirated, hydrocarbons interact with the fatty acid tail of surfactant, dissolving this protective substance and contributing to acute lung injury (Chaps. 79 and 102).

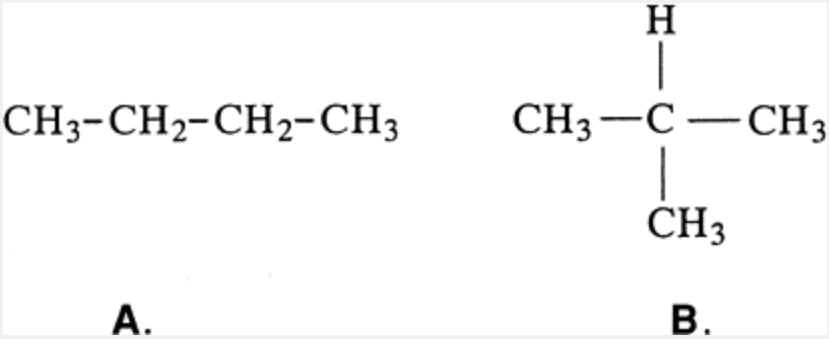


Figure 12-11. Two isomers of the 4 carbon alkane, butane. A. *n*-Butane. B. Isobutane.

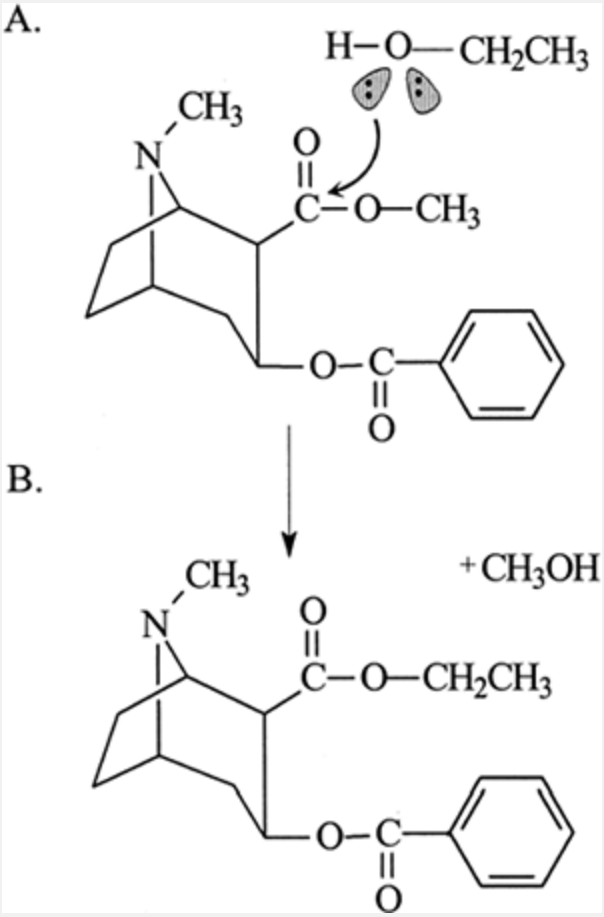


Figure 12-12. Reaction of cocaine with ethanol (A) to form cocaethylene and methanol (B).

Alcohols possess the hydroxyl (â€“OH) functional group, which adds polarity to the molecule and makes alcohols highly soluble in other polar substances, such as water. For example, ethane gas (CH_3CH_3) has negligible solubility in water, whereas ethanol (CH_3CH_2OH) is *miscible*, or infinitely soluble, in water. In biologic systems, alcohols are generally CNS depressants, but they can also act as nucleophiles. Ethanol may react with cocaine to form cocaethylene, a longer-acting and more vasoactive substance than cocaine itself (Fig. 12-12; see Chap. 74 for clinical details).

Alcohols can be primary, secondary, or tertiary, in which the reference carbon is bonded to 1, 2, or 3 carbons in addition to the hydroxyl group. Methanol, in which the reference carbon is bonded to no other carbons, is also a primary alcohol. The difference between primary, secondary, and tertiary structures is important, because although the alcohol functional group imparts many qualities to the molecule, the degree of substitution can affect the chemical reactivity. Primary alcohols can undergo multistep oxidation to form carboxylic acids, whereas secondary alcohols generally undergo one-step metabolism to form ketones, and tertiary alcohols do not readily undergo oxidation. This is a point of significant toxicologic importance, and is discussed in more detail later.

Alcohols can be named in many ways; the most common is to add *-ol* or *-yl alcohol* to the appropriate prefix. If the alcohol group is bonded to an interior carbon, the number to which the carbon is bonded precedes the suffix.

Carboxylic acids contain the functional group â€“COOH. As their name implies, they are acidic, and the pK_a of carboxylic acids are generally 4 or 5, depending on the substitution of the molecule. Carboxylic acids are capable of producing a significant anion gap metabolic acidosis, which is true whether the acids are endogenous or exogenous. Examples of endogenous acids are Î²-hydroxybutyric acid and lactic acid; examples of exogenous acids are formic acid (produced by the metabolism of methanol) and glycolic, glyoxylic, and oxalic acids (produced by the metabolism of ethylene glycol). Carboxylic acids are named by adding *-oic acid* to the appropriate prefix; the four-carbon straight-chain carboxylic acid is thus butanoic acid.

Thiols contain a sulfur atom, which usually functions as a nucleophile. The sulfur atom of *N*-acetylcysteine can regenerate glutathione reductase, and can also react directly with NAPQI to detoxify this electrophile. The sulfur atom of many chelating agents, such as dimercaprol and succimer, are nucleophiles that are very

effective at chelating electrophiles such as heavy metals. Thiols are generally named by adding the word *thiol* to the appropriate base. Thus, a 2-carbon thiol is ethane thiol.

As noted above, molecules with a given functional group often have more in common with molecules within the same functional group than they have in common with the molecules from which they were derived. The alkanes methane, ethane, and propane are straight chain hydrocarbons with similar properties. All are gases at room temperature, have almost no solubility in water, and have similar melting and boiling points. When these molecules are substituted with one or more hydroxide functional groups, they become alcohols: examples are methanol, ethanol, ethylene glycol (a *glycol* is a molecule that contains two alcohol functional groups), the primary alcohol 1-propanol, and the secondary alcohol 2-propanol (isopropanol). Each of these alcohols is a liquid at room temperature, and all are very water soluble. All have boiling points that are markedly different from the alkane from which they were derived, and quite close to each other.

In addition to conferring different physical properties on the molecule, the addition of the alcohol functional group also confers different chemical properties and reactivities. For example, methane, ethane, and propane are virtually incapable of undergoing oxidation in biologic systems. The alcohols formed by the addition of one or more hydroxyl groups, however, are readily oxidized by alcohol dehydrogenase (Fig. 12-13).

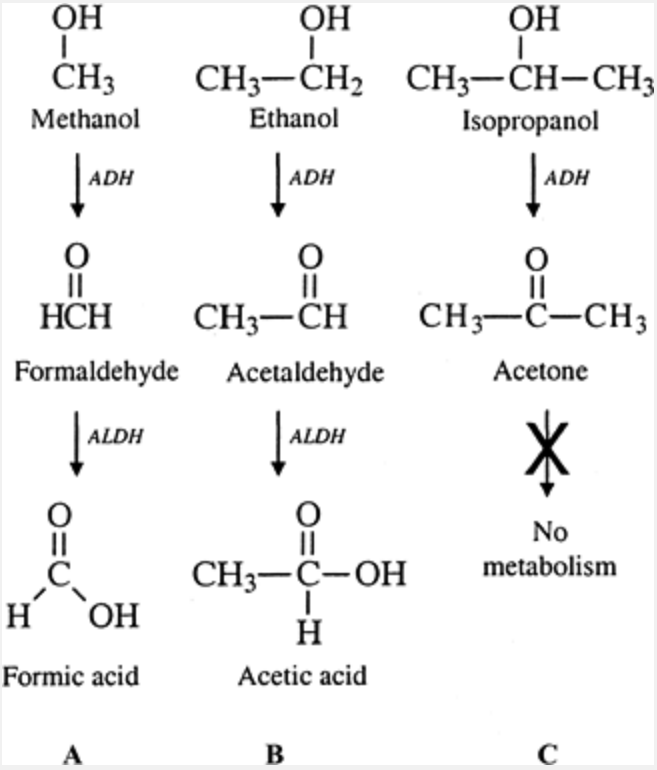


Figure 12-13. Oxidative metabolism of (A) methanol, (B) ethanol, and (C) isopropanol. Note that acetone does not undergo further oxidation in vivo. ADH = alcohol dehydrogenase; ALDH = aldehyde dehydrogenase.

As Figure 12-13 indicates, the oxidation of the primary alcohols methanol and ethanol results in the formation of *aldehydes* (an aldehyde is a functional group in which a carbon atom contains a double bond to oxygen and a single bond to hydrogen), whereas the oxidation of the secondary alcohol isopropanol resulted in the formation of a *ketone* (a ketone is a functional group in which a carbon is double-bonded to an oxygen atom and single-bonded to two separate carbon atoms). Although both aldehydes and ketones contain the *carbonyl group* (a carbon-oxygen double bond),

aldehydes and ketones are distinctly different functional groups, and have different reactivity patterns. For instance, aldehydes can undergo enzymatic oxidation to carboxylic acids (Fig. 12-13A and B), whereas ketones cannot (Fig. 12-13C).

It is here that recognition of functional groups helps to understand the potential toxicity of an alcohol. Methanol, ethanol, and isopropanol are all alcohols; as such, their toxicity before metabolism is expected to be (and in fact is) similar to that of ethanol, producing CNS sedation.

Because these toxins are primary and secondary alcohols, all three can be metabolized to a carbonyl compound, either an aldehyde or a ketone. Here, however, the functional groups on the molecules have changed; whereas aldehydes can be metabolized to carboxylic acids (which can, in turn, cause an anion gap acidosis), ketones cannot. It is for this reason that methanol and ethylene glycol can cause an anion gap acidosis, and isopropanol cannot (Chap. 103).

The concept of functional groups, however useful, has limitations. For example, although both formic acid and oxalic acid are organic acids, they cause different patterns of organ system toxicity. Formic acid is a mitochondrial toxin, and exerts effects primarily in areas (such as the retina or basal ganglia) that poorly tolerate an interruption in the energy supplied by oxidative phosphorylation. Conversely, oxalic acid readily precipitates calcium and is toxic to renal tubular cells, which accounts for the hypocalcemia and nephrotoxicity that are characteristic of severe ethylene glycol poisoning. The concept of the functional group is thus an aid to understanding chemical reactivity, but not a substitute for a working knowledge of the toxicokinetic or toxicodynamic effects of xenobiotics in living systems.

Summary

Understanding key principles in inorganic and organic chemistry

provides insight into the mechanisms by which xenobiotics act. The periodic table forms the basis for inorganic chemistry and provides insight into the expected reactivity, and to a large extent the clinical effects, of any element. A growing understanding of how reactive species are formed and how they interfere with physiologic processes has led to new insights in the pathogenesis and treatment of toxin-mediated diseases. Organic chemistry forms the basis of life, and is essential to an understanding of biochemistry and pharmacology. Because many xenobiotics are organic compounds there is direct relevance to medical toxicology.

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Chapter 13

Biochemical and Metabolic Principles

Kathleen A. Delaney

Xenobiotics are compounds that are foreign to a living system. Xenobiotic toxins injure living organisms by interfering with critical metabolic processes, by causing structural damage to cells, or by altering the cellular genetic material. The specific biochemical sites of actions that disrupt metabolic processes are well characterized for many xenobiotics although mechanisms of cellular injury are not. This chapter focuses on those general biochemical principles that are relevant to an understanding of the injurious effects of toxic xenobiotics. It also reviews the current understanding of the biotransformation enzymes and their clinical implications.

The capacity of a xenobiotic to produce injury in a living organism is affected by many factors that include its absorption, distribution, elimination, site of activation or detoxification, site of action, and capability to cross membranes to access a particular organ. Sites of action include the active sites of enzymes or receptor binding sites, DNA, and lipid membranes. The route of

exposure to a toxin may confine damage primarily to one organ: for example pulmonary injury that follows inhalation; GI injury that follows a caustic ingestion; or injury to the skin following dermal exposure. Hepatocellular injury results when a toxic xenobiotic is delivered to the liver, either by the portal venous system following ingestion, or by the hepatic artery that carries blood with xenobiotics absorbed from other sites of exposure. Various factors affect the ability of a toxin to access a particular organ. For example, many potentially toxic xenobiotics fail to produce injury because they cannot cross the bloodâ€“brain barrier. The negligible CNS effects of the mercuric salts when compared with organic mercury compounds are related to their inability to penetrate the CNS. Two potent biologic toxinsâ€”ricin (from *Ricinus communis*) and Î±-amanitin (from *Amanita phalloides*)â€”block protein synthesis through the inhibition of RNA polymerase. Their very different clinical effects are related to tissue accessibility. Ricin has a special binding protein that enables it to gain access to the endoplasmic reticulum in GI mucosal cells, where it inhibits cellular protein synthesis and causes severe diarrhea.[48] Î±-Amanitin is transported into hepatocytes by bile salt transport systems, where inhibition of protein synthesis results in cell death.[43 , 50] The electrical charge on a toxin also affects its ability to enter a cell. Unlike the ionized (charged) form of a xenobiotic, the uncharged form is lipophilic and passes easily through lipid cell membranes to enter the systemic circulation. The pK_a of an acidic xenobiotic (HA â† A^- + H^+) is the pH at which 50% of the molecules are charged (A^- form) and 50% are uncharged (HA form). A xenobiotic with a high pK_a is more likely to be absorbed in an acidic environment where the uncharged form predominates. Hence, the site of absorption of a toxin in the gastrointestinal tract; the acidic environment of the stomach or the alkaline environment of the small intestine; is affected by its pK_a . See Chap. 9 for a more extensive discussion of basic principles of pharmacokinetics.

General Enzyme Concepts

The capability to detoxify and eliminate both endogenous toxins and exogenous xenobiotics is crucial to the maintenance of physiologic homeostasis and normal metabolic functions for all organisms. A simple example is the detoxification of cyanide, a potent cellular poison that is ubiquitous in the environment and is also a product of normal metabolism. Mammals have evolved the enzyme rhodanese, which combines cyanide with thiosulfate to create the less toxic, renally excreted compound thiocyanate.[85]

The majority of xenobiotics have lipophilic properties that facilitate absorption across cell membranes in organs that are portals of entry to the body: the skin, GI tract, and lungs. The liver has the highest concentration of enzymes that metabolize xenobiotics. Enzymes found in the liquid matrix of hepatocytes that are specific for alcohols, aldehydes, esters, or amines act on many different substrates within these broad classes. Enzymes that act on more lipophilic xenobiotics, including the CYP (formerly cytochrome P450) enzymes, are embedded in the lipid membranes of the endoplasmic reticulum. When cells are mechanically disrupted and centrifuged, these membrane-bound enzymes are found in the pellet, or microsomal fraction; hence, they are called microsomal enzymes. Enzymes located in the liquid matrix of cells are called cytosolic enzymes and are found in the supernatant when disrupted cells are centrifuged. Cytosolic enzymes are present in all tissues.[42]

Biotransformation Overview

The term *biotransformation* refers to the alteration of a xenobiotic as a result of enzyme action.[51] Biotransformation usually results in â€œdetoxification,â€• a reduction in the toxicity of a substance and its removal from the body. In some cases, however, the metabolites produced may be more toxic than the parent

xenobiotic. In this case, the biotransformation results in â€œtoxicationâ€• or â€œmetabolic activation.â€•[82] A single xenobiotic may be a substrate for biotransformation by

several metabolic pathways, some resulting in detoxification and others in metabolic activation. The predominant pathway for the biotransformation of an individual toxin is determined by many factors that include the availability of cofactors, the effect of substrate concentration on the rate of substrate metabolism (reflected by the K_m [Michaelis-Menten dissociation constant] of the biotransformation enzyme and by saturation effects), changes in the concentration of the enzyme caused by induction, and the presence of inhibitors.[82] The production of toxic metabolites by a given biotransformation process is also affected by the concentration of protective agents such as glutathione.

The likelihood that a xenobiotic will undergo biotransformation depends on its chemical nature. Ionized compounds such as carboxylic acids are less likely to cross a lipid membrane to enter the body. When they do, the kidneys rapidly eliminate them. Very volatile compounds, such as dichloromethane, are expelled promptly via the lungs. Neither of these groups of xenobiotics undergo significant enzymatic metabolism. Nonpolar, lipophilic xenobiotics that are less soluble in aqueous fluids require biotransformation to more water-soluble compounds before they can be excreted.[51]

Most biotransformation reactions have two sequential phases. Phase I reactions add functional groups to lipophilic xenobiotics, converting them into more chemically reactive metabolites. This is usually followed by phase II reactions that conjugate the reactive products of phase I with other molecules that render them more water soluble, detoxifying the xenobiotic and facilitating its elimination. Some xenobiotics undergo only a phase I or a phase II reaction.

Oxidation Overview

Much of the activity that occurs during biotransformation or within critical metabolic pathways results in the oxidation or reduction of carbon. Oxidation involves the transfer of electrons from a substrate molecule to an electron-seeking (electrophilic) molecule, leading to reduction of the electrophilic molecule and oxidation of the substrate. These oxidation-reduction reactions are often coupled to the cyclical oxidation and reduction of a cofactor, such as the pyridine nucleotides, NADPH/$NADP^+$ (nicotinamide adenine dinucleotide phosphate) or NADH/NAD^+ (nicotinamide adenine dinucleotide). These nucleotides alternate between their reduced (NADPH, NADH) and oxidized ($NADP^+$, $NADH^+$) forms. The terminal transfer of electrons to oxygen also provides a mechanism for oxidation of substrates.

Electrons resulting from the catabolism of energy sources are extracted by NAD^+ , forming NADH. NADH transports the electrons into the mitochondria where they enter the cytochrome-mediated electron transport system. This results in the production of adenosine triphosphate (ATP), the reduction of molecular oxygen, and the regeneration of NAD^+ , a process that is critical to the maintenance of oxidative metabolism. NADPH serves primarily to carry electrons from the oxidative reactions of catabolism to the synthetic (anabolic) reactions of biosynthesis. NADPH is also coupled to the reduction of glutathione, which plays an important role in the protection of cells from oxidative damage. The main source of NADPH is the pentose phosphate pathway (also called the hexose-monophosphate shunt), an alternative pathway for the oxidation of glucose.

The oxidation state of a specific carbon atom can be determined by counting the number of carbon and hydrogen atoms to which the carbon atom is connected. The more reduced a carbon, the higher the number of carbon-hydrogen bonds. For example, the carbon in methanol (CH_3 OH) has three carbon-hydrogen bonds

and is more reduced than the carbon in formaldehyde (H_2 C = O), which has two. Carbon-carbon double bonds count as one bond.

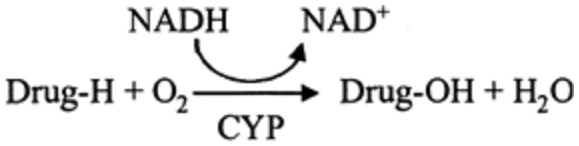

Figure 13-1. A common oxidation reaction catalyzed by CYP enzymes: the hydroxylation of Drug-H to Drug-OH.

Phase I Biotransformation Reactions

Phase I reactions are predominantly oxidation reactions that add functional groups suitable for conjugation during phase II. These include hydroxyl (-OH), sulfhydryl (-SH), amino (-NH_2), aldehyde (-COH), or carboxyl (-COOH) moieties.[42] Elements such as nitrogen, sulfur, and phosphorus that do not contain carbon are also oxidized in phase I reactions. Other phase I reactions result in hydrolysis, hydration, and dehalogenation.[82]

The CYP enzymes are cytochromes bound to the lipid membranes of the endoplasmic reticulum that use a cyclical transfer of electrons between oxidized (Fe^{3+}) or reduced (Fe^{2+}) forms of iron. They are responsible for the majority of phase I oxidative biotransformation reactions. Membrane-bound flavin monooxygenase (FMO), another NADPH-dependent oxidase located in the endoplasmic reticulum, makes an important contribution to the oxidation of amines and other compounds containing nitrogen, sulfur, or phosphorus.[51] A common oxidation reaction catalyzed by CYP enzymes is illustrated by the hydroxylation or monooxidation of a foreign compound R-H to R-OH (Fig. 13-1).[46]

The alcohol, aldehyde, and ketone oxidation systems are predominantly cytosolic enzymes that catalyze phase I oxidation-reduction reactions using NADH/NAD^+ .[30 , 44 , 49 , 82] Two classic phase I oxidation reactions are the metabolism of ethanol to

acetaldehyde by alcohol dehydrogenase (ADH) followed by the metabolism of acetaldehyde to acetic acid by aldehyde dehydrogenase (ALDH) (Fig. 13-2). Alcohol dehydrogenase, which oxidizes many different alcohols, is found in the liver, lungs, kidney, and gastric mucosa.[2 , 49] Females have less ADH in their gastric mucosa than males. This results in decreased first-pass metabolism of alcohol and increased alcohol absorption. Some populations, particularly Asians, are deficient in ALDH, resulting in increased acetaldehyde levels and symptoms of the acetaldehyde syndrome.[2 , 49]

$$CH_3CH_2OH + NADPH + H^+ + O_2 \xrightarrow{CYP2E1} CH_3CHO + NADP^+ + 2\,H_2O$$

$$CH_3CH_2OH + NAD^+ \xrightarrow{\text{Alcohol dehydrogenase}} CH_3CHO + NADH + H^+$$

Figure 13-2. Conversion of ethanol to acetaldehyde by CYP2E1 that uses reduced NADPH and oxygen and by alcohol dehydrogenase that uses oxidized NAD^- . This illustrates how NAD and NADP can function in oxidation reactions in both their oxidized and reduced forms. Alcohol dehydrogenase has a low K_m for ethanol and is the predominant metabolic enzyme in moderate drinkers.

Overview of the CYP Enzymes

The most numerous and important of the enzymes involved in phase I oxidation reactions are the CYP enzymes. This nomenclature derives from the complex cytochrome protein structure that is the basic unit of the enzyme and the spectrophotometric characteristics of its associated heme molecule. When bound to carbon monoxide, the maximal absorption spectrum of the reduced CYP (Fe^{2+}) enzyme occurs at 450 nm.[59 , 62] CYP enzymes, which incorporate 1 atom of oxygen

into the substrate and 1 atom into water, were once called â€œmixed-function oxidases.â€• This activity is now referred to as a â€œmicrosomal monooxygenation reaction.â€• [59, 82] These biotransformation CYP enzymes, bound to the lipid membranes of the smooth endoplasmic reticulum, are distinct from the cytochromes that comprise the mitochondrial electron transport chain.[59]

Although most of the CYP isozymes are found in the liver, high levels can be found in extrahepatic tissues, particularly the gastrointestinal tract.[19] The lungs,[54, 59] heart,[63] and brain[63] also have discernible amounts of CYP isozymes. Each tissue has a unique profile of CYP enzymes that determines its sensitivity to different xenobiotics.[19] The CYP enzymes in the enterocytes of the small intestine actually contribute significantly to â€œfirst-passâ€• metabolism of some xenobiotics.[41, 59] Corrected for tissue mass, the CYP enzyme system in the kidneys is as active as that in the liver. The activity of the renal CYP enzymes is decreased in patients with chronic renal failure, with relative sparing of CYP1A2, 2C19, and 2D6 compared with 3A4 and 2C9.[13]

More than 2500 different genes coding for CYP enzymes have been identified.[59, 60] CYP enzymes are categorized according to the similarities of their amino acid sequences. They are in the same â€œfamilyâ€• if they are more than 40% similar, and same â€œsubfamilyâ€• if they are more than 55% similar. Families are designated by an Arabic numeral, subfamilies by a capital letter, and each individual enzyme (or isozyme) by another numeral, resulting in the nomenclature CYPnXm for each isozyme. For example, CYP3A4 is an isozyme of the CYP3 family and of the CYP3A subfamily.[27, 58] CYP enzymes catalyze a diverse number of reactions that include both biosynthetic and xenobiotic biotransformation. Most xenobiotic metabolism is done by the CYP1, CYP2, and CYP3 families, with a small amount done by the CYP4 family.[13, 84] It is estimated that the total number of exogenous CYP enzyme substrates may exceed 200,000

chemicals.[47]

Nearly 90% of oxidative transformation of xenobiotics is accomplished by 6 CYP enzymes: 1A2, 2C9, C19, 2D6, 2E1, and 34A (Table 13-1).[59 , 75] The approximate amounts of liver CYP enzymes are 3A4 (40â€“55%), 2D6 (30%), 2C9 and 2C19 (10â€“20%), 2E1 (7%), and 1A2 (2%).[46 , 62]

Percent of liver CYPs
2%

10â€“20%
30%
7%
40â€“55%
Contribution to enterocyte CYPs
Minor
Minor
Minor
Minor
Minor
70%
Percent of metabolism of typically used drugs
2â€“15%
10%

25â€“30%

50â€“60%
Organs other than liver with isozyme
Lung, intestine, stomach
Nasal mucosa, stomach, heart, intestine
Nasal mucosa, heart, intestine
Lung, heart, intestine
Lung, intestine

Nasal mucosa, lung, stomach, intestine
Polymorphism[a]
No
Yes
Yes
Yes
No
No
Poor metabolizer
African American

1â€“2%
20%
2â€“8%

Asian

1â€“2%
15â€“20%
<1%

White

1â€“3%
3â€“5%
5â€“10%

Ultra extensive metabolizer
Asian

1%

Ethiopian

30%

Northern Europeans

1â€“2%

Southern Europeans

10%

[a] Enzyme variations can exist even in those listed as â€œNoâ€• for polymorphism.

Isozyme 1A2 2C9 2C19 2D6 2E1 3A4

TABLE 13-1. Characteristics of Different CYP Isozymes[1,13,19,46,47,54,59,62,63]

Substrate and CYP Enzyme Specificity

In vitro models, which are relatively inexpensive and involve no human subjects, have been used to define the specificities of CYP enzymes for their substrates and inhibitors.[28] Unfortunately, the ability of an enzyme to metabolize a substrate in a test tube does not always predict its role in the cell. These models use substrate and inhibitor concentrations that are much higher than would be encountered in vivo, and the mathematical models that extrapolate to clinically relevant processes produce conflicting results.[28] This has resulted in discrepancies in reported substrates, inhibitors, and inducers of specific CYP enzymes. Discordance between genetic type and phenotypic expression is routinely observed.[6]

The substrate specificity of a CYP enzyme greatly affects its role in biotransformation.[29] Some CYP enzymes, particularly those involved in biosynthesis, are highly selective. This is the case for CYP21A2, a mitochondrial enzyme that specifically catalyzes the 21-hydroxylation of progesterone, an important step in steroid synthesis.[31] Most CYP enzymes involved in xenobiotic biotransformation have low substrate specificity and can metabolize many substances.[29] This lack of substrate specificity allows the ongoing biotransformation of a substance in spite of deficiency or inhibition of a specific enzyme. When a substrate can be biotransformed by more than one CYP enzyme, the enzyme that has the highest affinity for the substrate usually predominates at low substrate concentrations, while enzymes with lower affinity may predominate at high concentrations. This transition is usually

concomitant with, but is not dependent on, the saturation of the catalytic capacity of the primary enzyme as it reaches its maximum rate of activity.[29, 31] The K_m, which is defined as the concentration of enzyme that results in 50% of maximal enzyme activity, describes this property of enzymes. For example, ADH in the liver has a very low K_m for ethanol, making it the primary

metabolic enzyme for ethanol when concentrations are low.[49] Ethanol is also biotransformed by the CYP2E1 enzyme. CYP2E1 has a high K_m for ethanol and only functions when ethanol levels are high. It accounts for only a small fraction of ethanol metabolism in moderate drinkers, but accounts for significantly more biotransformation in alcoholics. As another example, diazepam is metabolized by both CYP2C19 and CYP3A4. However, the affinity of CYP3A4 for diazepam is so low (ie, the K_m is high) that the majority of diazepam is metabolized by CYP2C19.[37]

The CYP enzymes that biotransform a specific xenobiotic cannot be predicted by its drug class. Whereas fluoxetine and paroxetine are both major substrates and potent inhibitors of CYP2D6, sertraline is not extensively metabolized and exhibits minimal interaction with other antidepressants.[5] The majority of Î²-hydroxy-Î²-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors are metabolized by CYP3A4 (lovastatin, simvastatin, and atorvastatin); however, fluvastatin is metabolized by CYP2D6 and pravastatin undergoes virtually no CYP enzyme metabolism at all.[32] Among angiotensin-II receptor blockers, losartan and irbesartan are metabolized by CYP2C9, while valsartan, eprosartan, and candesartan are not substrates for any CYP enzyme. In addition, losartan is a prodrug whose active metabolite provides most of the pharmacologic activity, while irbesartan is the primary active compound. For these two drugs the inhibition of CYP2C9 is predicted to have opposite effects.[24]

The specificity of enzyme inhibition may be affected by the concentration of an inhibitor. Omeprazole is a potent inhibitor of CYP2C19, CYP2C9, and CYP3A4.[32, 40] At lower concentrations omeprazole selectively inhibits CYP2C19, a specificity that is lost at higher concentrations.[28] The induction of CYP3A4 by rifampin in HIV-positive patients is associated with decreases in blood concentrations of the protease inhibitors saquinavir and ritonavir by 80% and 35%, respectively.[27]

The substrate selectivity of some CYP enzymes is determined by molecular, electrical, and physicochemical properties of the substrates. The CYP1A subfamily has greater specificity for planar polyaromatic substrates such as benzo[*a*]pyrene. The CYP2E subfamily targets low-molecular-weight, hydrophilic xenobiotics, whereas CYP3A4 has increased affinity for lipophilic compounds. Substrates of CYP2C9 are usually weakly acidic, whereas those of CYP2D6 are more basic.[47] High specificity can also result from key structural considerations such as stereoselectivity. Some xenobiotics are racemic mixtures of stereoisomers. These may be substrates for different CYP enzymes and have distinct affinities for the enzymes, resulting in different rates of metabolism. For example, R-warfarin is biotransformed by CYP3A4 and CYP1A2, whereas S-warfarin is metabolized by CYP2C9.[13 , 82]

Genetic Polymorphism

A simple model of the human genome has a DNA sequence for each gene, with a corresponding allele on each chromosome.[89] For enzymes, the translation of these DNA sequences into proteins results in the functionally defined phenotypic expression of the genes. When a genetic variation occurs, the result is either a rare defect or a polymorphism. A polymorphism is a genetic change that occurs in at least 1% of the human population.[89] A genetic change in a biotransformation enzyme may result in an alteration of the activity rate of that enzyme.[6 , 89]

The genetic polymorphism of human populations results in very significant differences in the abilities of individuals to biotransform specific xenobiotics. Differences in biotransformation capacity that lead to toxicity, once thought to be â€œidiosyncratic,â€• are likely caused by these inherited, unmeasured differences in the genetic complement of the individual. A familiar consequence of genetic polymorphism is the inheritance of rapid or slow â€œacetylatorâ€• phenotypes. Acetylation is a phase II

biotransformation that is especially important for the biotransformation of amines (R-NH_2) or hydrazines (NH_2 â€“NH_2). Slow acetylators may be at increased risk of toxicity associated with the slower biotransformation of nitrogen-containing xenobiotics such as isoniazid (INH), procainamide, hydralazine, and sulfonamides.[22 , 66]

Three major metabolizer phenotypes are recognized: extensive (normal), poor (slow), and ultraextensive (rapid).[46 , 58 , 89] The CYP2C19 and CYP2D6 genes are highly polymorphic (Table 13-1).[36] The CYP2D6 gene, which has 76 different alleles, is associated with ultraextensive metabolism in 30% of Ethiopians, 10% of Southern Europeans, and 1â€“2% of Northern Europeans.[36 , 46] It is associated with poor metabolism in 5â€“10% of whites, 2â€“8% of African Americans, and fewer than 1% of Asians.[13] The poor metabolizer phenotype of the CYP2C19 gene is found in 3â€“5% of whites, 15â€“20% of Asians, and 20% of African Americans. The CYP2C9 gene exhibits only mild polymorphism; poor metabolism occurs in 1â€–3% of whites and in 1â€–2% of Asians or African Americans.[13 , 59] Other CYP genes have varied degrees of polymorphism. In some cases there is discordance between the genetically determined biotransformation capacity and its phenotypic expression. This creates confusion when genotype alone is used to model expressions of human biotransformation capability.[6]

Inherited variations in the genes that code for enzymes in important metabolic pathways affect the toxicity of a xenobiotic by altering the response to or the disposition of the xenobiotic. A classic example of altered response to a xenobiotic is seen in glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD is a critical enzyme in the pentose phosphate shunt, a metabolic pathway located in the red blood cell (RBC) that produces NADPH, which is required to maintain RBC glutathione in a reduced state. In turn, reduced glutathione prevents hemolysis during oxidative stress.[82] In patients deficient in G6PD, oxidative stress produced

by electrophilic or oxidative xenobiotics results in hemolysis.

Besides being substrates, xenobiotics may induce or inhibit the activity of different CYP enzymes.[89] A xenobiotic may inhibit or induce the activity of an enzyme even though it is not a substrate at that CYP site. For example, quinidine is biotransformed by CYP3A4, but it is a potent inhibitor of CYP2D6.[54]

Heterogeneity of CYP enzymes results in differences in metabolic activity between individual patients. A prodrug may not be metabolized to its active form because the patient is a poor metabolizer or is taking a xenobiotic that inhibits the respective CYP enzyme.[27] Conversely, a drug may not reach a therapeutic level because the patient is an ultrarapid metabolizer or is taking a second drug that induces the respective CYP enzyme.[89]

Pharmacogenetics is the study of genetic variations that affect differences in individual responses to medications. This refers to the full spectrum of genes that determine drug efficacy and safety, including genetic factors that determine differences in drug distribution, target

proteins, and metabolism.[89] The goal of the study of pharmacogenetics is to characterize an individual patient's biotransformation enzyme genotype to allow prediction of toxicity and optimize the therapeutic effects of important drugs.[89]

Induction and Inhibition of CYP Enzymes

Enzyme induction is usually caused by increased expression of CYP genes, resulting in a net increase of enzyme protein synthesis. Induction of an enzyme results in more rapid biotransformation of a xenobiotic that is affected by the same enzyme. Inducer xenobiotics are often substrates for the affected CYP enzyme, amplifying the detoxification response during prolonged periods of

xenobiotic challenge.[86] Increased enzyme synthesis starts with the binding and activation of chromosomal â€œnuclear receptorsâ€• by inducer xenobiotics, which leads to increased transcription of gene specific messenger RNA.[46, 84] Nuclear receptors include PXR in the CYP3A family, CAR in the CYP family, and AhR in the CYP1A subfamily. The observation that the induction of CYP1A1 by omeprazole is not mediated by the AhR nuclear receptor suggests that there are other mechanisms of gene induction that do not use nuclear receptors.[58]

Because the clinical manifestations of enzyme induction rely on protein synthesis, there is a time delay in the onset and offset relative to starting and stopping the inducing xenobiotic. In addition, xenobiotics with long half-lives require longer periods to reach steady-state concentrations that maximize induction. CYP enzyme induction caused by xenobiotics with long half-lives, such as phenobarbital or fluoxetine, may fully manifest only after weeks of exposure. Conversely, xenobiotics with short half-lives, such as rifampin or venlafaxine, can reach maximum induction within days.[13, 27]

Similar pharmacokinetic considerations affect the clinical manifestations of enzyme inhibition. Competitive inhibition as a result of binding at substrate sites usually begins within hours.[13] Because the degree of inhibition correlates with the concentration of the involved xenobiotic, the time required to reach the maximal effect correlates with the half-life of the xenobiotic in question.[13] Although competitive inhibition is a common form of CYP enzyme function, it is the least likely mechanism of inhibition to be clinically relevant.[24]

Another mechanism of inhibition results from competition between one xenobiotic and a metabolite of a second xenobiotic at its CYP enzyme substrate binding site. For example, the metabolites of clarithromycin and erythromycin produced by CYP3A inhibit further CYP3A activity. The effect is reversible and usually increases with

repeated dosing. A relatively rare third mechanism is the irreversible inhibition of a CYP enzyme by the reactive metabolite of a second xenobiotic at its substrate binding site. This so-called suicide inhibition results in the destruction of the bound CYP enzyme. Biotransformation by the affected CYP enzyme does not resume until new enzyme is produced.[24 , 79]

Drugâ€“Drug and Drugâ€“Chemical Interactions with CYP Enzymes

Adverse reactions to medications, including drugâ€“drug interactions, are estimated to be one of the top 10 causes of death in hospitalized patients, the risk of which increases with the number of drugs taken. Fifty percent of adverse reactions are possibly related to pharmacogenetic factors.[89] The most significant interactions are mediated by CYP enzymes.[59]

Drugâ€“drug interactions that involve CYP enzymes can be either pharmacodynamic or pharmacokinetic in nature.[13] Pharmacodynamic interactions occur when the mechanism of action of one xenobiotic enhances or diminishes the effect produced by a second xenobiotic. Pharmacokinetic interactions occur when the effect of one xenobiotic alters the absorption, distribution, metabolism, and/or elimination of another, leading to a change in the effective concentration of the second xenobiotic at its site of action.[13] Drug interactions will be more significant if the xenobiotics have significant CYP enzyme specificity. For example, the potent and specific CYP3A inhibitor itraconazole prevents the metabolism of astemizole and simvastatin. Blockade of the biotransformation of these CYP3A-specific substrates has resulted in torsade de pointes dysrhythmias or rhabdomyolysis.[1]

Many drugâ€“drug interactions are not apparent in initial drug studies. Because of the overlapping substrate specificities of many CYP enzymes, drugâ€“drug interactions are not predictable even

when the specific enzyme responsible for the metabolism of a drug is known and can be quantitated. The life-threatening interactions between terfenadine and ketoconazole, both metabolized by CYP3A4, were not appreciated until 11 years after terfenadine was marketed.[59 , 75]

Many environmental and â€œnondrugâ€• xenobiotics interact with the CYP enzymes. St. John's wort, an herb marketed as a natural antidepressant, induces multiple CYP enzymes including 1A2, 2C9, and 3A4. The induction of CYP3A4 by St. John's wort is associated with a 57% decrease in effective serum levels of Indinavir when given comcomittantly.[65] Xenobiotics contained in grapefruit juice, such as naringin and furanocoumarins, are both substrates and inhibitors of CYP3A4. They inhibit the first-pass metabolism of CYP3A4 substrates by inhibiting CYP3A4 activity in both the gastrointestinal tract and the liver.[17] Polycyclic hydrocarbons found in charbroiled meats and in cigarette smoke induce CYP1A2. For smokers who drink coffee, levels of caffeine, a CYP1A2 substrate, will be increased following cessation of smoking.[46]

Specific CYP Enzymes

CYP1A2

This enzyme is involved in the metabolism of 15% of all pharmaceuticals used today.[13] As noted above, the CYP1 family is induced by polycyclic hydrocarbons found in cigarette smoke and charred food. This family bioactivates several procarcinogens including benzo[*a*]pyrene.[62] Xenobiotics activated by CYP1 enzyme in the gastrointestinal tract are linked to colon cancer.[59]

CYP3A4

CYP3A4 is the most abundant CYP in the human liver, comprising anywhere from 40â€“55% of the mass of hepatic CYP enzymes.[13 ,

[32, 46] The CYP3A4 enzyme is the most common one found in the intestinal mucosa and is responsible for much first-pass drug metabolism.[13]

More than 120 xenobiotics are metabolized by CYP3A4. It is involved in the biotransformation of 50â€“60% of all pharmaceuticals.[60, 86] Substrates include dihydropyridine calcium channel blockers, cyclosporine, cisapride, many opioids, and many HMG-CoA reductase inhibitors.[32] An excellent example of an adverse drug interaction related to this enzyme is the QT interval prolongation and spontaneous ventricular tachycardia that occurred in patients taking terfenadine or astemizole in combination with ketoconazole or erythromycin.[64, 75] Ketoconazole inhibits CYP3A4, causing a 15- to 72-fold increase in serum levels of terfenadine.[59]

Bioflavonoids in grapefruit juice decrease metabolism of some substrates by 5- to 12-fold.[13, 27, 59] The CYP3A4 enzyme does not exhibit genetic polymorphism; however, there are large interindividual variations in enzyme levels.[27]

CYP2D6

Approximately one-third of human CYP enzymes are in the CYP2 enzyme family, which, with 76 alleles, exhibits the greatest degree of genetic polymorphism.[46] Twenty-five percent of all drugs used today, including 50% of the commonly used antipsychotics, are substrates for CYP2D6. It is sometimes called debrisoquine hydrolase as it was first identified with studying the metabolism of the antihypertensive agent debrisoquine.[13, 36, 59]

Approximately 5â€“10% of whites and 2â€“8% of African Americans are poor metabolizers of CYP2D6 substrates.[13] Perhexiline, an antianginal agent marketed in Europe in the 1980s, caused severe liver disease and peripheral neuropathy in persons with a demonstrated inability to metabolize debrisoquine.[74]

Decreased activity of CYP2D6 was implicated in the development of severe lactic acidosis in some patients taking phenformin.[61]

CYP2E1

This enzyme comprises 7% of the total CYP enzyme content in the human liver.[62] Although not considered to demonstrate genetic polymorphism, genetic changes account for a 2-fold increase in nasopharyngeal cancer in Chinese persons who smoke. Besides CYP1A2, this is the only other CYP enzyme linked to cancer.[59] CYP2E1 is induced by a number of xenobiotics including ethanol, phenobarbital, isoniazid, phenytoin, and cigarette smoke.[45, 90] The induction of CYP2E1 is associated with increased liver injury by reactive metabolites of carbon tetrachloride and of bromobenzene (Chap. 26).[33] During the metabolism of substrates that include carbon tetrachloride, ethanol, acetaminophen, paranitrophenol, aniline, and *N* -nitrosomethylamine, CYP2E1 actively produces free radicals and other reactive metabolites associated with adduct formation and lipid peroxidation (Chap. 26).[20] CYP2E1 is inhibited by acute elevations of ethanol, an effect illustrated by the capacity of acute administration of ethanol to inhibit the metabolism of acetaminophen.[10] The chronic ingestion of ethanol hastens its own metabolism through enzyme induction.

CYP2C9

The CYP2C9 enzyme is the most abundant isozyme of the CYP2C enzyme family which, with CYP2C19, comprises approximately 10â€“20% of the CYP enzymes in the liver.[46] This enzyme is associated with polymorphism; poor metabolism occurs in 1â€“3% of whites and in 1â€–2% of Asians and African Americans.[13, 59] This enzyme biotransforms warfarin-S, the most active isomer of warfarin. There is an association between slow metabolism and an increased risk of bleeding in patients on warfarin.[3, 52]

Phase II Biotransformation Reactions

Phase II biotransformation reactions are synthetic reactions that catalyze rapid conjugation of the products of phase I reactions with endogenous molecules such as glucuronic acid, glutathione, sulfate, or some amino acids, such as glycine, glutamic acid, and taurine. This conjugation terminates the pharmacologic activity of the xenobiotic and greatly increases its water solubility and excretability.[51, 82] Most phase II reactions occur in the cytosol and are faster than phase I reactions.[51]

Glucuronides are the most common endogenous conjugating agents.[51] Glucuronyl transferase conjugates glucuronic acid donated by uridine diphosphate glucuronic acid (UDPG), with the nitrogen, sulfhydryl, hydroxyl, or carboxyl groups of foreign or endogenous compounds. The more polar conjugated xenobiotics are readily eliminated because of the ionized carboxyl group that is recognized by both biliary and renal organic acid active transport systems. Smaller conjugates usually undergo renal elimination, whereas larger ones undergo biliary elimination.[51]

Sulfate conjugates are highly ionized and very water soluble. The addition of sulfate donated by oxidized cysteine to the hydroxyl group of alcohols and aryl amines is a common mechanism for phase II detoxification.[51] The biotransformation of phenol is an interesting example of the effect of pharmacokinetics of biotransformation enzymes on the metabolism of an individual substrate. The affinity of sulfate for phenol is very high (the K_m is low), so that when low doses of phenol are administered, the predominant excretion product is the sulfate ester. Because the capacity of this reaction is readily saturated, when high doses of phenol are administered glucuronidation becomes the main method of detoxification.

Glutathione-S transferases catalyze the conjugation of the tripeptide glutathione (glycine-glutamate-cysteine, or GSH) with a

diverse group of reactive, electrophilic metabolites of phase I CYP enzymes. The reactive compounds initiate an attack on the sulfur group of cysteine, resulting in conjugation with GSH that detoxifies the reactive metabolite. Some GSH-conjugates are directly excreted. More commonly, the glycine and glutamate residues are cleaved and the remaining cysteine is acetylated to form an *N* -acetylcysteine (mercapturic acid) conjugate that is readily excreted in the urine. A familiar example of this detoxification is the avid binding of *N* -acetyl-*p* -benzoquinoneimine (NAPQI), the toxic metabolite of acetaminophen, by glutathione.[8, 11]

Mechanisms of Cellular Injury

Ideally, potentially toxic metabolites produced by phase I reactions are detoxified during the phase II reactions. When detoxification goes awry because of overproduction of a reactive intermediate or a deficiency of phase II substrates, toxic intermediates can cause cellular injury. The following sections review mechanisms of cellular injury related to xenobiotic biotransformation.

Synthesis of Toxins or â€œMistakenâ€• Toxins

Sometimes a xenobiotic is mistaken for a natural substrate by synthetic enzymes that act on the xenobiotic and facilitate its injurious effects. The incorporation of the rodenticide fluoroacetate into the tricarboxylic acid cycle is an example of this mechanism of toxic injury (Fig. 13-3). Another example is illustrated by analogs of purine or pyrimidine bases that are phosphorylated and inserted into growing DNA or RNA chains, resulting in mutations and disruption of cell division. This mechanism is used therapeutically with 5-fluorouracil (5-FU), an antitumor, pyrimidine base analog. When phosphorylated to 5-fluoro-dUTP and incorporated into

growing DNA chains, it causes structural instability of the cellular DNA and inhibits tumor growth.[72]

Injury by Metabolites at Distant Sites

Toxic metabolites may be synthesized at one site and transported to other target sites where they cause injury. Cyanide formed by the hepatic metabolism of acetonitrile nail removers produces toxicity

at distant sites.[15] Benzene is biotransformed in the liver to benzoquinone and dihydroxybenzene intermediates, which subsequently injure the bone marrow.[88] 2,5-Hexanedione, the neurotoxic metabolite of *n* -hexane and methyl-*n* -butyl ketone, is also produced in the liver, far from the site where injury occurs.[20]

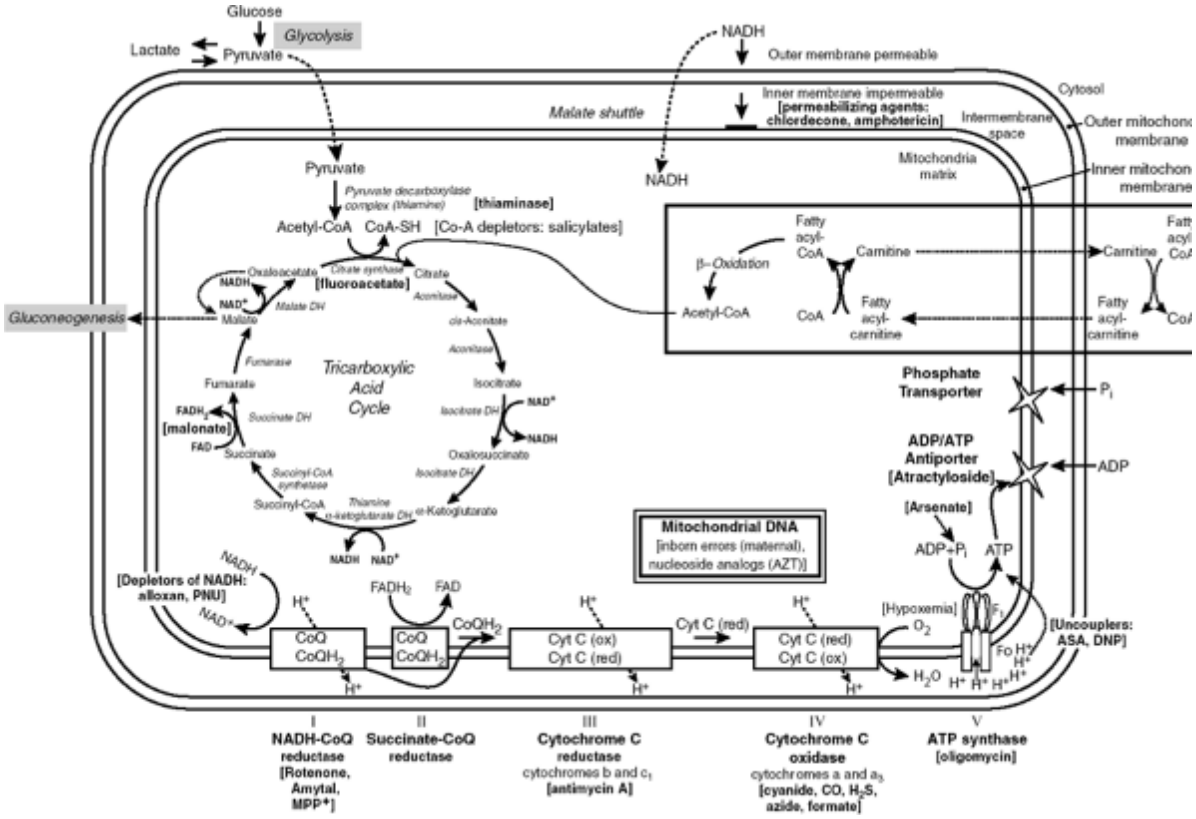

Figure 13-3. Pyruvate is converted to acetylcoenzyme A (acetyl-

CoA), which enters the Krebs cycle as shown. Reducing equivalents, in the form of NADH, and FADH, donate electrons to a chain of cytochromes beginning with NADH dehydrogenase. These reactions â€œcoupleâ€• the energy released during electron transport to the production of ATP. Ultimately, electrons combine with oxygen to form water. The sites of action of toxins that inhibit oxidative metabolism are shown. The sites where thiamine functions as a coenzyme are also illustrated. DH = dehydrogenase.

The toxicity of ingested xenobiotics may be altered by endogenous enzymatic activity or by the enzymatic activity of bacterial flora in the gastrointestinal tract. Laetrile (amygdalin) was used as an alternative treatment for cancer but caused deaths because of its biotransformation to cyanide. Amygdalin must be hydrolyzed in the gut to cyanide to exert its toxicity. When administered intravenously, amygdalin is not toxic.[34] Nitrates present in well water in farming communities are converted to nitrites by gut bacteria, leading to methemoglobinemia. A high gastric pH in very young infants allows the growth of enteric organisms in the stomach, making infants particularly susceptible to the toxic effects of ingested nitrates. Infants also have a reduced ability to detoxify nitrites.[69]

Injury by Metabolites of Biotransformation

The capacity of a tissue to biotransform certain toxins may be essential to the production of injury in that tissue. Highly reactive metabolites exert damage at the site where they are synthesized. Tissue injury by reactive metabolites occurs commonly in the liver, the major site of biotransformation of xenobiotics, but occurs in other organs as well (Chap. 26).[29 , 77] The lungs, skin, kidneys, gastrointestinal tract, and the nasal mucosa have the ability to biotransform xenobiotics to metabolites that result in local

injury.[12, 42] Overdoses of acetaminophen lead to excessive hepatic production of the highly reactive electrophile NAPQI, which initiates a damaging covalent bond with hepatocytes (Chap. 34).[8, 11] Acute renal tubular necrosis also occurs in patients with overdose of acetaminophen.[39] This is attributed to its biotransformation by prostaglandin H synthase within renal tubular cells to a highly reactive semiquinoneimine.[21]

Monoamine oxidases (MAOs) are mitochondrial enzymes present in many tissues. They oxidize a large number of different amines; including dopamine, epinephrine, and serotonin; and toxins such as primaquine and haloperidol. The metabolic activity of MAOs was responsible for the outbreak of parkinsonism associated with the use of methylphenyltetrahydropyridine (MPTP), an unintended byproduct of attempts to synthesize a â€œdesignerâ€• analog of meperidine, methylphenylpropionoxypiperidine (MPPP). After crossing the bloodâ€“brain barrier, MPTP is biotransformed by MAO in glial cells to methylphenyldihydropyridine ($MPDP^+$),

which is nonenzymatically converted to MPP^+ . The MPP^+ is subsequently taken up by specific dopamine transport systems into dopaminergic neurons in the substantia nigra, resulting in inhibition of oxidative phosphorylation and subsequent neuronal death.[26]

Free Radical Formation

Free radicals are compounds that have an unpaired electron and are very reactive with other species because they seek to obtain another electron. They include the superoxide anion O_2 Â·$^-$, which is produced by adding an electron to O_2 , and the highly reactive hydroxyl radical HOÂ·, which is produced by splitting (homolytic cleavage) the H_2 O_2 molecule. The H_2 O_2 molecule itself is reactive and is also associated with injury. The superoxide and hydroxyl radicals react with other molecules to generate other free radical

species. Some toxins promote the formation of reactive oxidizing species to the extent that defensive mechanisms against oxidants are overwhelmed, a condition called oxidative stress. Oxidative stress may result in oxidative damage to lipids, nucleic acids, and proteins. Free radicals are most destructive when they initiate chain reactions, such as when a free radical attacks polyunsaturated fatty acids in cellular membranes resulting in lipid peroxidation. This attack removes a hydrogen atom from a methylene carbon and leaves an unpaired electron, causing the formation of a lipid radical. This lipid free radical attacks other unsaturated fatty acid chains, causing a chain reaction that destroys the cellular membrane. Membrane degradation products initiate inflammatory reactions in the cells, resulting in further damage.[77]

Molecular oxygen (O_2) has two unpaired electrons in its orbits. Because oxygen is a relatively weak univalent electron acceptor (and most organic molecules are weak univalent electron donors), oxygen cannot efficiently oxidize amino acids and nucleic acids. However, the unpaired electrons of O_2 readily interact with the unpaired electrons of transition metals and organic radicals. Metals frequently catalyze the creation of oxygen free radicals. The following is an example of hydroxyl radical formation: (A) A first step is the addition of an electron to O_2 to create the superoxide ion. (B) The very reactive superoxide combines with hydrogen and another electron to produce hydrogen peroxide. (C) In the presence of a metal ion catalyst such as iron, hydrogen peroxide undergoes various reactions to produce the hydroxyl radical. The dot in these formulas represents an unpaired electron, the hallmark of a free radical.[35 , 51]

(A) $O_2 + e^- \longrightarrow O_2^{\bullet -}$

(B) $O_2^{\bullet -} + 2H^+ + e^- \longrightarrow H_2O_2$

(C) $H_2O_2 \xrightarrow[Fe^{2+}]{} OH^- + OH\bullet$ (Fenton)

$H_2O_2 + O_2^{\bullet -} \xrightarrow[Fe^{2+}]{} O_2 + OH^- + OH\bullet$ (Haber-Weiss)

The damaging effects of the free radicals can be minimized by reaction with antioxidants such as ascorbate, tocopherols, and glutathione.[51] Deficiencies of antioxidants, especially glutathione, are associated with increased oxidative damage. Free radicals are also neutralized by several enzymes, including peroxidase, superoxide dismutase, and catalase.

The ethanol-inducible CYP2E1 isozyme produces significant amounts of superoxide and peroxide free radicals, and, in the presence of iron, hydroxyl free radicals that readily initiate lipid peroxidation. This has been studied extensively in models of the metabolism of carbon tetrachloride, ethanol, and acetaminophen.[18] The formation of free radicals is implicated in the pulmonary injury caused by paraquat, the myocardial injury caused by doxorubicin, and the liver injury caused by carbon tetrachloride.[57 , 67] Paraquat reacts with NADPH to form a pyridinyl free radical, which, in turn, reacts with oxygen to generate the superoxide anion radical. Adriamycin is metabolized to a semiquinone free radical in the cardiac mitochondria, which, in the presence of oxygen, forms a superoxide anion radical that initiates myocardial lipid peroxidation.[57] Carbon tetrachloride (CCl_4) is metabolized to the trichloromethyl radical ($Â·CCl_3$) that binds covalently to cellular macromolecules. In the presence of oxygen, this is converted to the trichloromethylperoxyl radical ($Â·CCl_3\ O_2$) that can initiate lipid peroxidation (Fig. 13-4).[68] See Chap. 26 for a more extensive discussion.

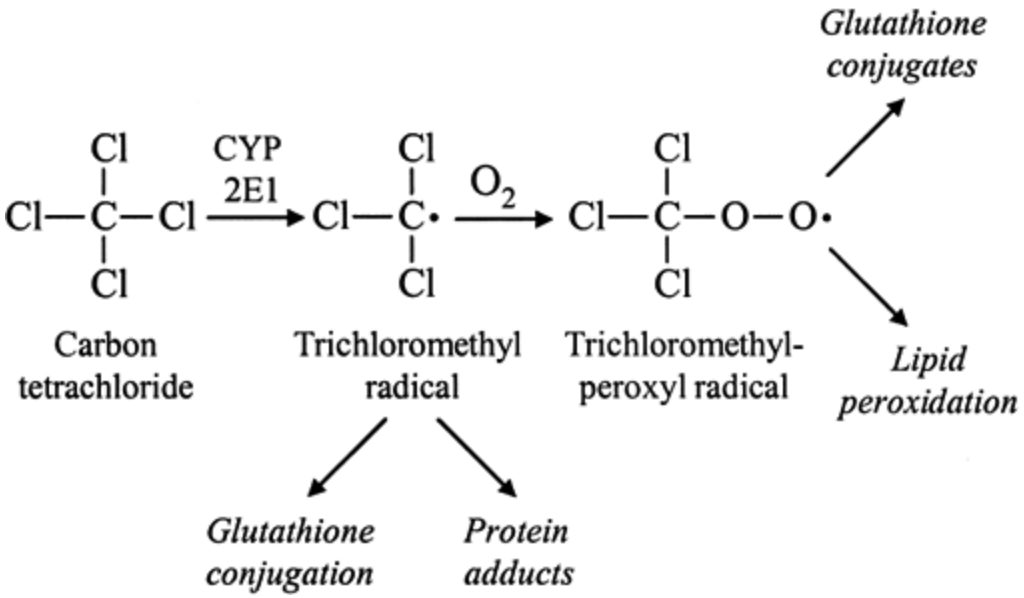

Figure 13-4. Carbon tetrachloride metabolism by the hepatocyte. Under hypoxic conditions, the CCl_3 radical is the predominant species formed. At higher oxygen tensions, CCl_3 radical is oxidized to the CCl_3 OO radical, which is more readily detoxified by glutathione. Both free radicals bind to hepatocytes and cause cellular injury.

Critical Biochemical Pathways and Toxins that Affect them

High-energy phosphate bonds, predominantly in the form of ATP, fuel all energy-dependent cellular processes such as synthesis, active transport, and maintenance of electrolyte balance and membrane integrity. When the production or use of ATP is inhibited, rapid cell death occurs. The ultimate goal of many metabolic processes is the production and mobilization of cellular energy. Numerous pathways interconnect glycogen, fat, and protein reserves in many tissues that store and retrieve ATP and glucose. The brain and red blood cells are entirely dependent on glucose for energy production, while other tissues can also use

ketone bodies and fatty acids to synthesize ATP.

Catabolic pathways that produce cellular energy include glycolysis, the tricarboxylic acid (TCA, or Krebs) cycle, and oxidative phosphorylation, which are mediated by the electron transport chain. Glycolysis occurs in the cytosol, while the TCA cycle and the electron transport chain are located within the mitochondria. Glycolysis produces small amounts of ATP through the anaerobic metabolism of glucose. Pyruvate, the end product of glycolysis, yields far more ATP when it is converted to acetylcoenzyme A (acetyl-CoA) and â€œprocessedâ€• aerobically by the oxygen-dependent TCA cycle. The TCA cycle and oxidative phosphorylation, which function only in the presence of oxygen, are the major pathways of oxidative metabolism and the synthesis of ATP (Fig. 13-3). Oxidative phosphorylation disposes of electrons or â€œreducing equivalentsâ€•

generated by the oxidative metabolism of cellular fuels, such as sugars and lipids, and converts their energy to ATP. Oxidative metabolism is highly energy efficient, producing 36 moles of ATP for each mole of glucose metabolized, compared to the 2 moles of ATP produced by glycolysis. The following sections review the basics of cellular energy metabolism and several important xenobiotics that affect these critical metabolic functions (Table 13-2).[38 , 56]

Glycolysis

Glycolysis is the first biochemical pathway in the metabolism of glucose. Other sugars enter the glycolytic pathway after conversion to glycolytic intermediates (Fig. 13-5). The glycolytic process converts one molecule of glucose to 2 pyruvate molecules + 2 ATP + 2 NADH. Pyruvate may follow many paths. Under anaerobic conditions, the 2 pyruvates produced from 1 glucose molecule are reduced by lactate dehydrogenase to 2 lactate

molecules in an NADH-requiring step that regenerates NAD+. Thus, anaerobic glycolysis yields 2 molecules of lactate + 2 ATP. When NAD^+ and oxygen are available, pyruvate is converted by pyruvate decarboxylase to acetyl-CoA, which is transported from the cytosol into the mitochondrion and condenses with oxaloacetate within the TCA cycle to form citrate (Fig. 13-3).[38, 56] In energy replete conditions, pyruvate molecules are used for fatty acid synthesis.

General
Oxygen becomes unavailable
Xenobiotics â†’respiratory paralysis
Xenobiotics â†’ischemia
Xenobiotics â†’ â†“hemoglobin oxygenation
Glycolysis
Inhibits NADH production
Iodoacetate (at GAPDH)
NO+ (at GAPDH)
Gluconeogenesis
Inhibits NADH production
4-(Dimethylamino)phenol *p* -benzoquinone
Hypoglycin
Fatty acid metabolism
Inhibits NADH production
Aflatoxin Protease inhibitors
Amiodarone Salicylates
Hypoglycin Tetracycline
Perhexiline Valproic acid
Pyruvate dehydrogenase
Inhibits NADH production
Arsenite
p -Benzoquinone
Tricarboxylic acid cycle
Inhibits NADH production
Fluoroacetate (at aconitase)

Electron-transport chain complex I
Inhibits electron transport at complex I
Rotenone, amytal, MPP+, paraquat
Electron-transport chain complex III
Inhibits electron transport at complex III
Antimycin-A, funiculosin, myxothiazole
Substituted phenols (are also uncouplers)
Di- and trivalent metal cations (Zn^{2+} , Hg^{2+} , Cu^{2+} , and Cd^{2+})
Electron-transport chain complex IV
Inhibits electron transport at complex IV
Cyanide H_2S
Azide Formate
Nitric oxide Carbon monoxide
Phosphine Protamine
Electron-transport chain at ATP synthase
Inhibits ATP production from ADP at ATP synthase
Mycotoxins (numerous, including oligomycin)
Organic chlorines (DDT and chlordecone)
Organotin agents (cyhexatin)
Propranolol
Paraquat
Mitochondria ADP/ATP antiporter
Disrupts the movement of ADP into and ATP out of the mitochondria at the ADP/ATP antiporter
Atractyloside
DDT
Free fatty acids and some compounds with similar structure
Mitochondria inner membrane
Uncouples oxidative phosphorylation by disrupting the proton gradient â†’ stops proton flow at ATP synthase â†’ stops ATP synthesis
Substituted phenols (pentachlorophenol, dinitrophenol)
Lipophilic amines (amiodarone, perhexiline, buprenorphine)
Benzonitrile

Thiadiazole herbicides
NSAIDs with ionizable groups (salicylates, diclofenac, indomethacin, piroxicam)
Valinomycin
Gramicidin
Calcimycin
Chlordecone
Mitochondria inner membrane
Diverts electrons to alternate pathways (vs. to the electron-transport chain)
Adriamycin
MPP^+
Naphthoquinones (menadione)
N -nitrosoamines
Paraquat
GAPDH = glyceraldehyde 3-phosphate dehydrogenase; MPP+ = 1-methyl-4-phenylpyridinium.

Step/Location Action Examples

TABLE 13-2. Inhibitors of Glucose Metabolism and ATP Synthesis

Arsenate has a toxic effect at the glycolytic step where 3-phosphoglyceraldehyde dehydrogenase (3-PGA) catalyzes the oxidation of glyceraldehyde-3-phosphate to 1,3-diphosphoglycerate; a reaction that preserves a high-energy phosphate bond used to synthesize ATP in the next step of glycolysis (Fig. 13-5).[14] As an analog of phosphate, arsenate acts as a substrate at this step. The resultant unstable intermediate is rapidly hydrolyzed, preventing the subsequent synthesis of ATP and interrupting glycolysis.[14]

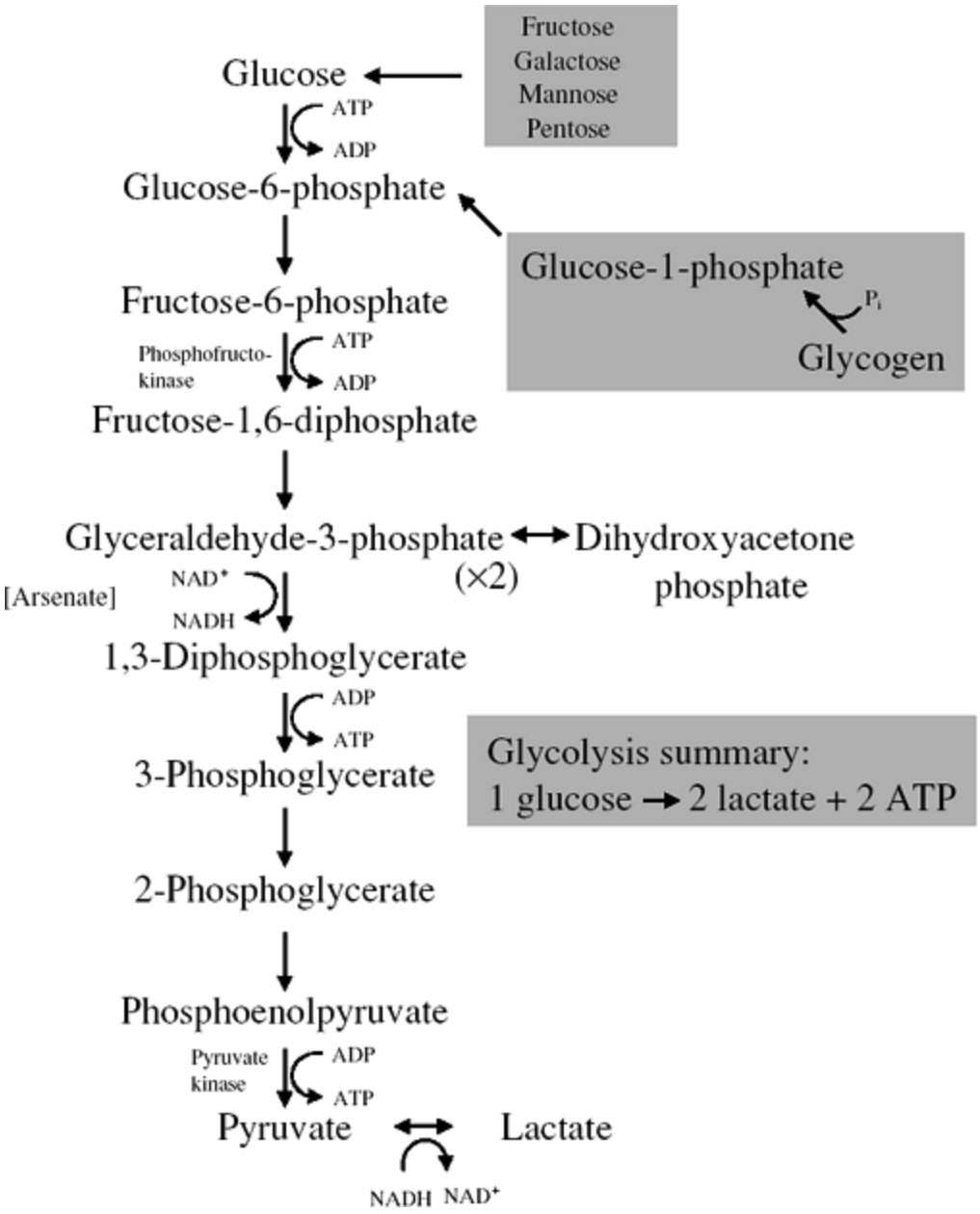

Figure 13-5. During glycolysis, the anaerobic metabolism of 1 mole of glucose to 2 moles of lactate results in the net production of 2 moles of ATP. Arsenic inhibits 3-phosphoglycerate dehydrogenase, which catalyzes the oxidation of glyceraldehyde-3-phosphate to 1,3-diphosphoglycerate.

Tricarboxylic Acid Cycle

The TCA cycle uses acetyl-CoA derived from glycolysis, fat, or protein to regenerate NADH from NAD^+ . The cycle is a major source of electrons (in the form of NADH) and is critical to the aerobic production of ATP (Fig. 13-3). Each acetyl-CoA molecule that is oxidized within the TCA cycle ultimately forms 1 molecule each of CO_2 and GTP (guanosine triphosphate), and, more importantly, 3 molecules of NADH and 1 molecule of flavin adenine dinucleotide (reduced form) ($FADH_2$), which enter the electron transport chain, and produce 15 molecules of ATP. In addition, the TCA cycle provides important intermediates for amino acid synthesis and for gluconeogenesis.[38]

Inhibitors of the TCA cycle are powerful toxins. Two highly toxic rodenticides, sodium fluoroacetate and fluoroacetamide, are incorporated as fluoroacetyl coenzyme A and enter the TCA cycle by condensation with oxaloacetate to form fluorocitrate. This blocks the conversion of citrate to isocitrate, which results in the accumulation of large amounts of citrate in the mitochondria, inhibition of the cycle, and termination of oxidative metabolism (Fig. 13-3) (Chap. 106).[82]

Thiamine is an important cofactor for two TCA cycle enzymes. It is required for the conversion of pyruvate to acetyl-CoA by pyruvate decarboxylase and for the conversion of (Î±-ketoglutarate to succinyl-CoA by (Î±-ketoglutarate dehydrogenase.[56] The life-threatening effects of thiamine deficiency are likely related to impairment of these enzyme functions (see Antidotes in Depth: Thiamine Hydrochloride).

The Electron Transport Chain

The success of aerobic metabolism requires disposal of electrons generated by oxidative metabolism so that new electrons can enter the pathway. The oxidative phosphorylation of adenosine

diphosphate (ADP) to ATP captures energy generated by the oxidative reactions of the TCA cycle in the high-energy phosphate bond of ATP (see Fig. 13-3). Oxidative phosphorylation of ADP to ATP occurs in the electron transport chain, which consists of a series of cytochrome-enzyme complexes within the inner mitochondrial membrane. Within these complexes, NADH is split into $NAD^+ + H^+ + 2$ electrons at two locations and $FADH_2$ is split into $FAD + H^+ + 2$ electrons at one position. These splits have two results. First, the regenerated NAD^+ and FAD are recycled back to the TCA cycle, enabling oxidative metabolism to continue. Second, these actions provide the energy required to pump protons (H^+) from the mitochondrial matrix into the intermembrane space. This action causes the matrix to become relatively alkaline compared to the now acidified intermembrane space; resulting in a proton gradient across the inner mitochondrial membrane. This gradient provides the energy needed to create the high-energy bonds of ATP. The final step in oxidative phosphorylation is the reduction of molecular oxygen to water by cytochrome a-a_3 (Fig. 13-3).[38 , 56]

Mitochondria oxidize substrates, consume oxygen, and make ATP. Toxins that interrupt oxidative phosphorylation impair ATP production by either inhibiting specific electron chain complexes or by acting as â€œuncouplers.â€• Both of these mechanisms result in rapid depletion of cellular energy stores, followed by failure of ATP-dependent active transport pumps, loss of essential electrolyte gradients, and increases in cell volume.[55]

â€œInhibitorsâ€• of specific cytochromes block electron transport and cause an accumulation of reduced intermediates proximal to the site of inhibition. This stops the use of oxygen and substrate. Failure to regenerate oxidized substrates for the TCA cycle, particularly NAD^+ and flavin adenine dinucleotide (FAD), further impairs oxidative metabolism. Cyanide, carbon monoxide, and hydrogen sulfide block the cytochrome a-a_3 -mediated reduction of O_2 to H_2 O. The very dramatic clinical effects of a significant cyanide exposure illustrate the importance of aerobic metabolism

(Chap. 121). Other xenobiotics have been less commonly associated with inhibition of the electron transport chain (Table 13-2).[83]

Severe metabolic acidosis is an unavoidable clinical manifestation of toxins that inhibit aerobic respiration. This metabolic acidosis is caused by the accumulation of protons in the mitochondrial matrix that are not used in the production of ATP, and not by the accumulation of lactic acid, which is only a marker for metabolic acidosis associated with the impairment of oxidative metabolism.[73]

Toxins that uncouple oxidative phosphorylation stop ATP synthesis by destroying the pH gradient across the mitochondrial

inner membrane. Protons continue to be pumped into the intermembrane space while oxygen and substrate consumption continue. Uncoupling agents allow the protons to cross back into the mitochondrial matrix, causing the loss of the proton gradient across the inner mitochondria membrane, which results in the loss of further ATP production. Thus, oxygen consumption is â€œuncoupledâ€• from ATP production. Energy created by electron transport that cannot be coupled to ATP synthesis is released as heat. Various xenobiotics â€œuncoupleâ€• ATP synthesis (Table 13-2). A classic one is dinitrophenol, used in the past as an herbicide and as a weight-loss product (Chaps. 39 and 111). Compounds that are capable of carrying hydrogen ions across membranes are generally lipophilic weak acids. These agents must have an acid-dissociable group to carry the proton, and a bulky lipophilic group to cross a membrane.[83] Dinitrophenol is able to carry its proton from the cytosol into the more alkaline mitochondrial matrix where it dissociates, acidifying the matrix and destroying the proton gradient across the inner mitochondrial membrane. Interestingly, the phenolate anion of dinitrophenol is relatively lipophilic and can cross back out to the cytosol where it gains a new proton and starts the process over again. Long-chain fatty acids uncouple oxidative phosphorylation by a similar

mechanism.[83] Fatal exposures to dinitrophenol and to pentachlorophenol, a wood preservative, are associated with severe hyperthermia attributed to heat generation by uncoupled oxidative phosphorylation.[53] Rats develop fatal hyperthermia following oral ingestion of dinitrophenol.[78] The hyperthermia and acidosis associated with severe salicylate poisoning are also attributed to its uncoupling of oxidative phosphorylation.[76]

Pentose Phosphate (Hexose Monophosphate) Shunt

The hexose monophosphate (HMP) shunt provides the only source of cellular NADPH. NADPH is used in biosynthetic reactions, particularly fatty acid synthesis, and is an important source of reducing power for the maintenance of sulfhydryl groups that protect the cell from free radical injury.[9, 35] As discussed earlier, G6PD is a key enzyme in the pathway (Fig. 13-6). Reduced glutathione, which is quantitatively the most important general antioxidant in cells, depends on the availability of NADPH. RBCs are especially vulnerable to deficiency of NADPH, which results in hemolysis during oxidative stress.

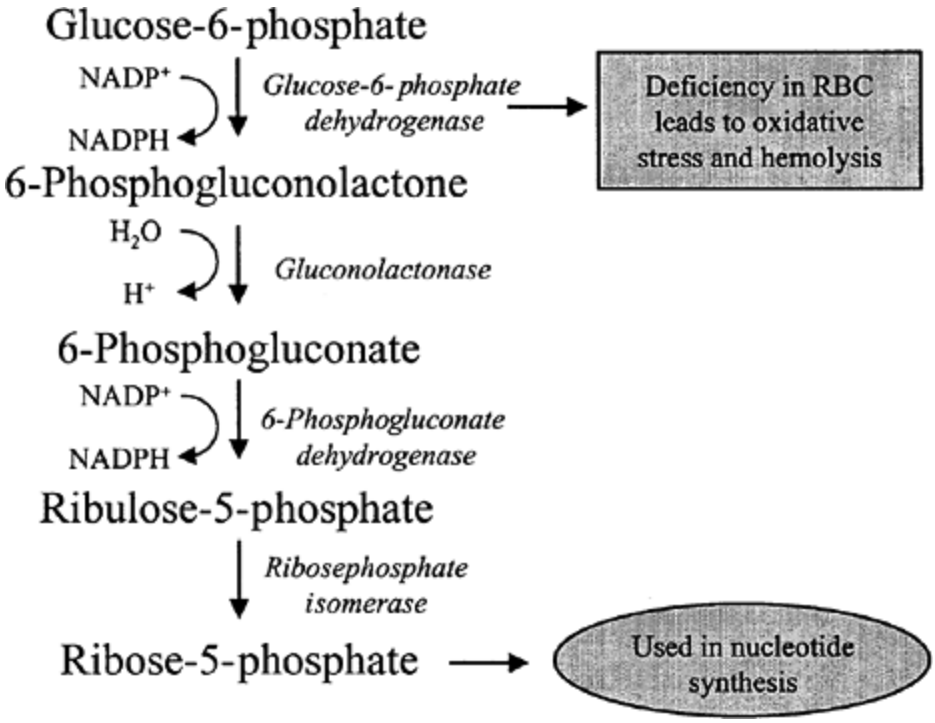

Figure 13-6. The oxidation reactions of the pentose phosphate pathway are an important source of NADPH for reductive biosynthesis and for protection of cells against oxidative stress. Deficiency of G6PD, the first enzyme in the pathway, may result in RBC hemolysis during oxidative stress.

Another manifestation of oxidative stress in RBCs is the oxidation of the iron in hemoglobin from Fe^{2+} to Fe^{3+}, producing methemoglobin that occurs both spontaneously and as a response to xenobiotics such as nitrites and aminophenols. Because most reduction of methemoglobin is done by NADH-dependent methemoglobin reductase, which is not deficient in persons who lack G6PD, such persons do not develop methemoglobinemia under normal circumstances. However, when oxidative stress is severe and methemoglobinemia develops, people who have G6PD deficiency have limited ability to use the alternative NADPH-dependent methemoglobin reductase (Chap. 122).[87]

Gluconeogenesis

Gluconeogenesis is a biochemical pathway localized predominantly in the liver that facilitates the conversion of amino acids and intermediates of the TCA cycle to glucose. It is an important source of glucose during fasting and enables maintenance of glycogen stores. Most of the steps in the synthesis of glucose from pyruvate are simply the reverse of glycolysis, with three irreversible exceptions: (a) the conversion of glucose-6-phosphate to glucose; (b) the conversion of fructose-1,6-diphosphate to fructose-6-phosphate; and (c) the synthesis of phosphoenolpyruvate from pyruvate. The synthesis of phosphoenolpyruvate from pyruvate is especially complex. Pyruvate is first converted to oxaloacetate within the mitochondria, then to malate, which is transported out of the mitochondria and converted in the cytosol back to oxaloacetate, and then to phosphoenolpyruvate (Fig. 13-7). Certain amino acids, notably alanine, glutamate, and aspartate, are readily converted to TCA cycle intermediates and can be used in the synthesis of glucose through this cycle.[38] Glycerol, produced by the breakdown of triglycerides in adipose tissue, is another substrate for gluconeogenesis.

The regulation of gluconeogenesis is opposite to that of glycolysis. Both glucagon and catecholamines stimulate gluconeogenesis, whereas insulin and hyperglycemia turn it off. Gluconeogenesis requires the presence of NAD^+ in the cytosol, which is necessary to oxidize lactate to pyruvate. It also requires the presence of NADH in the mitochondria. It is impaired by processes that increase the cytosol reducing potential as measured by the cytosol $NADH/NAD^+$ ratio (see discussion below).

A number of xenobiotics impair gluconeogenesis, resulting in hypoglycemia when glycogen stores are depleted (Table 13-2). Hypoglycin A, an unusual amino acid found in unripe ackee fruit that is the cause of Jamaican vomiting sickness, produces

profound hypoglycemia.[23, 76, 80] Its metabolite methylenecyclopropylacetic acid (MCPA) indirectly inhibits gluconeogenesis by blocking the oxidation of long-chain fatty acids, an important source of NADH in mitochondria. It also inhibits the metabolism of several glycogenic amino acids including leucine, isoleucine, and tryptophan, and blocks their entrance into the TCA cycle. MCPA may also prevent the transport of malate out of the mitochondria.[71, 80, 81] Significant hypoglycemia occurs in fasting patients with elevated ethanol levels.[7, 25, 49] This is likely a result of the impairment of gluconeogenesis by the increased cytosolic NADH:NAD^+ ratio associated with the metabolism of ethanol. This inhibits the two steps that require NAD^+ : the conversion of lactate to pyruvate and the conversion in the cytosol of malate to oxaloacetate.[4, 49, 68]

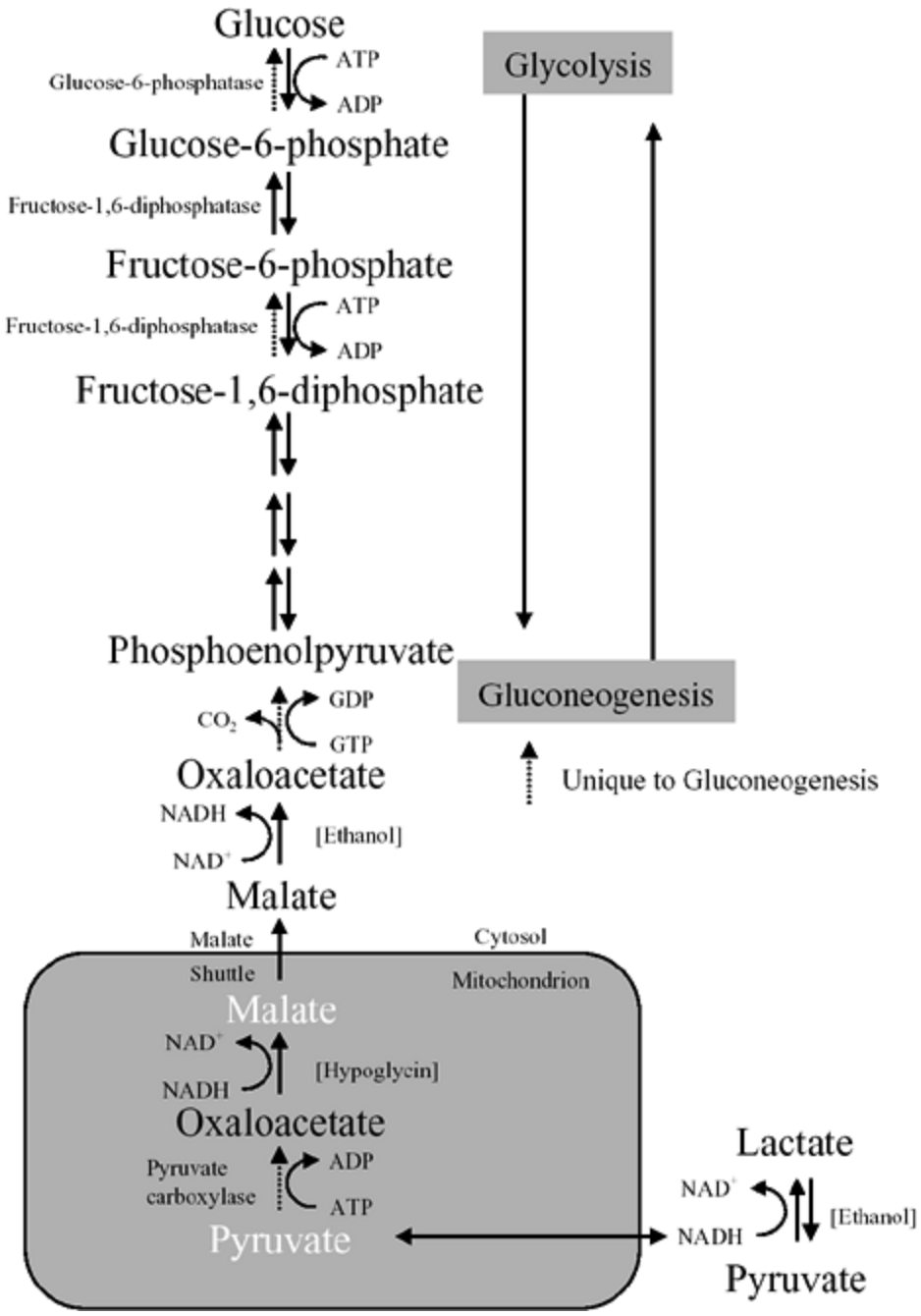

Figure 13-7. Gluconeogenesis reverses the steps of glycolysis, with the exception of the bypass of the three irreversible steps shown. The step from pyruvate to phosphoenolpyruvate involves both cytosolic and mitochondrial reactions that use ATP. Hypoglycin A inhibits the intramitochondrial conversion of oxaloacetate to malate by depleting NADH through interference

with Î²-oxidation of fatty acids. Ethanol decreases cytosolic supplies of NAD^+ . Pyruvate kinase (PK) and phosphofructokinase (PFK), the enzymes whose activities are regulated by glucagon via cyclic adenosine monophosphate (cAMP)-dependent phosphokinase, are shown.

Fatty Acid Metabolism

Fatty acid metabolism occurs primarily in hepatocytes. Fatty acids mobilized in adipose tissue enter hepatocytes by passive diffusion. Fatty acid synthesis is stimulated by insulin and inhibited by glucagon and epinephrine. Acetyl-CoA is the primary building block of free fatty acids (FFAs). In energy-repleted cells, fatty acids are combined with glycerol phosphate to form triacylglycerol (triglycerides), the first step in the synthesis of fat for storage. Hepatic triglycerides are bound to lipoprotein to form very-low-density lipoprotein (VLDL), then transported and stored in adipocytes. When hepatocytes are energy depleted, triglycerides are broken down to FFA and glycerol (Fig. 13-8). This process is suppressed by insulin, but supported by glucagon or epinephrine. FFAs undergo Î²-oxidation in the mitochondria, a process that breaks the FFA into acetyl-CoA molecules that can then enter the TCA cycle. FFAs require activation before transport into the mitochondria. This is accomplished by acylcoenzyme A (acyl-CoA) synthetase, which adds a CoA group to the FFA in an energy dependent synthetic reaction. These are transported into the mitochondria by a process that utilizes cyclical binding to carnitine, a â€œcarnitine shuttleâ€• (Fig. 13-3). Once inside the mitochondria, FFAs are converted to acetyl-CoA by Î²-oxidation, so-called because it involves the sequential removal of 2-carbon fragments, each time acting at the second carbon (the Î² carbon) position of the fatty acid. Each 2-carbon molecule removed from the FFA produces 1 NADH and 1 $FADH_2$, which enter oxidative

phosphorylation, and 1 mole of acetyl-CoA, which enters the TCA cycle. This process produces 1.3 times more ATP per molecule of carbon metabolized than does the oxidative metabolism of glucose or other carbohydrates.[38]

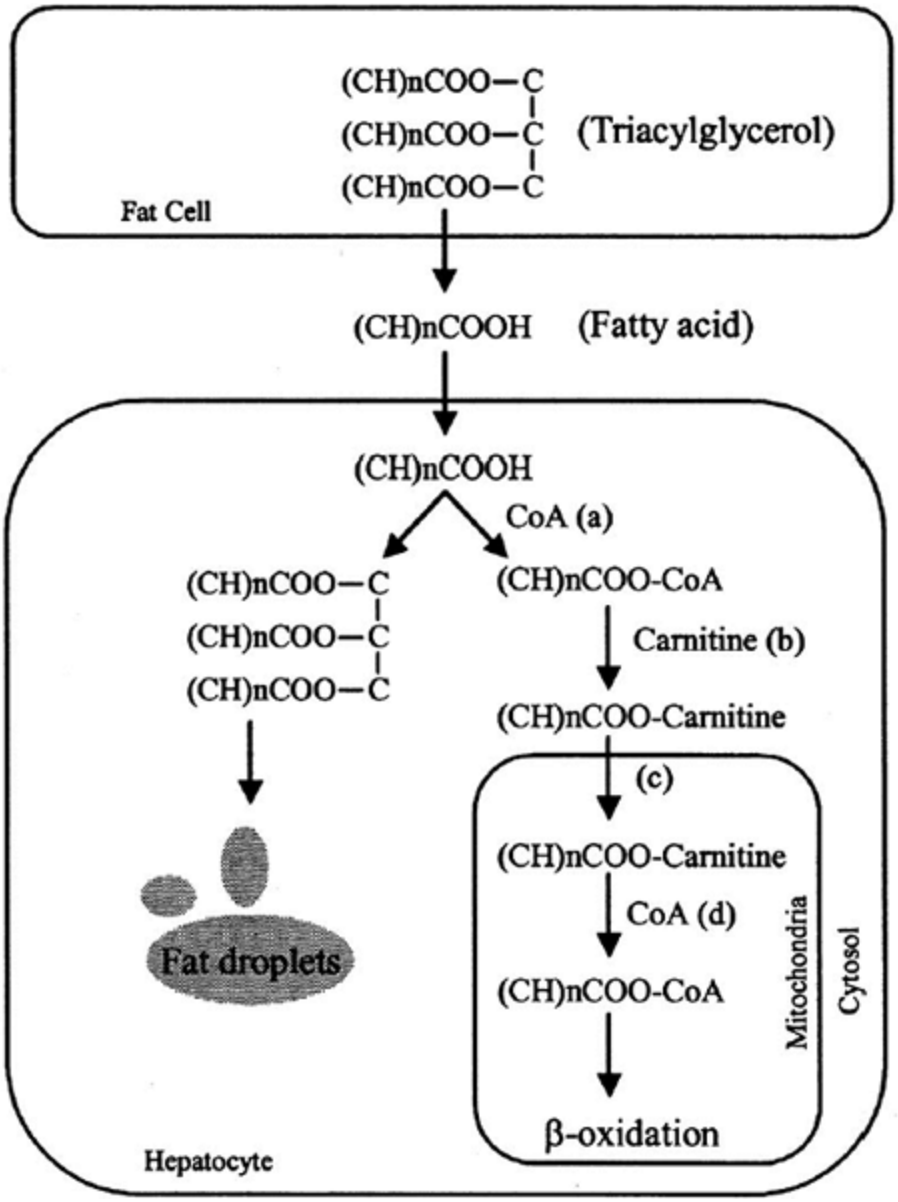

Figure 13-8. Steatosis, an accumulation of fat, results when toxins interfere with the oxidation of fatty acids. Other processes that may be associated with intracellular accumulation of fat include (a) impaired lipoprotein synthesis; (b) impaired lipoprotein

release; (c) increased mobilization of free fatty acids; (d) increased uptake of circulating lipids; and (e) increased production of triglycerides. Î²-Oxidation takes place in the mitochondria after transport of fatty acids from the cellular cytosol across the mitochondrial membrane. The enzymes involved are (a) acyl-CoA synthetase; (b) carnitine palmitoyltransferase I; (c) carnitine acylcarnitine translocase; and (d) carnitine palmitoyltransferase II. Acyl-CoA is the intramitochondrial substrate for Î²-oxidation. Potential mechanisms of inhibition of Î²-oxidation include induction of carnitine deficiency, inhibition of the transferase or translocase, and increased NADH:NAD^+ ratio via increased use of NAD^+ or by inhibition of NADH use. The specific site of action is not defined for many toxins that cause steatosis.

Many xenobiotics interrupt fatty acid metabolism at various steps, resulting in accumulation of triglycerides in the liver (Table 13-2). The mechanisms of disruption of fatty acid metabolism are poorly defined and numerous hypotheses are proposed.[16] Some agents, including ethanol, hypoglycin, and nucleoside analogs (Chap. 26), inhibit Î²-oxidation, at least indirectly, through effects on NADH concentrations. Protease inhibitors are associated with a syndrome of peripheral fat wasting, central adiposity, hyperlipidemia, and insulin resistance.

The condition of alcoholic ketoacidosis is related in part to inhibition of gluconeogenesis in the alcoholic patient and in part to an exuberant response to nutritional needs by the fatty acid machinery. Vomiting in the alcoholic patient leads to decreased intake of carbohydrate, which stimulates a starvation response with increases in serum glucagon, cortisol, growth hormone, and epinephrine concentrations, and decreases in serum insulin. When the need for carbohydrate is not met by gluconeogenesis, lipolysis, which is normally inhibited by insulin, is intensified and fatty acid mobilization progresses. Glucagon stimulates mitochondrial

carnitine acyltransferase, and Î²-oxidation of fatty acids is increased. The increased mitochondrial NADH:NAD^+ ratio favors the production of Î²-hydroxybutyrate over acetoacetate, its oxidized form. The administration of fluids, dextrose and thiamine to the alcoholic patient leads to correction of this process.[70]

Summary

Humans and other animals are exposed to a wide variety of xenobiotics. Some, including therapeutic drugs, are harmless at low doses and toxic only at high doses. The toxicity of those xenobiotics that interrupt important biologic functions or that result in cellular injury is dose-related and often rapidly evident. The diverse mechanisms of toxic injury have been discussed in general terms. The capacity of xenobiotics to cause injury is clearly a function of many factors specific to the xenobiotic, the tissue injured, and the individual animal or species.

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Chapter 14

Neurotransmitters and Neuromodulators

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Many poisonous substances produce their primary toxic effects by affecting neurotransmission. This chapter reviews the normal physiology of neurotransmission, the molecular action and biochemistry of several major neurotransmitters and their receptors, and the toxicologic mechanisms by which numerous substances act at the molecular level. Acetylcholine, norepinephrine, epinephrine, dopamine, serotonin, Î³-aminobutyric acid (GABA), Î³-hydroxybutyrate (GHB), glycine, glutamate, and adenosine are the neurotransmitters and neuromodulators of toxicologic interest that are discussed in this chapter.

When examining molecular actions of drugs and toxins on neurotransmitter systems, it is apparent that substances rarely possess single pharmacologic actions. For example, doxepin, in part, antagonizes voltage-gated sodium channels, histaminic H_1 and H_2

receptors, Î±-adrenoceptors, muscarinic acetylcholine receptors, dopamine D_2 receptors, and $GABA_A$ receptors; prevents potassium efflux; and inhibits norepinephrine, serotonin, and adenosine uptake. For obvious reasons, then, this chapter cannot include every action of every drug or toxin on the nervous system. Nor is it meant to be a complete discussion of toxic syndromes produced by various agents, as these are discussed in specific chapters. Rather, this chapter provides a general and basic understanding of the mechanisms of action of various toxic agents affecting neurotransmitter function and receptors, especially in the central nervous system. With this focus, the clinical effects produced by various toxins are more easily understood and predicted, and specific treatments aimed at reversing pharmacologic effects of the offending agents can be rationally undertaken.

Given the complexity of the nervous system and the numerous actions of a given drug, it is not always clear which neurotransmitter system is producing an observed effect during a particular toxicity. Therefore, pharmacologic agents discussed in this chapter may be found in several sections. An attempt is made to note what appears to be a drug or toxin's main mechanism of action, although other actions are noted when possible.

Neuron Physiology and Neurotransmission

Membrane Potentials, Ion Channels, and Nerve Conduction

Membrane-bound sodium-potassium adenosine triphosphatase (ATPase) moves three sodium ions (Na^+) from inside the cell to the interstitial space while pumping two potassium ions (K^+) into the cell. Because the cell membrane is not freely permeable to large, negatively charged molecules on the inside of the cell, such as

proteins, an equilibrium results in which the inside of the neuron is negative with respect to the outside. This typical neuronal resting membrane potential is â€“65 mV.

Sodium, calcium (Ca^{2+}), K^+, and chloride (Cl^-) ions move into and out of neurons through ion channels. Ions always move passively down electrochemical gradients through ion channels, which are long polypeptides comprising several subunits that span the plasma membrane several times. Many different ion channels are structurally comparable, sharing similar amino acid sequences.[17] Channels for a specific ion can also vary in structure, depending on the specific subunits that have combined to form the channel. Because of structural similarity of different channels, it is not surprising that many drugs or toxins are able to bind to more than one type of ion channel.

More than 40 different ion channels have been described in various nerve terminals,[99] and it is estimated that a human being contains hundreds of different varieties of ion channels for Na^+, Cl^-, Ca^{2+}, and K^+. Most ion channels fall into two general classes: voltage-gated (voltage-dependent) ion channels and ligand-gated ion channels.[99] Voltage-gated channels open or close in response to changes in membrane potential. Ligand-gated channels open or close when a ligand (eg, neurotransmitter) binds to the channel to change its configuration.

A commonly accepted model describes voltage-gated Na^+ channels and some other voltage-gated ion channels in three possible states. Using Na^+ channels as an example, the Na^+ channel is closed at rest and impermeable to sodium, preventing Na^+ from moving into the cell. When the channel undergoes activation, the channel opens, allowing Na^+ to move intracellularly, down its electrochemical gradient. The channel then undergoes a third conformational change by becoming inactivated, preventing further influx of Na^+. The term *recovery* describes the conversion of inactive channels back to the resting state, a process that requires repolarization of the cell

membrane.

Depolarization of a neuron usually results from an initial inward flux of cations (Na^+ or Ca^{2+}), or prevention of K^+ efflux. The fall in membrane potential (movement toward 0 mV) results in further activation of these voltage-dependent Na^+ channels, allowing yet a greater influx of cations. When the membrane

potential falls to threshold, Na^+ channels are activated en masse, and there is a large influx of Na^+.

Depolarization of a segment of the neurolemma causes the adjacent neuronal membrane to reach threshold, resulting in the propagation of an action potential down the neuron. Sodium channel activation is quickly followed by inactivation. Over the short-term, repolarization of the neuron occurring after inactivation of Na^+ channels mainly results from efflux of K^+ and some influx of Cl^-.

Neurotransmitter Release

Neurotransmitters are chemicals that are released from nerve endings into the synapse, where they produce effects by binding to receptors on postsynaptic and/or presynaptic cell membranes. The receptors may be on other neurons or effector organs such as smooth muscle. Concentrations of neurotransmitters in cytoplasm are usually low because of rapid degradation by various enzymes and because they diffuse out of the nerve ending. To provide a source of neurotransmitters that is protected from degradation and that can be rapidly released, neurotransmitters are concentrated and stored within vesicles in the axonal nerve terminal for release. As a wave of depolarization from Na^+ influx reaches the nerve ending, the membrane depolarization causes voltage-gated Ca^{2+} channels to open, allowing Ca^{2+} to move rapidly into the cell. This influx of Ca^{2+} triggers exocytosis of vesicle contents into the synapse. The voltage-gated Ca^{2+} channels responsible for inward Ca^{2+} currents that trigger neurotransmitter release are mainly of the N and P

subtypes.[103,121] Calcium channel blockers used in clinical practice (eg, verapamil, nifedipine) do not block these subtypes of voltage-dependent Ca^{2+} channels, but rather block the L-type. However, L-subtype Ca^{2+} channels reside elsewhere on neurons, which explains the ability of traditional Ca^{2+} channel blockers to affect some neurologic functions.

Vesicle Transport of Neurotransmitters

The pH inside neurotransmitter vesicles is about 5.5, lower than that in the cytoplasm. A vacuolar adenosine triphosphatase (V-ATPase) in the vesicular membrane is responsible for movement of protons into the vesicular lumen at the expense of adenosine triphosphate (ATP) hydrolysis. Vesicular uptake pumps that move neurotransmitters or their precursors from the cytoplasm into the vesicle lumen, in turn, are powered by the electrochemical H^+ gradient; that is, the movement of an H^+ out of the vesicle into the cytoplasm is coupled to the movement of a neurotransmitter from the cytoplasm into the vesicle. This is particularly true for vesicular transporters of GABA, glycine, dopamine, norepinephrine, and serotonin.

At least four unique *vesicular* transporters for neurotransmitters have been sequenced to date. VGAT transports GABA and glycine. VMAT2 transports all three monoamines, dopamine, norepinephrine, and serotonin (VMAT1 transports monoamines into nonneuronal vesicles). VAChT is responsible for acetylcholine (ACh) transport, and VGluT1 transports glutamate.

Neurotransmitters are confined within the vesicle, to a great extent, by ion trapping, as they are more ionized and less able to diffuse back out of the vesicle at the lower pH. Anything that causes a decrease in the pH gradient across the vesicle membrane results in the movement of neurotransmitters into the cytoplasm.[149] For example, amphetamines move into vesicles, where they buffer protons, causing the movement of monoamine neurotransmitters out of vesicles, and raising cytoplasmic concentrations of

neurotransmitters.[149,150]

Neurotransmitter Uptake

Although acetylcholine is inactivated in the synapse by enzymatic degradation, most neurotransmitters have their synaptic effects terminated by active uptake into neurons and/or glial cells. These plasma membrane neurotransmitter transporters are distinct from those transporters responsible for movement of neurotransmitters into vesicles within the cytoplasm. Cell membrane transporters (uptake pumps) for different neurotransmitters are Na^+-dependent transport proteins, during which the uptake of neurotransmitters is accompanied by the movement of Na^+ across the synaptic membrane.[2]

Neurotransmitter uptake transporters have been subdivided into two main families.[2] One family includes structurally similar uptake pumps for Î³-aminobutyric acid, glycine, norepinephrine, dopamine, and serotonin. They generally comprise 600â€“700 amino acids and form loops spanning the plasma membrane 12 times.

GAT-1 transports GABA into neurons, while GAT-2, GAT-3 and GAT-4 transport GABA into glial cells and, possibly, into postsynaptic neurons. DAT, SERT, and NET are responsible for uptake of dopamine, serotonin, and norepinephrine, respectively. GLYT-1 (at least three isoforms) transports glycine into neurons and astrocytes, while GLYT-2 transports glycine into glycinergic neurons.

The second family comprises 5 glutamate uptake transporters (excitatory amino acid transporters), which appear to traverse the plasma membrane 10 times. EAAT1 resides in cerebellar glial cells; EAAT2 in forebrain glia; EAAT3 in cortical neurons; EEAT4 in cerebellar Purkinje cells; and EAAT5 in the retina. Each time a glutamate moves into a neuron or glial cell, it is accompanied by 3 Na^+ and 1 proton. At the same time, a K^+ is extruded with each cycle.

Several properties make transporter proteins of particular toxicologic significance. First, they are capable of moving neurotransmitters in either direction; when cytoplasmic neurotransmitter concentrations are significantly elevated, neurotransmitters can be transported back into the synapse. Second, these transporters are not always completely specific for a particular substance. For instance, the uptake transporter for norepinephrine can pump dopamine and other biogenic amines into the neuron. Third, a drug or toxin that acts at the level of the membrane transporter may affect functions of several different neurotransmitters, depending on its specificity for a particular transporter. As an example, fluoxetine is fairly specific at inhibiting uptake of serotonin, whereas cocaine inhibits the uptake of serotonin, norepinephrine, and dopamine.

Neurotransmitter Receptors

Channel Receptors

The first general class of neurotransmitter receptors comprise ligand-gated ion channels (channel receptors or ionotropic receptors) in which the receptor for the neurotransmitter is part of an ion channel. These channels comprise multiple subunits which combine in various combinations to create channels that vary in their response to a given neurotransmitter or other agonist/antagonist. By binding to its receptor, the neurotransmitter allosterically changes the configuration of the ion channel so that ions can more easily traverse the channel and enter or leave the cell. As an example, the acetylcholine nicotinic receptor at the neuromuscular junction is a ligand-gated Na^+ channel. When

acetylcholine binds to the nicotinic receptor, the channel's configuration changes, allowing Na^+ to move into the cell and trigger an action potential. (The action potential then propagates down muscle via voltage-gated Na^+ channels.) Table 14-1 lists other

examples of channel receptors.

TABLE 14-1. Types of Neurotransmitter and Neuromodulator Receptors

Ion Channel	Linked to G Protein
ACh nicotinic	ACh muscarinic
$GABA_A$, $GABA_C$	$GABA_B$
Glycine (inhibitory)	Dopamine
Glutamate AMPA	Norepinephrine
Glutamate NMDA	$5\text{-}HT_{1,2,4â€“7}$
Glutamate kainate	Adenosine
$5\text{-}HT_3$	Glutamate metabotropic

ACh = acetylcholine; AMPA = amino-3-hydroxy-5-methyl-4-isoxazole propionate; GABA = Î³-aminobutyric acid; 5-HT = 5-hydroxytryptamine (serotonin); NMDA = *N*-methyl-D-aspartate.

G Protein Receptors

The second general class of neurotransmitter receptors are linked to

G proteins, which are part of a superfamily of proteins with guanosine triphosphatase (GTPase) activity responsible for signal transduction across plasma membranes.[140] G proteins comprise 3 polypeptide subunits: Î±, Î², and Î³ chains. These chains span the plasma membrane several times, and they associate with a separately transcribed neurotransmitter receptor that spans the cell membrane 7 times, with an external binding site for neurotransmitters. Some receptors (eg, $GABA_B$ receptor) coupled to G proteins are dimers comprising two separate proteins, both of which must be present for activity.

Both the Î± subunit and the Î²Î³ subunit of a G protein may account for activity resulting from a neurotransmitter binding to its receptor. The Î± chain normally binds guanosine diphosphate (GDP) in the cytoplasm and is inactive. When a neurotransmitter binds to its receptor on the outside of the cell membrane, GDP dissociates from the Î± chain and guanosine triphosphate (GTP) binds in its place, activating the Î± subunit. The activated Î± chain then dissociates from receptor and from the Î² and Î³ chains. Both the activated Î± subunit and Î²Î³ subunits modulate effectors in the plasma membrane.[140] The effector influenced by Î± or Î²Î³ subunits may be an enzyme that the subunits stimulate or inhibit (eg, adenylate cyclase) or an ion channel that is opened or closed directly or through other chemical reactions (eg, channel phosphorylation).[30] Intrinsic GTPase activity in the Î± chain eventually converts the GTP to GDP, inactivating the Î± subunit and allowing it to reassociate with the Î² and Î³ chains and the neurotransmitter receptor, terminating the action of the subunits.[140]

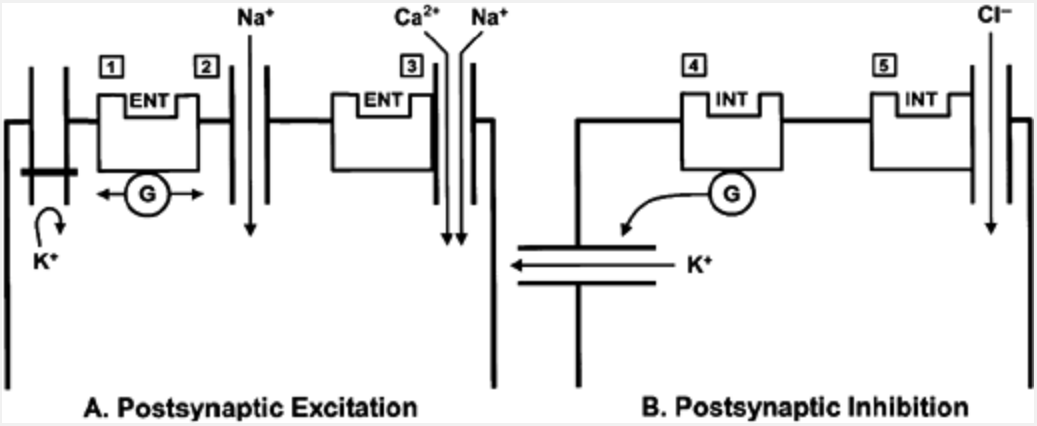

Figure 14-1. Common mechanisms of postsynaptic excitation and inhibition. A. An excitatory neurotransmitter (ENT) binds to receptors linked to G proteins to prevent K^+ efflux [1] or to allow Na^+ influx [2], producing membrane depolarization. An ENT may bind to and activate a cation channel [3] to allow Na^+ and/or Ca^{2+} influx with resultant membrane depolarization. B. An inhibitory neurotransmitter (INT) hyperpolarizes the membrane (makes membrane potential more negative) by binding to receptors linked to G proteins to enhance K^+ efflux [4], or to Cl^- channels to allow Cl^- influx [5]. Some chloride channels are regulated by G proteins as well. G = G protein.

G proteins are mainly categorized by the type of Î± chain they contain. The three main families of G proteins coupled to neurotransmitter receptors are G_s (containing the Î± subunit $Î±_s$), $G_{i/o}$ (containing $Î±_i$ or $Î±_o$), and G_q (containing $Î±_q$). G_s is a positive allosteric effector of membrane-bound adenylate cyclase; activation of a neurotransmitter receptor coupled to G_s causes a rise in intracellular 3â€², 5â€²-cyclic adenosine monophosphate (cAMP) concentration.[89] Neurotransmitter receptors activating G_i may inhibit adenylate cyclase or modulate K^+ and Ca^{2+} channels. Receptors coupled to $G_{q/11}$ act through membrane-bound phospholipase C to

increase intracellular calcium concentrations.

Table 14-1 lists the neurotransmitter receptors coupled to G proteins. A given neurotransmitter can activate different classes of receptors (eg, channel and G protein) or different types of receptors in the same class. For example, $GABA_A$ receptors are Cl^- channels, whereas $GABA_B$ receptors are coupled to G proteins. Dopamine D_1 receptors are linked to G_s, whereas D_2 receptors are linked to G_i or G_o.

Neuronal Excitation and Inhibition

Excitatory neurotransmitters usually act postsynaptically by causing Na^+ or Ca^{2+} influx, or by preventing K^+ efflux, triggering depolarization and an action potential (Fig. 14-1). These effects may be mediated by channel or G protein-coupled receptors.

Postsynaptic inhibition can be mediated by channel receptors or by receptors coupled to G proteins (Fig. 14-1). Inhibition is usually accomplished by movement of Cl^- into the neuron or by movement of K^+ out of the neuron. Both processes hyperpolarize the neuron and move membrane potential farther away from

threshold, making it more difficult for a given stimulus to depolarize the membrane to threshold voltage.

Presynaptic inhibition, the prevention of neurotransmitter release, is usually mediated by receptors coupled to G proteins. When a neurotransmitter released from a neuron binds to a receptor on that same neuron to limit further neurotransmitter release, the receptor is termed an *autoreceptor*.[133] Autoreceptors reside on dendrites, cell bodies, axons, and presynaptic terminals. Autoreceptors on dendrites and cell bodies (somatodendritic autoreceptors) usually inhibit further neurotransmitter release by increasing K^+ efflux, hyperpolarizing the neuron away from threshold (Fig. 14-2). However, activation of autoreceptors found on presynaptic terminals

(terminal autoreceptors) usually limits increases in intracellular Ca^{2+} concentration by limiting Ca^{2+} influx or preventing release from intracellular Ca^{2+} stores, impairing exocytosis of neurotransmitter vesicles (Fig. 14-2). Types of neurotransmitter receptors that serve as autoreceptors also usually reside postsynaptically, where they may mediate different physiologic effects.

Presynaptic nerve terminal inhibition of neurotransmitter release is not limited to actions by autoreceptors. Presynaptic terminal inhibitory receptors for various neurotransmitters may be found on a single neuron (heteroreceptors). For example, not only does stimulation of an $Î±_2$ autoreceptor on a noradrenergic nerve limit norepinephrine release, but stimulation of presynaptic $Î±_2$ receptors found on postganglionic parasympathetic nerve terminals prevents acetylcholine release.

Finally, stimulation of receptors on presynaptic nerve endings may enhance, rather than inhibit, neurotransmitter release. Such receptors also are usually coupled to G proteins. For example, stimulation of a $Î²_2$ receptor on an adrenergic nerve terminal enhances norepinephrine release.

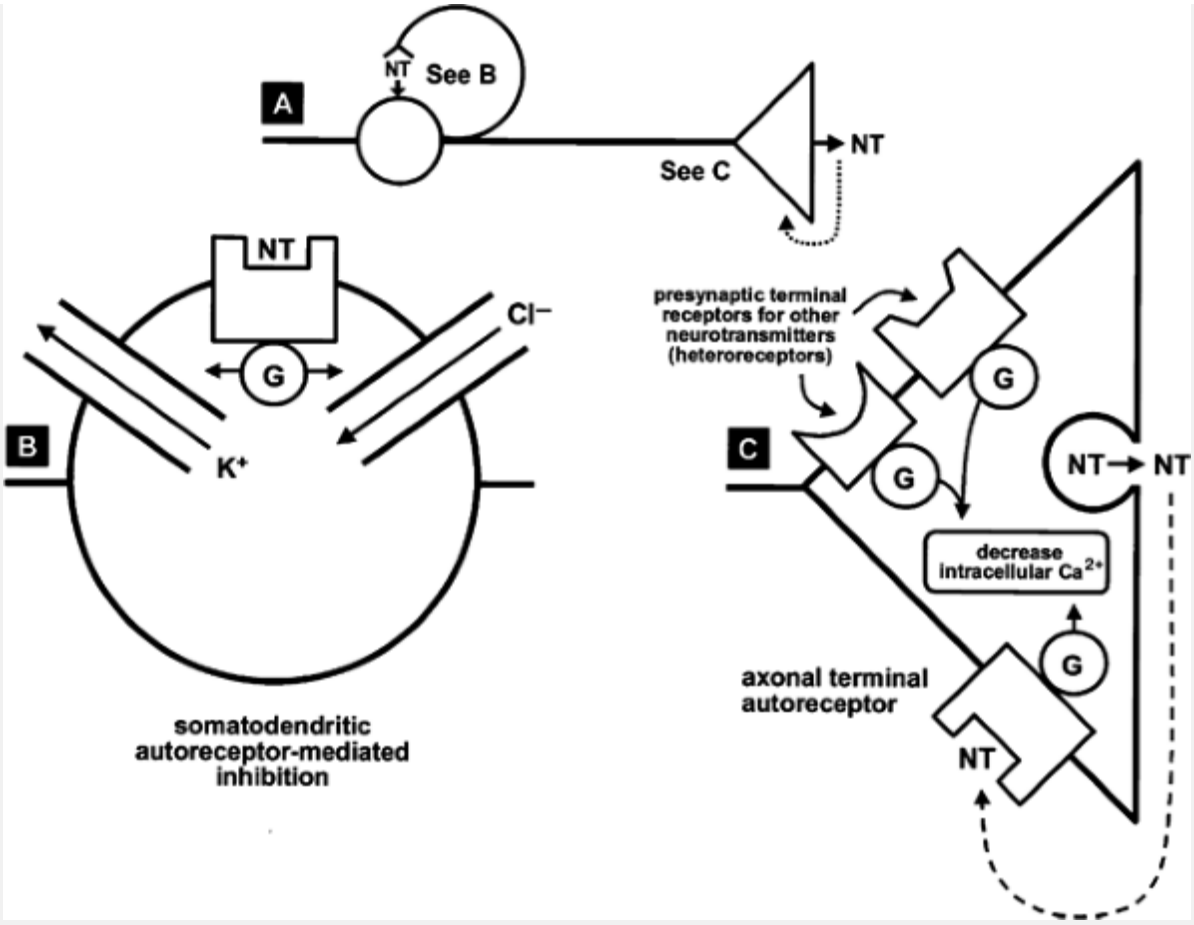

Figure 14-2. Common mechanisms of presynaptic inhibition (the inhibition of neurotransmitter [NT] release). A. Neuron A releases NT, which returns to activate receptors on the cell body or dendrites (somatodendritic autoreceptors), or on the axonal terminal (terminal autoreceptors). Such activation limits further release of NT by completing a negative feedback loop. B. At somatodendritic autoreceptors, NT binding produces activation of G proteins, which promote either K^+ efflux or Cl^- influx; both processes hyperpolarize the neuron away from threshold. C. At terminal autoreceptors, NT binding activates G proteins, which, through various mechanisms, lower intracellular Ca^{2+} concentrations to prevent exocytosis of NT vesicles, despite depolarization. Presynaptic inhibitory receptors for other types of

NTs (heteroreceptors) are illustrated in C. Excitatory axonal terminal autoreceptors and heteroreceptors that serve to enhance (not inhibit) neurotransmitter release are not shown. G = G protein.

Acetylcholine

ACh is a neurotransmitter of the central and peripheral nervous system. Centrally, it is found in both brain and spinal cord; cholinergic fibers project diffusely to the cerebral cortex. Peripherally, ACh serves as a neurotransmitter in autonomic and somatic motor fibers (Fig. 14-3).

Synthesis, Release, and Inactivation

Acetylcholine is synthesized from acetylcoenzyme A and choline. Acetylcholine moves into synaptic vesicles via the vesicular membrane transporter VAChT, where it is stored before release into the synapse by Ca^{2+}-dependent exocytosis. Acetylcholine undergoes degradation in the synapse to choline and acetic acid by acetylcholinesterase. An Na^{+}-dependent transporter in the neuronal membrane then pumps choline back into the cytoplasm to be used again as a substrate for ACh synthesis (Fig. 14-4). Pseudocholinesterase (plasma cholinesterase) is made in the liver and

plays no role in the degradation of synaptic ACh. However, it does metabolize some drugs, including cocaine and succinylcholine.

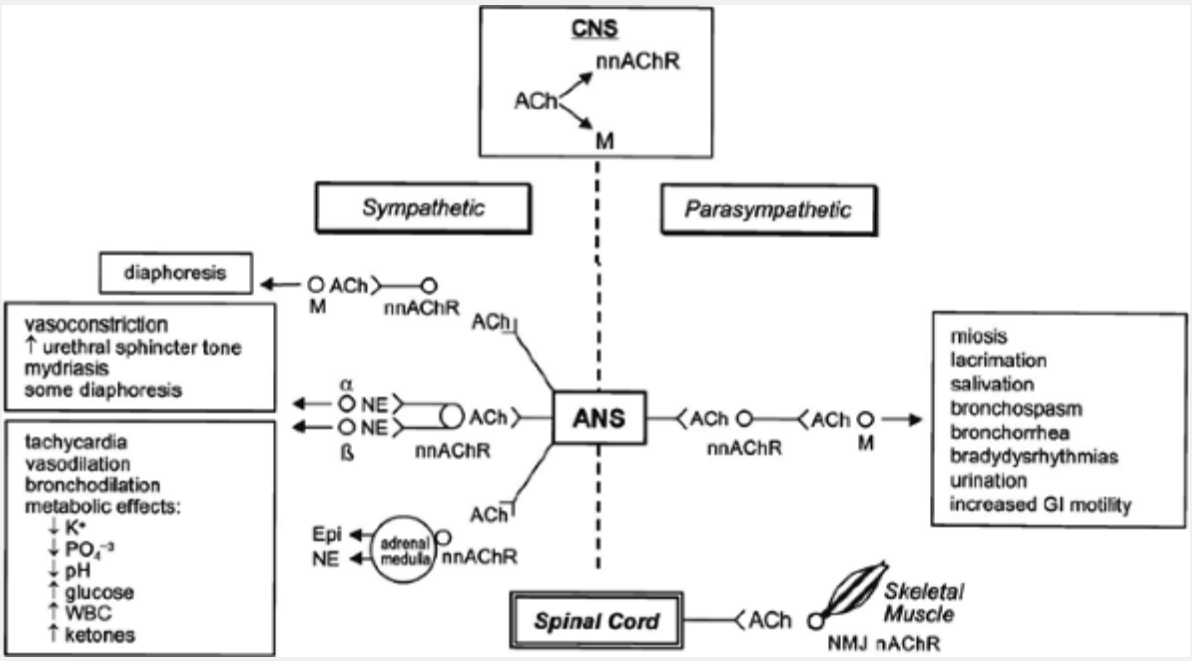

Figure 14-3. Diagram of the cholinergic nervous system, including adrenergic involvement in the autonomic nervous system. ACh binds to CNS, ganglionic, and adrenal neuronal nicotinic receptors (nnAChRs) and to neuromuscular junction nicotinic receptors (NMJ nAChRs). ACh also binds to various subtypes of muscarinic (M) receptors in the CNS and on effector organs innervated by postsynaptic parasympathetic neurons and to most sweat glands. NE and/or EPI released in response to ganglionic ACh stimulation of nnAChRs activates Î±- and Î²-adrenoceptors. ACh =acetylcholine; ANS = autonomic nervous system; CNS =central nervous system; EPI =epinephrine; NE =norepinephrine.

Acetylcholine Receptors

Nicotinic Receptors

After release from cholinergic nerve endings, ACh activates two main types of receptors: nicotinic and muscarinic.[85] Nicotinic receptors (nAChRs) reside in CNS (mainly in spinal cord), on postganglionic autonomic neurons (both sympathetic and parasympathetic), and at skeletal neuromuscular junctions, where they mediate muscle contraction (Fig. 14-3).

Nicotinic receptors at neuromuscular junctions (NMJ nAChRs) are part of an Na^+ channel made of five protein subunits and are thus channel receptors. Stimulation of these receptors by ACh results mainly in Na^+ influx, depolarization of the endplate, and triggering of an action potential that is propagated down muscle by voltage-gated Na^+ channels.

Nicotinic receptors on central or peripheral neurons or in the adrenal gland are termed neuronal nAChRs. Neuronal nAChRs are also ion channels, although in some cases Ca^{2+} influx through the receptor may be more important than Na^+ influx. Neuronal nAChRs also comprise five protein subunits.

Muscarinic Receptors

Muscarinic receptors reside in the CNS (mainly in the brain), on end organs innervated by postganglionic parasympathetic nerve endings, and at most postganglionic sympathetically innervated sweat glands (Fig. 14-4). At least five subtypes of muscarinic receptors, $M_{1â€“5}$, are recognized and linked to several G proteins. For example, in the heart, ACh released from the vagus nerve binds to M_2 receptors linked to G_i. G_i opens K^+ channels, allowing efflux of K^+ down its concentration gradient, which makes the inside of the cell more negative and more difficult to depolarize, slowing heart rate. Different subtypes of muscarinic receptors also act as autoreceptors in various locations, M_1 being the most common.

Chemical Agents

Table 14-2 provides examples of agents that affect cholinergic neurotransmission.

Modulators of Acetylcholine Release

Figure 14-4 illustrates sites of actions of numerous agents that influence the cholinergic nervous system. Botulinum toxins, some neurotoxins from pit vipers, and elapid Î²-neurotoxins prevent release of ACh from peripheral nerve endings.[61] This results in ptosis, other cranial nerve signs, weakness, and respiratory failure. Hypermagnesemia also inhibits acetylcholine release, probably by inhibiting Ca^{2+} influx into the nerve endings.[85]

Guanidine, aminopyridines, and black widow spider venom enhance the release of ACh from nerve endings. Guanidine has been unsuccessfully tried as a treatment for botulism. Aminopyridines block voltage-gated K^+ channels to prevent K^+ efflux; the resultant action potential widening (delayed repolarization) causes prolongation of Ca^{2+} channel activation, enhancing influx of Ca^{2+} and promoting neurotransmitter release. Aminopyridines have been used therapeutically in Lambert-Eaton syndrome, myasthenia gravis, and multiple sclerosis, and experimentally in calcium channel blocker overdose.

Black widow spider venom causes acetylcholine release with resultant muscle cramping and diaphoresis.[6] Carbachol, a nicotinic and muscarinic agonist, also probably causes ACh release.

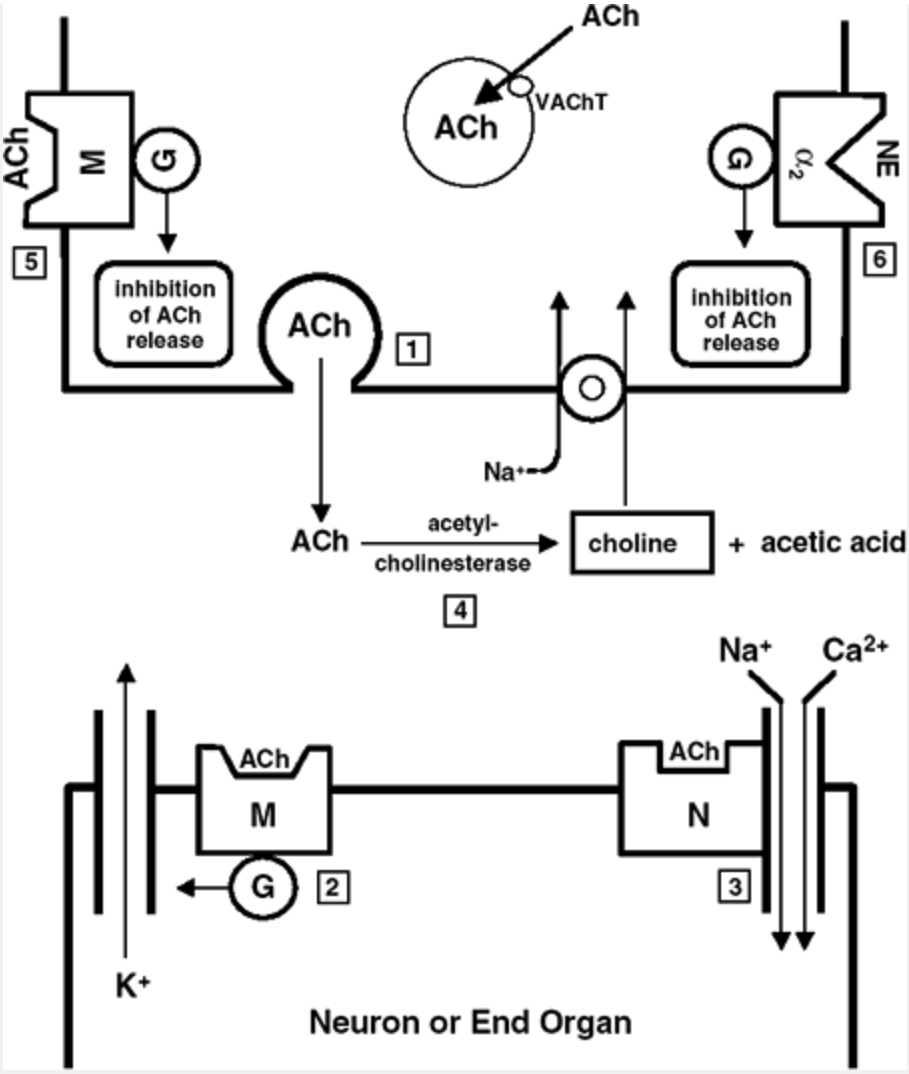

Figure 14-4. Cholinergic nerve ending. Activation of postsynaptic muscarinic receptors hyperpolarizes the postsynaptic membrane through G-protein-mediated enhancement of K^+ efflux. Several subtypes of muscarinic receptors coupled to various G proteins existâ€”a muscarinic receptor coupled to a G protein that opens K^+ channels is shown only as an example. Postsynaptic nicotinic receptor activation causes Na^+ influx and membrane depolarization. Importantly, Ca^{2+} influx appears to be the main cation involved with some neuronal nicotinic receptors. Presynaptic muscarinic and Î±$_2$-

adrenoceptor activation prevents ACh release through lowering of intracellular Ca^{2+} concentrations. The agents listed in Table 14-2 may act to enhance or prevent release of ACh [1]; activate or antagonize postsynaptic muscarinic (M) receptors [2]; activate or antagonize nicotinic (N) receptors [3]; inhibit acetylcholinesterase [4]; prevent ACh release by stimulating presynaptic muscarinic autoreceptors [5] or Î±$_2$-adrenergic heteroreceptors [6]; or enhance ACh release by antagonizing presynaptic autoreceptors [5] or by antagonizing presynaptic Î±$_2$-adrenergic heteroreceptors [6] (on parasympathetic postganglionic terminals). ACh =acetylcholine; G = G protein; NE =norepinephrine; VAChT = vesicular transporter for ACh.

Nicotinic Receptor Agonists and Antagonists

Agents that bind to and activate nicotinic receptors may stimulate postganglionic sympathetic and parasympathetic neurons, skeletal muscle endplates, and neurons within the CNS (Fig. 14-3). Prolonged depolarization at the receptor eventually causes blockade of nicotinic receptors.[113] For example, poisoning by nicotine, both a neuronal and NMJ nAChR agonist, produces hypertension, tachycardia, vomiting, diarrhea, muscle fasciculations, and convulsions (excitation), followed by hypotension, bradydysrhythmias, paralysis, and coma (blockade). Nicotinic agonists include nicotine alkaloids (eg, nicotine, coniine, lobeline), carbachol (mainly muscarinic effects), and methacholine (slight effect). Succinylcholine is a neuromuscular blocking agent that initially stimulates and then blocks NMJ nAChRs.

TABLE 14-2. Examples of Xenobiotics That Affect Cholinergic Neurotransmission

Cholinomimetics	Cholinolytics
Cause ACH release	Direct nicotinic antagonists
Î±$_2$-Adrenergic antagonists[a]	Î±-Bungarotoxin[c]
Aminopyridines	Coniine
Black widow spider venom	Cytisine
Carbachol	Gallamine
Guanidine	Hexamethonium
	Lobeline
Anticholinesterases	Mecamylamine
Echothiophate iodide	Nicotine
Edrophonium	Nondepolarizing neuro-
Galantamine	muscular blocking agents

N-methylcarbamate insecticides	Succinylcholine[b]
Metrifonate	Trimethaphan
Neostigmine	
Organic phosphorus insecticides	Indirect neuronal nicotinic
Physostigmine	antagonists
Pyridostigmine	Physostigmine
Rivastigmine	Tacrine
Tacrine	Galantamine
Direct nicotinic agonists	Direct muscarinic antagonists
Carbachol	Amantadine
Coniine	Antihistamines
Cytisine	Atropine
Lobeline	Benztropine

Nicotine	Carbamazepine
Succinylcholine (initial)[b]	Clozapine
	Cyclobenzaprine
Indirect neuronal nicotinic agonists	Disopyramide
Chlorpromazine	Glutethimide
Corticosteroids	Orphenadrine
Ethanol	Phenothiazines
Ketamine	Procainamide
Local anesthetics	Quinidine
Phencyclidine	Scopolamine
Volatile anesthetics	Tricyclic antidepressants
	Trihexyphenidyl
Direct muscarinic agonists	
Arecoline	Inhibit ACh release

Bethanechol	Î±2-Adrenergic agonists[d]
Carbachol	Botulinum toxins
Methacholine	Crotalidae venoms
Muscarine	Elapidae Î²-neurotoxins
Pilocarpine	Hypermagnesemia

ACh = acetylcholine
[a]Antagonism of Î±2-adrenoceptors enhances ACh release from parasympathetic nerve endings.
[b]Depolarizing neuromuscular blocking agent.
[c]Î±-Bungarotoxin exemplifies many elapid Î±-neurotoxins that produce paralysis and death from respiratory failure.
[d]Stimulation of presynaptic Î±2-adrenoceptors on parasympathetic nerve endings prevents ACh release.

Agents that block NMJ nAChRs without stimulation at skeletal neuromuscular junctions produce weakness and paralysis. Examples include curare and atracurium. Î±-Neurotoxins from elapids (eg, Î±-bungarotoxin) directly antagonize NMJ nAChRs,

producing ptosis, weakness, and respiratory failure from paralysis.[164]

Chemicals blocking peripheral neuronal nAChRs produce autonomic ganglionic blockade. Trimethaphan is used as a pharmacologic ganglionic blocker; however, trimethaphan is not entirely specific for neuronal nAChRs. Occasional patients develop weakness and

paralysis from NMJ nAChR blockade.

Recent studies demonstrate that the function of neuronal nAChRs can be modulated by a variety of compounds that do not bind to the ACh binding site, but bind instead to a number of distinct allosteric sites on the neuronal nAChR. For example, aside from their ability to inhibit acetylcholinesterase, physostigmine, tacrine, and galantamine bind to a noncompetitive allosteric activator site on neuronal nAChRs to enhance channel opening and ion conductance (there is evidence suggesting that serotonin may bind here as well). Furthermore, a diverse range of compounds, including chlorpromazine, phencyclidine, ketamine, local anesthetics, and ethanol bind to a noncompetitive negative allosteric site(s) to inhibit inward ion fluxes without directly affecting ACh binding. Steroids can desensitize neuronal nAChRs by binding to yet an additional allosteric site. Finally, a dihydropyridine calcium channel blocker binding site has been described, but remains poorly understood.[115]

Muscarinic Receptor Agonists and Antagonists

Peripheral muscarinic agonists produce bradycardia, miosis, salivation, lacrimation, vomiting, diarrhea, bronchospasm, bronchorrhea, and micturition. Central muscarinic agonists produce sedation, extrapyramidal dystonias and rigidity, coma, and convulsions. Examples of direct muscarinic agonists include muscarine (from mushrooms), bethanechol, pilocarpine, carbachol, arecoline, and methacholine.

Anticholinergic poisoning syndrome results from blockade of muscarinic receptors and is more appropriately referred to as antimuscarinic poisoning syndrome.[136] Central nervous system muscarinic blockade produces confusion, agitation, myoclonus, tremor, picking movements, abnormal speech, hallucinations, and coma. Peripheral antimuscarinic effects include mydriasis, anhidrosis, tachycardia, and urinary retention. Muscarinic antagonists number in

the hundreds; Table 14-2 lists examples.

Acetylcholinesterase Inhibition

Agents inhibiting acetylcholinesterase raise ACh concentrations at both nicotinic and muscarinic receptors, producing a variety of CNS, sympathetic, parasympathetic, and skeletal muscle signs and symptoms.[32] Anticholinesterases include organic phosphorus compounds and *N*-methylcarbamates. Organic phosphorus compounds are usually encountered as insecticides, although topical medicinal organic phosphorus compounds are used for the treatment of glaucoma and lice. *N*-methylcarbamates are found as insecticides and pharmaceutics. Medicinal *N*-methylcarbamates include physostigmine, pyridostigmine, rivastigmine, and neostigmine. Edrophonium, galantamine, tacrine, and metrifonate are noncarbamate, reversible anticholinesterases.

Î ±$_2$-Adrenoceptor Agonists and Antagonists

Agonists and antagonists of Î±$_2$-adrenoceptors are discussed in detail below. Briefly, stimulation of presynaptic Î±$_2$-adrenoceptors on postganglionic parasympathetic nerve endings decreases ACh release. Conversely, presynaptic Î±$_2$ antagonism increases ACh release (Fig. 14-4).

Norepinephrine and Epinephrine

Norepinephrine (NE), epinephrine (EPI), dopamine (DA), and serotonin (5-hydroxytryptamine; 5-HT) have historically been referred to as biogenic amines, and their neurotransmitter systems are similar in many respects. Neurotransmitter synthesis, vesicle transport and storage, uptake, and degradation share many enzymes and structurally similar transport proteins. Cocaine, reserpine, amphetamines, and monoamine oxidase inhibitors (MAOIs) affect all four types of neurons. In addition, these agents produce several

different effects in the same system. For example, in the noradrenergic neuron, amphetamines work mainly by causing the release of cytoplasmic norepinephrine, but they also inhibit norepinephrine uptake, and their metabolites inhibit monoamine oxidase. Actions of drugs that affect all biogenic amine neurotransmitters are described in the most detail for noradrenergic neurons. For the sake of brevity, similar mechanisms of action are simply noted in discussions of dopaminergic and serotonergic neurotransmission.

Norepinephrine is released from postganglionic sympathetic fibers (Fig. 14-3) and is also found in the CNS. The adrenal gland, acting as a modified sympathetic ganglion, releases epinephrine and lesser amounts of norepinephrine in response to stimulation of neuronal nAChRs. Epinephrine-containing neurons also reside in the brainstem.

The locus ceruleus is the main noradrenergic nucleus in the brain, comprising about 12,500 neurons in the floor of the fourth ventricle on each side of the pons. Axons radiate from this nucleus out to all layers of the cerebral cortex, to the cerebellum, and to other structures. Norepinephrine demonstrates both excitatory and inhibitory actions in the CNS. Norepinephrine released from locus ceruleus projections in the hippocampus increases cortical neuron activity through Î²-adrenoceptor activation and G protein-mediated inhibition of K^+ efflux. Norepinephrine released in outer cortical areas produces inhibitory effects mediated by Î±-adrenoceptor agonism. At this level, norepinephrine produces slow cortical neuron hyperpolarization and decreased rates of spontaneous firing. Consistent with this, norepinephrine demonstrates anticonvulsant actions in animals. Carbamazepine's anticonvulsant action may be partly a result of inhibition of norepinephrine uptake.[45] Despite antagonistic actions on different cortical neurons, electrical stimulation of the locus ceruleus produces widespread cortical activation and excitation. This overall effect probably explains a great deal of the hyperattentiveness and lack of fatigue that

accompanies use of agents that mimic or increase noradrenergic activity in the brain. Locus ceruleus neuronal firing increases during waking and dramatically falls during sleep.

Synthesis, Release, and Uptake

Figure 14-5 is a representation of a noradrenergic neuron. Tyrosine hydroxylase is the rate-limiting enzyme in norepinephrine synthesis and is sensitive to negative feedback by norepinephrine. This enzyme requires Fe^{2+} as a cofactor and exists as a homotetramer and is upregulated by chronic exposure to caffeine and nicotine. Under normal dietary conditions tyrosine hydroxylase is completely saturated by tyrosine, and increasing dietary tyrosine intake does not appreciably increase dopa synthesis. Dopa undergoes decarboxylation by L-amino acid decarboxylase to dopamine. L-Amino acid decarboxylase (dopa decarboxylase) is not specific for dopa. For example, it also catalyzes the formation of serotonin from 5-hydroxytryptophan.

About one-half of cytoplasmic dopa is actively pumped into vesicles containing the enzyme dopamine-Î²-hydroxylase by VMAT2. The remaining dopamine is quickly deaminated.

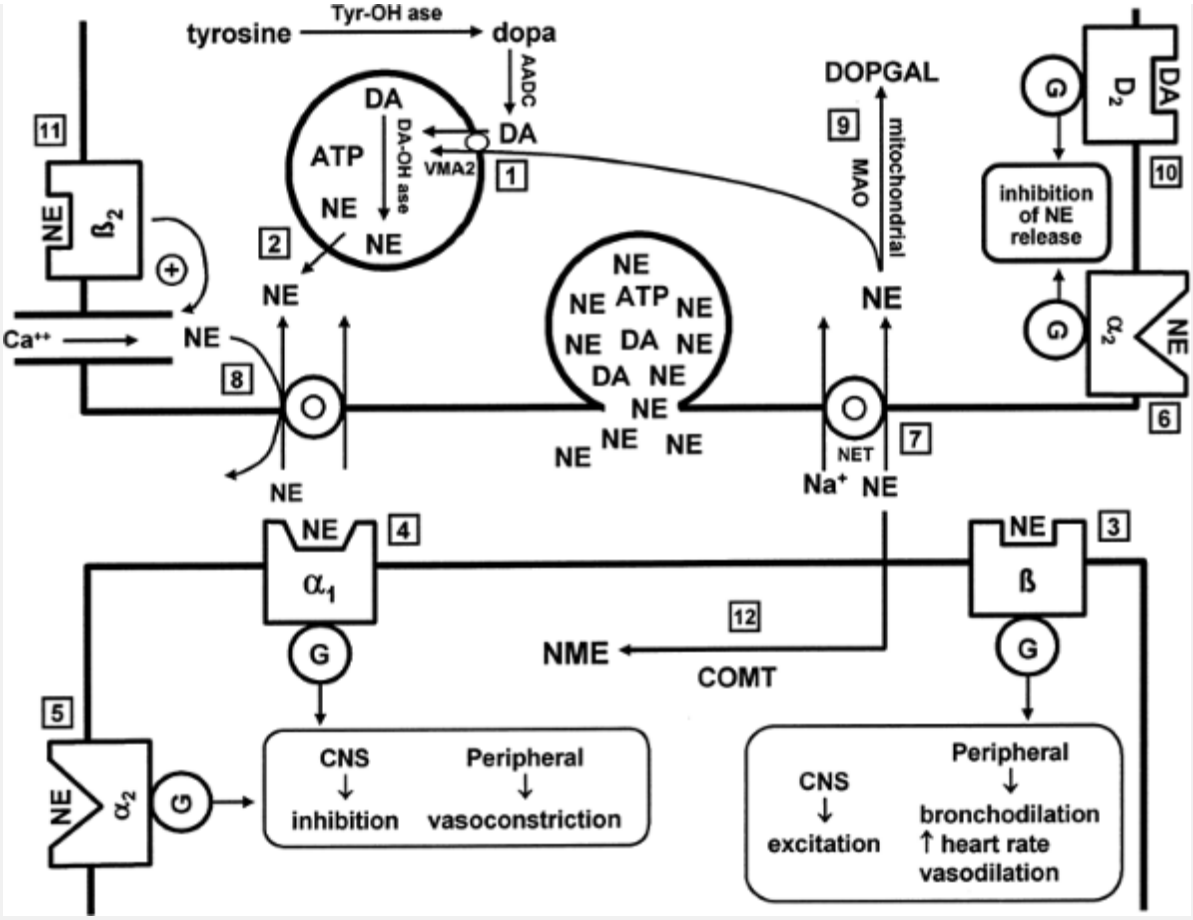

Figure 14-5. Noradrenergic nerve ending. The postsynaptic membrane may represent an end organ or another neuron in the CNS. Brief examples of effects resulting from postsynaptic receptor activation are shown. Agents in Tables 14-4 and 14-5 produce effects by inhibiting transport of dopamine (DA) or norepinephrine (NE) into vesicles through VMA2 [1]; causing movement of NE from vesicles into the cytoplasm [2]; activating or antagonizing postsynaptic Î±- and Î²-adrenoceptors [3â€“5]; modulating NE release by activating or antagonizing presynaptic $Î±_2$-autoreceptors [6], $dopamine_2$ (D_2) heteroreceptors [10], or $Î²_2$-autoreceptors [11]; blocking uptake of NE (NET inhibition) [7]; causing reverse transport of NE from the cytoplasm into the synapse via NET by raising cytoplasmic NE concentrations [8]; inhibiting monoamine oxidase (MAO) to prevent NE degradation

[9]; or inhibiting COMT to prevent NE degradation [12]. COMT is not found in neurons in large amounts. AADC =aromatic L-amino acid decarboxylase; ATP =adenosine triphosphate; DA-OHase = dopamine-Î²-hydroxylase; COMT = catechol-*O*-methyltransferase; CNS =central nervous system; DOPGAL = 3,4-dihydroxyphenylglycoaldehyde; G = G protein; NET =membrane NE uptake transporter; NME = normetanephrine; Tyr-OHase = tyrosine hydroxylase; VMA2 =vesicle uptake transporter for NE.

In the vesicle, dopamine is converted to norepinephrine by dopamine-Î²-hydroxylase, an enzyme requiring Cu^{2+} and ascorbic acid. Vesicles isolated from peripheral nerve endings contain dopamine, norepinephrine, dopamine-Î²-hydroxylase, and ATP, and all of these substances are released into the synapse during Ca^{2+}-dependent exocytosis triggered by neuronal firing. (Whether dopamine-Î²-hydroxylase is released into CNS synapses has not been determined.) In neurons containing epinephrine as a neurotransmitter, norepinephrine is released from vesicles into the cytoplasm, where it is converted to epinephrine by phenylethanolamine-*N*-methyl-transferase. Epinephrine is then transported back into vesicles before synaptic release.[85]

Norepinephrine is removed from the synapse mainly by uptake into the presynaptic neuron by the norepinephrine transporter (NET). Although this transporter has great affinity for norepinephrine, it also transports other amines, including dopamine, tyramine, MAOIs, and amphetamines. Once pumped back into the cytoplasm, norepinephrine can either be transported back into vesicles for further storage and release, or can be quickly enzymatically degraded by monoamine oxidase (MAO), an enzyme expressed on the outer mitochondrial membrane.

MAO resides in sympathetic postganglionic neurons, intestinal mucosa, liver, kidney, lung, and brain, but also extracellularly. It

exists as two isozymes, MAO-A and MAO-B,[98] each with relatively separate affinities for various substrates (Table 14-3). Neuronal MAO degrades cytoplasmic amines, including neurotransmitters, to

prevent elevated cytoplasmic concentrations of biogenic amines. Hepatic and intestinal MAO prevent large quantities of dietary bioactive amines from entering the circulation and producing systemic effects.

TABLE 14-3. Characteristics of Monoamine Oxidase (MAO) Isozymes

	MAO Isozymes	
	MAO-A	MAO-B
Location		
Brain	+	+++
Intestine	+++	+
Liver	++	++
Platelets	0	++++
Placenta	++++	0
Substrates		

Norepinephrine	+ + + +	+
Epinephrine	+ +	+ +
Dopamine	+ +	+ +
Serotonin	+ + + +	+
Tyramine	+ +	+ + +

Catechol-*O*-methyltransferase (COMT), found in the synaptic cleft, also metabolizes norepinephrine and epinephrine. In other tissue, COMT metabolizes catecholamines, including those that have entered the systemic circulation.

Adrenergic Receptors

The two main types of adrenoceptors are Î±-adrenoceptors and Î²-adrenoceptors. All adrenoceptors are linked to G proteins.

Î²-Adrenoceptors

Î²-Adrenoceptors are divided into three major subtypes ($Î²_1$, $Î²_2$, and $Î²_3$), depending on their affinity for various agonists and antagonists.[28,66,68,89] $Î²_1$- and $Î²_2$-adrenoceptors are linked to G_s, and their stimulation raises cAMP concentration and/or activates protein kinase A, which, in turn, produces several effects, including regulation of ion channels. At least some $Î²_3$-adrenoceptors may be coupled not only to G_s, but also to receptors for $G_{i/o}$ proteins.

The Î²-adrenoceptors are polymorphic, with genetic variation in the human population.[26] Polymorphism influences response to medications, regulation of receptors, and clinical course of

disease.[26,68,89] In general, peripheral Î²$_1$-adrenoceptors are found mainly in the heart (along with Î²$_2$ receptors), whereas peripheral Î²$_2$-adrenoceptors also mediate additional adrenergic effects.[68] Presynaptic Î²$_2$-adrenoceptor activation causes release of norepinephrine from nerve endings (positive feedback). Î²$_3$-Adrenoceptors reside mainly in fat, but they also reside in skeletal muscle, gallbladder, and colon where they regulate metabolic processes. Activation of cardiac Î²$_3$-adrenoceptors might produce negative inotropic effects in some circumstances. Î²$_3$-Adrenoceptors' polymorphism may contribute to clinical expressions of nonâ€“insulin-dependent diabetes and obesity.[26,148,165]

Î±-Adrenoceptors

Î±-Adrenoceptors are linked to G proteins that inhibit adenylate cyclase and lower cAMP levels, affect ion channels, increase intracellular calcium through inositol triphosphate and diacylglycerol production, or produce other actions. These receptors are divided into two main types, Î±$_1$ and Î±$_2$, and at least six subtypes, Î±$_{1A}$, Î±$_{1B}$, Î±$_{1D}$, Î±$_{2A}$, Î±$_{2B}$, and Î±$_{2C}$.[39,66] Most Î±$_1$ adrenoceptors are coupled to G_q, whereas most Î±$_2$ adrenoceptors are coupled to G_i.

In peripheral tissue, Î±$_1$-adrenoceptors reside on the postsynaptic membrane in continuity with the synaptic cleft. Stimulation of these receptors on blood vessels commonly results in vasoconstriction. Most Î±$_1$ receptors are coupled to G_q.

Î±$_2$-Adrenoceptors reside on both sides of the synapse. Presynaptic Î±$_2$-adrenoceptor activation mediates negative feedback, limiting further release of norepinephrine (Fig. 14-5). Postganglionic parasympathetic neurons (cholinergic) also contain presynaptic Î±$_2$-adrenoceptors that, when stimulated, prevent release of ACh (Fig. 14-4).

Postsynaptic Î±$_2$-adrenoceptors on vasculature also can mediate vasoconstriction. Initially, it was suggested that postsynaptic Î±$_2$-adrenoceptors resided mainly outside of the synapse and mediated

vasoconstrictive responses to circulating Î± agonists such as norepinephrine, whereas postsynaptic $Î±_1$-adrenoceptors responded to norepinephrine released from nerve endings. However, it has been demonstrated that in at least some tissues (eg, saphenous vein), norepinephrine released following nerve stimulation produces vasoconstriction through action at $Î±_2$-adrenoceptors, making the previous differentiation not as distinct.[39,74] Because both $Î±_1$- and $Î±_2$-adrenoceptors on noncerebral vasculature mediate vasoconstriction, a patient with hypertension from high concentrations of circulating catecholamine (eg, pheochromocytoma or clonidine withdrawal) or from extravasation of norepinephrine from an intravenous line commonly needs both $Î±_1$- and $Î±_2$-adrenoceptor blockade to vasodilate adequately (eg, phentolamine). Stimulation of postsynaptic $Î±_2$-adrenoceptors in the brainstem inhibits sympathetic output and produces sedation (Fig. 14-6). In fact, dexmedetomidine, an imidazole and potent $Î±_{2A}$-adrenergic agonist, is used for sedation in intensive care patients, although hypotension and bradycardia occur as expected side effects.[13]

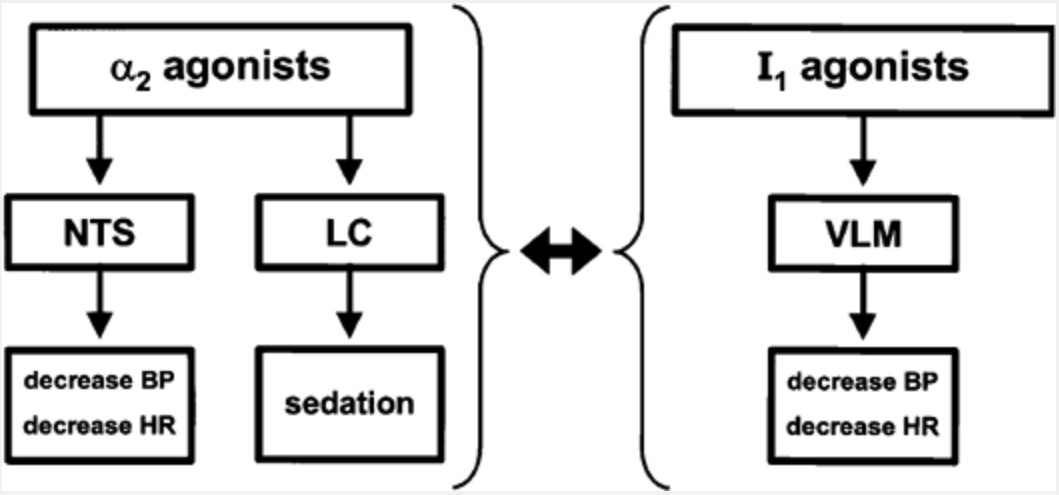

Figure 14-6. Central action of agents that activate $Î±_2$-adrenoceptors or that bind to type 1 imidazoline binding sites (I_1). There are poorly understood interactions between

imidazoline binding sites and Î±$_2$-adrenoceptors that make delineation of specific effects difficult to attribute to specific receptor activation. BP = blood pressure; HR = heart rate; LC =locus ceruleus; NTS = nucleus tractus solitarius; VLM =ventrolateral medulla.

Chemical Agents

Chemicals producing pharmacologic effects that result in or mimic increased activity of the adrenergic nervous system are *sympathomimetics* (Table 14-4). Those with the opposite effect are *sympatholytics* (Table 14-5).

Sympathomimetics

Direct-Acting Agents

Drugs or chemicals whose sympathomimetic actions result from direct binding to Î±- or Î²-adrenoceptors are called direct-acting sympathomimetics. Most of these drugs do not cross the bloodâ€“brain barrier in significant quantities.

Indirect-Acting Agents

Agents that produce sympathomimetic effects by causing the release of cytoplasmic norepinephrine from the nerve ending in the absence of vesicle exocytosis are called indirect-acting sympathomimetics. Amphetamine is the prototype of indirect-acting agents and is used for the discussion of what is known about their mechanism of action. In general, mechanisms of indirect release of norepinephrine by amphetamines, cocaine, phencyclidine, MAOIs, and mixed-acting agents noted in Table 14-4 are similar in that their actions depend on their ability to produce elevated cytoplasmic norepinephrine concentrations.

Amphetamine and structurally similar indirect-acting agents move into the neuron mainly by the membrane transporter that pumps norepinephrine into the neuron. (Lipophilic indirect-acting

agents move into the neuron by diffusion.) From the cytoplasm, amphetamines are transported into neurotransmitter vesicles, where they buffer hydrogen ions to raise intravesicle pH. As noted earlier, much of the vesicle's ability to concentrate norepinephrine (and other neurotransmitters) is a result of ion trapping of norepinephrine at the lower pH. The rise in intravesicle pH produced by amphetamines causes norepinephrine to leave the vesicle and move into the cytoplasm.[149,150] Such movement may be caused by diffusion and/or reverse transport of norepinephrine by VMAT2. In the cytoplasm, amphetamines also compete with norepinephrine and dopamine for transport into vesicles, which further contributes to elevated cytoplasmic norepinephrine concentrations. In the case of amphetamine, the rise in cytoplasmic concentrations of norepinephrine may be enhanced by the ability of amphetamine metabolites to inhibit MAO, which impairs norepinephrine degradation.

TABLE 14-4. Examples of Sympathomimetics

Direct acting
Î²-Adrenoceptor agonists
Albuterol
Dobutamine
Epinephrine
Isoproterenol
Metaproterenol
Norepinephrine
Ritodrine

Terbutaline
Î±-Adrenoceptor agonists
Dobutamine
Epinephrine
Ergot alkaloids
Methoxamine
Norepinephrine
Phenylephrine
Indirect acting
Amphetamines
Cocaine
Fenfluramine
MAOIs
Methylphenidate
Pemoline
Phencyclidine
Phenmetrazine
Propylhexedrine
Tyramine
Mixed acting
Dopamine
Ephedrine
Mephentermine
Phenylpropanolamine
Pseudoephedrine
Selective $Î±_2$-adrenoceptor antagonists
Idazoxan
Yohimbine
Imidazoline binding-site antagonists
Idazoxan
MAOIs
Amphetamine metabolites
Clorgyline[a]
Isocarboxazid

Linezolid
Moclobemide[a]
Pargyline
Phenelzine
Selegiline[b]
Tranylcypromine
Inhibit NE Uptake
Amphetamines
Atomoxetine
Benztropine
Bupropion
Carbamazepine
Cocaine
Diphenhydramine
Duloxetine
Orphenadrine
Pemoline
Reboxetine
Tramadol
Tricyclic antidepressants
Trihexyphenidyl
Venlafaxine

MAOIs = monoamine oxidase inhibitors; NE = norepinephrine.
[a] Mainly inhibit MAO-A at low doses.
[b] Mainly inhibit MAO-B at low doses.

Every time the Na^+-dependent uptake transporter, NET, moves, a bioactive amine (eg, tyramine) into the neuron where it is released, a binding site for norepinephrine on NET transiently faces inward and becomes available for reverse transport of norepinephrine out of the neuron. The normally low concentration of cytoplasmic norepinephrine prevents significant reverse transport. In the face of

elevated cytoplasmic norepinephrine concentrations produced by indirect-acting agents as described earlier, NET moves norepinephrine out of the neuron and back into the synapse, where the neurotransmitter stimulates adrenoceptors (indirect action). This process is sometimes referred to as facilitated exchange diffusion, or displacement, of norepinephrine from the nerve ending. Evidence supporting reverse transport produced by amphetamines is that inhibitors of the transporter (eg, tricyclic antidepressants) prevent amphetamine-induced norepinephrine release.

While all indirect-acting agents cause reverse norepinephrine transport by increasing cytoplasmic norepinephrine concentrations, those that move into the neuron by the membrane transporter (eg, amphetamines, MAOIs, dopamine, tyramine) further enhance reverse transport because their uptake may cause more norepinephrine binding sites on NET to face inward per unit time.

Although cocaine does inhibit NET, it also causes some norepinephrine release. In fact, cocaine similarly lessens pH gradients across vesicle membranes[150] to raise cytoplasmic concentrations of

norepinephrine. That cocaine produces less norepinephrine release than amphetamines is partly explained by cocaine-induced inhibition of the membrane transporter and by the fact that cocaine does not move into the neuron by active uptake (ie, does not increase the number of norepinephrine binding sites facing inward), but diffuses into the neuron. (Most of cocaine's severe sympathomimetic effects probably result from cocaine's action on the brain rather than peripheral nerve endings.[155])

TABLE 14-5. Examples of Sympatholytics

Î±-Adrenoceptor antagonists	Penbutolol[a]
Clozapine	Pindolol[a]
Doxazosin	Practolol[a]
Droperidol	Propranolol
Ergot alkaloids	Sotalol
Labetalol	Timolol
Olanzapine	
Phenothiazines	Prevent NE release with
Phenoxybenzamine	depolarization
Phentolamine	Bretylium[b]
Prazosin	Reserpine[b]
Quinidine	
Risperidone	Î±2-Adrenoceptor agonists[d]
Terazosin	Î±-Methyldopa[c]

Tolazoline	Brimonidine
Trazodone	Clonidine
Tricyclic antidepressants	Dexmedetomidine
Urapidil	Guanabenz
	Guanfacine
Inhibit dopamine-Î²-hydroxylase	Moxonidine
Diethyldithiocarbamate	Naphazoline
Disulfiram	Oxymetazoline
MAOIs	Rilmenidine
	Tetrahydralazine
Î²-Adrenoceptor antagonists	Xylometazoline
Acebutolol[a]	
Alprenolol[a]	Imidazoline binding-site agonists[d]
Atenolol	Clonidine

Betaxolol	Guanabenz
Bisoprolol	Guanfacine
Carteolol	Moxonidine
Carvedilol	Naphazoline
Esmolol	Oxymetazoline
Labetalol	Rilmenidine
Metipranolol[a]	
Metoprolol	Inhibitors of vesicle uptake
Nadolol	Reserpine[b]
Oxprenolol[a]	Tetrabenazine

NE = norepinephrine; MAOIs = monoamine oxidase inhibitors.
[a] Partial Î²-agonist.
[b] Causes transient NE release after initial dose.
[c] Metabolized to Î±-methylnorepinephrine, which activates Î±$_2$-receptors.
[d] Agents in these categories vary in their relative selectivity for Î±$_2$-adrenoceptors or imidazoline binding sites.

Phencyclidine (PCP) is a hallucinogen that possesses multiple pharmacologic actions. Like toxicity from many hallucinogens, PCP

toxicity is accompanied by increased adrenergic activity, which results, in part, from PCP-induced decreases in pH gradients across the vesicle membrane[150] and indirect release of norepinephrine. Like cocaine, PCP moves into the neuron by diffusion rather than uptake through the membrane transporter, at least partly explaining less PCP-induced norepinephrine release than is typically seen in amphetamine poisoning.

Reserpine, guanethidine, and bretylium cause neurotransmitter release either with initial doses or early in overdose before their primary sympatholytic effects are observed. Presumably this is a result of transient rises in cytoplasmic norepinephrine concentrations.

In addition to causing ACh release, black widow spider venom causes vesicle exocytosis of norepinephrine, producing hypertension and diaphoresis over the palms, soles, upper lip, and nose. All of the aforementioned indirectly acting agents, except black widow spider venom, enter the CNS.

Mixed-Acting Agents

Mixed-acting sympathomimetics act directly and indirectly. For example, large doses of phenylpropanolamine indirectly cause norepinephrine release and act directly as Î±-adrenoceptor agonists. Intravenously administered dopamine indirectly causes norepinephrine release, explaining most of its vasoconstricting activity, but also directly stimulates dopaminergic and Î²-adrenoceptors. Direct Î±-agonism occurs at high doses. Except for dopamine, these agents also cross the bloodâ€“brain barrier to produce central effects.

Uptake Inhibitors

Inhibitors of norepinephrine uptake raise concentrations of norepinephrine in the synapse to produce excessive stimulation of

adrenoceptors.

There are two main mechanisms of action for inhibitors of biogenic amine uptake: competitive and noncompetitive. Noncompetitive inhibitors, such as cyclic antidepressants, carbamazepine, venlafaxine, methylphenidate, and cocaine, bind at or near the carrier site on NET to prevent NET from moving norepinephrine and other agents into or out of the neuron. These inhibitors are not transported into the neuron by this mechanism; lipophilic agents diffuse into the neuron. Various drugs used for their antimuscarinic effects also block NET noncompetitively. These include benztropine, diphenhydramine, trihexyphenidyl, atomoxetine, and orphenadrine.[105]

The second mechanism, competitive inhibition of NET, characterizes most indirect-acting agents, including amphetamines and structurally similar compounds (eg, mixed-acting agents, MAOIs). These agents prevent norepinephrine uptake by competing with synaptic norepinephrine for binding to the carrier site on NET, the mechanism by which these agents move into the neuron. In fact, an additional adrenergic action of amphetamines, mixed-acting agents, MAOIs, and tyramine is to raise synaptic norepinephrine concentrations by competing with norepinephrine for uptake, thereby compounding their indirect and/or direct actions.

MAOIs

MAOIs are transported by NET into the neuron, where they act through several mechanisms.[98] Inhibition of MAO, their main pharmacologic effect, results in increased cytoplasmic concentrations of norepinephrine and some indirect release of neurotransmitter into the synapse. As a minor effect they also may displace norepinephrine from vesicles by raising pH in a manner similar to amphetamines. These actions explain the initial hyperadrenergic findings following MAOI overdose and probably also account for occasional and unpredictable adrenergic crises in patients taking these agents,

despite the patients' compliance with diet.

Nonspecific MAOIs inhibit both isozymes of MAO, preventing intestinal and hepatic degradation of bioactive amines as well. A person taking such an MAOI who then ingests food or receives drugs containing indirect-acting sympathomimetics (eg, tyramine, phenylpropanolamine, dopamine, amphetamines) has a much larger cytoplasmic concentration of norepinephrine to transport into the synapse and may therefore develop central and peripheral hyperadrenergic findings. Although MAOIs specific for the MAO-B isozyme are less likely to predispose to food or drug interactions by maintaining significant hepatic MAO activity, isozyme specificity is lost as the dose of the MAOI is increased. In fact, selegiline, currently marketed as a selective MAO-B inhibitor, partially inhibits MAO-A activity at therapeutic doses. Specificity may lack importance when indirect-acting agents are administered systemically (eg, intravenous dopamine or amphetamines). Several amphetamine metabolites are capable of inhibiting MAO, contributing to their sympathomimetic activity. Linezolid is an antibiotic that produces weak MAO inhibition.

Occasionally, patients suffering from refractory depression respond to a combination of MAOIs and tricyclic antidepressants. This combination therapy is usually unaccompanied by excessive adrenergic activity because the inhibition of the membrane uptake transporter by the tricyclic antidepressant attenuates excessive reverse transport of elevated cytoplasmic norepinephrine concentrations produced by MAOIs. In animals, tricyclic antidepressants that prevent norepinephrine uptake or cocaine, also an norepinephrine uptake inhibitor, protect against drug and food interactions with MAOIs by inhibiting the uptake transporter, thus inhibiting reverse transport.

COMT Inhibitors

Inhibitors of COMT are administered in the treatment of Parkinson

disease to prevent the catabolism of concomitantly administered L-dopa. Entacapone only acts peripherally, whereas tolcapone also crosses the bloodâ€“brain barrier.

Î ±$_2$-Adrenoceptor Antagonists

Yohimbine blocks Î±$_2$-adrenoceptors to produce a mixed clinical picture. Peripheral postsynaptic Î±$_2$ blockade produces vasodilatation. Blockade of presynaptic Î±$_2$-adrenoceptors on cholinergic nerve endings (Fig. 14-4) enhances ACh release, occasionally producing bronchospasm[82] and contributing to diaphoresis. Similar presynaptic actions on peripheral noradrenergic nerves enhance catecholamine release (Fig. 14-5). Blockade of central Î±$_2$-adrenoceptors in the locus ceruleus results in CNS stimulation, whereas blockade of postsynaptic Î±$_2$-adrenoceptors in the nucleus tractus solitarius may enhance sympathetic output (Fig. 14-6). The final result includes hypertension, tachycardia, anxiety, fear, agitation, mania, mydriasis, diaphoresis, and bronchospasm.[90] Yohimbine does not block

imidazoline receptors (see Imidazoline and Î±$_2$-Adrenoceptor Agonists below). One action of the antidepressant mirtazapine is Î±$_2$-adrenoceptor blockade.

Sympatholytics

Direct Antagonists

Direct Î±- and Î²-adrenoceptor antagonists are noted in Table 14-5. In overdose, and sometimes at therapeutic doses, any Î²-adrenoceptor selectivity becomes insignificant. Some Î²-adrenoceptor antagonists also are partial agonists.

Drugs That Prevent Norepinephrine Release

Drugs that prevent the release of norepinephrine, despite membrane depolarization, include guanethidine and bretylium. Both drugs initially cause release of norepinephrine and can produce transient sympathomimetic effects. Drugs that block the vesicle uptake transporter prevent the movement of norepinephrine into vesicles and deplete the nerve ending of this neurotransmitter, also preventing norepinephrine release after depolarization. Examples include rauwolfia alkaloids (reserpine), tetrabenazine, and guanethidine (in part). Reserpine and ketanserin inhibit both VMAT1 and VMAT2, whereas tetrabenazine only inhibits VMAT2. Like guanethidine, reserpine causes transient norepinephrine release with initial dose or early in overdose. Î²-Adrenoceptor antagonists block presynaptic $Î²_2$-adrenoceptors to limit catecholamine release from nerve endings, although this does not appear to be their main mechanism of action.

Imidazoline and $Î±_2$-Adrenoceptor Agonists

Numerous imidazoline derivatives (eg, clonidine) and structurally similar compounds are used as centrally acting antihypertensive agents or long-acting topical vasoconstrictors. These agents are currently divided into first-generation agents (eg, clonidine) that are thought to act at both $Î±_{2A}$-adrenoceptor and imidazoline binding sites, and second-generation agents (eg, rilmenidine) that express much greater affinity for imidazoline binding sites than for $Î±_{2A}$-adrenergic receptors.

The ventromedial (depressor) and the rostral-ventrolateral (pressor) areas of the ventrolateral medulla (VLM) are responsible for the central regulation of cardiovascular tone and blood pressure. They receive afferent fibers from the carotid and aortic baroreceptors, which form the tractus solitarius via the nucleus tractus solitarius (NTS).[73]

The hypotensive actions of $Î±_2$-adrenoceptor agonists were previously attributed entirely to brainstem $Î±_2$-adrenoceptor

activation, because stimulation of postsynaptic Î±$_2$-adrenoceptors in the NTS decreased sympathetic output (Fig. 14-6).[22] The discovery of imidazoline binding sites, however, led to a more complicated analysis. It was discovered that imidazolines and related substances produced hypotension when applied to the VLM, whereas catecholamines capable of activating Î±$_2$-adrenoceptors were claimed to be incapable of producing effects at this site. This led to the hypothesis that receptors specific for imidazoline-like compounds, different from Î±$_{2A}$-adrenoceptors, must exist. Decreased sympathetic output could result from activation of imidazoline binding sites in the VLM and from Î±$_2$-adrenoceptor activation in the NTS; sedation and respiratory depression were attributed to Î±$_2$-adrenoceptor activation in the locus ceruleus.[47]

Imidazoline binding sites have been characterized and subdivided into I_1, I_2 (with subtypes), and I_3.[42] I_1 binding sites reside on neuronal plasma membranes and are involved in controlling systemic blood pressure. I_2 sites are allosteric sites found on the external membrane of mitochondria and modulate MAO-A and MAO-B.[22,42] The putative I_3 sites are thought to modulate insulin secretion via ATP-sensitive potassium channels in Î²-islet cells.

The molecular structure of the imidazoline binding sites has not been identified and it is unclear whether these sites act through ion channels, through G proteins, or through some other mechanism. An endogenous ligand for these binding sites has been discovered. Agmatine, originally identified as a *clonidine-displacing substance*, is synthesized by decarboxylation of arginine. It appears to function as a neurotransmitter, and it binds all subclasses of both Î±$_2$-adrenoreceptors and I-binding sites, as well as block *N*-methyl-D-aspartate (NMDA) glutamate receptors. Other physiologic functions of agmatine continue to be investigated.[10,124]

Functional studies suggested that the hypotensive effects of clonidine-like drugs involved imidazoline binding sites, while most of the side effects involved Î±$_{2A}$-adrenoceptors.[47] Consequently, drugs

such as rilmenidine, possessing much greater activity at imidazoline binding sites than at Î±$_{2A}$-adrenoceptors, were developed. However, functional evidence suggests that there is significant interaction between the imidazoline sites and Î±$_{2A}$-adrenoceptors, and that this interaction is necessary to trigger hypotensive effects.[21,47] As examples, there appears to be a close relationship between â€œpresynapticâ€• imidazoline sites and â€œdownstreamâ€• Î±$_{2A}$-adrenoceptors in the VLM mediating hypotension;[62] Î±$_{2A}$-adrenoceptors in the VLM appear to be activated as a consequence of imidazoline site activation. Although second-generation agents (rilmenidine and moxonidine) preferentially act via imidazoline binding sites, and although Î±$_{2A}$-adrenoceptors are important for the hypotension produced by first-generation agents (clonidine and Î±-methyldopa), hypotension produced by all of these agents is dependent on central noradrenergic pathways.[21,62] Some studies report that yohimbine, an Î±$_2$-adrenoceptor antagonist, reverses the hypotensive effect of both clonidine and rilmenidine-like drugs, when given at high doses. Thus, it appears that there is significant interaction between imidazoline sites and Î±$_{2A}$-adrenoceptors, and that centrally acting antihypertensive agents with relatively high affinity for imidazoline binding sites may require both imidazoline-specific sites and functional Î±$_{2A}$-adrenoceptors to produce their hypotensive actions.

Ingestions of agents that activate Î±$_{2A}$-adrenoceptors and imidazoline binding sites (Table 14-5) produce a mixed picture. Peripheral postsynaptic Î±$_2$-adrenoceptor stimulation produces vasoconstriction, pallor, and hypertension, often with reflex bradycardia (Fig. 14-5). Peripheral presynaptic Î±$_2$-adrenoceptor stimulation prevents norepinephrine release (Fig. 14-5), whereas central Î±$_2$-adrenoceptor stimulation in the locus ceruleus accounts for CNS and respiratory depression (Fig. 14-6). Stimulation of postsynaptic Î±$_2$-adrenoceptors in the NTS and, with some agents, of central I_1 receptors in the VLM are thought to inhibit sympathetic output and enhance parasympathetic tone, explaining hypotension

with bradycardia (Fig. 14-6).[73] Both first- and second-generation agents produce dry mouth.[22,42]

Dopamine-Î²-Hydroxylase Inhibition

Inhibition of dopamine-Î²-hydroxylase (Fig. 14-5) prevents the conversion of dopamine to norepinephrine, resulting in less norepinephrine release and less Î±- and Î²-adrenoceptor stimulation with neuronal firing. Disulfiram produces such inhibition.[44] Because norepinephrine release mediates most of dopamine's ability to cause vasoconstriction, norepinephrine is the vasopressor of choice in a hypotensive patient taking disulfiram. Diethyldithiocarbamate, used in metal

chelation and by some AIDS patients, is a disulfiram metabolite that produces similar actions. MAOIs and Î±-methyldopa also inhibit dopamine-Î²-hydroxylase, although this is not their main mechanism of action.[98]

Dopamine is relatively contraindicated in hypotensive patients who have overdosed on MAOIs. First, dopamine acts indirectly and its administration might produce excessive adrenergic activity and exaggerated rises in blood pressure. Second, even if an adrenergic storm does not occur, most of dopamine's Î±-mediated vasoconstriction is secondary to norepinephrine release. In the presence of MAOIs, norepinephrine synthesis may be impaired from concomitant dopamine-Î²-hydroxylase inhibition, and dopamine may not reliably raise blood pressure if cytoplasmic and vesicular stores have been depleted. In the presence of impaired norepinephrine release or Î±-adrenoceptor blockade by any cause, unopposed dopamine-induced vasodilatation from action on peripheral dopamine and Î²-adrenoceptors may paradoxically lower blood pressure further. Norepinephrine and epinephrine can be used to support blood pressure relatively safely in patients taking MAOIs, because these vasopressors have little or no indirect action and are

metabolized by COMT when given intravenously.

Dopamine

Because dopamine is the direct precursor of norepinephrine, noradrenergic vesicles contain dopamine. The release of norepinephrine from peripheral sympathetic nerves, therefore, always results in release of some dopamine (Fig. 14-5), as does the release of norepinephrine and epinephrine from the adrenal gland, explaining the normal presence of dopamine in blood. In peripheral tissues, activation of dopamine receptors cause vasodilatation of mesenteric, and coronary vascular beds. Dopamine can also stimulate Î²-adrenoceptors and, at high doses, can directly stimulate Î±-adrenoceptors. When dopamine is administered intravenously, most vasoconstriction is caused by dopamine-induced norepinephrine release.

Dopamine accounts for about one-half of all catecholamines in the brain and is present in greater quantities than norepinephrine or 5-HT. In contrast to the diffuse projections of noradrenergic neurons, dopaminergic neurons and receptors are highly organized and concentrated in several areas, especially in the basal ganglia and limbic system.[81,135]

Excessive dopaminergic activity in the neostriatum and/or other areas from any cause (eg, increased release, impaired uptake, increased receptor sensitivity) can produce acute choreoathetosis[75] and acute Gilles de la Tourette syndrome, with tics, spitting, and cursing. Excessive dopaminergic activity in the limbic system and, perhaps, in other areas, produces paranoid psychosis that is indistinguishable from paranoid schizophrenia and is thought responsible for much of the drug craving and addictive behavior in patients abusing sympathomimetic drugs. Diminished dopaminergic tone (eg, impaired release, receptor blockade) in the neostriatum produces various extrapyramidal disorders such as acute dystonias and parkinsonism.[123,145,158]

Synthesis, Release, and Uptake

The steps of dopamine synthesis and vesicle storage are the same as those for norepinephrine, except that dopamine is not converted to norepinephrine after transport into vesicles (Fig. 14-7). Dopamine is removed from the synapse via uptake by DAT, the membrane-bound dopamine transporter. DAT and NET exhibit 66% homology in their amino acid sequences. Like NET, DAT is not completely specific for dopamine, but transports drugs such as amphetamines and other structurally similar sympathomimetics.

Cytoplasmic dopamine has a fate similar to norepinephrine. It is pumped back into vesicles by VMAT2 (brain) and VMAT1 (neuroendocrine tissue, adrenal glands) or degraded by MAO and COMT.

Dopamine Receptors

All dopamine receptors are coupled to G proteins and are divided into two main groups, depending on whether they raise or lower cAMP concentrations. Dopamine D_1-like receptors (D_1 and D_5) are expressed as various subtypes and are linked to G_s to stimulate adenylate cyclase and to raise cAMP concentrations.[81] Dopamine is 5â€“10 times more potent at D_5 receptors than it is at D_1 receptors.

D_2-like receptors (D_2, D_3, D_4) are linked to $G_{i/o}$, to produce several actions, including inhibition of adenylate cyclase and the lowering of cAMP levels. Again, numerous subtypes of receptors exist (eg, D_{2S}, D_{2L}). D_2 receptors are concentrated in the basal ganglia and limbic system. Some D_2 receptors also reside on presynaptic membranes, where their activation limits neurotransmitter release, including the peripheral release of norepinephrine (Figs. 14-5 and 14-7). D_3 receptors are concentrated in the hypothalamic and limbic nuclei, whereas D_4 receptors are concentrated in the frontal cortex and limbic nuclei (rather than basal ganglia nuclei). Most agonists bind to

the D_3 receptors with higher affinity than to D_2 receptors, whereas most antagonists bind preferentially to D_2 receptors.[81,135] Most agonists and antagonists express a lower affinity for D_4 receptors than they express for D_2 receptors; a notable exception is clozapine.

Chemical Agents

Table 14-6 provides examples of chemical agents that affect dopaminergic neurotransmission.

Dopamine Agonism

Indirect- and Mixed-Acting Agents

Most indirect- and mixed-acting sympathomimetics cause dopamine release. The mechanism of action is similar to that causing norepinephrine release. These agents diffuse into the neuron or undergo uptake by DAT before being transported into vesicles by VMAT2 where they buffer protons and displace dopamine into the cytoplasm for reverse transport by DAT into the synapse. Benztropine, diphenhydramine, trihexyphenidyl, and orphenadrine also cause dopamine release, perhaps contributing to their abuse potential, which is noted below.[105] Excessive dopaminergic activity following therapeutic doses or overdoses of decongestants (eg, pseudoephedrine), amphetamines, methylphenidate, and pemoline can produce acute choreoathetosis and Tourette syndrome.[24,91] Parkinsonian patients ingesting excessive doses of L-dopa (which is converted to dopamine) may present with similar symptoms.

Direct Agonists

Bromocriptine is an ergot derivative that directly activates dopamine receptors (mainly D_2). Toxic effects include those described above for indirect-acting agents. Apomorphine directly activates D_2 receptors. Such action at the chemoreceptive triggering zone

produces vomiting, whereas agonism in the basal ganglia explains apomorphine's use in the treatment of Parkinson disease. Fenoldopam is a D_1 agonist used as a vasodilator in the treatment of hypertensive emergencies.

D_1 and D_2-like receptor activation is the predominant mediator of locomotor effects from dopamine agonists. Activation of either D_1- or D_2-like receptors produces antiparkinsonian effects.[63,135] Cabergoline, ropinirole, and pramipexole are D_2-like agonists used to treat Parkinson disease.[8,42,60] Dihydrexidine is a D_1-like agonist that has been used for the same purpose.

Uptake Inhibition

Agents inhibiting DAT prevent dopamine uptake and include cocaine, amphetamines, methylphenidate, and probably amantadine. Increased dopaminergic activity from cocaine toxicity may produce choreoathetosis (â€œcrack dancingâ€•) and Tourette syndrome. In general, antidepressants are not strong dopamine uptake blockers. However, bupropion appears to be more active in this regard.[131]

As noted earlier, much of the drug craving and addiction produced by sympathomimetics probably results from excessive dopaminergic activity in the mesolimbic system.[145] Interestingly, the anticholinergic drugs benztropine, diphenhydramine, trihexyphenidyl, and orphenadrine are also dopamine uptake inhibitors, possibly explaining their abuse.[105,141] In fact, benztropine is one of the most potent dopamine uptake inhibitors known. Amantadine, an antiparkinsonian agent that causes dopamine release and some inhibition of dopamine uptake (as well as being anticholinergic), is also abused.

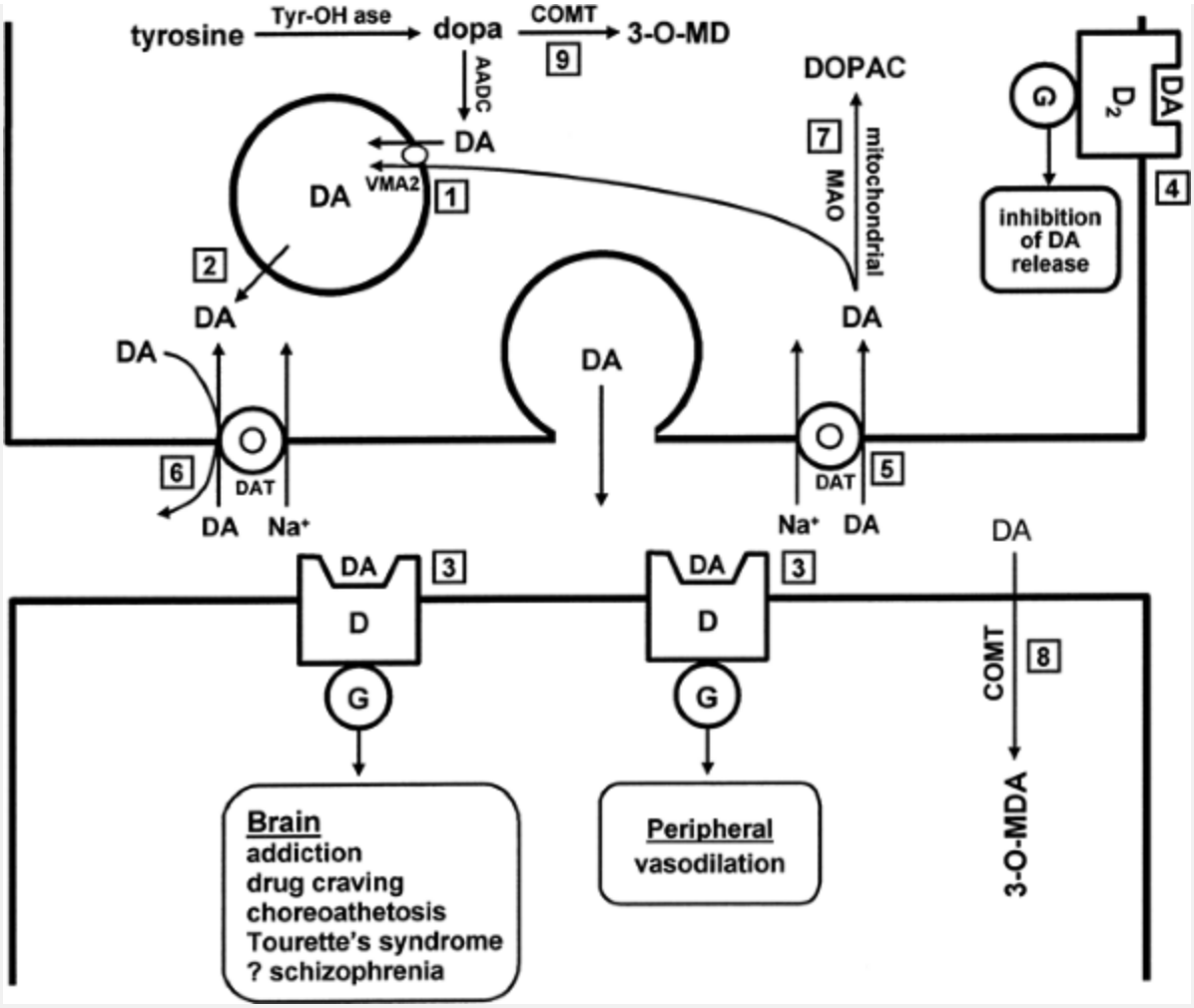

Figure 14-7. A dopaminergic nerve ending and postsynaptic membrane. Dopamine (DA) released from nerve endings binds to various postsynaptic DA receptors (D) on neurons or peripheral end organs. Stimulation of presynaptic D_2 receptors [4] lessens DA release. Agents in Table 14-6 may act to inhibit vesicle uptake [1]; cause DA to leave the vesicle and move into the cytoplasm [2]; activate or antagonize DA receptors [3,4]; inhibit DAT to prevent DA uptake [5]; cause reverse transport of cytoplasmic DA (via DAT) into the synapse by raising cytoplasmic DA concentrations [6]; prevent DA degradation by inhibiting monoamine oxidase (MAO) [7]; prevent DA degradation by inhibiting catechol-*O*-methyltransferase (COMT) [8]; or prevent

dopa metabolism by inhibiting COMT [9]. Both DA and dopa are substrates for COMT. For purposes of illustration, dopa metabolism is shown presynaptically, and DA metabolism is shown postsynaptically. 3-*O*-MD =3-*O*-methyldopa; 3-*O*-MDA =3-*O*-methyldopamine; AADC = L-aromatic amino acid decarboxylase; DAT =membrane DA uptake transporter; DOPAC =3,4-dihydroxyphenylacetic acid; Tyr-OHase =tyrosine hydroxylase; VMA2 = vesicle membrane uptake transporter.

Increase of Receptor Sensitivity

Several drugs are thought to increase sensitivity of dopamine receptors, resulting in choreoathetosis, even with therapeutic doses (eg, phenytoin). Evidence exists that increased dopamine receptor sensitivity may be responsible for movement disorders resulting from amphetamines.[29] Tardive dyskinesia (discussed below) may also result from increased dopamine receptor sensitivity.

MAO Inhibition

MAOIs inhibit the breakdown of cytoplasmic dopamine. Part of the food and drug interactions with MAOIs results from excessive release of dopamine from nerve endings.

COMT Inhibition

Peripheral COMT inhibitors (eg, entacapone, tolcapone) are given with levodopa to patients with Parkinson disease to prevent peripheral degradation of levodopa to 3-*O*-methyldopa. This allows more levodopa to traverse the bloodâ€“brain barrier and to be converted to dopamine by neuronal dopa decarboxylase. Tolcapone also inhibits COMT in the brain.[71] Other substrates of COMT include dopa, dopamine, norepinephrine, epinephrine, and

their hydroxylated metabolites. COMT inhibitors might potentiate the effects of these drugs when administered intravenously.[71]

TABLE 14-6. Examples of Xenobiotics That Affect Dopaminergic Neurotransmission

Dopamine agonism	Bupropion
Direct stimulation of dopamine receptors	Cocaine
Apomorphine	Diphenhydramine
Bromocriptine	Methylphenidate
Cabergoline	Orphenadrine
L-Dopa[a]	Pemoline
Fenoldopam	Trihexyphenidyl
Lisuride	
Pergolide	Increase dopamine receptor sensitivity
Pramipexole	
Ropinirole	Amphetamines

	Antipsychotics
Inhibit dopamine metabolismâ€”MAOIs	Metoclopramide
Clorgyline	Phenytoin
Isocarboxazid	
Linezolid	Dopamine antagonism
Moclobemide	Block dopamine receptors
Pargyline	Amoxapine
Phenelzine	Buspirone
Selegiline	Clozapine
Tranylcypromine	Droperidol
	Haloperidol
Inhibit dopamine metabolismâ€”COMTs	Loxapine
Entacapone	Metoclopramide
Tolcapone	Molindone

	Olanzapine
Indirect acting	Phenothiazines
Amantadine	Pimozide
Amphetamines	Quetiapine
Benztropine	Risperidone
Decongestants	Thioxanthenes
Diphenhydramine	Trazodone
MAOIs	Tricyclic antidepressants[b]
Methylphenidate	Ziprasidone
Orphenadrine	
Pemoline	Destroy dopaminergic neurons
Phencyclidine	
Trihexyphenidyl	MPTP

Inhibit dopamine uptake	Prevent vesicle dopamine uptake
Amantadine	
Amphetamines	Reserpine
Benztropine	Tetrabenazine

COMTs = catechol-*o*-methyltransferase inhibitors; MAOIs 5 monoamine oxidase inhibitors; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

[a] Metabolized to dopamine, which acts as an agonist.

[b] Relatively weak D_2 receptor antagonists.

Dopamine Antagonism

Direct Receptor Blockade

Blockade of dopamine receptors is the specific aim when using many therapeutic agents. The neuroleptic actions of butyrophenones, phenothiazines, and other antipsychotics mainly correlate with their ability to block D_2-like receptors, probably in the mesolimbic system. Many phenothi-azines block both D_1-like and D_2-like receptors, whereas haloperidol mainly blocks D_2-like receptors. Unfortunately, antipsychotics and metoclopramide also block dopamine receptors in the striatum, producing various extrapyramidal symptoms, including acute parkinsonism and dystonias.

In the last decade, several â€œatypicalâ€• antipsychotics have been marketed that produce fewer extrapyramidal effects and are thought to carry less risk of producing tardive dyskinesia.[127] The relative

affinity of an antipsychotic for 5-HT_{2A} receptors over D_2 receptors has predictive value for atypical agents with a lower risk of extrapyramidal symptoms.[118] Such agents include clozapine, olanzapine, quetiapine, risperidone, and ziprasidone.

The ratio of muscarinic (M_1) blockade to D_2-receptor blockade is also important in limiting extrapyramidal symptoms. Antipsychotic agents exhibiting strong antimuscarinic effects (eg, olanzapine, clozapine, thioridazine) are also less likely to induce extrapyramidal symptoms.[127]

Buspirone, an antianxiety agent, antagonizes D_2 receptors, which explains occasional extrapyramidal reactions. Various cyclic antidepressants, especially amoxapine, block D_2 receptors to some extent.

The chronic use of dopamine-blocking agents causes upregulation of dopamine receptors. The continued use or, especially, withdrawal of dopamine antagonists (antipsychotics, metoclopramide, and occasionally antidepressants) might result in excessive dopaminergic activity and tardive dyskinesia, characterized by choreiform movements typical of excessive dopaminergic influence in the neostriatum.

The blockade of dopamine receptors by numerous agents, including butyrophenones, phenothiazines, and metoclopramide, can produce a poorly understood disorder called *neuroleptic malignant syndrome*. Neuroleptic malignant syndrome also follows acute withdrawal of dopamine agonists (eg, stopping L-dopa or bromocriptine in a patient prior to surgery). Neuroleptic malignant syndrome is characterized, in part, by mental status changes, autonomic instability, rigidity, and hyperthermia.

Indirect Antagonism

Reserpine and tetrabenazine inhibit VMAT to prevent transport of dopamine into storage vesicles and deplete nerve endings of

dopamine. In fact, reserpine was used as an antipsychotic agent before the introduction of phenothiazines. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a meperidine analog, undergoes activation by MAO to a metabolite that causes death of dopaminergic neurons. Both MPTP and its metabolite undergo uptake not only by DAT, but also by NET and SET, making their way into all biogenic amine neurons. The reasons that dopaminergic neurons are selectively damaged remains unknown. Both MAOIs and inhibitors of dopamine transporters prevent MPTP-induced destruction of dopaminergic neurons.

Serotonin

Serotonin (5-HT, 5-OH-tryptamine) is a ubiquitous indole alkyl-amine found in nature (animals, plants, venoms) that acts as a neurotransmitter centrally, but is also found peripherally. In fact, less than 2% of the body's 5-HT is found within the CNS.

In the CNS, several hundred thousand serotonergic neurons lie in or in juxtaposition to numerous midline nuclei in the brainstem (9 raphe nuclei), from which they project to virtually all areas of the brain, including the basal ganglia. Serotonin is involved with mood, personality, affect, appetite, motor function, temperature regulation, sexual activity, pain perception, sleep induction, and other basic functions. Serotonin is not essential for any of these processes but modulates their quality and extent. The serotonergic system is extremely diverse, with 14 types of receptors that act to stimulate or inhibit neurons, including those

of other neurotransmitter systems. Serotonin is also the precursor for the pineal hormone melatonin.[50]

Peripherally, 5-HT is produced mainly in the enterochromaffin cells of the intestine. Local release contributes to peristalsis. Platelets take up 5-HT while passing through the enteric circulation. Serotonin is released from activated platelets to interact with other platelet

membranes (promote aggregation) and with vascular smooth muscle (vasoconstriction in most vascular beds).

Experimentally, 5-HT exhibits diverse effects on the cardiovascular and peripheral nervous systems, although the importance of these actions remains uncertain in the normal physiologic state. Serotonin vasoconstricts (stimulation of 5-HT_2, 5-HT_{1B}, and 5-HT_{1D} receptors) most vascular beds except for coronary arteries and skeletal muscle, where it produces vasodilatation in the presence of intact endothelium. 5-HT_{1B} and 5-HT_{1D} agonists (eg, sumatriptan) might produce coronary vasoconstriction as an adverse effect to their desired actions on cranial vasculature.[59]

Centrally, it is particularly difficult to ascribe a specific symptom or physical finding to serotonergic neurons because of the diversity of their physiologic actions. However, 5-HT definitely plays an important role in the action of many hallucinogenic or illusionogenic drugs, which act as partial agonists at cortical 5-HT_2 receptors.[88] Proserotonergic agents are used to treat depression, whereas agents that antagonize 5-HT receptors (5-HT_2) have greater importance in the management of schizophrenia.

Generally, 5-HT acts in opposition to dopamine. For example, 5-HT serves to increase prolactin, adrenocorticotropic hormone (ACTH), and growth hormone secretion, whereas dopamine decreases prolactin secretion. As another example, activation of basal ganglial 5-HT_{2A} receptors inhibits dopamine release. However, well-known exceptions exist, such as cortical 5-HT_3 receptors, whose activation promotes dopamine release.[88]

Synthesis, Release, and Uptake

Figure 14-8 illustrates 5-HT synthesis. Tryptophan-5-hydroxylase is the rate-limiting enzyme of 5-HT synthesis and is free from negative feedback influences by the end product, 5-HT. Thus, increases in tryptophan are predictably accompanied by increased 5-HT

production. L-Amino acid decarboxylase (dopa decarboxylase) converts 5-hydroxytryptophan to 5-HT. Cytoplasmic 5-HT is transported into vesicles by VMAT2, where it is concentrated by ion trapping before release by Ca^{2+}-dependent exocytosis. In contrast to vesicles containing dopamine or norepinephrine, 5-HT vesicles contain almost no ATP. After release into the synapse, a transporter (SERT) in the neuronal membrane transfers 5-HT back into the neuron, where it reenters vesicles or is degraded by MAO.

Serotonin is preferentially metabolized by the MAO-A isozyme. Paradoxically, the serotonergic nerve terminal is almost devoid of MAO-A but contains abundant amounts of MAO-B. It has been hypothesized that the large amounts of MAO-B metabolize other agents that might inappropriately promote serotonin release (eg, dopa). However, the small amount of MAO-A found in serotonergic neurons provides adequate degradation of 5-HT.[50]

Serotonin Receptors

Most authors identify seven major functioning receptors ($5\text{-}HT_1$ through $5\text{-}HT_7$) and numerous subtypes.[9]

$5\text{-}HT_1$ Receptors

Receptors in the $5\text{-}HT_1$ class are coupled to G proteins and commonly increase K^+ efflux and decrease cAMP concentrations. Members of the $5\text{-}HT_1$ receptor class express greatest affinity for 5-HT and are thus biologically active under normal physiologic conditions. $5\text{-}HT_{1A}$ receptors reside predominantly on raphe nuclei, where they act as somatodendritic autoreceptors. Hippocampal $5\text{-}HT_{1A}$ receptors reside postsynaptically, where they also inhibit through similar mechanisms.[83]

Central $5\text{-}HT_{1D}$ and $5\text{-}HT_{1B}$ receptors primarily act as inhibitory terminal autoreceptors and heteroreceptors. They are found less commonly on postsynaptic membranes. Originally $5\text{-}HT_{1B}$ receptors

were not believed to exist in humans. However, most of the actions described in older literature regarding 5-HT_{1D} receptors can now be attributed to 5-HT_{1B} receptors. Unfortunately, this distinction will continue to lead to confusion for some years to come. Cranial blood vessels (eg, meninges) possess 5-HT_{1D} and 5-HT_{1B} receptors, whose activation produces vasoconstriction and decreased inflammation.[57,59]

5-HT_{1E} and 5-HT_{1F} receptors are more recently discovered members of the 5-HT_1 receptor class. 5-HT_{1F} receptors reside on presynaptic membranes and may act in a similar fashion to 5-HT_{1D} and 5-HT_{1B} receptors.[9]

5-HT_2 Receptors

The three subtypes of 5-HT_2 receptors are coupled to G proteins, thus serving to decrease K^+ efflux and/or increase intracellular Ca^{2+} concentration by raising concentrations of inositol triphosphate and diacylglycerol.[130] The three subtypes of 5-HT_2 receptors are so similar in characterization that investigational agents have great difficulty in distinguishing the subtypes. 5-HT_{2A} receptors are most concentrated in the cerebral cortex, where they serve as excitatory postsynaptic receptors. Their activation increases glutamate release from pyramidal cells, but also can lead to release of GABA.[1,86] 5-HT_{2A} receptors also reside on platelets, where their activation produces platelet aggregation. 5-HT_{2C} receptors (previously 5-HT_{1C}) reside on the choroid plexus, where they regulate cerebrospinal fluid production. Peripherally, 5-HT_{2C} activation also promotes penile erection. Activation of 5-HT_{2B} receptors in the GI tract promotes colonic contraction.[86]

5-HT_3 Receptors

5-HT_3 receptors are isopentameric ligand-gated cation channels that are structurally similar to ACh nicotinic receptors, $GABA_A$ Cl^- channels, and NMDA glutamate receptors.[3] They have been localized

to both presynaptic and postsynaptic membranes. Upon activation, they stimulate the neuron by opening the channel to cause depolarization through Na^+ and/or Ca^{2+} influx. In addition, these channels are normally blocked by Mg^{2+} in a voltage-dependent manner similar to glutamatergic NMDA receptors (see Glutamate below). Centrally, 5-HT_3 receptors are expressed diffusely, but are especially concentrated in the chemoreceptive triggering zone, where their activation induces emesis. In the cerebral cortex, their activation leads to increased release of dopamine and decreased release of ACh. Cortical 5-HT_3 receptors are frequently identified on GABA interneurons where they increase inhibitory, GABAergic tone. In contrast to cerebral actions, activation of peripheral 5-HT_3 receptors on cholinergic nerves in the gut enhances ACh release to increase gastrointestinal motility.[9,18]

5-HT_4 Receptors

5-HT_4 receptors are coupled to G proteins (G_s). Their activation leads to increased cAMP concentrations. 5-HT_4 receptors are scattered diffusely throughout the brain, and their exact role remains undefined. Peripheral 5-HT_4 receptors reside in the heart, intestines, and adrenal gland where their activation can be demonstrated to produce tachycardia, aldosterone and cortisol release, and contraction of gut and bladder smooth muscle. Again,

whether these actions are important under normal physiologic conditions is not clear. Both central and peripheral 5-HT_4 receptors promote the release of acetylcholine.[41]

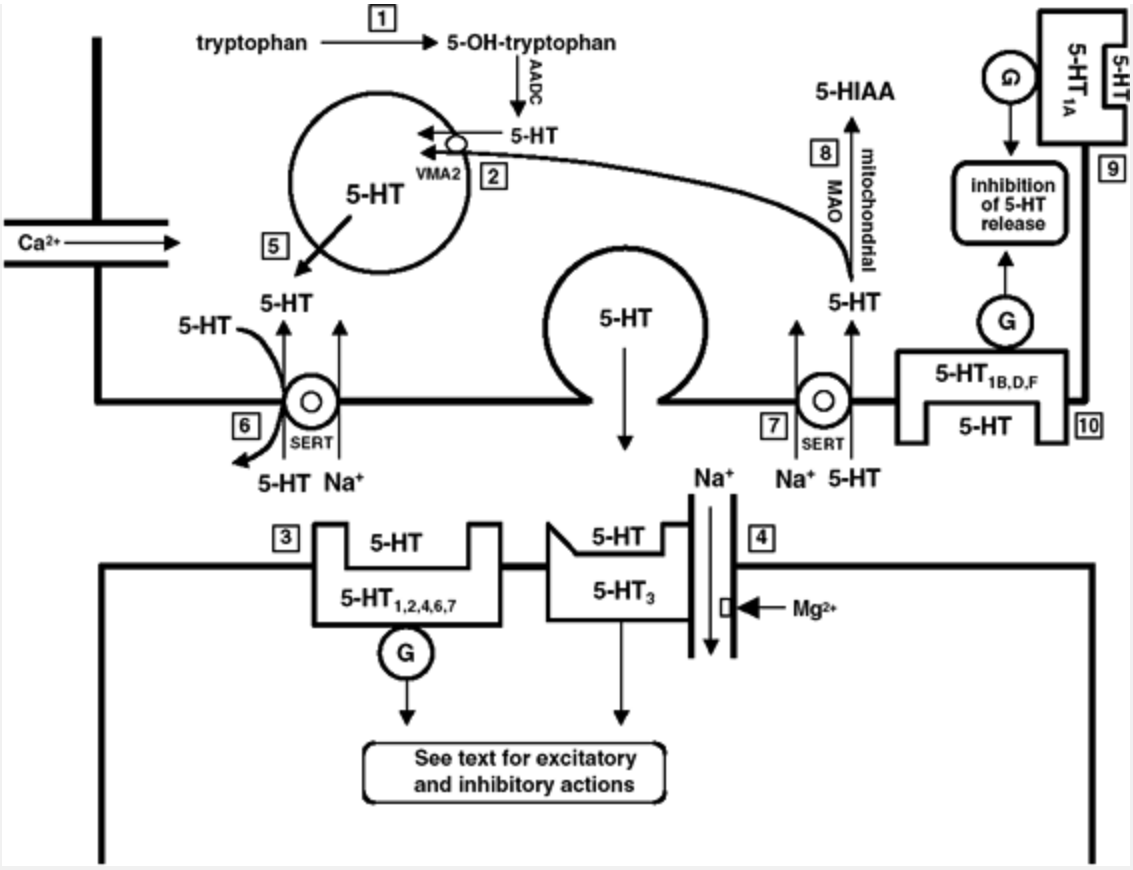

Figure 14-8. A serotonergic nerve ending and postsynaptic membrane. Tryptophan hydroxylase [1] converts tryptophan to 5-hydroxytryptophan (5-OH-tryptophan). Aromatic L-amino acid decarboxylase (AADC) then metabolizes 5-OH-tryptophan to serotonin (5-HT). Serotonin is concentrated within vesicles through uptake by VMA2 before exocytosis [2]. After uptake into the neuron by SERT [7], 5-HT is transported back into vesicles or undergoes degradation by monoamine oxidase (MAO) to an intermediate compound, which is converted to 5-hydroxyindoleacetic acid (5-HIAA) [8]. $5\text{-HT}_{1,2,4,6,7}$ receptors [3,9,10] are coupled to G proteins, while 5-HT_3 receptors [4] are ligand-gated cation channels that may conduct Na^+ and/or Ca^{2+}. 5-HT_3 cation channels also appear to be blocked by Mg^{2+} until the cell is depolarized, allowing Mg^{2+} to dissociateâ€”a mechanism similar to that found at NMDA glutamate receptors. In

addition to residing on postsynaptic membranes, 5-HT_{1A}, 5-HT_{1B}, 5HT_{1D}, and 5-HT_{1F} receptors serve as presynaptic autoreceptors that, when stimulated, decrease further release of 5-HT [9,10]. Presynaptic 5-HT_{1A} receptors mainly serve as somatodendritic autoreceptors, whereas presynaptic 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors serve as terminal autoreceptors. Agents in Table 14-7 act to enhance 5-HT synthesis [1]; inhibit VMA2 to prevent vesicle uptake of 5-HT [2]; raise cytoplasmic concentrations of 5-HT, resulting in reverse transport of 5-HT into the synapse by SERT [6] by displacing 5-HT from vesicles [5] or inhibiting MAO [8]; activate or antagonize 5-HT receptors [3,4,9,10]; or by inhibiting 5-HT uptake [7]. G =G protein; SERT =membrane 5-HT uptake transporter; VMA2 =vesicle membrane uptake transporter.

5-HT_5 Receptors

5-HT_5 receptors exist in the form of at least two subtypes, one of which may be coupled to G_s. Their mechanism of activation remains unknown. 5-HT_5 receptor agonists or antagonists are not readily available.[9]

5-HT_6 and 5-HT_7 Receptors

5-HT_6 and 5-HT_7 receptors are positively coupled to cAMP formation through G proteins. Their distribution is poorly defined. However, many antidepressant and antipsychotic agents antagonize these receptors. They are currently a source of great interest because of the possibility of avoiding dopamine blockade to achieve antipsychotic activity. The 5-HT_7 receptor may be particularly important in regulating circadian rhythms.[78]

Chemical Agents

Table 14-7 provides examples of chemical agents that affect serotonergic neurotransmission.

Serotonin Agonists

The ingestion of tryptophan is thought to increase 5-HT production and was commonly used as an unproved sleep aid until it was associated with the eosinophilia myalgia syndrome. 5-Hydroxytryptophan (5-HTP) is the immediate precursor to 5-HT. 5-HTP is commonly available without a prescription. The antianxiety agents buspirone, gepirone, and ipsapirone act as partial agonists at somatodendritic and postsynaptic 5-HT_{1A} receptors.[9] Sumatriptan, an antimigraine agent, mainly activates 5-HT_{1D} and 5-HT_{1B} receptors. Sumatriptan's action may result from vasoconstriction of meningeal and other cranial, extracerebral vasculature; no impairment of cerebral blood flow follows the use of this agent. Other members of the triptan class of drugs include rizatriptan, zolmitriptan, and naratriptan.[59]

Metoclopramide, cisapride, zacopride, renzapride, and tegaserod are prokinetic drugs that activate 5-HT_4 receptors to increase gut motility.[41,60,84] Because 5-HT_4 receptors are also found in the heart and urinary bladder detrusor muscle, 5-HT_4 agonists occasionally produce bladder incontinence and tachycardia.

Numerous indoles and phenylalkylamines, including ergot alkaloids, lysergic acid diethylamide (LSD), psilocybin, and mescaline, exhibit both agonistic and antagonistic properties at multiple 5-HT receptors. Their hallucinogenic/illusionogenic action is best

explained by partial agonism at 5-HT_{2A} receptors. Some substituted amphetamines (eg, methylenedioxymethamphetamine) directly stimulate serotonin receptors.[1,88]

TABLE 14-7. Examples of Xenobiotics That Affect Serotonergic Neurotransmission

Serotonin agonism	Citalopram
Enhance 5-HT synthesis	Cocaine
L-Tryptophan	Dextromethorphan
5-Hydroxytryptophan	Duloxetine
	Escitalopram
Direct 5-HT agonists	Fluoxetine
Buspirone	Fluvoxamine
Cisapride	Lamotrigine
Ergots and indoles[a]	Meperidine
Flesinoxan	Milnacipran
Gepirone	Nefazodone
Hallucinogenic substituted	Reboxetine
amphetamines	Sertraline

Ipsapirone	Tramadol
mCPP	Trazodone
Mescaline[a]	Tricyclic antidepressants[b]
Metoclopramide	Venlafaxine
Naratriptan	
Renzapride	Serotonin Antagonism
Rizatriptan	Direct 5-HT antagonists
Sulpiride	Alosetron
Sumatriptan	Amisulpride
Tandospirone	Clozapine
Tegaserod	Cyproheptadine
Urapidil	Dolasetron
Zacopride	Ergots and indoles (eg,
Zolmitriptan	LSD)[a]

	Granisetron
Increase 5-HT release	Haloperidol
Amphetamines	Ketanserin
Cocaine	Mianserin
Codeine derivatives	Mescaline[a]
Dexfenfluramine	Methysergide
Dextromethorphan	Metoclopramide
L-Dopa	Mirtazapine
Fenfluramine	Nefazodone
MDMA	Olanzapine
Mirtazapine	Ondansetron
Reserpine (initial)	Phenothiazines
	Phentolamine
Increase 5-HT tone by unknown	Pindolol

mechanism	Propranolol
Lithium	Quetiapine
	Risperidone
Inhibit 5-HT breakdown (MAOIs)	Ritanserin
Clorgyline	Sertindole
Isocarboxazid	Trazodone
Linezolid	Tricyclic antidepressants
Moclobemide	Tropisetron
Pargyline	Ziprasidone
Phenelzine	Zotepine
Tranylcypromine	
Selegiline	Enhance 5-HT uptake
	Tianeptine
Inhibit 5-HT uptake	

Amoxapine	Inhibit vesicle uptake
Amphetamines	Reserpine
Atomoxetine	Ketanserin
Carbamazepine	Tetrabenazine

5-HT = serotonin; LSD = lysergic acid diethylamide; MAOIs = monoamine oxidase inhibitors; *m*CPP = *m*-chlorophenylpiperazine (metabolite of trazodone and nefazodone); MDMA = methylenedioxymethamphetamine.
[a] Indoles and phenylalkylamines activate and antagonize various 5-HT receptors. Their hallucinogenic/illusionogenic effects mainly result from partial agonism at 5-HT_2 receptors.
[b] Clomipramine is the most potent 5-HT uptake inhibitor of the tricyclic antidepressants.

Cocaine and indirect-acting sympathomimetics, especially amphetamines, cause serotonin release as previously described. Other releasing agents are dextromethorphan and codeine derivatives. Centrally, dopamine undergoes uptake into serotonergic neurons to displace 5-HT from the neuron. Ingestion of L-dopa or other agents that increase CNS dopamine concentrations can cause 5-HT release.[104]

Inhibitors of 5-HT uptake include amphetamines, cocaine, various antidepressants, meperidine, and dextromethorphan.[104] Several antidepressants specifically inhibit 5-HT uptake. Examples of selective serotonin reuptake inhibitors (SSRIs) include fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram. The use of SSRIs sometimes produces extrapyramidal side effects[5] for reasons that

remain unclear because of the numerous actions of 5-HT in the basal ganglia. Two anticonvulsants, carbamazepine and lamotrigine, appear to inhibit 5-HT uptake.[144] Again, reserpine and tetrabenazine prevent 5-HT uptake into vesicles.

MAO-A accounts for most 5-HT degradation, and nonspecific MAOIs and MAO-A inhibitors (clorgyline, moclobemide) both raise 5-HT concentrations and, through indirect action, probably cause 5-HT release.[53,104]

Serotonin Antagonists

Trazodone and nefazodone act mainly as antagonists at 5-HT_2 receptors, but are also weak uptake inhibitors. Both undergo metabolism to *m*-chlorophenylpiperazine (mCPP), which activates most 5-HT receptors, but is especially active at 5-HT_{2C} receptors. Ketanserin and ritanserin specifically antagonize 5-HT_{1D} receptors while methysergide and cyproheptadine antagonize 5-HT_1 and 5-HT_2 receptors.[53,104]

Mirtazapine exhibits complex actions, including antagonism of 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptors.[86] Mirtazapine also indirectly increases 5-HT_{1A} activity and enhances release of norepinephrine through antagonism of Î±$_2$-adrenoceptors. Mirtazapine also demonstrates potent antagonism of histaminic, muscarinic, and Î±-adrenoceptors.[53]

Most antipsychotics and tricyclic antidepressants antagonize 5-HT_{2A} and, to a lesser extent, 5-HT_{2C} receptors. In fact, investigators are interested in developing antipsychotic agents similar to risperidone that possess potent antagonistic properties at 5-HT_2 receptors without accompanying dopamine receptor antagonism in order to limit extrapyramidal side effects. These investigations have resulted in the introduction of olanzapine, sertindole, ziprasidone, zotepine, quetiapine, and amisulpride.[16]

Ondansetron, granisetron, tropisetron, dolasetron, and alosetron

antagonize 5-HT_3 receptors. Their antiemetic action is thought to be explained by several mechanisms. Central antagonism at the chemoreceptor triggering zone lessens vomiting. Peripheral 5-HT_3 receptor antagonism in the gut prevents ACh release, decreasing gut motility. Finally, antagonism of vagal 5-HT_3 receptors decreases afferent stimulatory signals to the vomiting center in the brainstem.[9] Ondansetron and other experimental 5-HT_3 antagonists are being studied in the treatment of schizophrenia because of their ability to prevent dopamine release. Metoclopramide antagonizes 5-HT_3 and D_2 receptors.

Tianeptine is an antidepressant that enhances 5-HT uptake, thus lowering synaptic 5-HT concentrations.[112]

Serotonin Syndrome

Excessive stimulation of 5-HT_{1A} receptors and, to a lesser extent, 5-HT_2 receptors, causes serotonin

syndrome.[104] Briefly, this disorder is characterized by shivering, myoclonus, tremor, and rigidity (especially of legs), along with hyperthermia, tachycardia, diaphoresis, confusion, agitation, convulsions, and coma. This iatrogenic, idiosyncratic syndrome results most commonly from the combined use of two serotonergic drugs (eg, SSRI and lithium, SSRI and MAOI, MAOI and clomipramine). Reports indicate that serotonin syndrome may occur following the isolated use or overdose of a single seroto-nergic agent (eg, venlafaxine or fluvoxamine). Drugs that act to increase CNS dopamine concentrations, such as levodopa and bromocriptine, have potential to precipitate serotonin syndrome by indirect serotonin release.[104] Adverse effects (eg, rigidity, hyperthermia) resulting from interactions between MAOIs and meperidine, dextromethorphan, or codeine may result from excessive serotonergic activity, as well, because all of these agents enhance serotonergic tone (Table 14-7).

Î³-Aminobutyric Acid

GABA is one of two main inhibitory neurotransmitters of the central nervous system (glycine is discussed below; see Glycine as an Inhibitory Neurotransmitter). Drugs that enhance GABA activity are generally used as anticonvulsants, sedative-hypnotics, and general anesthetics. Agents that antagonize GABA activity typically produce CNS excitation and convulsions. GABA is synthesized from glutamate, the brain's main excitatory neurotransmitter.

In general, GABA inhibition predominates in the brain. In the spinal cord, through mono- and polysynaptic reflex pathways, GABA mediates a number of physiologically minor peripheral effects outside the CNS (eg, vasodilatation, bladder relaxation). Spinal cord GABA is important in attenuating skeletal muscle reflex arcs.[96]

Synthesis, Release, and Uptake

Figure 14-9 illustrates GABA synthesis. Glutamic acid decarboxylase (GAD) requires pyridoxal phosphate (PLP) as a cofactor. Pyridoxal phosphate is synthesized from pyridoxine (vitamin B_6) by the enzyme pyridoxine kinase (PK).[102] VGAT, a vesicle-bound transporter comprising about 130 amino acids and crossing the vesicle membrane about 10 times, transports GABA into vesicles from where it is released through Ca^{2+}-dependent exocytosis into the synapse.[96] Uptake of GABA from the synapse back into the presynaptic neurons is mediated by the Na^+-dependent transporter, GAT-1, whereas uptake into glial cells and possibly postsynaptic neurons is mediated by GAT-2, GAT-3, and GAT-4. Evidence also suggests that GABA is released into the synapse from cytoplasm by reverse transport under some conditions. In glial cells, cytoplasmic GABA can undergo degradation by GABA-transaminase (GABA-T) to succinic semialdehyde (SSA), part of which then undergoes oxidation to succinate. GABA-T also requires PLP as a cofactor.[109] The transamination of GABA to SSA by GABA-T results in the conversion of Î±-ketoglutarate to glutamate, which then moves back into

neurons to be used for resynthesis of GABA.

GABA Receptors

There are three main types of GABA receptors (Table 14-8).[20] $GABA_A$ receptors are Cl^- channels that mediate postsynaptic inhibition by allowing Cl^- to move into and hyperpolarize the postsynaptic neuron. Situated at various sites in relation to the GABA recognition site on the Cl^- channel are sites for exogenous and endogenous modulatory agents (Fig. 14-10) where numerous excitatory and depressant drugs bind, and through which $GABA_A$ receptor responsiveness is regulated under normal physiologic conditions. The common denominator for modulation at the $GABA_A$ complex is an increase or decrease in inward Cl^- current.

Throughout the CNS there are regional variations in expressions of multiple subunit genes for the $GABA_A$ complex. $GABA_A$ receptors exist as pentamers, composed most commonly of 1 to 3 Î± subunits, 1 to 3 Î² subunits, and either a Î³ or Î´ subunit. The most common combination appears to be 2Î±-2Î²-1Î³. Multiple subtypes of subunits exist (eg, $Î±_1$â€“$Î±_6$), but within a single receptor, the subtypes of individual subunits appear to be identical. Nevertheless, given the large numbers of subtypes and different combinations of subunits, more than 2000 different $GABA_A$ Cl^- channels theoretically could form, with different pharmacologic affinities for certain ligands, including anesthetics, benzodiazepines, barbiturates, and for GABA itself.[8,139] It appears highly unlikely, however, that this many different types of $GABA_A$ receptors are found in mammalian brains.

The second type of GABA receptor, $GABA_B$, is found on both pre- and postsynaptic membranes. The $GABA_B$ receptors are heterodimers, with companion proteins linked to the receptors, and are coupled to G proteins (probably $G_{i/o}$) that mediate both presynaptic and postsynaptic inhibition.[23] Presynaptic inhibition results from preventing Ca^{2+} influx so as to impair exocytosis of neurotransmitter vesicles, including those containing excitatory amino acids (eg,

glutamate). Postsynaptic inhibition is mediated by increasing K^+ efflux through K^+ channels, resulting in hyperpolarization of the membrane away from threshold. Through presynaptic actions, $GABA_B$ receptors also serve as autoreceptors, where their activation in response to synaptic GABA provides feedback inhibition of further neurotransmitter release (Fig. 14-9).

A third GABA receptor, $GABA_C$, is a Cl^- channel that, when activated, allows increased Cl^- influx. The $GABA_C$ receptors are thought to comprise 5 ligand-binding sites, whereas $GABA_A$ receptors have 2 ligand-binding sites.[20] $GABA_C$ receptors are composed of Ï• subunits (Ï•$_1$â€“Ï•$_3$). Ï•$_1$ subunits are located in the mammalian retina, Ï•$_2$ subunits are present in most brain regions, and Ï•$_3$ subunits are found in the hippocampus. Ï•$_1$ and Ï•$_2$ receptors have also been found outside the CNS.[69] $GABA_C$ receptors are sensitive to *cis*-4-aminocrotonic acid (CACA), are insensitive to baclofen, bicuculline, benzodiazepines, and barbiturates, and are less sensitive to neuroactive steroids and to picrotoxin (Table 14-8).[69] $GABA_C$ receptors are activated at 40-fold lower GABA concentrations than $GABA_A$ receptors, are less liable to desensitization, and remain open longer than $GABA_A$ Cl^- channels.

Chemical Agents

Table 14-9 provides examples of chemical agents that affect GABAergic neurotransmission.

Modulation of GABA Production and Degradation

Isoniazid (INH) and other hydrazines (eg, monomethylhydrazine from mushrooms) lower CNS GABA concentrations by several mechanisms. Most important, they compete with pyridoxine for binding to PK, impairing PLP production.[102] Pyridoxal phosphate binding to the GAD complex is easily reversible.[109] The acute decrease in PLP

concentration, then, is rapidly accompanied by impaired GABA synthesis and a decrease in GABA concentration. Lack of normal GABA inhibition produces seizures typical of hydrazine intoxications. Although PLP is also required for GABA degradation by GABA-T, acute decreases in PLP do not affect this enzyme nearly as much, because PLP is more

tightly bound to the GABA-T complex and remains associated with the enzyme.[109] To a lesser extent, isoniazid binds to the GAD-PLP complex to prevent GABA formation.

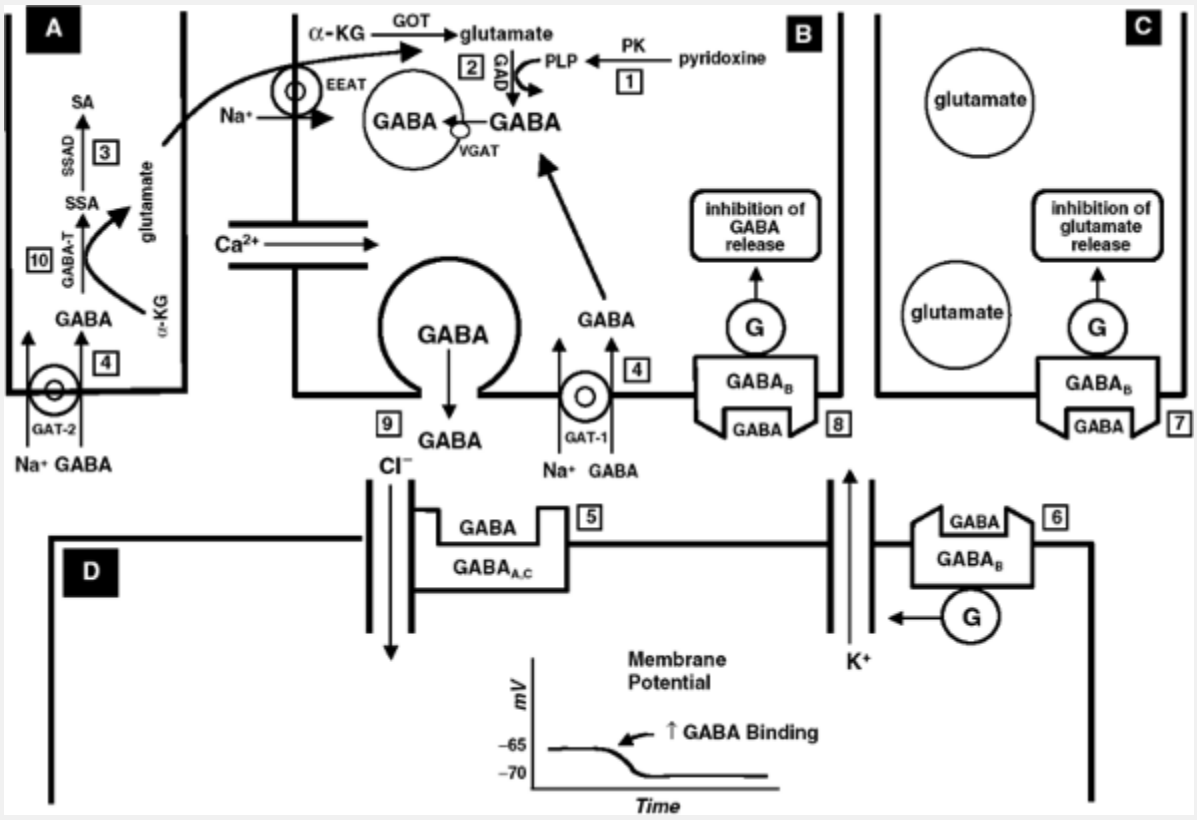

Figure 14-9. GABAergic neurotransmission. GABA (Î³-aminobutyric acid) released from a presynaptic neuron (B) binds to postsynaptic $GABA_A$, $GABA_B$, or $GABA_C$ receptors to hyperpolarize and inhibit neuron D [5,6] or to presynaptic $GABA_B$

heteroreceptors on neuron C [7] to inhibit neurotransmitter release by blocking Ca^{2+} influx (an excitatory glutamatergic neuron is shown as an example). Stimulation of $GABA_B$ autoreceptors on neuron B [8] also reduces further release of GABA. Synaptic GABA undergoes uptake into the presynaptic neuron by GAT-1, and uptake into glial cells and possibly postsynaptic neurons by GAT-2, GAT-3, and GAT-4 (GAT-2 is shown mediating uptake into glial cell A as an example.) Acute falls in pyridoxal phosphate (PLP) lead to impaired glutamic acid decarboxylase (GAD) activity and low GABA concentrations. Although GABA-transaminase (GABA-T) also requires PLP, acute falls in PLP do not affect this enzyme as dramatically because of tight PLP binding to the GABA-T complex. Agents in Table 14-9 act to impair PLP formation by inhibiting pyridoxine kinase (PK) [1]; to increase GABA concentrations by either stimulating GAD [2] or inhibiting SSAD [3]; to inhibit GABA uptake [4]; to stimulate or block GABA receptors [5â€“8]; to cause GABA release [9]; or to inhibit GABA-T [10]. Glutamic-oxaloacetic transaminase (GOT), GABA-T, and SSAD are mitochondrial enzymes. Î±-KG = Î±-keto-glutarate; G = G protein; GAT = membrane GABA uptake transporter; SA = succinic acid; SSA = succinic semialdehyde; SSAD = SSA dehydrogenase; VGAT = vesicle membrane GABA uptake transporter.

Cyanide inhibits numerous enzymes besides cytochrome oxidase. Inhibition of GAD with a resultant fall in GABA concentration may partly explain seizures that occur in cyanide-poisoned patients. Domoic acid (see Glutamate below) may inhibit GAD.[35]

TABLE 14-8. GABA Receptors and Their Characteristics

	$GABA_A$	$GABA_B$	$GABA_C$
Receptor	Cl^- channel	G-protein-coupled	Cl^- channel
Bicuculline antagonism	Yes	No	No
Baclofen agonism	No	Yes	No
Benzodiazepine agonism	Yes	No	No
Barbiturate agonism	Yes	No	No
Picrotoxin antagonism	Yes	No	Slight

The most important mechanism for valproate's anticonvulsant action is unknown. In vitro studies demonstrate its ability to increase brain GABA concentrations either by inhibition of succinic semialdehyde dehydrogenase or by activation of GAD.[70] Gabapentin's ability to increase the rate of GABA synthesis in the brain also may result from stimulation of GAD.[153] Vigabatrin, an anticonvulsant, acts by irreversibly inhibiting GABA-T.[147]

$GABA_A$ Agonism

Figure 14-10 schematically illustrates the $GABA_A$ receptor complex. In general, substances that increase $GABA_A$ complex activity cause CNS depression, ranging from mild sedation and nystagmus to ataxia, stupor, coma, and even general anesthesia. Most indirect agonists that bind to the $GABA_A$ complex have no activity in the absence of GABA. With some exceptions,

their pharmacologic actions require the binding of GABA to its receptor and do not result from a direct effect on Cl^- conductance exclusive of GABA binding. Many of these drugs demonstrate additional actions that are not mediated through the $GABA_A$ complex.

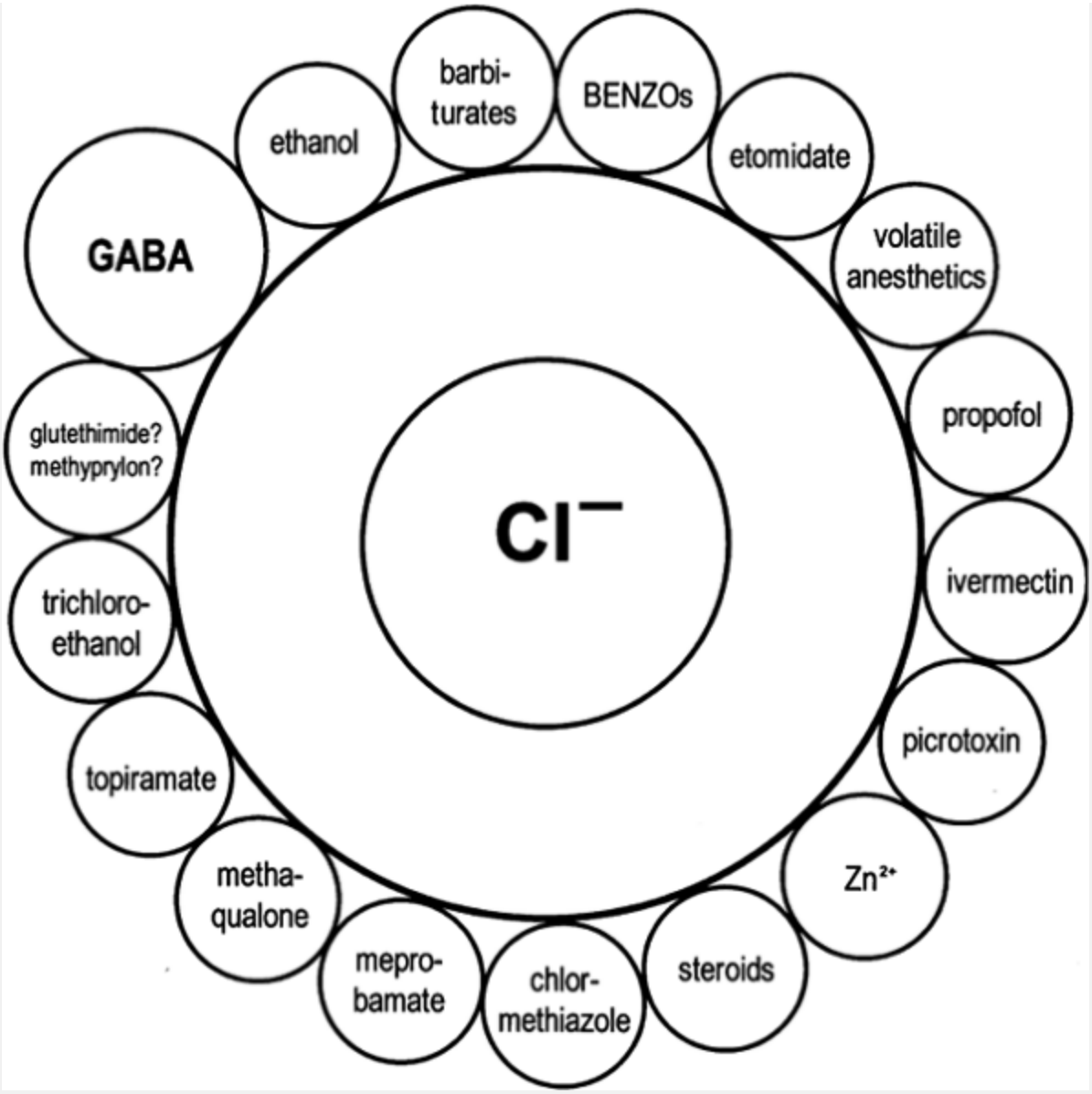

Figure 14-10. Representation of the $GABA_A$ Cl^- channel receptor complex. Benzodiazepines (BENZOs), barbiturates, picrotoxin, steroids, and GABA (Î³-aminobutyric acid) clearly bind to different sites on the channel. Although separate circles represent different agents capable of binding to and of modulating Cl^- influx through the $GABA_A$ receptor complex, it is not always apparent where these agents bind on the channel. For example, general anesthetics and ethanol may produce their

effects by interacting with the steroid binding site. Chloral hydrate undergoes metabolism to trichloroethanol, which interacts with the $GABA_A$ receptor complex. Zolpidem, zopiclone, and zaleplon are nonbenzodiazepines that bind to the benzodiazepine site. Given the structural similarity of glutethimide and methyprylon to barbiturates, it is speculated that their action may be mediated at $GABA_A$ receptors.

Direct GABA Agonists

The main direct GABA agonist of toxicologic interest is muscimol, found in some poisonous mushrooms. Muscimol binds to the GABA receptor on the $GABA_A$ complex to mimic the action of GABA.[110] Ibotenic acid, a direct glutamate agonist found in the same mushrooms, is decarboxylated to muscimol just as glutamate is decarboxylated to GABA.

Indirect GABA Agonists

Benzodiazepines bind to benzodiazepine receptors on $GABA_A$ complexes to increase the affinity of GABA for its receptor and to increase the frequency of Cl^- channel opening in response to GABA binding.[138] The benzodiazepine binding site on the $GABA_A$ receptor is located in a pocket between an Î± subunit and a Î³ subunit.[161] Benzodiazepines also inhibit adenosine uptake apart from $GABA_A$ activity (see Adenosine below).

Various isoforms of $GABA_A$ Cl^- channels differ in their affinity for different benzodiazepines. $GABA_A$ receptors containing $Î³_2$ subunits are more sensitive to benzodiazepines than are $GABA_A$ receptors containing $Î³_1$ and $Î³_3$ subunits. Sensitivity and response to benzodiazepine binding is also highly dependent on the specific Î± subunit composition of the $GABA_A$ receptor. $GABA_A$ receptors containing an $Î±_4$ or $Î±_6$ subunit are completely insensitive to and

will not bind benzodiazepines, whereas $GABA_A$ receptors containing $Î±_1$, $Î±_2$, $Î±_3$, or $Î±_5$ subunits are sensitive to benzodiazepine binding. In addition, specific Î± subunits may mediate different effects of benzodiazepines. For example, sedative effects are mediated through binding to $Î±_1$ subunits while anxiolytic effects appear to be mediated by binding to $Î±_2$ subunits.[49]

Zolpidem, an imidazopyridine, and zaleplon, a pyrazolopyrimidine, are nonbenzodiazepine agents that act as agonists at the

benzodiazepine binding site on the $GABA_A$ receptor. These agents exhibit a high selectivity for the $Î±_1$ subunit and low selectivity for $Î±_2$, $Î±_3$, and $Î±_5$ subunits.[142,161] This selective binding to $Î±_1$ subunits is thought to account for relatively selective sedative properties of zaleplon and zolpidem at therapeutic doses, as compared to benzodiazepines.

TABLE 14-9. Examples of Xenobiotics That Affect GABAergic Neurotransmission

GABA agonism	GABA antagonism
Stimulate GAD	Direct $GABA_A$ antagonists
Valproate	Bicuculline
Gabapentin	Cephalosporins
	Ciprofloxacin
Direct $GABA_A$ agonists	Enoxacin

Muscimol	Imipenem
Progabide[a]	Nalidixic acid
	Norfloxacin
Indirect $GABA_A$ agonists	Ofloxacin
Avermectin	Penicillins
Barbiturates	
Benzodiazepines	Indirect $GABA_A$ antagonists
Chloral hydrate	Aztreonam
Clomethiazole	Clozapine
Ethanol	Flumazenil
Etomidate	Lindane
Felbamate	MAOIs
Ivermectin	Maprotiline
Meprobamate	Organochlorine insecticides

Methaqualone	Penicillins
Propofol	Pentylenetetrazol
Steroids	Picrotoxin
Topiramate	Tricyclic antidepressants
Trichloroethanol	
Volatile anesthetics	Inhibit GAD
Zaleplon	Cyanide
Zolpidem	Domoic acid
Zopiclone	Hydrazines
	Isoniazid
Direct $GABA_B$ agonists	
Baclofen	Direct $GABA_B$ antagonists
GHB	Phaclofen[b]
Progabide[a]	Saclofen[b]

Inhibit GABA-T	Inhibit PK
Vigabatrin	Hydrazines[c]
	Isoniazid[c]
Inhibit GABA uptake	
Guvacine	
Tiagabine	
Valproate	

GABA = Î³-aminobutyric acid; GABA-T = GABA transaminase; GAD = glutamic acid decarboxylase; GHB = Î³-hydroxybutyric acid; PK = pyridoxine kinase; MAOIs = monoamine oxidase inhibitors.

[a] Directly activate $GABA_A$ and $GABA_B$ receptors as well as being metabolized to GABA.

[b] Thought not to cross bloodâ€“brain barrier in meaningful amounts.

[c] Major site of action is PK inhibition, though some direct GAD inhibition occurs.

Numerous steroids, such as alphaxalone and naturally occurring analogs, bind to more than one site on the $GABA_A$ complex to inhibit or enhance the action of GABA.[55,138]

The synthesis of neuroactive steroids is partly regulated by benzodiazepine binding to mitochondrial benzodiazepine receptors

(MBRs) apart from the $GABA_A$ complex.[80,138] These mitochondrial benzodiazepine binding sites are found both within and outside the CNS and were originally called peripheral benzodiazepine receptors. Mitochondrial benzodiazepine binding sites comprise three subunits: a voltage-dependent anion channel; an adenine nucleotide carrier; and a binding site for PK 11195, an isoquinoline carboxamide derivative.[54] Benzodiazepines vary in their affinity for mitochondrial binding. On binding, benzodiazepines appear to enhance the movement of cholesterol into mitochondria to begin steroid synthesis. Some of carbamazepine's action may be a result of binding at mitochondrial benzodiazepine receptors.[45]

Barbiturates bind to the $GABA_A$ complex to produce several effects.[77,138] All barbiturates enhance the action of GABA by producing more Cl^- influx for a given amount of GABA binding by increasing the duration of Cl^- channel opening. Whereas phenobarbital does not change the affinity of GABA or benzodiazepines for their binding sites, depressant barbiturates, such as pentobarbital, do increase GABA and benzodiazepine receptor affinities for their ligands, further enhancing inward Cl^- currents. At high concentrations, at least some barbiturates directly open Cl^- channels to cause Cl^- influx.[77] In addition, barbiturates possess other actions that depress all excitable membranes, including cardiac and smooth muscle.

The intravenous anesthetics propofol and etomidate enhance inward $GABA_A$ Cl^- currents, and at high concentrations they directly open chloride channels in the absence of GABA.[7] The anesthetic effects of etomidate are mediated by $Î²_3$ subunits, while agonism at $Î²_2$ subunits may contribute to etomidate's sedative effect.[111,125,142] Volatile general anesthetics also directly activate $GABA_A$ Cl^- channels.

Some of ethanol's action is mediated through binding to the $GABA_A$ complex. The degree to which ethanol enhances the effect of GABA on Cl^- influx depends on the $GABA_A$ receptor subunit composition. For

example, receptors with an Î±4 or Î±6 subunit and a Î´ subunit respond to very low concentrations of ethanol.[151,163]

Methaqualone produces at least part of its pharmacologic effect through indirect $GABA_A$ activity. Little is known of glutethimide's and methyprylon's mechanism of action. Their structural similarities to barbiturates suggest that much or most of them reside at the $GABA_A$ receptor. Trichloroethanol, a metabolite of chloral hydrate, and clomethiazole interact at the $GABA_A$ complex in a manner similar to barbiturates, although it is not clear whether they are binding to an identical site on the Cl^- channel.[166] Ivermectin, an antihelminthic, activates $GABA_A$ Cl^- channels by increasing GABA binding. Meprobamate displays barbiturate-like action at the $GABA_A$ receptor, and, at high concentrations, is able to cause Cl^- influx in the absence of GABA.[126] High concentrations of felbamate also cause inward Cl^- currents in the presence of GABA, although this seems unimportant at therapeutic doses.[126] Part of topiramate's anticonvulsant action may result from enhanced Cl^- influx through binding to $GABA_A$ receptors.[137]

Inhibition of GABA Uptake

Valproate and the anticonvulsants guvacine and tiagabine work, in part, by inhibiting GABA uptake. Although valproate is structurally similar to GABA, its inhibition of the GABA transporter does not appear to be competitive.[108]

$GABA_A$ Antagonism

Direct $GABA_A$ Antagonists

Substances that act by any mechanism to decrease $GABA_A$ activity can cause CNS excitation and convulsions by preventing inhibitory inward Cl^- currents. Direct antagonists bind to the same site as GABA to prevent GABA binding, the prototype being the convulsant bicuculline. Various antibiotics interact with the $GABA_A$ receptor to

antagonize the action of GABA. In a dose-dependent manner, both imipenem and cephalosporins appear to directly antagonize GABA binding and can produce seizures at high doses or at therapeutic doses in susceptible individuals.[162] Evidence suggests that penicillin may also directly antagonize GABA binding. Electrophysiologic and radioligand binding studies indicate that norfloxacin, ciprofloxacin, ofloxacin, and enoxacin all combine with the GABA binding site to prevent GABA binding.[162] Theophylline and at least some nonsteroidal antiinflammatory agents markedly enhance GABA antagonism by some fluoroquinolones in vitro.[162] Virol A, from *Cicuta virosa*, appears to directly antagonize binding of GABA to its receptor on the $GABA_A$ complex.[156]

Indirect $GABA_A$ Antagonists

Penicillin is well known for producing convulsions at high doses (eg, >20 million units of penicillin per day with renal insufficiency), and both penicillin and aztreonam, a monobactam, appear to block the Cl^- channel to prevent GABA-mediated inward Cl^- currents.[162]

Picrotoxin, from *Anamirta cocculus* (fish berries), and the experimental convulsant pentylenetetrazol bind to the picrotoxin site of the $GABA_A$ receptor complex to inhibit the action of GABA. Excessive doses produce CNS excitation and convulsions. Some organochlorine insecticides (eg, lindane) also inhibit the action of GABA by binding to what appears to be the picrotoxin site.[92] Convulsions characterize acute poisonings by these agents. Both Î±-thujone, the active component in wormwood oil, and cicutoxin from the water hemlock noncompetitively antagonize $GABA_A$ activity.[64,157]

Flumazenil competitively antagonizes benzodiazepines, zolpidem, zaleplon, and zopiclone at their receptors to reverse their pharmacologic effects.[20,139] Paradoxically, large doses of flumazenil exhibit anticonvulsant activity in animals. This is explained by flumazenil's ability to inhibit adenosine uptake, not by partial agonism at the benzodiazepine receptor.[117]

Cyclic antidepressants, including amoxapine and maprotiline, and at least two MAOIs (isocarboxazid and tranylcypromine) inhibit GABA-mediated Cl^- influx at $GABA_A$ receptors.[95,146] Their potency at inhibiting Cl^- influx correlates with the frequency of seizures that occur in patients taking therapeutic doses of these medications. Impaired $GABA_A$ activity may contribute to or be primarily responsible for seizures seen in patients who overdose on these agents. The exact binding site of these drugs on the $GABA_A$ receptor complex is not yet known, although some evidence suggests at least indirect activity at the picrotoxin binding site.

Some subtypes of $GABA_A$ receptors are susceptible to inhibition by zinc ions.[138] What role this plays in normal physiology or toxicology is not established.

$GABA_A$ Withdrawal

Acute withdrawal from all $GABA_A$ direct and indirect agonists appears almost identical except for time course; in all cases, a common denominator is impaired Cl^- influx. Withdrawal of all $GABA_A$ agonists can cause tremor, hypertension, tachycardia, respiratory alkalosis, diaphoresis, agitation, hallucinations, and convulsions. When $GABA_A$ receptors are chronically exposed to an agonist, changes in gene expression of receptor subunits occur which lessens Cl^- influx in response to GABA or drug binding, producing tolerance. Importantly, withdrawal of the agonist produces yet further changes in subunit expression. For example, benzodiazepine-insensitive $Î±_4$-subunit expression is increased following withdrawal of many GABA agonists, including benzodiazepines, zolpidem, zaleplon, neuro-steroids, and ethanol. (Expression of other subunits, including $Î±_1$, $Î³_2$, $Î²_2$, and $Î²_1$ also change in response to exposure and/or withdrawal of $GABA_A$ agonists.[49]) Alterations in $GABA_A$ receptor subunit composition following chronic exposure to and withdrawal of an agonist can, therefore, affect the ability to successfully treat withdrawal

symptoms. While any $GABA_A$ receptor agonist may be used to treat withdrawal from another, some agents work better than others in different clinical settings. For example, patients experiencing severe alcohol withdrawal may have an increased proportion of $GABA_A$ receptors containing benzodiazepine-insensitive Î±4 subunits, and contain fewer $GABA_A$ receptors with benzodiazepine-sensitive Î±1 subunits.[27] Even extremely high doses of benzodiazepines in these patients may not effectively control severe alcohol withdrawal. A better treatment option in such a setting would be $GABA_A$ agonists such as propofol or phenobarbital that act either on a different site on the $GABA_A$ receptor or directly open the Cl^- channel.[7,27] Phenytoin and carbamazepine do not stop $GABA_A$ withdrawal seizures because their pharmacologic effects are independent of $GABA_A$ agonism.

$GABA_B$ Agonists

The main $GABA_B$ receptor agonist of toxicologic significance is baclofen. Coma, hypothermia, hypotension, bradydysrhythmias, and seizures characterize its toxicity. The convulsions that occur in patients with baclofen overdose are thought to result from disinhibition (inhibition of inhibitory neurons). Carbamazepine's activation of $GABA_B$ receptors has been demonstrated, although this is not thought to explain most of its anticonvulsant action. Some of Î³-hydroxybutyrate's actions following pharmacologic doses may be mediated through activation of $GABA_B$ receptors.

$GABA_B$ Withdrawal

Baclofen withdrawal is similar clinically to $GABA_A$ withdrawal. Hallucinations, agitation, tremor, increased sympathetic activity, and convulsions are the main characteristics of baclofen withdrawal. Withdrawal from chronic intrathecal baclofen administration may also be accompanied by large swings in autonomic tone (hypotension, hypertension, tachycardia, bradycardia) and transient cardiomyopathy and shock. Reinstitution of oral baclofen therapy

following oral withdrawal, or intrathecal baclofen following intrathecal withdrawal is the definitive treatment of choice.[96]

Î³-Hydroxybutyrate

Î³-Hydroxybutyrate (GHB; Î³-hydroxybutyric acid) exists endogenously but toxicologic interest stems from its use as a drug of abuse and as a treatment for narcolepsy.[11,46,87] GHB is rapidly absorbed and freely crosses the blood-brain barrier. Toxicity resulting from ingestion of GHB is explained by GHB receptor and $GABA_B$ receptor activation, and comprises agitation, tremor, rapid onset of coma, vomiting, bradycardia, hypotension, hypotonia, and apnea that usually resolve within several hours. Although seizure activity has been noted in experimental animals, it is debated whether GHB causes true convulsive activity in human beings. Human experiments with â€œtherapeuticâ€• doses of GHB have not found EEG changes consistent with seizure activity.[87] Some authors have reported â€œgeneralized seizuresâ€• occurring in patients presenting after GHB overdose. Interestingly, patients with the rare inborn error of metabolism, succinic semialdehyde dehydrogenase (SSAD) deficiency, have elevated GHB concentrations and tend to experience seizures.[56] Valproate similarly elevates endogenous GHB concentrations by inhibiting SSAD.

Controversy exists as to whether GHB should be considered a neurotransmitter or simply a neuromodulator because it is unclear whether this substance is concentrated within vesicles for synaptic release. There is evidence demonstrating a sodium-dependent uptake transporter for GHB.

GHB receptors appear to be heterogeneously distributed throughout the brain, with highest concentrations in the hippocampus, cortex, limbic areas, and thalamus, as well as in regions innervated by dopaminergic terminals and dopaminergic nuclei. GHB receptors exist on neurons, mainly at the synaptic level, but are absent from glial or peripheral cells.

At least two general GHB receptors have been described thus far, based on binding affinity for GHB and other ligands. High-affinity receptors for GHB do not respond to GABA, GABAergic agonists, Î³-butyrolactone, or dopamine. Similarly, GHB does not activate $GABA_A$ Cl^- channels. Flumazenil and baclofen fail to antagonize GHB binding to its binding site.[11]

Although Î³-butyrolactone (GBL) does not express affinity for GHB binding sites, GBL rapidly undergoes hydrolysis to form GHB by peripheral Î³-lactonase.[11,94] 1,4-Butanediol undergoes conversion to GHB via alcohol dehydrogenase and aldehyde dehydrogenase.

Several proposed pathways for endogenous GHB formation exist (Fig. 14-11).[11] Evidence exists for GHB's metabolism back to GABA, although this appears minimal at physiologic GHB concentrations.[46] However, effects resulting from pharmacologic doses of GHB may result, in part, from secondary GABA formation.

Although normal endogenous GHB concentrations are probably not high enough to activate $GABA_B$ receptors, such receptor activation may occur with exogenous administration of GHB. Furthermore, there appears to be functional interplay between GHB and $GABA_B$ receptors.[11]

Specific interactions between GHB and dopamine are complex and not fully delineated. Treatment with GHB appears to inhibit dopamine release, probably via stimulation of $GABA_B$ receptors.[168] GHB also affects the firing rates of dopaminergic neurons, dopamine synthesis, and levels of dopamine and its major metabolites. GHB is thought to affect sleep cycles, temperature regulation, cerebral glucose metabolism and blood flow, memory, and emotional control, and it may be neuroprotective.

Although GHB can suppress alcohol withdrawal, GHB is also addictive, and both tolerance and a withdrawal syndrome have been described. Withdrawal is characterized, in part, by insomnia, cramps, paranoia, hallucinations, tremor, and anxiety.

Glycine as an Inhibitory Neurotransmitter

Glycine acts as a postsynaptic inhibitory neurotransmitter in the spinal cord and lower brainstem. In the CNS, serine is converted to glycine by serine hydroxymethyltransferase (SHMT).

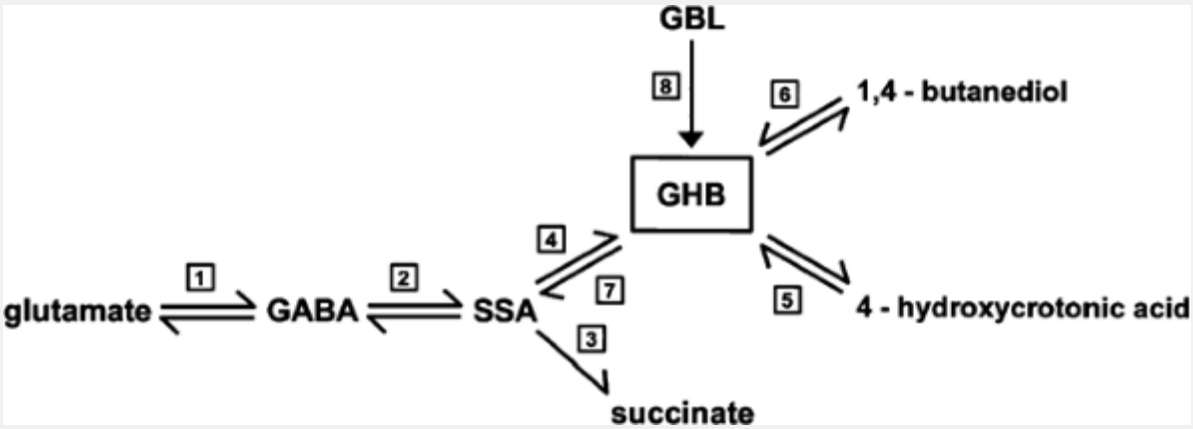

Figure 14-11. Potential pathways of GHB (Î³-hydroxybutyrate) synthesis and degradation. GABA = Î³-aminobutyric acid; GBL = Î³-butyrolactone; SSA =succinic semialdehyde; [1] =glutamic acid decarboxylase; [2] = GABA-transaminase; [3] =succinic semialdehyde dehydrogenase; [4] =specific succinic semialdehyde reductase and/or nicotinamide adenine dinucleotide phosphate (NADPH)-dependent aldehyde reductase 2; [5] = mitochondrial Î² oxidation; [6] =alcohol dehydrogenase and aldehyde dehydrogenase; [7] =GHB dehydrogenase; [8] = Î³-lactonase.

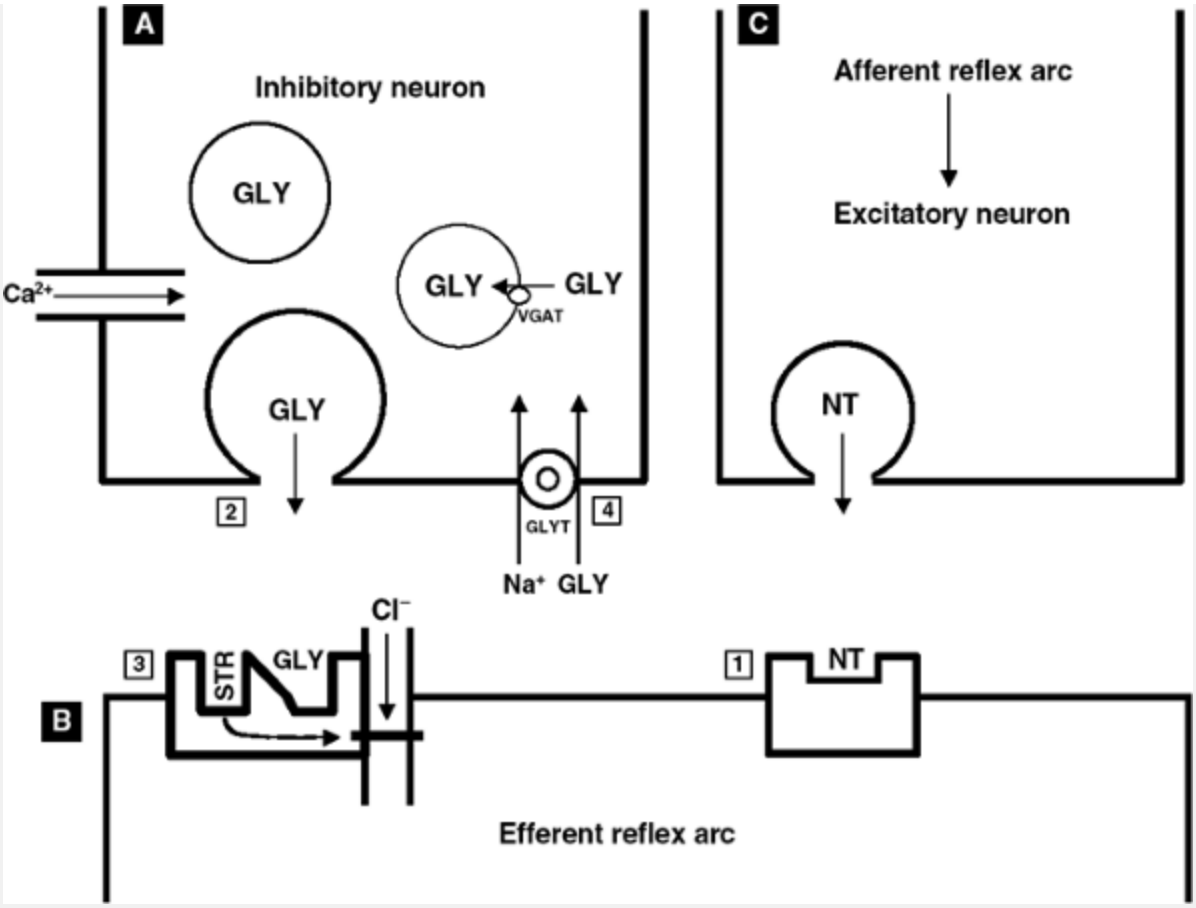

Figure 14-12. Inhibitory glycinergic neurotransmission. Glycine is concentrated within vesicles by uptake via VGAT, the vesicle membrane transporter. Signals from the afferent limb of a reflex arc (neuron C) cause the release of an excitatory neurotransmitter (NT) that crosses the synapse to bind to neuron B in the efferent limb of the reflex arc [1]. To prevent excessive neuronal firing and motor activity, glycine (GLY) released from inhibitory neuron A [2] binds to glycine Cl^- channel receptors on neuron B [3] and causes inhibition by hyperpolarization through Cl^- influx. Synaptic glycine is transported back into the neuron by at least two subtypes of membrane glycine transporters, GLYT-1 and GLYT-2 [4]. Strychnine (STR) binds to the glycinergic Cl^- channel to decrease glycine's binding, which prevents Cl^- influx. Although strychnine is shown to bind to a separate site from

glycine, there is evidence that these sites may overlap.

Release and Uptake

Glycine is transported into storage vesicles by VGAT and undergoes Ca^{2+}-dependent exocytosis upon neuronal depolarization (Fig. 14-12). Glycine is removed from the synapse through uptake by a Na^{+}-dependent transporter into presynaptic neurons and into glial cells. Two glycine membrane transporters have been cloned,

and share homology with GABA uptake transporters. GLYT-1 is found both in astrocytes and neurons, whereas GLYT-2 is localized on axons and terminal boutons of neurons that contain vesicular glycine. Although both transporters are found associated with glycinergic neurons in the brainstem and spinal cord, GLYT-1 is also found in the forebrain in regions devoid of glycinergic neurotransmission. At the latter location, GLYT-1 may regulate extracellular glycine that is available for NMDA receptor activation, and GLYT-1 inhibitors, then, could enhance NMDA responses (see NMDA Receptor Antagonists below). Glycine transporters can also function in reverse, pumping glycine out of the cell when the intracellular sodium concentrations rise.[4]

Glycine Receptors

Like $GABA_A$, the glycine receptor is a Cl^- channel on the postsynaptic membrane. $GABA_A$ Cl^- channels and glycinergic Cl^- channels share significant amino acid homology. Glycine receptors are pentameric proteins made up of Î± and Î² subunits. Four isoforms of the Î± subunit and one isoform of the Î² subunit have been described.[101]

Glycine receptor activation causes an inward Cl^- current that hyperpolarizes the membrane. It appears that three glycine molecules must bind to sites on the Cl^- channel to produce inhibitory

Cl^- influx.

Chemical Agents

Table 14-10 provides examples of chemical agents that affect inhibitory glycine Cl^- channels. The amino acids D-alanine, taurine, L-alanine, L-serine, and proline can activate glycinergic Cl^- channels. Both ethanol and propofol potentiate glycine-mediated inward Cl^- currents through action at the Î± subunit of the glycine receptor, just as they do at $GABA_A$ Cl^- channels.[97,101] Clozapine inhibits glycine uptake.[67]

Strychnine is the main toxicologic agent affecting glycinergic transmission. Strychnine binds to the Î± subunit of the glycine receptor to prevent glycine's action on Cl^- influx,[3] at least in part by decreasing glycine's binding to its receptors. This physiologic antagonism of glycine's action produces increased muscle tone, rigidity, opisthotonus, trismus, and death from respiratory failure and rhabdomyolysis. Given the similarity in Cl^- channels, it is not surprising that strychnine binds to the $GABA_A$ complex in vitro. However, strychnine's affinity for this complex is less than that for glycine receptors, and most of its toxicologic action is a result of physiologic antagonism of glycine's inhibitory action.

Picrotoxin binds to the glycine receptor to impair Cl^- influx.[93] Tetanus toxin produces rigidity and trismus by preventing glycine release from nerve endings in the spinal cord and brainstem.

TABLE 14-10. Examples of Xenobiotics That Affect Inhibitory Glycine Chloride Channels

Glycine agonists	Glycine antagonists
Ethanol	Strychnine
Propofol	Picrotoxin
D-Serine	Glycine uptake inhibitor
	Clozapine

Ethanol and propofol enhance Cl^- influx through glycine Cl^- channels, although they do not appear to act as direct agonists. Evidence exists for picrotoxin's direct antagonism at the glycine binding site(s) in contrast to $GABA_A$ Cl^- channels, where it acts at a site separate from where GABA (Î³-aminobutyric acid) binds.

Glutamate

Glutamate is the main excitatory neurotransmitter in the CNS. Up to 66% of all brain energy expenditure is attributed to uptake and recycling of glutamate.[67] Aspartate displays similar actions although its exact role as a neurotransmitter is not as well defined because it is only active at certain types of glutamate receptors. Glutamate and aspartate are commonly referred to as excitatory amino acid (EAA) neurotransmitters. Glutamate is essential for memory, learning, perception, and locomotion.[38,76]

Glutamatergic neurotransmission has been a subject of intense research because of its role in mediating neuronal damage in degenerative neurologic diseases and during times of trauma, ischemia, hypoglycemia, and status epilepticus. Although glutamate receptor stimulation is necessary for normal brain activity, excessive glutamate receptor activation endogenously or by glutamate agonists can produce convulsions, neuronal damage, and death. Conversely, glutamate antagonists demonstrate anticonvulsant activity and neuroprotective action in animal models of brain and spinal cord injury. Glutamate may also play an important role in the development of drug abuse and subsequent withdrawal symptoms. Glutamate antagonists decrease drug craving and withdrawal symptoms in patients addicted to ethanol, benzodiazepines, and opioids.[14]

Synthesis, Release, and Uptake

Glutamate is a nonessential amino acid that does not cross the bloodâ€“brain barrier. It must, therefore, be synthesized from products of glucose metabolism or other precursors that enter neurons. Glutamate is primarily synthesized from glutamine by the enzyme glutaminase located within the mitochondrial compartment. Other amino acids, such as aspartate, also serve as sources for glutamate production. Glutamate stored within vesicles is released into the synapse by Ca^{-2}-dependent exocytosis.[38] Five different EAA uptake transporters have been identified, and glutamate undergoes uptake both by neuronal and glial cells.[134] Synaptic glutamate transported into glial cells undergoes conversion back to glutamine by the enzyme glutamine synthase. Glial cells then release glutamine back into the synapse for uptake by neurons and recycling back to glutamate and then into storage vesicles (Fig. 14-13). Reverse transport of glutamate from the cytoplasm into the synapse by the membrane transporter may occur under some circumstances.[38] Glutamate also serves as the precursor for GABA's synthesis.

Glutamate Receptors

The EAA receptor system is the most complex of all neurotransmitters. This complexity is necessary for protection against the devastating effects of uncontrolled excitatory neurotransmission. At present, 11 different glutamate receptors are recognized. Three ionotropic glutamate receptors are cation channels, and 8 metabotropic receptors are linked to G proteins.[38]

A single neuron may express numerous types of glutamate receptors. Postsynaptic glutamate receptors are usually excitatory, although some inhibitory actions have been demonstrated. Presynaptic terminal glutamate receptors appear mainly to inhibit release of various neurotransmitters, including glutamate (Fig. 14-13).[118]

Ionotropic Glutamate Receptors

Three ionotropic glutamate receptors have been identified. All allow for excitation through cation

influx. These receptors are further categorized and named by their abilities to be activated or antagonized by various substances: kainate, AMPA (Î±-amino-3-hydroxy-5-methyl-4-isoxazole propionate), and NMDA (*N*-methyl-D-aspartate).

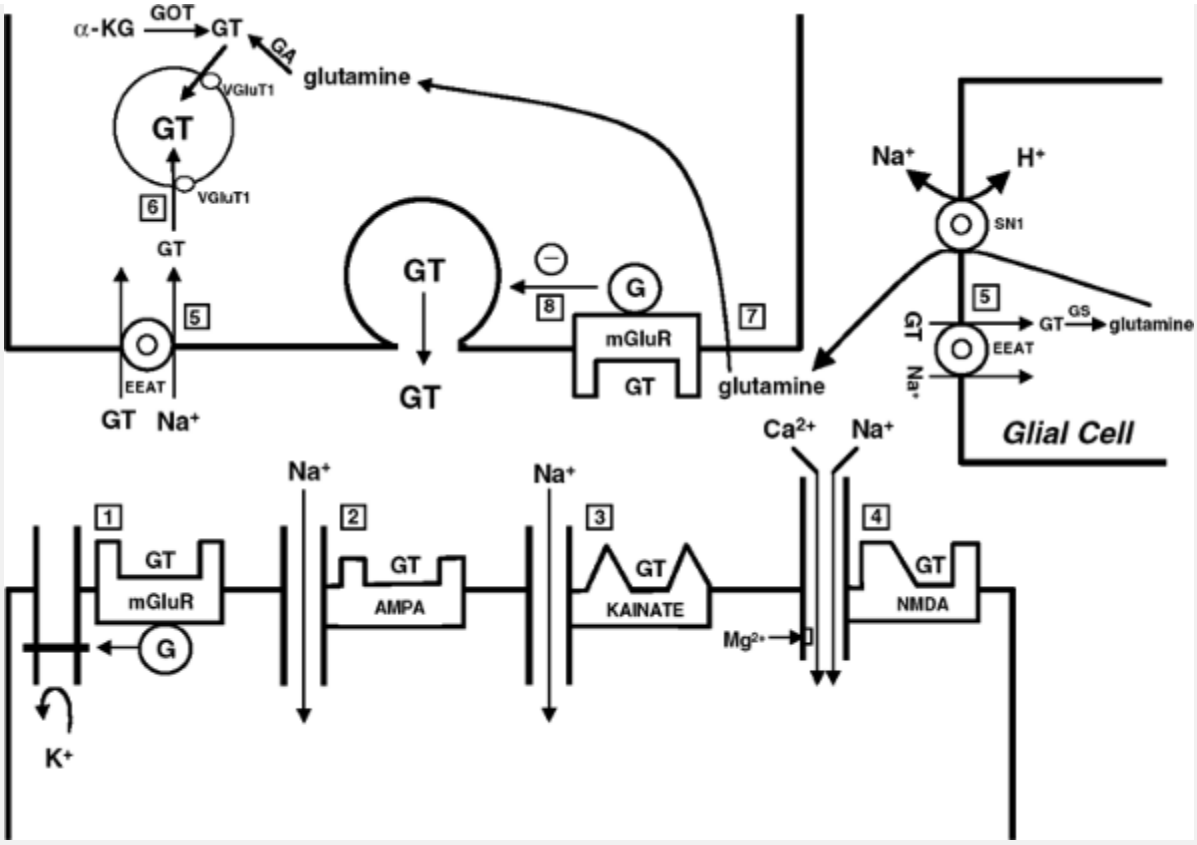

Figure 14-13. Glutamatergic neurotransmission. Glutamic-oxaloacetic transaminase (GOT) converts Î±-ketoglutarate (Î±-KG) to glutamate (GT) in mitochondria. GT also forms from glutamine via mitochondrial glutaminase (GA). Glutamate is transported into vesicles [6] by VGlut1 (or possibly other subtypes) for exocytotic release into the synapse. Synaptic glutamate activates four main types of receptors. AMPA [2], kainate [3], and NMDA [4] receptors are cation channels. Membrane depolarization in response to their activation causes neuronal excitation through cation influx. Metabotropic receptors (mGluR) [1,8] are coupled to G proteins and are expressed on pre- and postsynaptic membranes. In addition, some mGluRs reside outside of the synapse. Postsynaptic mGluR excitation in this example [1] results from preventing K^+ efflux, but other mechanisms of excitation exist. Presynaptic mGluRs act to inhibit

[8] glutamate (and other neurotransmitter) release through modulating intracellular Ca^{2+} concentrations. Figure 14-14 provides a more detailed illustration of the NMDA receptor. Excessive influx of Ca^{2+} through NMDA receptors (and through some AMPA and kainate receptors) causes neuronal damage and cell death. An Mg^{2+} ion normally blocks the NMDA receptor channel to prevent Ca^{2+} influx despite glutamate binding. However, depolarization of the neuronal membrane by cation influx resulting from activation of any of the other receptor types causes Mg^{2+} to dissociate from the NMDA receptor and to allow potentially damaging inward Ca^{2+} currents. Glutamate undergoes uptake by neurons and glial cells by various subtypes of EEAT, the membrane bound glutamate transporter [5]. In glial cells, GT is converted to glutamine by glutamine synthase (GS), and glutamine is transported out of glial cells by system N-1 (SN1), a Na^{+}- and H^{+}-dependent pump that is structurally similar to VGAT, the vesicle membrane GABA transporter. Glutamine then moves back into neurons [7] where it undergoes conversion back to glutamate. Various agents in Table 14-11 affect glutamatergic neurotransmission, in part, by stimulating or blocking the various glutamate receptors [1â€“4,8] or by preventing glutamate uptake [5]. G =G protein.

Kainate receptors are named for their affinity for kainic acid found in seaweed and comprise GluR5â€“7, KA1, and KA2 subunits.[72] Activation allows Na^{+} influx and a small amount of K^{+} efflux, resulting in neuronal depolarization. Some kainate receptors in the hippocampus also appear to allow Ca^{2+} influx following activation. Kainate receptors are the only ionotropic glutamate receptors, to date, found presynaptically, although they are much more prevalent on postsynaptic neuronal membranes.[52]

The AMPA receptor is an ion channel structurally similar to the kainate receptor that also mediates Na^{+} influx (and lesser amounts

of K^+ efflux) on postsynaptic membranes, triggering neuronal depolarization.[12] AMPA receptors are composed of GluR1â€“3 subunits.[72] The AMPA receptor is the most common ionotropic glutamate receptor found in the brain and appears to account for most glutamatergic excitation under normal conditions. A subtype of AMPA receptors in the hippocampus may also allow Ca^{2+} influx after activation.[129]

The NMDA receptor, the most studied of all glutamate receptors, is a Ca^{2+} channel whose activation allows for inward Ca^{2+} and Na^+ currents (and some K^+ efflux), resulting in neuronal depolarization

and excitation (Fig. 14-14). NMDA receptors comprise NR1, $NR2_{Aâ€“D}$, and $NR3_{Aâ€“B}$ subunits.[72] Excessive stimulation of NMDA receptors by glutamate released during times of ischemia, trauma, hypoglycemia, or convulsions triggers damaging rises in intracellular Ca^{2+} concentrations, activation of numerous enzymes, and free radical formation, all of which incite cell death.[76] Antagonists of NMDA Ca^{2+} channels demonstrate anticonvulsant and neuroprotective activity during times of neuronal insult.

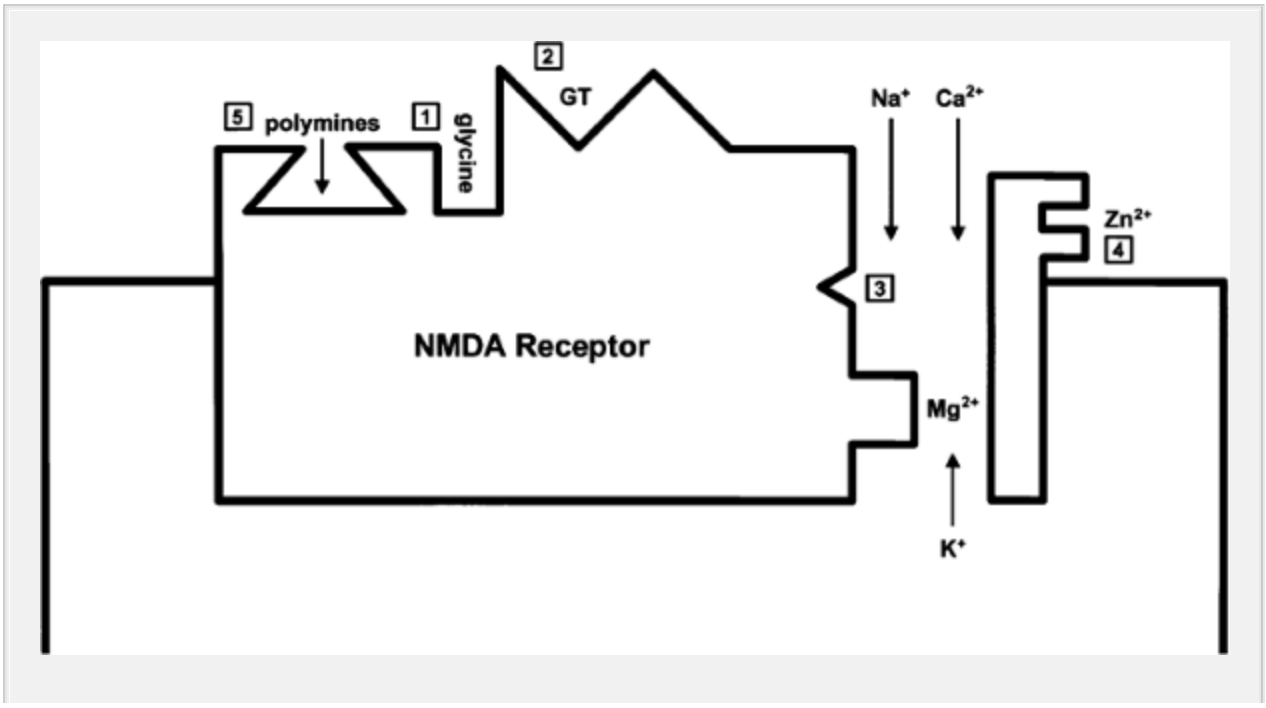

Figure 14-14. Representation of the NMDA glutamate receptor. The NMDA receptor is a voltage-gated and ligand-gated Ca^{2+} channel. Glutamate (GT) binds to its receptor on the channel [2] to open the Ca^{2+} channel and to allow Ca^{2+} and Na^{+} influx and lesser amounts of K^{+} efflux. Mg^{2+} normally blocks the Ca^{2+} channel, preventing cation influx in response to glutamate binding. Mg^{2+} leaves the channel when the membrane is depolarized by 20â€“30 mV. Glycine must also bind to its site on the NMDA receptor complex for successful glutamate agonism. Polyamines bind on the extracellular surface of the receptor [5]. Zn^{2+} binds [4] to inhibit Ca^{2+} influx. The phencyclidine (PCP) binding site [3] lies within the channel. Agents in Table 14-11 may antagonize glycine binding [1]; block the Ca^{2+} channel by binding to the PCP binding site [3]; bind to the polyamine binding site [5]; or directly stimulate the glutamate binding site [2].

The NMDA Ca^{2+} channel is normally blocked by Mg^{2+} in a voltage-dependent manner, preventing Ca^{2+} influx despite glutamate binding (Fig. 14-14).[128] Only when the neuronal membrane is depolarized by at least 20â€“30 mV through some other mechanism (eg, activation of another type of glutamate receptor) will Mg^{2+} leave the channel and allow Ca^{2+} influx in response to glutamate binding. Thus, the NMDA glutamate receptor is both a ligand-gated and voltage-gated ion channel. Many neurons express both NMDA and non-NMDA receptors for glutamate. Excessive stimulation of kainate or AMPA receptors by glutamate causes cell damage through Na^{-} (and in some instance, Ca^{2+}) influx, because the membrane depolarization they produce causes Mg^{2+} to leave the NMDA receptor and allows for potentially damaging inward Ca^{2+} currents.[38] Calcium ion influx through voltage-gated ion channels (including the L subtype) on cell bodies that open in response to depolarization also contributes to accumulation of intracellular calcium and cell damage. Consequently, excessive activation of any excitatory glutamate receptor has the

potential to produce neuronal cytotoxicity.[76] Glutamate alone is incapable of activating NMDA receptors, even after Mg^{2+} has dissociated from the ion channel. Glycine also must bind to its specific receptor on the NMDA receptor complex for successful glutamate agonism (Fig. 14-14), making glycine an indirect agonist of excitatory neurotransmission.[38] Strychnine does not antagonize glycine's excitatory action at NMDA receptors, explaining why glycine NMDA receptors are also known as strychnine-insensitive glycine receptors.

Zinc ions normally bind to the NMDA receptor complex to antagonize the action of glutamate. Binding of spermine or spermidine to a polyamine binding site on the extracellular side of the NMDA receptor results in increased affinity of glycine and glutamate for their binding sites. However, polyamine agonism is not essential for glutamate activation of NMDA receptors.[65]

Metabotropic Glutamate Receptors

Metabotropic glutamate receptors (mGluRs) are linked to various G proteins on post- and presynaptic membranes (Fig. 14-13). Eight different receptors have been isolated. In contrast to ionotropic glutamate receptors, mGluRs may excite or inhibit at postsynaptic membranes, and appear mainly to inhibit at presynaptic locations. Postsynaptic excitation most commonly results from prevention of K^+ efflux or activation of phospholipase C, which serves to raise intracellular Ca^{2+} concentration. Postsynaptic inhibition usually results from enhanced K^+ efflux.[100]

Metabotropic glutamate receptors are commonly subdivided into three main groups based on their sequence homology, intracellular signaling mechanisms and response to specific experimental agonists.[106] As a general rule, group I receptors (mGlu1, mGlu5) reside postsynaptically; activation produces excitation through blockade of K^+ efflux or by activating phospholipase C, producing rises in intracellular Ca^{2+}.[152] In animal experiments, agonists of

group I receptors produce convulsions, while antagonists display anticonvulsant effects.[106]

Groups II (mGlu2, mGlu3) and III (mGlu4, mGlu6, mGlu7, mGlu8) receptors most commonly serve as presynaptic autoreceptors and heteroreceptors and, when activated, inhibit adenylate cyclase activity. This, in turn, prevents Ca^{2+} influx and serves to inhibit release of neurotransmitters, including glutamate, GABA, dopamine, and adenosine. Group II presynaptic autoreceptors may play an especially important role in decreasing further glutamate release during pathologic conditions when the extracellular

concentration of glutamate exceeds normal physiologic levels.[152] Agonists of groups II and III metabotropic receptors produce anticonvulsant effects in animals.[106]

TABLE 14-11. Examples of Xenobiotics That Affect Glutamatergic Neurotransmission

Glutamate agonism	NMDA receptor antagonists
Direct glutamate receptor agonists	Amantadine
BMAA	Dextrorphan
BOAA	Dizocilpine (MK801)
Domoic acid	Ketamine

Ibotenic acid	Memantine
Willardine	Orphenadrine
	Pentamidine
Glycine NMDA receptor agonists	Phencyclidine
D-Cycloserine	Ethanol[a]
Milacemide	
	NMDA glycine antagonists
Glutamate uptake inhibitor	Felbamate
Clozapine	Kynurenic acid
	Meprobamate
Glutamate antagonism	
Prevent glutamate release	Polyamine antagonists
Lamotrigine	Ifenprodil
Nimodipine	Eliprodil

Riluzole	

BMAA = Î±-amino-Î²-methylaminopropionic acid; BOAA = Î²-*N*-oxalylamino-L-alanine; NMDA 5 *N*-methyl-D-aspartate.
[a] Ethanol antagonizes glutamate's action at NMDA receptors through an unknown mechanism.

Chemical Agents

Table 14-11 provides examples of chemical agents that affect glutamatergic neurotransmission.

Glutamate Agonism

Domoic acid produces amnestic shellfish poisoning, partly characterized by confusion, agitation, convulsions, memory disturbance, neuronal damage, and death.[58] The structural similarity between domoic acid and glutamate is thought to explain excessive activation of kainate receptors with secondary NMDA receptor activation and neuronal damage.

Investigators hypothesize that other naturally occurring glutamate receptor agonists produce additional neurologic diseases. The neurogenic form of lathyrism results from using chickling peas (*Lathyrus sativus*) as a food staple. Chickling peas contain Î²-*N*-oxalylamino-L-alanine (BOAA), an agonist of AMPA receptors.[38,79] Neurogenic lathyrism was common in German concentration and prisoner of war camps during World War II and still occurs regularly in some parts of the world. Ibotenic acid, from poisonous mushrooms, activates NMDA and some metabotropic glutamate receptors.[38,79] It undergoes decarboxylation to muscimol, a direct agonist at $GABA_A$ receptors. Clozapine inhibits glutamate uptake.[67]

Because noncompetitive NMDA receptor antagonism reproduces many

signs and symptoms of schizophrenia, investigators are directing efforts at increasing glutamate's activity at NMDA channels in an effort to treat the disease. After crossing the bloodâ€“brain barrier, milacemide undergoes conversion to glycine, which is required for NMDA receptor activation. D-Cycloserine also crosses the bloodâ€“brain barrier to stimulate glycine receptors on NMDA calcium channels.[38]

Glutamate Antagonism

Prevention of Glutamate Release

Riluzole, used for the treatment of amyotrophic lateral sclerosis, indirectly prevents release of glutamate. Lamotrigine diminishes glutamate release through blockade of voltage-gated Na^+ channels. Blockade of voltage-gated Ca^{2+} channels by nimodipine also appears to impair glutamate release.[154]

NMDA Receptor Antagonists

Although some experimental agents and pharmaceutics antagonize the action of glutamate, most of our knowledge concerns antagonism at NMDA receptors. Phencyclidine and ketamine appear to bind within the ion channel (PCP binding site) to block Ca^{2+} influx following glutamate binding (Fig. 14-14).[76] Both agents possess other pharmacologic actions and can produce convulsions in overdose. However, in animal models of seizures and neuronal insult, both drugs are neuroprotective and anticonvulsant.

Dextromethorphan and its first-pass metabolite, dextrorphan, exhibit anticonvulsant activity in animals. Dextrorphan's anticonvulsant activity results, in part, from blockade of NMDA receptor Ca^{2+} channels by binding to the PCP binding site. Dextromethorphan does not bind to the NMDA complex but, like dextrorphan, can directly block N- and L-type voltage-dependent Ca^{2+} channels.[29]

Dizocilpine (MK-801) is an NMDA receptor antagonist that binds to the PCP binding site in the NMDA Ca^{2+} channel. Human trials of dizocilpine resulted in adverse effects similar to those produced by phencyclidine, preventing further use in humans as a neuroprotective agent. Amantadine, memantine, and orphenadrine act as low-affinity antagonists at the PCP site but are not associated with psychotomimetic adverse effects. Part of amantadine's effectiveness in the treatment of Parkinson disease may be related to NMDA antagonism. Pentamidine also antagonizes glutamate binding at NMDA channels.[154]

Ethanol competitively inhibits NMDA receptor stimulation by an unknown mechanism, resulting in upregulation of this glutamatergic system. It does not appear to act through currently recognized binding sites.[167] In some animal models of ethanol withdrawal seizures, NMDA receptor antagonists demonstrate better anticonvulsant action than $GABA_A$ agonists.

Glycine Antagonists

Felbamate's anticonvulsant activity may result, in part, from antagonism of glycine at NMDA receptors.[100] Kynurenic acid, a metabolite of L-tryptophan, prevents NMDA activation through glycine antagonism. Meprobamate also antagonizes NMDA glutamate receptors by a yet-to-be-determined mechanism. However, given the structural similarity to felbamate, meprobamate may act by antagonizing the action of glycine.[126]

Polyamine Antagonism

Ifenprodil and eliprodil antagonize glutamate's action at NMDA channels by preventing polyamine binding.[100]

Adenosine

The overall action of adenosine throughout the body is to lessen

oxygen requirements and to increase oxygen and substrate delivery. In keeping with the paradigm, adenosine functions in the CNS as an extremely important inhibitory neuromodulator and vasodilator.

Synthesis, Release, and Uptake

Normal intracellular concentrations of adenosine range from 50 to 300 nM. An Na^+-dependent purine uptake transporter moves

adenosine into the neuron (Fig. 14-15). During times of adequate oxygen delivery and oxidative phosphorylation, intracellular ATP concentrations are normally many fold greater than those of adenosine. Adenosine begins conversion to ATP by adenosine kinase, but adenosine can also be metabolized to inosine by adenosine deaminase, a less important pathway.[25,120]

ATP is commonly coreleased with other neurotransmitters (eg, norepinephrine, ACh, glutamate) into the synapse where it can be degraded to adenosine monophosphate (AMP) (Fig. 14-15). When oxygen delivery remains adequate to meet metabolic demands, most synaptic adenosine arises from the extracellular dephosphorylation of AMP by ectosolic 5-nucleotidase.[25]

During increased cellular catabolism, especially during inadequate oxygen delivery, intracellular adenosine concentrations rapidly rise as phosphorylated adenosine species are degraded to adenosine. The rise in intracellular adenosine concentration results in reverse transport of adenosine into the synapse by the purine uptake transporter (Fig. 14-15). Synaptic adenosine, then, activates adenosine receptors on neuronal and nonneuronal tissue (eg, vasculature). Adenosine's actions are terminated by uptake into glial cells and neurons (Fig. 14-15).[25]

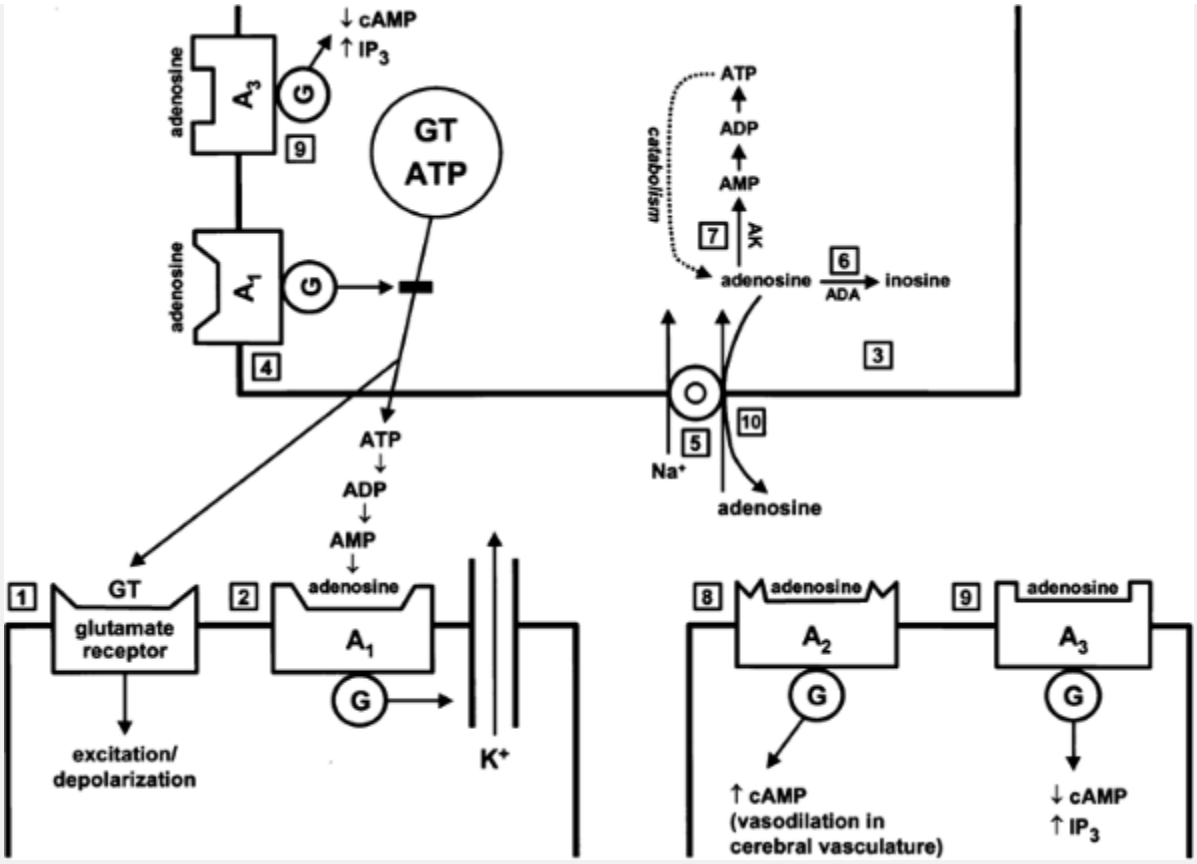

Figure 14-15. Adenosine's role in regulating excitatory neurotransmission, using glutamate as an example. In this example, glutamate (GT) excites a postsynaptic neuron by activating glutamate receptors [1]. Adenosine triphosphate (ATP) enters the synapse when glutamate is released. Adenosine formed from metabolism of ATP within the synapse binds to postsynaptic A_1 receptors [2], which open K^+ channels to inhibit the neuron through hyperpolarization. Adenosine also activates presynaptic A_1 receptors [4] to lower intracellular Ca^{2+} concentrations, thereby impairing further glutamate release. After uptake [5], adenosine is acted upon either by adenosine kinase (AK) [7] to form adenosine monophosphate (AMP), or by adenosine deaminase (ADA) [6] to form inosine. Adenosine also binds to neuronal A_2 receptors (especially in the striatum) and to vascular A_2 receptors to cause vasodilatation [8]. A_3 receptors

[9] are not activated by normal concentrations of adenosine. During times of excessive catabolism (eg, seizures, hypoglycemia, stroke) when intracellular adenosine concentrations rise markedly, adenosine moves into the synapse through reverse transport via the purine uptake transporter [10]. Resultant stimulation of A_1 and A_2 receptors results in inhibitory actions to decrease oxygen requirements and to increase substrate delivery through vasodilatation as described above. However, the resultant stimulation of A_3 receptors [9] may contribute to neuronal damage and death. Agents in Table 14-12 act to inhibit adenosine uptake [5]; to inhibit ADA [6]; to inhibit AK [7]; to increase adenosine release; and to antagonize A_1 [2,4] and A_2 [8] receptors. ADP = adenosine diphosphate; ATP =adenosine triphosphate; cAMP =cyclic adenosine monophosphate; G =G protein; IP_3 =inositol triphosphate.

Exogenously administered adenosine used in the treatment of supraventricular tachycardia does not cross the bloodâ€“brain barrier and therefore is centrally inactive. The half-life of adenosine in the blood is less than 10 seconds.

Adenosine Receptors

The purine P_1 receptor family comprises four adenosine receptor subtypes linked to G proteins: A_1, A_{2A}, A_{2B}, and A_3.[122] Postsynaptic A_1

stimulation results in K^+ channel opening and K^+ efflux with subsequent hyperpolarization of the neuron (Fig. 14-15). Evidence suggests that G protein-mediated Cl^- influx may explain postsynaptic hyperpolarization by A_1 activation in some cases. Presynaptic A_1 stimulation modifies voltage-dependent Ca^{2+} channels, lessening Ca^{2+} influx during depolarization, which limits exocytosis of neurotransmitter. Therefore, activation of A_1 receptors prevents

release of neurotransmitters presynaptically and inhibits their response postsynaptically.[122,159]

In the central and autonomic nervous systems, A_1 receptors reside on presynaptic and postsynaptic membranes, where they serve as inhibitory modulators for numerous neurotransmitter systems; they are particularly prevalent in association with glutamatergic neurons in the CNS.[159] A_1 receptor stimulation also produces sedation and is important in sleep regulation.[120] Other functions attributed to A_1 receptors include neuroprotection, anxiolysis, temperature reduction, anticonvulsant activity, and spinal analgesia.

Peripheral A_1 receptor activation produces bronchoconstriction, decreased glomerular filtration, decreased heart rate, slowed atrioventricular conduction, and decreased atrial myocardial contractility.[36] In the heart, almost all A_1 receptors reside in the atria.[19]

In the CNS, A_{2A} receptors demonstrate limited distribution. They are concentrated on cerebral vasculature and produce vasodilatation when stimulated.[122,159] Additionally, A_{2A} receptors are especially prevalent on neurons in the striatum where they inhibit the activity of D_2 receptors.[48] Striatal A_{2A} receptors decrease GABA effects while enhancing cholinergic, glycinergic, and glutamatergic neurotransmission.[40] Some A_2 receptors are found presynaptically where they serve to increase glutamate release upon activation.[19]

A_{2B} receptors are expressed diffusely throughout the brain, and are most commonly identified on glial cells. A_{2B} receptors demonstrate low affinity for adenosine, and little is known of their physiologic role.[22] Both A_{2A} and A_{2B} receptors are coupled to G_s. The rise in cAMP concentration resulting from A_{2A} activation on cerebral vasculature and elsewhere explains vasodilatation.[122] For example, peripheral A_2 receptor activation also results in coronary artery vasodilation.[33]

A_3 receptors reside diffusely throughout the CNS and express low

affinity for adenosine. A_3 receptors act through G proteins to decrease adenylate cyclase activity and increase phospholipase C activity.[160] The low concentrations of adenosine found during normal metabolism minimally activate A_3 receptors to produce inhibitory effects. During times of excessive adenosine accumulation (eg, hypoxia, seizures), adenosine accumulates at and activates A_3 receptors to produce complex responses that appear to enhance ischemic cellular injury and death, at least in part through disinhibition of presynaptic metabotropic glutamate receptor responses. Thus, A_3 receptor antagonists are being examined for neuroprotective actions.[160]

Adenosine and Seizure Termination

In humans and in animal models of status epilepticus, including those from drugs and toxins, there are two alternating phases of electrical activity noted on electroencephalography. Periods of high-frequency spike activity accompanied by marked increases in cerebral oxygen consumption and metabolic requirements alternate with interictal periods of isolated spike waves during which metabolic demands are less. The high-frequency phase lasts only a few minutes before suddenly terminating, sometimes with a few seconds of electrocerebral silence. A gradual increase in electrical activity during the interictal phase eventually leads to a recurrence of high-frequency spike activity.

These periodic spontaneous self-terminations of high-frequency electrical activity initially occur before neurons exhaust oxygen and energy supplies. These punctuations result from adenosine release from depolarizing neurons (and probably glial cells).[43] Adenosine acts on presynaptic receptors to prevent further release of excitatory neurotransmitters and acts on postsynaptic receptors to inhibit their actions.

Any agent that directly or indirectly enhances adenosine's action at A_1 receptors in the brain will usually exhibit anticonvulsant activity.

Conversely, A_1 receptor antagonists lower the seizure threshold and make seizure termination more difficult and less likely to respond to anticonvulsants.

Agents that antagonize A_{2A} receptors produce cerebral vasoconstriction and may limit oxygen delivery during times of increased demand. Antagonism of A_{2A} receptors in the striatum increases dopamine-mediated motor activity.

Chemical Agents

Table 14-12 provides examples of chemical agents that affect adenosine receptors.

Direct Adenosine Agonists

ADAC (adenosine amine congener) is a direct A_1 receptor agonist used in the treatment of Huntington disease.[19] Tecadenoson is a selective A_1 receptor agonist that is used for treatment of supraventricular tachycardia.[19]

Indirect Adenosine Agonists

Papaverine and dipyridamole inhibit adenosine uptake.[116] Like other adenosine agonists, papaverine and dipyridamole demonstrate anticonvulsant activity when injected into the CNS. Such actions are not achievable with safe systemic doses.

In addition to their actions at $GABA_A$ receptors, benzodiazepines inhibit adenosine uptake.[34,117] This may explain observations that methylxanthines, potent adenosine receptor antagonists, reverse benzodiazepine-induced sedation in humans. The potencies of benzodiazepines as inhibitors of adenosine uptake show

good correlation with clinical anxiolytic and anticonflict potencies, suggesting that such inhibition contributes to their action. The anticonvulsant effect of large doses of flumazenil also results from

inhibition of adenosine uptake. Carbamazepine inhibits adenosine uptake, although this is not thought to account for most anticonvulsive action.

TABLE 14-12. Examples of Xenobiotics That Affect Adenosine Receptors

Adenosine agonism	Inhibit ADA
Direct agonists	Acadesine
Adenosine	Dipyridamole
ADAC (adenosine amine congener)	Pentostatin
Tecadenoson	
	Inhibit AK
Inhibit uptake	Acadesine
Acadesine	
Acetate[a]	Increase adenosine release
Benzodiazepines	Opioids

Calcium channel blockers	
Carbamazepine	Adenosine antagonism
Dipyridamole	A_1 blockade
Ethanol[a]	Caffeine
Flumazenil	Carbamazepine
Indomethacin	Theophylline
Papaverine	
Propentofylline	A_2 blockade
Tricyclic antidepressants	Caffeine
	Theophylline

ADA = adenosine deaminase; AK = adenosine kinase.
[a] Ethanol is metabolized to acetate, which inhibits adenosine uptake.

Adenosine may mediate many of the acute and chronic motor effects of ethanol on the brain. Ethanol, probably through its metabolite, acetate, prevents adenosine uptake, raising synaptic adenosine concentrations.[28] Excessive stimulation of several adenosine receptors in the cerebellum may explain much of the motor impairment from low ethanol concentrations. In fact, animals made

tolerant to ethanol develop cross-tolerance to adenosine agonists. In mice, adenosine receptor agonists increase ethanol-induced incoordination while adenosine antagonists decrease this intoxicating response.[37]

Numerous other agents are inhibitors of adenosine uptake, including propentofylline, nimodipine, tricyclic antidepressants, and other calcium channel blockers.[114,116]

A_1 receptors located at the spinal cord level are important modulators of pain transmission by limiting release of substance P.[132] Tricyclic antidepressants-induced inhibition of adenosine uptake may explain some of their effectiveness in treating neuropathic pain.[132] The analgesic effectiveness of opioids can be partially attributed to their ability to increase the release of adenosine within the spinal cord.[143]

Dipyridamole inhibits adenosine deaminase, raising adenosine concentrations. During times of elevated adenosine levels that occur with cardiac or cerebral ischemia, acadesine further enhances adenosine's beneficial actions by three mechanisms: inhibition of adenosine kinase (AK), inhibition of adenosine deaminase (ADA), and inhibition of adenosine uptake.[107]

Adenosine Antagonists

The main adenosine antagonists of toxicologic concern are methylxanthines. Theophylline and caffeine are selective P_1 antagonists, blocking both A_1 and A_2 receptors.[159] The response to methylxanthines by A_3 receptors varies widely depending on the species. Human A_3 receptors demonstrate very low affinity for methylxanthines.[160]

Peripherally, methylxanthines produce excessive release of catecholamines from peripheral nerve endings (and probably the adrenal gland) by blocking presynaptic A_1 receptors. In turn, catecholamine-mediated responses are exaggerated by blockade of

inhibitory postsynaptic A_1 receptors on end organs.[51]

Centrally, enhanced release and actions of excitatory neurotransmitters (eg, glutamate) and resultant lack of periodicity probably explain convulsions that are frequently refractory to anticonvulsants in methylxanthine poisoning. The reasons why theophylline convulsions carry such a high mortality stem from a lack of self-termination (continual high-frequency spike activity and large metabolic demands) that has resulted from A_1 antagonism, compounded by vasoconstriction caused by blockade of A_2 receptors.[119] $GABA_A$ receptor agonism, especially by barbiturates, most effectively prevents and terminates methylxanthine-induced seizures. Phenytoin not only is ineffective in treating theophylline-induced seizures, but may actually increase the likelihood of seizures and mortality.[15]

Like phenytoin, carbamazepine's major anticonvulsant effect results from Na^+ channel blockade. Unlike phenytoin, carbamazepine appears to antagonize A_1 receptors.[31,34] This may explain the higher frequency of seizures after carbamazepine overdose than after phenytoin overdose. The absence of A_2 blockade by carbamazepine theoretically allows for increases in cerebral blood flow to meet metabolic demands of the seizing brain.

Summary

Neurotransmitter systems share common physiologic features, including neurotransmitter uptake, vesicle membrane pumps, ion trapping of neurotransmitters within vesicles, calcium-dependent exocytosis, and receptors coupled to either G proteins or to ion channels. It is not surprising, then, that a single pharmacologic agent frequently produces effects on several different neurotransmitter systems.

As the number of new drugs and toxins encountered by man continues to grow, an understanding of their molecular actions in the

nervous system helps the physician to anticipate and better understand various pharmacologic and adverse effects resulting from therapeutic or toxic doses.

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Chapter 15
Withdrawal Principles

Richard J. Hamilton

In the central nervous system, excitatory neurons fire regularly, and inhibitory neurons inhibit the transmission of these impulses. Whenever action is required, the inhibitory tone diminishes, permitting the excitatory nerve impulses to travel to their end organs. Thus, all action in human neurophysiology is disinhibition.[50,95,100]

Tonic activity of a xenobiotic produces an adaptive change in the neuron. For example, tonic stimulation of an inhibitory neuron reduces the activity of that neuron so that the baseline level of function is again attained. A withdrawal syndrome occurs when the constant presence of this xenobiotic is removed or reduced and the adaptive changes persist. This produces a dysfunctional state in which there is significantly reduced inhibitory neurotransmission, essentially producing excitation (Fig. 15-1). Every withdrawal syndrome has two characteristics: (a) a preexisting physiologic adaptation to a xenobiotic, the continuous presence of which prevents withdrawal, and (b) decreasing concentrations of that

xenobiotic. In contrast, simple tolerance to a drug is characterized as a physiologic adaptation that shifts the doseâ€“response curve to the right; that is, greater amounts of xenobiotic are required to achieve a given effect. Patients with withdrawal syndromes have often developed tolerance, but tolerance does not require the continued presence of the xenobiotic to prevent withdrawal.[38,86]

The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) provides a helpful and descriptive set of criteria that mesh with our understanding of the pathophysiology of withdrawal syndromes.[30] According to DSM-IV, withdrawal is manifested by either of the following: (a) a characteristic withdrawal syndrome for the substance or (b) the same (or a closely related) substance is taken to relieve withdrawal symptoms. Note that either criterion fulfills this definition. Logically, all syndromes have the first criterion, and so it is the presence of the second criterion that is critical to understanding physiology and therapy.

For the purposes of defining a unifying pathophysiology of withdrawal syndromes, this chapter considers syndromes in which both features are present. An analysis from this perspective distinguishes xenobiotics that affect the inhibitory neuronal pathways from the effects of those agents that stimulate the excitatory neuronal pathways, such as cocaine. Cocaine does not produce a withdrawal syndrome using this definition, but rather a postintoxication syndrome that often results in lethargy, hypersomnolence, movement disorders, and irritability. This syndrome does not meet the second of the DSM-IV criteria for a withdrawal syndrome because the same (or a closely related) substance is not taken to relieve or avoid withdrawal symptoms. This postintoxication syndrome, the so-called â€œcrack crashâ€• or â€œwashed-out syndrome,â€• is caused by prolonged use of the drug, and patients return to their premorbid function without intervention.[74,87,98] This distinction is important for toxicologists, because (a) withdrawal syndromes that demonstrate both features of the DSM-IV criteria are treated with reinstatement and gradual withdrawal of a xenobiotic that has an effect on the

receptor and (b) withdrawal syndromes that do not demonstrate the second feature require only supportive care and resolve spontaneously.

Finally, withdrawal syndromes are best described and treated based on the class of receptors that are affected because this concept also organizes the approach to patient care. For each receptor and its agonists, research has identified genomic and nongenomic effects that produce neuroadaptation and withdrawal syndromes. There appear to be six mechanisms involved: (a) genomic mechanisms via mRNA; (b) second messenger effects via protein kinases, cyclic adenosine monophosphate (cAMP),[43] and calcium ions; (c) receptor endocytosis; (d) expression of various receptor subtypes depending on location within the synapse (synaptic localization); (e) intracellular signaling via effects on other receptors; and (f) neurosteroid modulation. All or some of these mechanisms are already demonstrated in each of the known withdrawal states.[51] These mechanisms develop in a surprisingly rapid fashion and modify the receptor and its function in such complex ways as to depend on the continued presence of the substance to prevent dysfunction.[49,63,67,69,85,99,103]

$GABA_A$ Receptors (Barbiturates, Benzodiazepines, Ethanol, Volatile Solvents)

Î³-Aminobutyric acid type A ($GABA_A$) receptors have separate binding sites for GABA, barbiturates, benzodiazepines, and picrotoxin, to name only a few xenobiotics (Chap. 14). Barbiturates and benzodiazepines bind to separate receptor sites and enhance the affinity for $GABA_A$ at its receptor site. $GABA_A$ receptors are part of a superfamily of ligand-gated ion channels, including nicotinic acetylcholine receptors and glycine receptors, that exist as pentamers arranged around a central ion channel.[89] When activated,

they hyperpolarize the postsynaptic neuron by facilitating an inward chloride current (without a G protein messenger), decreasing the likelihood of the neuron firing an action potential.[50,80]

The GABA receptor is a pentamer comprised of two Î± subunits, two Î² subunits and an additional subunit, most commonly Î³, which

is a key element in the benzodiazepine binding site. The two GABA-binding sites per receptor are located in a homologous position to the benzodiazepine site between the Î± and Î² subunits. Although the mechanism is unclear, benzodiazepines have no direct functional effect without the presence of GABA. Conversely, certain barbiturates, or perhaps all in a dose-dependent manner, can increase the frequency of channel opening producing a net increase in current flow without GABA binding.[36,67]

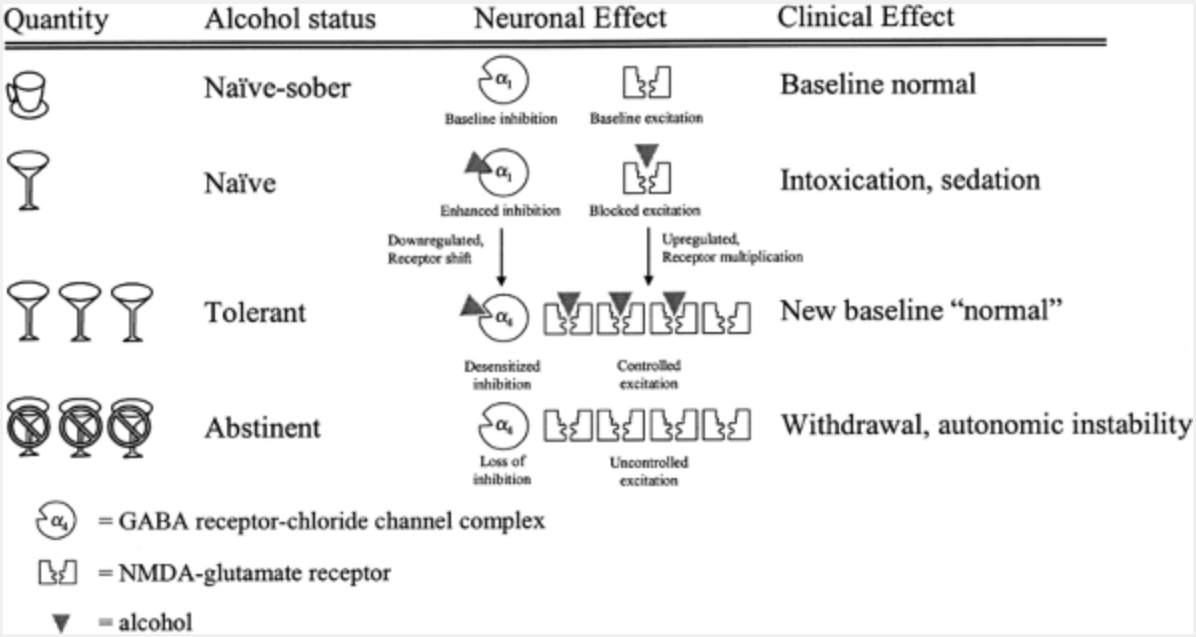

Figure 15-1. Alcohol intoxication, tolerance, and withdrawal. Alcohol consumption in alcohol-naive persons produces intoxication and sedation by simultaneous agonism at the Î³-

aminobutyric acid (GABA) receptor-chloride channel complex and antagonism at the *N*-methyl-D-aspartate (NMDA)-glutamate receptor. Continuous alcohol consumption leads to the development of tolerance through changes in both the GABA receptor-chloride channel complex (a subunit shift from Î±$_1$ to Î±$_4$, results in reduced sensitivity to the sedating effects of alcohol) and the NMDA subtype of glutamate receptor (upregulation in number, resulting in enhanced wakefulness). There is conceptually a level at which the tolerant patient may appear clinically normal despite having an elevated blood alcohol concentration. Tolerant patients who are abstinent lose the tonic effects of alcohol on these receptors, resulting in withdrawal.

Recent evidence demonstrates that this prototypical pentameric $GABA_A$ receptor assembly is derived from a permutation and combination of two, three, four, or even five different subunits. The subtypes of GABA receptors can even vary on the same cell.[67] In fact, GABA receptors are heterogeneous receptors with different subunits and distinct regional distribution. Although the preponderance of subtypes Î±$_1$Î²$_2$Î³$_2$, Î±$_2$Î²$_3$Î³$_2$, and Î±$_3$Î²$_3$Î³$_2$ account for 75% of GABA receptors, there are at least 16 others of import.[103] The recognition of additional subunits of $GABA_A$ receptors, such as Ï‰, has permitted the development of targeted pharmaceuticals.[7] For example, the drug zolpidem achieves its effect of hastened onset of sleep by targeting the Ï‰$_1$ receptor subunit of $GABA_A$.[84]

Previously, ethanol was thought to have GABA-receptor activity, although a clearly identified binding site was not evident (Chap. 75). Traditional explanations for this effect included (a) enhanced membrane fluidity and allosteric potentiation (so-called cross-coupling) of the 5 proteins that construct the $GABA_A$ receptor; (b) interaction with a portion of the receptor; and/or (c) enhanced GABA release.[18,50,52,83] Research with chimeric reconstruction of $GABA_A$

and *N*-methyl-D-aspartate (NMDA) channels demonstrates highly specific binding sites for high doses of ethanol which enhance $GABA_A$ and inhibit NMDA receptor-mediated glutamate neurotransmission.[68] However, research has not clarified whether ethanol at low doses is a direct agonist of $GABA_A$ receptors or a potentiator of $GABA_A$ receptor binding.[53,67,73,76]

Ethanol exhibits all 6 mechanisms of adaptation to chronic exposure, and is the prototypical substance for studying neuroadaptation and withdrawal.[51] These 6 mechanisms appear to apply to benzodiazepines as well.[3,48,73,76] The mechanisms are (a) altered $GABA_A$ receptor gene expression via alterations in mRNA and peptide concentrations of $GABA_A$ receptor subunits in numerous regions of the brain (genomic mechanisms); (b) posttranslational modification through phosphorylation of receptor subunits with protein kinase C (second-messenger effects); (c) subcellular localization by an increased internalization of $GABA_A$ receptor $Î±_1$-subunit receptors (receptor endocytosis); (d) modification of receptor subtypes with differing affinities for agonists to the synaptic or nonsynaptic sites (synaptic localization); (e) regulation via intracellular signaling by the NMDA, acetylcholine, serotonin, and $Î²$-adrenergic receptors; and (f) neurosteroid modulation of GABA-receptor sensitivity and expression.[17,31,34,46,52,53,78,101]

Intracellular signaling via NMDA subtype of the glutamate receptor appears to explain the â€œkindlingâ€• hypothesis, in which successive withdrawal events become progressively more severe.[8,10,12,15,33,55,102] The activity of an excitatory neurotransmission increases the more it fires, a phenomenon known as long-term potentiation, and is the result of increased activity of mRNA and receptor protein expression, a genomic effect of intracellular signaling.[38] As

NMDA receptors increase in number and function (upregulation)[42] and $GABA_A$ receptor activity diminishes, withdrawal becomes more severe.[28,55,65,78] The dizocilpine (MK-801) binding site of the NMDA

receptor appears to be the major contributor, and this effect is recognized in neurons that express both NMDA and $GABA_A$ receptors.[4,101,105] Interestingly, animal models suggest that chronic ethanol use induces alterations in the receptor subunit composition of the $GABA_A$ receptor, which may be partly responsible for the development of ethanol tolerance, withdrawal, and kindling.[20,55]

In summary, it is an over simplification to view $GABA_A$ receptors as a homogenous and static collection of cell-surface proteins that are stimulated by sedatives. $GABA_A$ agonists induce modulatory changes in the receptors through genomic and nongenomic mechanisms that ultimately alter their function. In this way, withdrawal symptoms represent the clinical manifestation of a change in GABA-receptor-complex characteristics.[19,44] When alcohol or any xenobiotic with GABA agonist activity is withdrawn, inhibitory control of excitatory neurotransmission, such as that mediated by the now upregulated NMDA receptors, is lost.[34,63,81] This results in the clinical syndrome of withdrawal: CNS excitation (tremor, hallucinations, seizures), and autonomic stimulation (tachycardia, hypertension, hyperthermia, diaphoresis) (Chap. 76).[39,50,85]

Volatile solvents, such as gasoline, ether, and toluene, are widespread substances of abuse whose effects appear to be mediated by the GABA receptor; all of these solvents have a well-established abuse potential, especially in adolescents. These solvents can produce CNS inhibition and anesthesia at escalating doses via the $GABA_A$ receptor. Elaboration of the mechanism specific for solvent abuse awaits further study, although it is logical to assume that they act in a similar fashion as ethanol and other xenobiotics with the $GABA_A$ receptor.[9] They also appear to initiate the same dopamine reward system as other drugs of abuse.[77,91]

$GABA_B$ Receptors (GHB and Baclofen)

$GABA_B$ agonists such as Î³-hydroxybutyric (GHB) acid and baclofen have similar clinical characteristics with regard to adaptation and

withdrawal.[11,24,37,104] The $GABA_B$ receptor is a heterodimer of the $GABA_{B(1)}$ and $GABA_{B(2)}$ receptor. Unlike $GABA_A$, the $GABA_B$ receptor couples to various effector systems through a signal-transducing G protein. $GABA_B$ receptors mediate presynaptic inhibition (by preventing Ca^{2+} influx) and postsynaptic inhibition (by increasing K^+ efflux). The postsynaptic receptors appear to have a similar inhibitory effect as the $GABA_A$ receptors. The presynaptic receptors provide feedback inhibition of GABA release. Unlike $GABA_A$ receptors, these are mediated through G protein messengers.[13,62,104]

GHB is a naturally occurring inhibitory neurotransmitter with its own distinct receptor. Physiologic concentrations of GHB activate at least two subtypes of a distinct GHB receptor (antagonist-sensitive and antagonist-insensitive). However, at supraphysiologic concentrations, such as those that occur after overdose and abuse, GHB also binds directly to the $GABA_B$ receptor and is also metabolized to GABA (which then activates the $GABA_B$ receptor). Endogenous GHB activates a presynaptic GHB receptor to modulate GABA and glutamate release and inhibits dopamine release by the $GABA_B$ receptor.[6] The GHB withdrawal syndrome clinically resembles the withdrawal syndrome noted from ethanol and benzodiazepines. Distinctive clinical features of GHB withdrawal are the relatively mild and brief autonomic instability with the persistence of psychotic symptoms.[97]

Baclofen is also a $GABA_B$ agonist. The pre- and postsynaptic inhibitory properties of baclofen allow it, paradoxically, to cause seizures in both acute overdose (because of decreased release of presynaptic GABA via autoreceptor stimulation) and withdrawal. Withdrawal is probably a result of the loss of chronic inhibitory effect of baclofen on postsynaptic $GABA_B$ receptors. On discontinuation, this produces hyperactivity of neuronal Ca^{2+} channels (N, P/Q type),[27] leading to seizures, hypertension, hallucinations, psychosis, and coma. However, these manifestations may not differ from the withdrawal symptoms of $GABA_A$ agonists.[79,92]

Typically, the development of a baclofen withdrawal syndrome occurs 24â€“48 hours after discontinuation of baclofen. Case reports highlight the development of seizures, hallucinations, psychosis, dyskinesias, and visual disturbances. The intrathecal baclofen pump has become an effective replacement for oral dosing, but withdrawal can occur following use of this modality as well. Reinstatement of the prior baclofen-dosing schedule appears to resolve these symptoms within 24â€“48 hours. Benzodiazepines and $GABA_A$ agonists (not phenytoin) are the appropriate treatment for seizures induced by baclofen withdrawal.[72]

Opioid Receptors (Opiates and Opioids)

Similar to ethanol and $GABA_A$ receptors, opioid binding to the opioid receptors result in a series of genomic and nongenomic neuroadaptations, especially via second-messenger effects. When opioids bind to opioid receptors they alleviate pain by inhibiting neurons. They also activate G_S proteins, and stimulate K^+ efflux currents. The opioid receptors are also linked to the $G_{i/o}$ proteins. These act through adenyl cyclase and activate inward Na^+ current, thus enhancing the intrinsic excitability of a neuron (Chap. 38).[23]

Chronic exposure to opiates and opioids (all drugs with opioid-receptor affinity) results in a decreased efficacy of the receptor to open potassium channels by genomic mechanisms and second-messenger effects. Following chronic opioid exposure, the expression of adenyl cyclase increases through activation of the transcription factor known as cAMP response element-binding protein (CREB).[64,70] (Fig. 15-2) This results in an upregulation of cAMP-mediated responses such as

the inward Na^+ channels responsible for intrinsic excitability. The net effect is that, only higher levels of opioids result in analgesia and other opioid effects. In the dependent patient, when opioid levels drop, inward Na^+ flux occurs unchecked, and the patient experiences

the opioid withdrawal syndrome. The clinical findings associated with this syndrome are largely a result of uninhibited activity at the locus caeruleus.[21,49,64,66,70]

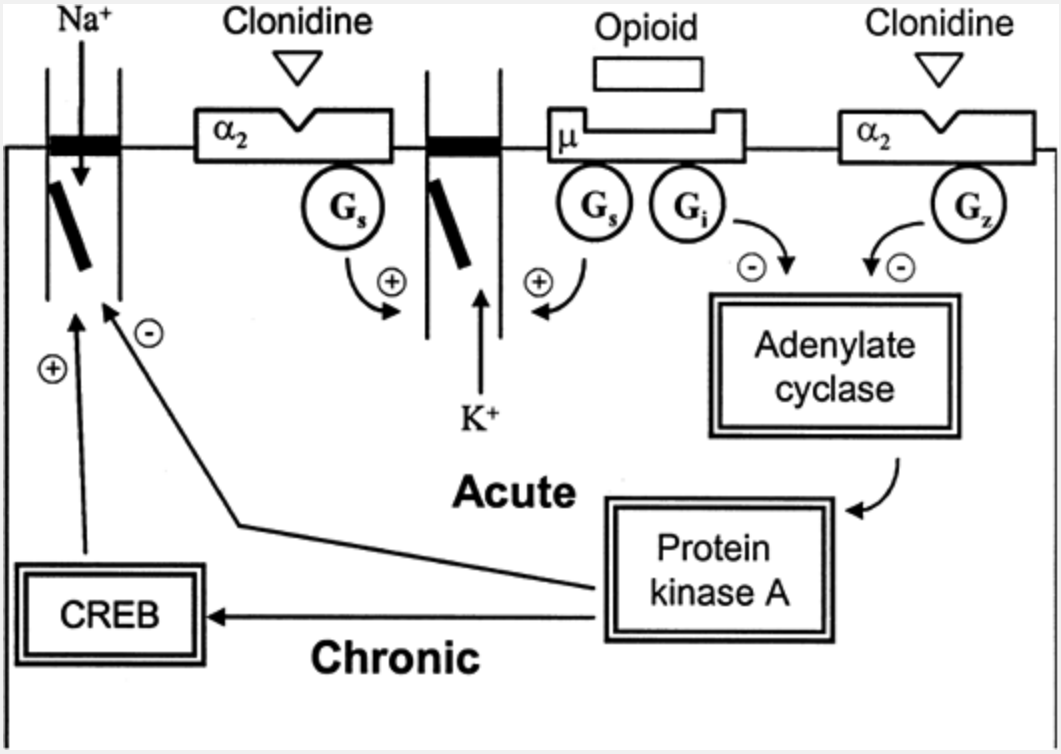

Figure 15-2. Immediate and long-term effects of opioids. The acute effects of both opioids and Î±2-adrenergic agonists are to increase inhibition through enhanced potassium efflux and inhibited sodium influx. Chronic effects alter gene expression to enhance sodium influx and restore hemeostasis. CREB (cAMP response element-binding protein).

Furthermore, opioid receptors and central Î±2-adrenergic receptors both exert a similar effect on the potassium channel in the locus ceruleus. Clonidine binds to the central Î±2-adrenergic receptor and stimulates potassium efflux, as do opioids, and produces similar

clinical findings.[2] This explains why clonidine has some efficacy in treating the opioid withdrawal syndrome. In addition, the antagonistic effect of naloxone at the opioid receptor seems to reverse the effect of clonidine on this shared potassium efflux channel.[2,35,40]

Rapid opioid detoxification is a form of iatrogenic withdrawal that uses drugs with antagonist activity to accelerate a return to premorbid receptor states. In theory, inducing opioid withdrawal under general anesthesia with high-dose opioid antagonists permits the transition from drug dependency to naltrexone maintenance without drug withdrawal symptoms.[56,57,58] Naltrexone blocks the euphoric effects of continued opioid use and discourages recidivism by blunting drug craving.[47,59,60,61] Although the mechanism by which naltrexone blocks drug craving is not entirely clear, the speculation is that mere receptor occupancy by an antagonist is sufficient to blunt cravings. However, withdrawal symptoms may still be intense and persist for up to 1 week after rapid detoxification, suggesting that clinical recovery from the changes induced by chronic opioid use is slow.[22,41,84,90,94]

Î ±$_2$-Adrenergic Receptors (Clonidine)

Î ±$_2$-Adrenergic receptors are located in the central and peripheral nervous system. Clonidine is a central and peripheral Î ±$_2$-adrenergic agonist. Stimulation of central presynaptic Î ±$_2$-adrenergic receptors inhibits sympathomimetic output and results in bradycardia, and hypotension.[32] Within 24 hours after the discontinuation of clonidine, norepinephrine concentrations rise as a result of enhanced efferent sympathetic activity.[82] This results in hypertension, tachycardia, anxiety, diaphoresis, and hallucinations.[16]

Adenosine (A) Receptors (Caffeine)

The release of neurotransmitters is accompanied by passive release

of adenosine as a by-product of adenosine triphosphate (ATP) breakdown. The released adenosine binds to postsynaptic A_1 receptors where it typically has inhibitory effects on the postsynaptic neuron. It also binds to presynaptic A_1 autoreceptors to limit further release of neurotransmitters. A_2 receptors are found on the cerebral vasculature and peripheral vasculature where stimulation promotes vasodilation.[26,45] Caffeine and other methylxanthines, such as theophylline, antagonize the inhibitory effect of adenosine, primarily on postsynaptic A_1 receptors. As a result, acute exposure results in increases in heart rate, ventilation, gastrointestinal motility, gastric acid secretion, and motor activity. Chronic caffeine exposure results in tolerance to the clinical effects of large, acute doses of caffeine. Chronic caffeine exposure regulates A_1 receptors by a variety of mechanisms, including increases in receptor number, increases in receptor affinity, enhancing receptor coupling to the G protein, and increases in G protein-stimulated adenyl cyclase.[54] An animal study demonstrates that the adenosine receptor has a 3-fold increase in affinity for adenosine at the height of withdrawal symptoms. This model suggests that chronic caffeine administration results in increase in receptor affinity for adenosine, thus restoring a state of physiologic balance (normal motor inhibitory tone). When caffeine is withdrawn, the enhanced receptor affinity results in a strong adenosine effect and clinical symptoms of withdrawal: headache (cerebral vasodilation), fatigue, and hypersomnia (motor inhibition).[69,93,96]

Acetylcholine Receptors (Nicotine)

Nicotinic receptors are a type of acetylcholine receptors located in the autonomic ganglia, adrenal medulla, CNS, spinal cord, neuromuscular junction, and carotid and aortic bodies. Nicotinic receptors are fast-response cation channels that are not coupled to G proteins, distinguishing them from muscarinic receptors, which are coupled to G proteins. Nicotinic acetylcholine receptors have both excitatory and inhibitory effects. As in other withdrawal syndromes,

changes brought on by chronic use of nicotinic agonists, such as nicotine in cigarettes, appear to be related to selective upregulation of cAMP. Much remains unknown about these receptors and how they affect addiction and withdrawal.[71,99]

SSRI Discontinuation Syndrome

Upon discontinuation of chronic selective serotonin reuptake inhibitor (SSRI) therapy, patients develop a characteristic syndrome. This syndrome complies with the definition of withdrawal syndromes in that symptoms begin when drug concentrations drop, and the syndrome abates when the drug is reinstated. Headache, nausea, fatigue, dizziness, and dysphoria are commonly described symptoms. The condition appears to be uncomfortable but not life-threatening, rapidly resolves with reinstatement of a drug of the same class, and slowly resolves when the drug is discontinued after a more gradual taper (Chap. 70).[14,24,75]

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Chapter 16 Thermoregulatory Principles

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Despite exposure to wide fluctuations of environmental temperatures, human body temperature is maintained within a narrow range.[20,130] Elevation or depression of body temperature occurs when (a) thermoregulatory mechanisms are overwhelmed by exposure to extremes of environmental heat or cold; (b) endogenous heat production is either inadequate, resulting in hypothermia, or exceeds the physiologic capacity for dissipation, resulting in hyperthermia; or (c) disease processes or drug effects interfere with normal thermoregulatory responses to heat or cold exposure.

Methods of Heat Transfer

Heat is transferred to or away from the body through radiation, conduction, convection, and evaporation. *Radiation* involves the transfer of heat from a body to the environment, and from warm objects in the environment, for example, from the sun to a body.

Conduction involves the transfer of heat to solid or liquid media in direct contact with the body. Water immersion or wet clothing in contact with the body conducts significant amounts of heat away from the body. This effect facilitates cooling in a swimming pool on a hot summer day, or may lead to hypothermia despite moderate ambient temperatures on a rainy day. The amount of heat lost through conduction and radiation depends on the temperature gradient between skin and surroundings, cutaneous blood flow, and insulation such as subcutaneous fat, hair, clothing, or fur in lower animals.[144] In the respiratory tract, heat is lost by conduction to water vapor or gas. In animals unable to sweat, this represents the primary method of heat loss. The amount of heat lost through the respiratory tract depends on the temperature gradient between inspired air and the environment, as well as the rate and depth of breathing.[144] *Convection* is the transfer of heat to the air surrounding the body. Wind velocity and ambient air temperature are the major determinants of convective heat loss. *Evaporation* is the process of vaporization of water, or sweat. Large amounts of heat are dissipated from the skin during this process, resulting in cooling. Ambient temperature, rate of sweating, air velocity, and relative humidity are important factors in determining how much heat is lost through evaporation. On a very humid day, sweat may pour off, rather than evaporate from a person exercising in a hot environment, thereby accomplishing little heat loss. In very warm environments, thermal gradients may be reversed, leading to transfer of heat to the body by radiation, conduction, or convection.[159,190]

Physiology of Thermoregulation

In the normal human, stimulation of peripheral and hypothalamic temperature-sensitive neurons results in autonomic, somatic, and behavioral responses that lead to the dissipation or conservation of heat. Thermoregulation is the complex physiologic process that serves to maintain hypothalamic temperature within a narrow

range of 98.6 Â± 0.8Â°F (37 Â± 0.4Â°C) known as the set point.[308] This hypothalamic set point is influenced by factors such as diurnal variation, the menstrual cycle and others. Maintaining, raising, or lowering the set point results in many outwardly visible physiologic manifestations of thermoregulation such as sweating, shivering, flushing, or panting. In the central nervous system, thermosensitive neurons are located predominantly in the preoptic area of the anterior hypothalamus, although some are found in the posterior hypothalamus. These neurons may be divided into those that are warm-sensitive, cold-sensitive, or temperature-insensitive. Approximately 30% of preoptic neurons are warm-sensitive. These increase their firing rate during warming and decrease their firing rate during cooling.[32] Warming of the hypothalamus in conscious animals results in vasodilation, hyperventilation, salivation, and increases in evaporative water loss, as well as a reduction of cold-induced shivering and vasoconstriction.[128] Cooling of the hypothalamus in conscious animals causes shivering, vasoconstriction, and increased metabolic rate, even if the environment is hot.[119] How these temperature-sensitive neurons of the hypothalamus detect temperature changes and effect neuronal transmission is unclear. Altered action potential initiation and propagation caused by temperature-dependent changes in membrane potential, changes in

the ratios of Na^+ to Ca^{2+} ions which alter neuronal excitability and neurotransmitter release, or effects on the Na^+K^+-ATPase (adenosine triphosphatase) pump, may be involved.[144] Drugs that increase intracellular cyclic adenosine monophosphate (cAMP) increase the thermosensitivity of warm-sensitive neurons.[32] In the brainstem, warm- and cold-sensitive neurons are located in the medullary reticular formation, where information from cutaneous receptors, spinal cord, and preoptic area of the anterior hypothalamus is integrated.[24,106,130,134]

The spinal cord also manifests thermosensitivity. Heat- and cold-sensitive ascending spinal impulses are conducted in the spinothalamic tract. As in the hypothalamus, local heating or cooling of the spinal cord results in thermoregulatory responses.[128] In addition to the hypothalamus, brainstem, and spinal cord, there is evidence of thermosensitivity in the deep abdominal viscera.[115,128,242] Intra-abdominal heating or cooling results in thermoregulatory responses. Cold- and warm-sensitive afferent impulses can be recorded from the splanchnic nerves in animals.[115,244] Finally, the skin also contains heat and cold thermosensitive neurons. Cold receptors are free nerve endings that protrude into the basal epidermis, whereas warm-sensitive receptors protrude into the dermis.[127,129] Cutaneous thermoreceptor output is affected by the absolute temperature of the skin, rate of temperature change, and area of stimulation.[128] Cutaneous cold receptors are AÎ´ and C nociceptor afferent fibers. AÎ´ fibers are small-diameter thinly myelinated fibers that conduct at 5â€“30 m/sec, and C-fibers are small-diameter unmyelinated fibers that conduct at 0.5â€“2 m/sec.[122] Afferents from heat receptors are primarily C fibers. Cutaneous thermoreceptive neurons respond to external temperature change as well as rate of temperature change, sending early warning to the central nervous system (CNS) via afferent impulses, allowing rapid and transient thermoregulatory responses before brain temperature changes (Fig. 16-1).

Vasomotor and Sweat Gland Function

Vasomotor responses to thermoregulatory input differ according to location. The normal thermoregulatory response to heat stress is mediated primarily by heat-sensitive neurons in the hypothalamus. Increased body-core temperature results in active vasodilation in the extremities and is under noradrenergic control; increasing sympathetic stimulation results in vasoconstriction, and decreasing sympathetic control results in vasodilation. Vasodilation in the

head, trunk, and proximal limbs is not a result of decreased sympathetic tone; instead, it is a result of an active process that is under the influence of cholinergic sudomotor nerves and local effects of temperature on venomotor tone. Sweat glands release local transmitters, such as vasoactive intestinal polypeptide (VIP) or bradykinins, and vasodilation results. Areas of the body such as the forehead, where sweating is most prominent during heat stress, correspond to areas where active vasodilation is greatest. The neurotransmitters involved in the regulation of relationships between vasodilation and sweating as a response to heat stress are not fully elucidated, but animal evidence suggests the presence of specific vasodilator nerves.[128]

Sweat glands are controlled by sympathetic postganglionic nerve fibers, which are cholinergic, and large amounts of acetylcholinesterase as well as other peptides involved in neural transmission.[127,128]

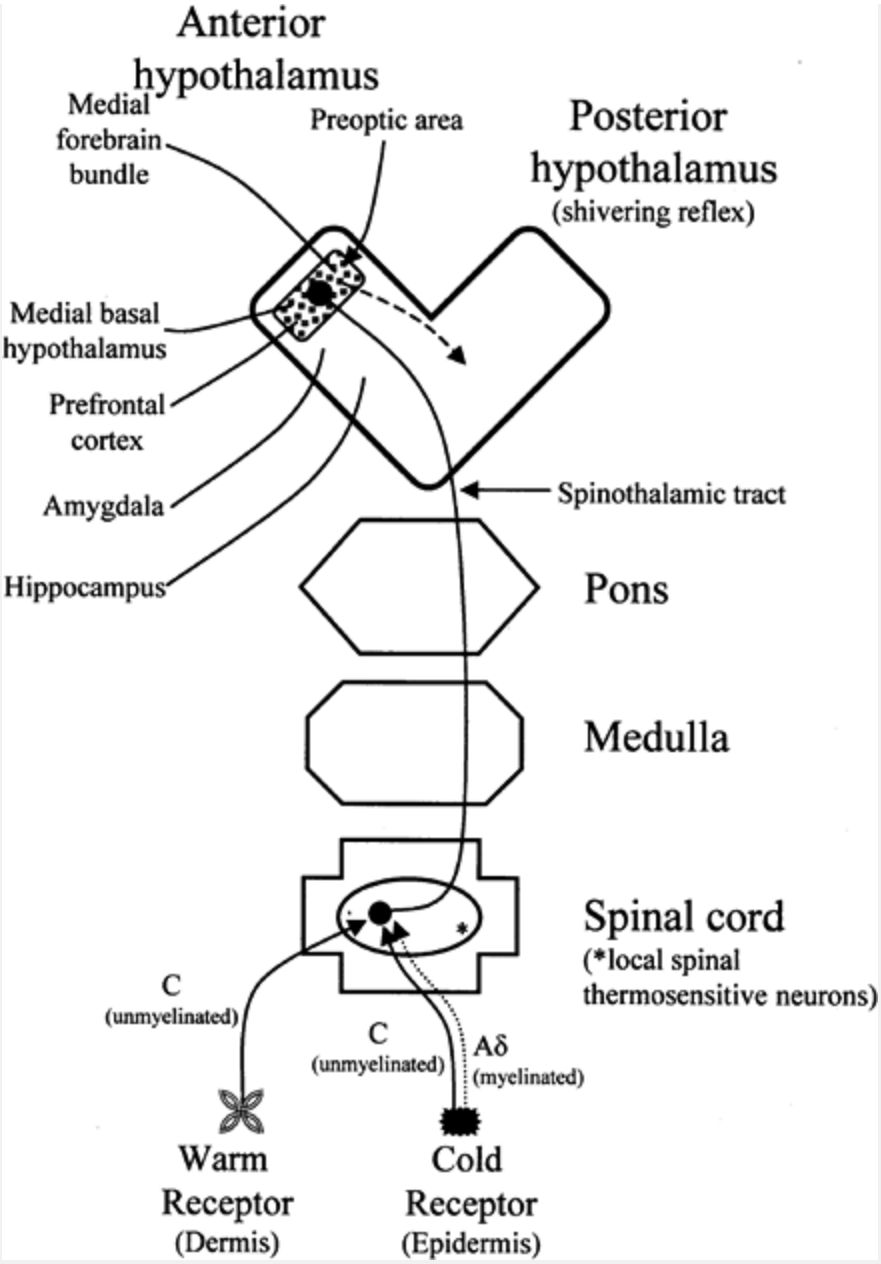

Figure 16-1. A representation of the response of cutaneous thermoreceptive neurons to external temperature change as an early warning to the central nervous system.

Neurotransmitters and Thermoregulation

The neurotransmitters involved in thermoregulation include serotonin, norepinephrine, acetylcholine, dopamine, prostaglandins, Î²-endorphins, and intrinsic hypothalamic peptides such as arginine vasopressin, adrenocorticotropic hormone, thyrotropin-releasing hormone, and Î±-melanocyteâ€“stimulating hormone.[52,230] Studies on the effects of individual neurotransmitters in thermoregulation yield contradictory results, depending on the animal species and the route of administration of the exogenous neurotransmitter. Refinements in techniques of microinjection of neurotransmitters into the hypothalamus of animals, rather than intraventricular instillation, have elucidated microanatomic sites where neurotransmitters are active. More research is needed, however, as interspecies variations and theoretical differences in response to exogenous versus endogenous peptides makes this area of study complex.

Apomorphine is a mixed dopamine agonist that has been shown to cause hypothermia in animals; studies using selective D_1- and D_2-receptor agonists and antagonists suggest that the hypothermic effect of apomorphine is a result of its effects on D_2 receptors, with some modulation by D_1 receptors in the hypothalamus.[205] Stimulation of D_2 receptors appears to mediate the hypothermia induced

by the peptide sauvagine.[35] Dopamine D_3 receptors undoubtedly play a role, as well; stimulation of D_3 by specific agonists caused hypothermia in an animal model.[206,207] There appears to be a link between dopamine D_2 receptors and norepinephrine receptors in the hypothalamus, perhaps leading to vasodilation and hypothermia. The effect of clozapine in producing hypothermia in the rat was demonstrated to be caused by D_1 and D_3 stimulation.[206,255] Lesser-known peptides appear to be involved in

thermoregulation. For example, neuropeptide Y is an amino acid neurotransmitter that occurs in high concentrations in the preoptic area of the anterior hypothalamus. Administration of neuropeptide Y caused a reduction in core temperature when administered with adrenoceptor antagonists such as prazosin, an Î±$_1$-adrenergic antagonist, propranolol, a Î²-adrenergic antagonist, and clonidine, a central Î±$_2$-adrenergic agonist.[87,253] The administration of synthetic cannabinoids induces hypothermia in animals, an effect that is antagonized by adrenergic agonists and enhanced by adrenergic antagonists.[237] Finally, studies on muscarinic receptors suggest the involvement of muscarinic M_2 and M_3 receptors in the production of hypothermia when agonists to these receptors are administered centrally.[256] Blockers of adenosine triphosphate (ATP)-sensitive K^+ channels can reverse the effect of cholinomimetic drugs in producing hypothermia.[239]

Drug effects on Thermoregulation

Many drugs and toxins have pharmacologic effects that interfere with thermoregulatory responses (Tables 16-1 and 16-2).[187,191,292] Î±-Adrenergic agonist agents prevent vasodilation in response to heat stress. Increased endogenous heat production in the setting of increased motor activity also occurs in patients poisoned with cocaine or amphetamines. Life-threatening hyperthermia has been associated with the use of these agents. Î²-Adrenergic antagonists and calcium channel blockers diminish the cardiac reserve available to compensate for heat-induced vasodilation, whereas diuretics decrease cardiac reserve through their effects on intravascular volume.[67] Î²-Adrenergic antagonists also interfere with the capacity to maintain normothermia under conditions of cold stress, possibly related to their interference with the mobilization of substrates required for thermogenesis.[128,191] Opioids, and diverse sedative-hypnotics, depress hypothalamic function and predispose to hypothermia in the overdose setting.[89] Carbon monoxide poisoning must also be considered in the

hypothermic patient. Organic phosphorous insecticides and other agents that cause cholinergic stimulation cause hypothermia by stimulation of inappropriate sweating and possibly through depression of the endogenous use of calorigenic substrates.[191] Drugs with anticholinergic effects decrease sweating and predispose to hyperthermia during environmental heat exposure or exercise. Phenothiazines appear to interfere with normal response to both heat and cold. Severe hyperthermia associated with the absence of sweating is frequently described in patients using phenothiazines and may be a consequence of their anticholinergic effects.[257,310] Effects on cold tolerance are attributed to their Î²-adrenergic antagonist effects, which prevent vasoconstriction in response to cold stress.[189] In addition, hyperthermia associated with severe extrapyramidal rigidity may occur in patients on antipsychotic agents.[178] This rigidity is attributed to the dopamine-blocking effects of this class of drugs.

TABLE 16-1. Effects of Xenobiotics that Predispose to Hyperthermia

I. Impaired cutaneous heat loss
A. Vasoconstriction through Î±-adrenergic stimulation
Amphetamine and derivatives
Cocaine
Ephedrine
Phenylpropanolamine
Pseudoephedrine
B. Sweat gland dysfunction by anticholinergic effects
Antihistamines
Belladonna alkaloids
Cyclic antidepressants
Phenothiazines
II. Myocardial depression

A. Decreased cardiac output
Antidysrhythmics
Î²-Adrenergic antagonists
Calcium channel blockers
B. Reduced cardiac filling by dehydration
Diuretics
Ethanol

III. Hypothalamic depression
Antipsychotics

IV. Impaired behavioral response
Ethanol
Opioids
Phencyclidine
Sedative-hypnotics
Cocaine

V. Uncoupling of oxidative phosphorylation
Pentachlorophenol
Dinitrophenol
Salicylates

VI. Increased muscle activity through agitation, seizures, or rigidity
Amphetamine derivatives
Caffeine
Cocaine
Isoniazid
Lithium
Monoamine oxidase inhibitors
Phencyclidine
Strychnine
Sympathomimetics

VII. Dystonia
Butyrophenones
Phenothiazines

VIII. Withdrawal

Dopamine agonists
Ethanol
Sedative-hypnotics

Ethanol

Ethanol is the most common xenobiotic related to the occurrence of hypothermia in an urban setting.[64,301] The mechanism by which ethanol predisposes to hypothermia is said to be by virtue of its effects on CNS depression, vasodilation, and blunting of behavioral

responses to cold. However, thermoregulatory dysfunction associated with ethanol intoxication is undoubtedly more complex.

TABLE 16-2. Effects of Xenobiotics that Predispose to Hypothermia

Impaired nonshivering thermogenesis
Î²-Adrenergic antagonists
Cholinergics
Hypoglycemics
Impaired perception of cold
Carbon monoxide
Ethanol
Hypoglycemics
Opioids
Sedative-hypnotics
Impaired shivering by hypothalamic depression
Carbon monoxide

Ethanol
General anesthetics
Opioids
Phenothiazines
Sedative-hypnotics

Impaired vasoconstriction
Î±-Adrenergic antagonists
Ethanol
Phenothiazines

In animal models, ethanol leads to hypothermia, the extent of which is partly dependent on ambient temperature.[224,245,246] In mice, as the dose of ethanol increased, body temperature decreased and the rate of this decline in body temperature was faster at higher ethanol doses.[219] The decline in body temperature could be reversed by increasing ambient temperature; increasing ambient temperature to 96.8Â°F (36Â°C) caused an immediate rise in the body temperature.[219] The poikilothermic effect of ethanol was not a result of hypoglycemia. Poikilothermia is the variation in body temperature greater than Â±3.6Â°F (Â±2Â°C) on exposure to environmental temperature changes. Rats treated with equipotent amounts of sodium pentobarbital showed the same effects on body temperature as rats treated with ethanol, suggesting a similar central mechanism of central nervous system depression resulting in altered thermoregulation.[219]

Numerous mechanisms are involved in the â€œethanol-induced depression of central nervous system function.â€•[250] Genetic factors influence the role of ethanol in the production of hypothermia. Mouse strains bred for sleep times differed in sensitivity to the effect of ethanol on temperature.[103,210,219] Mice can be selectively bred for genetic sensitivity or insensitivity to acute ethanol-induced hypothermia, and the differences appear to

be mediated by the serotonergic systems.[90] Histidyl-proline diketopiperazine (cyclo His-Pro or CHP), another neurotransmitter that is found in many animal species, acts at the preoptic-anterior hypothalamus to modulate body temperature.[42,137] Exogenous administration of this neuropeptide produced a dose-dependent decrease in ethanol-induced hypothermia. Attenuation of hypothermia resulted from passive immunization with CHP antibody.[42,137] Ethanol effects may be mediated through modulation of endogenous opioid peptides, as high-dose (10 mg/kg) naloxone reverses ethanol-induced hypothermia in animals.[234]

Pharmacokinetic characteristics of ethanol metabolism change in the presence of hypothermia. Hypothermic piglets infused with ethanol showed slower ethanol metabolism and a smaller volume of distribution and, as a result, higher ethanol levels than normothermic controls. Ethanol elimination and metabolism decreased as temperature fell.[165]

Tolerance develops to the effect of ethanol in producing hypothermia in all species.[92,224] The degree of tolerance is proportional to the dose and duration of treatment with ethanol and is not explained by the increased rate of metabolism with chronic exposure.[144] Age is a factor in the development of tolerance; older animals do not display the same degree of tolerance to the hypothermic effects of chronic ethanol administration as do younger animals.[216,233,307] The development of tolerance to ethanol-induced hypothermia is affected by genetic factors. Experimentally, tolerance to ethanol-induced hypothermia increases the incorporation of certain amino acids into proteins in the rat brain. The formation of new proteins in ethanol-tolerant rats suggests stimulation of gene expression related to the tolerant state.[144,295] Deficits in *N*-methyl-D-aspartate (NMDA) receptor systems may also be implicated in the development of ethanol tolerance. In addition, altered nicotinamide adenine dinucleotide (NADH) oxidation to NAD^+, diminished blood flow to

the liver, or slowing of metabolism through the microsomal enzyme system may be involved.[250]

Hypothermia alters the breathâ€”ethanol partition in the alveolus, and the temperature of expired breath alters breath-alcohol analysis results. In patients with mild hypothermia, ethanol breath analysis results in lower values by 7.3% per degree centigrade (or 1.8Â°F) decrease in body temperature.[95] Whether breath-alcohol analysis is also affected by hyperthermia in the test subject remains to be studied.[95]

Disease Processes and Thermoregulation

Many disease processes interfere with normal thermoregulation, limiting an individual's capacity to prevent hypothermia or hyperthermia. Extensive dermatologic disease or cutaneous burns impair sweating and vasomotor responses to heat stress.[37] Patients with autonomic disturbances such as diabetes or peripheral vascular disease also have altered vasomotor responses that impair vasodilation and sweating.[243] Extensive surgical dressings may preclude the evaporation of sweat in an otherwise normal patient. Heat-stressed persons with poor cardiac reserve may not be able to sustain a skin blood flow high enough to maintain normothermia.[77,276] Intense motor activity may lead to excessive endogenous heat production in patients with Parkinson disease or hyperthyroidism. Patients with agitated delirium or seizures also have significantly elevated rates of endogenous heat production. Hypothalamic injury caused by cerebrovascular accidents, trauma, or infection may disturb thermoregulation.[76,183] Hypothalamic dysfunction can lead to high, unremitting fevers and insufficient stimulation of heat loss mechanisms such as sweating. Hypothalamic damage may predispose to hypothermia by interference with centrally mediated heat conservation.[76,183,258,259] Fever, the normal response to

stimulation of the hypothalamus by pyrogens, results in an elevated physiologic temperature set point and is a disadvantage in the heat-stressed individual.[128]

Hypothermia

Epidemiology

Hypothermia is defined as an unintentional lowering of the core body temperature to <95Â°F (<35Â°C). Between 1979 and 2002, 16,555 people died of hypothermia in the United States, an average of 689 per year.[48] In 2002, 646 hypothermia-related deaths were reported,[48] 66% of which were in males. The majority of deaths were in individuals 65 years of age or older.

Medical factors increase the risk in the frail elderly, including limited mobility, impaired shivering, chronic illness, confusion, decreased protective fat, and slower metabolic rates. Social isolation and deprivation, poor nutrition, and inadequate access to or use of indoor heating, often because of financial concerns, are additional factors associated with the development of hypothermia.[46,132,153] Other risks associated with hypothermia in all groups are ethanol use, mental illness, use of antipsychotic medication, hypothyroidism, starvation, immobilization, dehydration, poverty, and homelessness (Table 16-3).[45]

Most hypothermic deaths occur in the winter months; however, mildly cool environments and windy wet conditions are also frequently associated with hypothermia. In 2002, Alaska, New Mexico, North Dakota, and Montana had the greatest overall death rates from hypothermia. States with milder climates, such as North and South Carolina, and western states, such as Arizona, with high elevations and cold nighttime temperatures, also reported hypothermia-related deaths.[48]

Response to Cold

The normal physiologic response to cold is initiated by stimulation of cold-sensitive neurons in the skin, so that the onset of the body's response to cold occurs prior to cooling of central blood. Cold-sensitive neurons in the skin send afferent impulses to the hypothalamus, resulting in shivering and piloerection. Shivering is the main thermoregulatory response to cold in humans, except in neonates, where nonshivering thermogenesis prevails. Shivering is initiated in the posterior hypothalamus when impulses from cold-sensitive thermoreceptors are integrated in the anterior hypothalamus and communicated to the posterior hypothalamus, or when cold-sensitive neurons in the posterior hypothalamus are activated directly. Efferent stimuli from the posterior hypothalamus travel through the midbrain tegmentum, pons, and lateral medullary reticular formation to the motor pathways of the tectospinal and rubrospinal tracts, resulting in shivering.[25] A mechanism of stimulation of shivering that usually occurs later when core temperature drops is the local cooling of the spinal cord, which leads to shivering by increasing excitability of motor neurons.

Heat produced without muscle contraction is known as nonshivering thermogenesis.[36,128] Nonshivering thermogenesis is mediated by the sympathetic nervous system.[58] Catecholamines activate adenylate cyclase, increasing cAMP, resulting in mobilization of fat and glucose stores (Î²-adrenergic receptors).[191,252] Nonshivering thermogenesis is blocked by Î²-adrenergic receptor antagonism and increased by administration of norepinephrine. Brown adipose tissue is the most important site of nonshivering thermogenesis. In humans, brown fat is found primarily in neonates, although in cold-acclimatized people there may be small amounts found on autopsy.[36] Brown adipose tissue functions as a thermoregulatory effector organ, producing heat by the oxidation of fatty acids when the tissue is stimulated by

norepinephrine.[41]

TABLE 16-3. Factors Predisposing to Hypothermia

Advanced age
Decreased metabolic rate
Decreased temperature discrimination
Decreased ability to shiver
Reduced peripheral blood flow
Central nervous system depression
Ethanol
Hypothalamic dysfunction
Infection
Intracranial bleeding
Stroke
Xenobiotics
Endocrine
Diabetic ketoacidosis
Hyperosmolar coma
Hypopituitarism
Hypothyroidism
Environmental
Homelessness
Unintentional
Hepatic failure
Immobilization
Central nervous system dysfunction
Illness
Spinal cord injury

Trauma

Nutritional
Hypoglycemia
Glycogen depletion
Starvation
Thiamine deficiency

Sepsis

Social
Failure to use indoor heating
Homelessness
Inadequate indoor heating
Poverty
Social isolation

Uremia

In addition to shivering and nonshivering thermogenesis, efferent sympathetic fibers from the hypothalamus stimulate peripheral vasoconstriction (Î±-adrenergic receptors). Piloerection and vasoconstriction result in decreased heat loss from the body. Intense vasoconstriction shunts blood away from the periphery to the core and antidiuretic hormone antagonism results in increased urine output and hemoconcentration.

Disease Processes and Hypothermia

Several disease processes commonly result in an inability to maintain a normal body temperature in a cool environment. Hypothermia may develop in association with sepsis,[180] hypothyroidism, hypoglycemia, uremia, hepatic failure, or poor nutrition.[240,243] Hypothalamic injury

may result in chronic poikilothermia.[189] Thiamine deficiency adversely affects the hypothalamus, perhaps because of inefficient glucose metabolism, and leads to hypothermia.[164] Spinal cord transections above the first thoracic segment interrupt hypothalamic-sympathetic outflow pathways, resulting in hypothermia.[243] The frail elderly are at greater risk of hypothermia because of decreased vasomotor responses and decreased capacity to shiver.[58,61] Mentally and physically compromised patients may be unable to make appropriate behavioral responses to hot or cold environments.

Evaluations to determine the presence of underlying diseases are often difficult in the hypothermic patient.[93,180] The mental status may be markedly altered by hypothermia but is not usually abnormal until the temperature falls below 90Â°F (32.2Â°C). If normal mental status is not regained when the temperature reaches 90Â°F (32.2Â°C) during rewarming, underlying CNS structural, toxic, or metabolic problems must be considered.[93,240] Failure of the patient to rewarm quickly suggests the presence of underlying disease. In one study, hypothermic patients without underlying disease are reported to rewarm at a rate of 1.0â€“3.7Â°F/h (0.6â€“2.1Â°C/h) (average, 2.1Â°F/h; 1.2Â°C/h), whereas patients with significant underlying disease (sepsis, gastrointestinal hemorrhage, diabetic ketoacidosis, pulmonary embolus, myocardial infarction) warmed at a rate of 0.25â€“1.8Â°F/h (0.1â€“1.0Â°C/h) (average, 1Â°F/h; 0.6Â°C/h).[300]

Alteration of Drug Metabolism in Hypothermia

Metabolism of drugs is altered in the setting of hypothermia. In hypothermic piglets, the volume of distribution and the clearance of fentanyl are decreased.[166] Similarly, in piglets given

gentamicin, the volume of distribution and clearance rate decreased in direct proportion to the decrease in cardiac output and glomerular filtration rate.[165] Hypothermic puppies given intravenous lidocaine showed slower rates of disappearance of the drug than when normothermic.[211] Humans and animals given propranolol showed a reduced volume of distribution and decreased total body clearance, resulting in higher than expected propranolol levels.[197,198,222] Decreased hepatic metabolism of propranolol during hypothermia has been shown in vitro.[198] Hypothermia prolongs neuromuscular blockade with *d*-tubocurarine,[117] and increases neuromuscular blockade with suxamethonium.[304] Phenobarbital metabolism and volume of distribution decreased with hypothermia in children.[143] The lethal dose of digoxin was doubled in hypothermic dogs.[21] Digoxin-like substances are present during hypothermia.[99,131]

Reasons for altered metabolism in hypothermia include delayed distribution of the drug and altered enzyme function with temperature and pH changes. Volume of distribution changes, in part, because of peripheral vasoconstriction. Cardiac output decreases, leading to decreased liver perfusion and decreased delivery of drug to hepatic microsomal enzymes.[117,146,147 and 148,231] Plasma volume decreases as free water moves intracellularly, causing hemoconcentration and further decreasing organ perfusion.[306] Biliary excretion of atropine, procaine, and sulfanilamide decreases in vitro.[146,147 and 148] The glomerular filtration rate decreases in hypothermia.[33] In vitro, the activity of metabolic pathways, including acetylation and hydrolysis, decrease with cooling.[146,147]

Clinical Findings

The clinical effects of hypothermia are related to the membrane-depressant effects of cold, which result in ionic and electrical conduction disturbances in the brain, heart, peripheral nerves, and

other major organs (Table 16-4).[133] Cold tissues are protected by decreases in tissue oxygen requirements. As body temperature decreases, metabolic activity declines at a rate of approximately 7% per 1.8Â°F (1Â°C).[306] This effect provides significant protection to vital organs despite the potentially deleterious effects of membrane suppression.

TABLE 16-4. Physiologic and Clinical Manifestations of Hypothermia

Cardiovascular
Normal, decreased, or increased cardiac output
Normal heart rate or tachycardia, then bradycardia
Vasoconstriction and central shunting of blood
ECG
Prolongation of intervals
Atrial fibrillation
Increased ventricular irritability
J-point elevation â€œOsborn wavesâ€•
Central nervous system
Mild: 90â€“95Â°F (32â€“35Â°C)
Normal mentation or slightly slowed
Moderate: 80â€“90Â°F (27â€“32Â°C)
Lethargic but verbally responsive
Severe: 68â€“80Â°F (20â€“27Â°C)
Unlikely to respond verbally, purposefully to noxious stimuli
Profound: <68Â°F (<20Â°C)
Unresponsive, may appear dead
Gastrointestinal tract

Decreased motility
Depressed hepatic metabolism

Hematologic
Hemoconcentration
Left shift of oxyhemoglobin dissociation curve

Kidneys
Cold-induced diuresis
Antidiuretic hormone antagonism

Lungs
Respiratory rate variable
Bronchorrhea

Metabolic
Metabolic acidosis
Increased glycogenolysis
Increased serum free fatty acids
Normal thyroid and adrenal function

Effects on the central nervous system are temperature-dependent and predictable. Mild hypothermia (90â€“95Â°F; 32.2â€“35Â°C) usually results in relatively benign clinical manifestations. Ataxia, slight clumsiness, slowed response to stimuli, and dysarthria are common.[93] As cooling continues, the mental status slowly deteriorates. In moderate hypothermia (80â€“90Â°F; 27â€“32.2Â°C), the patient is usually lethargic but still likely to respond verbally. In severe hypothermia (68â€“80Â°F; 20â€“26.6Â°C) the patient is unlikely to respond verbally, but will react purposefully to noxious stimuli.[93,124] In profound hypothermia (<68Â°F; <20Â°C), the patient is unresponsive to stimuli. Pupils may be fixed and dilated and the patient may appear dead.[124] However, standard criteria of brain death do not

apply to hypothermic patients. The hypothermia itself protects

against cerebral hypoxic damage.[133] Temperature drop inhibits the release of the excitatory neurotransmitter glutamate and attenuates the release of dopamine in brain ischemia animal models, suggesting a protective effect of hypothermia in brain injury.[40] Ventricular cerebrospinal fluid glutamate concentrations were lower in patients showing benefit from mild induced hypothermia after brain injury when compared to brain-injured patients kept normothermic.[194] However, a subsequent report of 392 patients failed to detect a benefit of induced hypothermia after acute brain injury.[5,54,123]

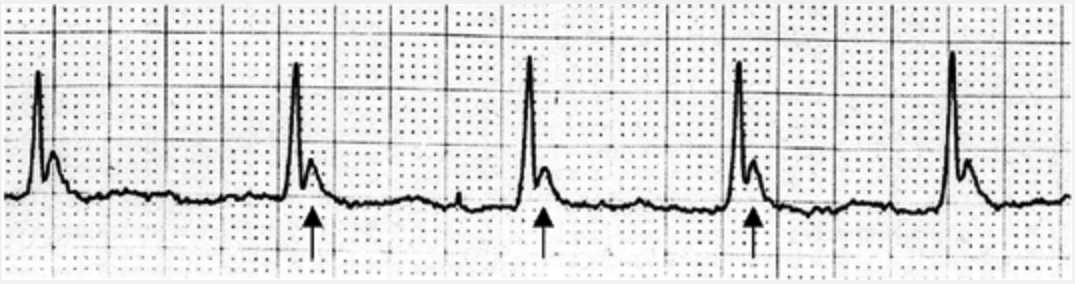

Figure 16-2. A characteristic electrocardiographic finding in the patient with profound hypothermia. The terminal phase of the QRS complex shows a typical elevation of the J-point Osborn wave (â†‘).

Under controlled circumstances patients have survived with body temperatures as low as 48.2Â°F (9Â°C).[96] Vigorous resuscitation is required for these patients. In particular, cardiac resuscitation should not be terminated in the field, where temperatures are

seldom taken. The adage that a patient cannot be considered dead until the patient is warm and dead is critical to providing appropriate management. This approach may lead to hours of cardiopulmonary resuscitation of hypothermic patients with ventricular fibrillation, ventricular tachycardia, or asystole, but may be ultimately successful in resuscitating patients initially presumed to be dead.[274]

The cardiac and hemodynamic effects of cold correlate closely with body temperature. As cooling begins there is a transient increase in cardiac output. Tachycardia develops secondary to shivering and sympathetic stimulation. At about 81Â°F (27.2Â°C) shivering ceases. Bradycardia develops with maintenance of a normal cardiac stroke volume.[38] This bradycardia is responsible for the decreased myocardial oxygen demand which may be protective in the setting of hypothermia.[38] In profound hypothermia, bradycardia may progress to asystole and death.

Unlike cerebral circulation, where autoregulation is preserved during cooling, coronary autoregulation is disturbed during hypothermia, and myocardial injury may ensue.[38] Attempts to maximize myocardial oxygenation through administration of oxygen and volume replacement to increase diastolic filling pressure are appropriate. Pharmacologic or electrical attempts to increase heart rate may dangerously increase myocardial oxygen demand.

The initial respiratory response to hypothermia is hyperventilation. As temperature continues to decrease, hypoventilation develops, which may progress to apnea and death. In animal models, this has been attributed to cold-induced failure of phrenic nerve conduction.[156]

The Electrocardiogram

The most common ECG abnormality in hypothermia is generalized,

progressive depression of myocardial conduction. Because myocardial oxygen demand remains unchanged in spite of cooling, and stroke volume is preserved, the number of beats per minute decreases as a means of decreasing myocardial oxygen requirements. PR, QRS, and QTc intervals are all prolonged, and increasingly profound hypothermia may lead to gradual progression to asystole.[74,288] Ventricular fibrillation occurs in an irritable myocardium most commonly at temperatures less than 86Â°F (30Â°C) resulting in a high O_2 consumption dysrhythmia. Atrial fibrillation is the most common dysrhythmia occurring in the presence of hypothermia.[94,232] Shivering may not be clinically evident, but a fine muscular tremor frequently produces a mechanical artifact in the baseline of the electrocardiogram.[80] A deflection occurring at the junction of the QRS and ST segment is invariably present in patients with temperatures <86Â°F (<30Â°C) (Fig. 16-2). First described in a single patient in 1938, the J-point deflection is commonly known as the *Osborn wave*.[81,235,284] The J-point deflection, thought to be a â€œcurrent of injuryâ€• associated with CO_2 retention under hypothermic conditions, was believed to be a poor prognostic sign.[235] Subsequent study has refuted its prognostic significance, as the J-point deflection is invariably found in the hypothermic patient when multiple electrocardiographic leads are obtained.[79,81,286,293] The size of the J-point deflection increases as body temperature decreases.[232,293] Atrial dysrhythmias that occur in the absence of underlying heart disease invariably disappear solely with rewarming.

Management

After blood specimens have been drawn, the hypothermic patient should be given 0.5â€“1.0 g dextrose/kg of body weight as $D_{50}W$ (50% dextrose in water) and 100 mg of thiamine IV. If hypoglycemia is the cause of the hypothermia, the response to dextrose may be dramatic, heralded by the onset of shivering and

rapid return to normal body temperature. Wernicke encephalopathy is uncommon, but may be associated with mild hypothermia; thermoregulation and normal ocular motion may return after the initiation of thiamine therapy.[164]

Hypothermia shifts the oxygen dissociation curve to the left (Chap. 22), resulting in decreased oxygen unloading to tissues; therefore, oxygen administration may be of benefit.[69] If clinically indicated for airway protection or inadequate ventilation or oxygenation, endotracheal intubation should be performed and can be done without complication.[64,173,208] However, there are case reports of ventricular fibrillation occurring during endotracheal intubation.[17,102,124,236,302] Every effort should be made to limit patient

activity and stimulation during the acute rewarming period, as activity may increase myocardial oxygen demand or alter myocardial temperature gradients, increasing the risk of iatrogenic ventricular fibrillation. Although pulmonary artery catheters and central venous lines have been inserted without complications, they should be avoided unless absolutely essential, so as not to precipitate ventricular dysrhythmias.[121,174,285] If a central venous catheter is considered necessary, it should not be allowed to touch the endocardium.[287] Patients who develop ventricular fibrillation are difficult to manage. In these instances, cardiopulmonary resuscitation (CPR) should be initiated, and the patient intubated and ventilated to maintain a pH of 7.40, uncorrected for temperature. Active internal rewarming should be instituted because standard therapy for ventricular fibrillation is often unsuccessful until rewarming is achieved. Patients should be supported, then defibrillated; if unsuccessful, defibrillation should not be attempted again until the patient has been warmed several degrees centigrade. Defibrillation may not be successful until the temperature exceeds 86Â°F (30Â°C); however, defibrillation can be successfully accomplished in animals and patients with

temperatures of less than 86Â°F (30Â°C).[7,17,66,215] The pneumatically powered â€œthumperâ€• and cardiopulmonary bypass devices are used successfully during prolonged hypothermic cardiopulmonary arrests.[17,57,177,275,285] Transesophageal echocardiographic examination of 7 hypothermic patients demonstrated that the thoracic pump mechanism is important for forward blood flow during CPR. The thoracic pump theory states that forward blood flow is caused by blood forced out of the heart and thoracic aorta by a general increase in intrathoracic pressure. Doppler studies demonstrate forward blood flow across the open mitral valve during external chest compression.[192]

Arterial Blood-Gas Physiochemistry

Assessment of the adequacy of ventilation and oxygenation in the hypothermic patient often poses a dilemma to clinicians, as chemical effects of cold on arterial pH and blood gases lead to confusion in the interpretation of arterial blood-gas values. Cold inhibits the dissociation of water molecules, causing pH to increase as cooling occurs. In vitro, the pH change of blood as it is cooled increases parallel to the pH change of neutral water. The partial pressures of CO_2 and O_2 decrease as cooling occurs, even as the blood content of those gases remains unchanged. Blood in a syringe taken from a patient whose body temperature is 98.6Â°F (37Â°C) yields a pH of 7.40 and a PCO_2 of 40 mm Hg in the blood-gas machine at 98.6Â°F (37Â°C), but yields a pH of 7.72 and a PCO_2 of 14 mm Hg if the blood is cooled to 61Â°F (16Â°C) and the values are measured at that temperature. Specially calibrated laboratory equipment, not routinely available, is required to measure blood-gas values directly at other than normal body temperature. A patient whose body temperature is 61Â°F (16Â°C) and whose actual in vivo blood-gas values are pH 7.72 and PCO_2 14 mm Hg will have values of pH 7.40 and PCO_2 40 mm Hg when the blood is warmed to 98.6Â°F (37Â°C) and measured in the

standard laboratory blood-gas machine. Because the machine measures pH and blood-gas pressures only in blood warmed to 98.6Â°F (37Â°C) (the uncorrected values), the actual in vivo values in hypothermic patients can be approximated using mathematically derived corrected values. Because the pH of neutrality has also increased, it is unclear what clinical meanings these corrected values have. The uncorrected values indicate what the pH and PCO_2 would be if the patient were normothermic. At first glance, the clinician might be content to learn that a hypothermic patient at 61Â°F (16Â°C) has a corrected pH of 7.47 and PCO_2 of 40 mm Hg. However, the uncorrected values of pH 7.18 and PCO_2 111 mm Hg indicate that the patient has a significant respiratory acidosis. Attempts to maintain a corrected pH of 7.40 may lead to hypoventilation and risk alveolar collapse and impairment of oxygenation. The preponderance of evidence in the anesthesia and cardiovascular surgery literature suggests that maintenance of ventilation is associated with a decreased incidence of myocardial injury and a decreased incidence of ventricular fibrillation.[69] pH and PCO_2 blood-gas values should be left uncorrected after the blood sample is warmed in the blood-gas machine and interpreted in the same way as in the normothermic patient.[69] In a study of hemodynamically stable hypothermic pigs, intraosseous blood-gas values of PCO_2 and pH correlated well with mixed venous blood samples.

Hypotension

When hypotension occurs in hypothermia, it is usually a result of the presence of bradycardia and the commonly associated volume depletion. Fluid depletion in hypothermia occurs as a result of a variety of mechanisms, including central shunting of blood by vasoconstriction and cold-induced diuresis. Cold diuresis occurs when increases in central blood volume result in inhibition of antidiuretic hormone. Impairment of renal enzyme activity and decreased renal tubular reabsorption contribute to the large

quantities of dilute urine known as cold diuresis.[118,122,174,306] Normal saline should be given to expand intravascular volume. Urine output is an important indicator of organ perfusion and the adequacy of intravascular volume in the hypothermic patient, although the initial cold diuresis may lead to underestimation of fluid needs.[306]

Pharmacologic Interventions

The best means to effect resuscitation of the hypothermic victim in ventricular fibrillation is controversial. The most recent recommendations for the treatment of cardiac arrest when the body core temperature is <86Â°F (<30Â°C) does not include the administration of a vasopressor drug or antidysrhythmic.[8] There is no data to support this recommendation. There is data, however, that suggests the possibility of improved chance of resuscitation with the use of antidysrhythmics.

Epinephrine and Vasopressin

The administration of vasopressin to pigs in hypothermic cardiac arrest increased coronary perfusion pressure and improved defibrillation success.[266] However, because of defibrillation, there was no difference in the 1-hour return in spontaneous circulation.[266] When using warmed thoracic lavage, vasopressin increased coronary perfusion pressure and increased the 1-hour survival.[265] Compared with the administration of saline that resulted in zero episodes of successful defibrillation, 8 of 8 vasopressin-treated pigs had restoration of spontaneous circulation after electrical defibrillation and improved short-term survival. The whole-body temperature was not increased, but the authors postulated there may be myocardial warming.[265] In another study in which epinephrine was given to one group of pigs and vasopressin to another, increased coronary perfusion pressure and return of spontaneous circulation (ROSC) resulted in both

groups.[169] In contrast, body temperature significantly increased during CPR with thoracic lavage, and epinephrine increased coronary perfusion pressure, but no improvement in ROSC occurred.[167] The length of time of cardiac arrest, the doses of drug, and the efforts

to rewarm differed in these studies. In one 19-year-old patient with prolonged hypothermic cardiopulmonary arrest who had received epinephrine 2 mg with no improvement, the administration of vasopressin was followed by immediate restoration of spontaneous circulation.[280] Interactions with epinephrine, vasopressin, and ischemia during CPR are complex and incompletely understood.[170] In normothermic patients with asystolic cardiac arrest, vasopressin followed by epinephrine was more effective in restoring spontaneous cardiac activity than epinephrine alone.[299]

Amiodarone

Amiodarone is recommended in the current for ventricular fibrillation in normothermia. In one study comparing the use of amiodarone, bretylium, and placebo in a hypothermic dog model, amiodarone showed no statistical improvement in causing ROSC. There was no significant difference between the groups; only 1 of 10 amiodarone-treated dogs demonstrated ROSC, versus 3 of 10 in the placebo group and 4 of 10 in the bretylium-treated dogs.[279]

Bretylium

Bretylium tosylate is a benzyl quaternary ammonium compound with a biphasic action, initially causing release of norepinephrine and then blocking its release. This may cause transient hypertension, but hypotension is the most common result.[215,234] Hypothermic dogs given bretylium had significantly lower mean arterial pressures and systemic and pulmonary vascular resistance

as compared to controls.[234] The mechanism of the antidysrhythmic effect of bretylium in normothermia may be related to its ability to increase the myocardial refractory period.[234]

Bretylium may be of benefit in the treatment of ventricular fibrillation in the hypothermic patient. The antidysrhythmic effect of bretylium is poorly understood. It prolongs the cardiac action potential and reduces heterogeneity of repolarization times.[248] The net effect seems to be stabilization of the cardiac rhythm. Bretylium is found to increase the fibrillation threshold in hypothermic cats given bretylium 50 mg/kg,[223] and in hypothermic dogs given bretylium 15 mg/kg,[39] whereas bretylium 7.5 mg/kg was found to increase the threshold prior to cooling.[234] In a canine study,[215] cooling occurred and either a 0.9% NaCl solution placebo or bretylium 40 mg/kg was administered prior to an attempt to induce ventricular fibrillation. Six of 11 dogs given placebo developed ventricular fibrillation, whereas only 1 of the 11 dogs pretreated with bretylium developed ventricular fibrillation following attempted induction. In this study, 3 dogs receiving pretreatment with bretylium fibrillated during the infusion, prior to maneuvers. Of the 6 dogs given placebo that developed ventricular fibrillation, all were successfully resuscitated, although 4 required bretylium to do so. This study did not attain statistical significance, and bretylium infusion both resulted in ventricular fibrillation and was effective in chemical defibrillation of ventricular fibrillation.[215] A single case of successful chemical defibrillation with bretylium is reported in an environmentally exposed patient with a core temperature of 85.1Â°F (29.5Â°C).[65] Given the difficulty of treating ventricular fibrillation once it occurs during hypothermia, the preponderance of evidence suggests a role for the use of bretylium. However, bretylium has been removed from the American Heart Association guidelines for advanced cardiac life support and may no longer be available in some institiutions.[8]

Dopamine

Dopamine increases cardiac output, mean arterial pressure, heart rate, and stroke volume in dogs cooled to 77Â°F (25Â°C), and stabilizes pulmonary arterial wedge pressure.[221] In a canine hypothermia model, dopamine infusions provided some protection from ventricular fibrillation. Dopamine lowered the temperature at which ventricular fibrillation occurred and reduced the incidence of ventricular fibrillation, as did infusion of norepinephrine.[11] The added benefit of dopamine in hypothermia may be a result of its renal and splanchnic vasodilating properties, increasing renal perfusion and supporting urine output.[106] Dopamine increases myocardial oxygen demand and decreases peripheral perfusion, potentially detrimental effects in the hypothermic patient.[11] Nevertheless, after the administration of intravenous fluids, dopamine infusion during hypothermia is indicated in the patient requiring blood pressure support.

Rewarming

Three types of rewarming modalities are used in the management of hypothermic patients.[60,181] *Passive external rewarming* involves covering the patient with blankets and protecting the patient from further heat loss. Passive external rewarming uses the patient's own endogenous heat production for rewarming and is most successful in healthy patients with mild to moderate hypothermia whose capacity for endogenous heat production is intact.[122] Passive external rewarming is reported to be successful in hypothermic patients with temperatures as low as 69Â°F (20.6Â°C).[283,293,301] Advocates of passive external rewarming argue that it allows vasoconstriction to persist and it decreases the afterdrop and shock from vasodilation associated with active skin rewarming.[122,208,283]

Active external rewarming involves the external application of heat to the patient. There is disagreement about the possible

detrimental effects of active external rewarming. For example, skin warming may lead to a physiologically detrimental suppression of shivering.[122] Acute vasodilation of peripheral vessels could cause hypotension and an increased peripheral demand on the persistently cold myocardium. The return of cold blood from the extremities to the heart is suggested to exacerbate intramyocardial temperature gradients, which could cause ventricular irritability during hypothermia.[186] However, in pigs, blood returning to the heart was found to be warm before warming of central organs occurred.[107]

Afterdrop is the continuing decrease in temperature once rewarming begins. Some authors (including the American Heart Association Advanced Cardiac Life Support [ACLS] guidelines)[8] recommend that rewarming of the extremities should be delayed by application of heat to the trunk only, rather than to the trunk and extremities, in an attempt to avoid the complications of afterdrop and intramyocardial temperature gradients.[171] However, there is no scientific evidence to suggest that this drop in temperature is more dangerous than the very temperature that had existed originally.[185] In addition, there is no evidence of pooling of blood in the periphery, nor of increased flow during surface rewarming.[185,260] Flow studies in the hand, arm, calf, and foot demonstrate that afterdrop has already occurred and is completed before any increase in blood flow occurs in the limbs.[185,297] Initial experiments demonstrating afterdrop were done in inanimate objects and reflected continued cooling of central structures before heat from external sources reached the core.[107,185,297]

Treatment including complete submersion is available in some institutions. Eighteen patients with temperatures of 78.8â€“91.4Â°F (26â€“33Â°C) were successfully warmed in a Hubbard tank, although one fatality not associated with rewarming occurred.[309] Submersion must be used with caution, however, because of the inherent

difficulties of controlling agitated patients and monitoring and resuscitating patients in water.

Mortality rates for active external rewarming are frequently reported to be higher than for passive external rewarming,[243] but case selection is not controlled in these series. It is possible that sicker patients who fail to rewarm passively are then actively rewarmed and have a higher mortality rate caused by their underlying disease, rather than by the method of therapy selected. The published series and case reports do not allow for an analysis of this hypothesis. Selection of either passive or active external rewarming in treatment of mild to moderate hypothermia does not appear to influence the prognosis as much as the presence or absence of underlying disease.[136,208,300] In our experience, active external rewarming has not resulted in mortality, except in those patients with severe underlying disease.[293]

Active internal rewarming involves attempts to increase central core temperature directly, by warming the heart prior to the extremities or periphery. The administration of heated, humidified oxygen delivered by face mask is considered part of active internal rewarming. Additional minimally invasive modalities of active internal rewarming include endotracheal intubation with warmed, humidified oxygen,[125] and gastric lavage with warmed fluids. Transcutaneous pacing was successful in improving hemodynamic parameters and speeding rewarming in an animal model.[76] More invasive modalities, those procedures that are fundamental to the rewarming controversy, include peritoneal lavage with warmed dialysate,[141,226] and the rerouting of blood through external blood rewarming equipment via cardiopulmonary or femoral-femoral bypass and hemodialysis.[43,130,217] Heparin-coated bypass systems are available, which avoids systemic anticoagulation, thus decreasing the risk of bleeding complications. It is suggested that extracorporeal venovenous rewarming and continuous arteriovenous rewarming show improved rewarming rates when

compared to standard techniques such as saline lavage of the bladder, stomach, or peritoneal cavity.[100] Extracorporeal methods of active internal rewarming should be reserved for severely hypothermic patients (<80Â°F or <27Â°F) or those with unstable cardiac rhythms (ventricular fibrillation or tachycardia, or asystole) attributed to hypothermia.[7,68,119] The evidence for the benefit of extracorporeal methods in those patients with stable rhythms is not yet available. In patients with stable rhythms, studies are essential to resolve the debate over the merits of passive or active external rewarming versus active internal rewarming.

Unfortunately, current ACLS guidelines for the management of hypothermia make several recommendations that are not supported by the literature. The most glaring area of controversy is the recommendation of extracorporeal rewarming for stable patients based on a temperature of 86Â°F (30Â°C) or less. ACLS guidelines assert that passive rewarming is ineffective in the stable patient with severe hypothermia, which is defined as a temperature below 86Â°F (30Â°C). However, many patients with temperatures below 86Â°F (30Â°C) have been successfully treated with passive external rewarming with, at most, the addition of warm, humidified oxygen.[293,301] Patient temperature correlates poorly with outcome.[7,66,173,285,288] Treatment recommendations should not be based solely on temperature. Stability of the vital signs and cardiac rhythm, and the underlying cause of hypothermia, are much more critical considerations in management. It is hard to imagine a patient with a stable cardiac rhythm and core temperature of 80â€“86Â°F (26.6â€“30Â°C) in whom extracorporeal rewarming with cardiopulmonary bypass is indicated.

Additionally, ACLS guidelines state that significant hyperkalemia may develop during rewarming, suggesting that this is a complication of rewarming. Hyperkalemia is not described as a consequence of rewarming.[64] In all of the evidence collected with

regard to hyperkalemia, this abnormality was present as a consequence of the hypothermia and not the rewarming.[124,192,262]

These are ideal subjects for intensive evidence-based investigations to resolve the science versus myth in hypothermia resuscitation.

Prognosis in Hypothermia

Except in cases of profound hypothermia,[124] the prognosis is most closely correlated with the presence or absence of underlying disease.[136,208,229,300,301] In patients with hypothermia alone, in the absence of underlying disease, mortality is 0â€“10%. In the presence of an underlying disease, mortality rises to 75â€“90%. Morbidity results from associated frostbite and trauma.

Prolonged cardiopulmonary arrest and absolute temperature are not predictive of poor outcome.[7,66,173,285,288] In severely hypothermic patients, profound hyperkalemia (K^+>10 mEq/L) is associated with unsuccessful resuscitation.[124,192,262]

Frostbite

Hypothermia may be accompanied by frostbite when patients are exposed to environmental temperatures that are less than 20Â°F (6.7Â°C).[209] Frostbite should be managed by rapid rewarming. The extremity involved may be placed in a large, soft basin of warm water (100â€“108Â°F; 38â€“43Â°C) for 30 minutes. The water temperature must be frequently adjusted, as the frozen extremity will have the effect of ice cubes, and with time, will cool the water in the basin. Parenteral analgesics may be necessary, as the rewarming process is often painful. Frostbitten areas should never be rubbed, as the tissue is particularly sensitive to trauma. Dextran, alcohol, vasodilators, and anticoagulants have not proven useful. Sympathectomy in this situation is also of unproven benefit and remains highly controversial.[157,172,200]

Prevention

Because many patients may not wear (and may not possess) adequate clothing, it is essential that they be assessed for social services support after the acute episode is resolved. In addition, many of these patients live in substandard, inadequately heated (often unheated) housing. Patients should be advised to wear comfortable, warm clothing to prevent future episodes of hypothermia. Adequate clothing is particularly important for patients traveling by automobile during inclement weather conditions. The importance of adequate nutrition should also be stressed.

Hyperthermia

Definition of Heatstroke

Heatstroke is defined by a rectal temperature greater than 106Â°F (41.1Â°C) in the setting of a neurologic disturbance manifested by psychosis, delirium, stupor, coma, and/or convulsions.[159] Temperature criteria cannot be absolute, as information regarding the patient's temperature is rarely available at the time of onset of heatstroke. In some instances the temperature may not be measured for several hours, during which time cooling may have been instituted or occurred spontaneously.[151,152] When appropriate environmental conditions prevail, the diagnosis of heatstroke should be made liberally. Although the absence of sweating was once thought to be an essential component of the definition of heatstroke,[55,227]

many patients with heatstroke have been noted to maintain the ability to sweat on presentation.[63,193,270,294]

Epidemiology of Heatstroke

Hundreds of people die annually of heatstroke in the United States, and 80% of the victims are older than age 50 years. Several studies show mortality rates from heatstroke to be 5.6â€“80%. Thousands of other victims survive with significant heat-related morbidity.[10,30,75,142,155,276] The high morbidity and mortality of heatstroke markedly contrast with those of profound hypothermia, in which the prognosis is related not to the temperature itself, but to the underlying etiology. The overall prognosis in heatstroke depends primarily on how long the temperature has been elevated prior to cooling, the maximum temperature reached, and the affected individual's premorbid health.

Heat-related deaths are preventable, and the public health preparedness of cities and healthcare workers is essential.[19,44] Mortality during heat waves is increased in urban areas where a heat wave has not occurred for several years.[53,78,142,264] Mortality is decreased when public health interventions improve preparedness. The city of Milwaukee experienced a heat wave in 1995 that resulted in numerous public health and preparedness responses; this may have led to the number of heat-related deaths and emergency medical service runs in the heat wave of 1999 being 49% lower than predicted.[298] After the Chicago heat wave of 1995, public policies targeting the elderly of Chicago may have contributed to a change in the demographics of those who succumbed during a subsequent heat wave in Chicago in 1999. The dead in 1999 were younger; more that 50% of those who died were younger than age 65 years. More than half of the dead were seen or spoken to on either the day of or the day before their death. Psychiatric illness was almost twice as prevalent in the younger victims, compared to those older than 65 years of age.[220]

Heat waves are meteorologic events characterized by air temperatures that are â‰¥90Â°F (â‰¥32.2Â°C) for 3 or more consecutive days.[47] During the summer of 2003, Europe experienced record high temperatures for many consecutive days.

The prolonged heat caused extreme increases in mortality across Europe. In France, there were 14,800 excess deaths caused by heat. This is equivalent to a total mortality increase of 60% between August 1 and August 20, 2003.[175,290] Italy reported 1094 excess deaths from June to August 2003, a 23% increase compared with the average annual number of deaths from 1995â€“2002.[44] Increased mortality was associated with risk factors previously reported, including old age, limited access to care, poor living conditions and social isolation.[267,291]

Socially isolated individuals or those with preexisting illness, as well as the physically compromised and frail elderly, are at greatest risk of death during heat waves. Confinement to bed was the strongest predictor of death in the Chicago heat wave of 1995, and living alone doubled the risk of death. There were fewer deaths among people with working air conditioners or who had access to an air-conditioned environment.[249,267] A working air conditioner was found to be the strongest protective factor against heat-related death 4 years later in the next deadliest heat wave in Chicago in a decade.[220] Although fans may seem to improve comfort, they do not prevent heat-related illness and may contribute to heat stress when temperatures and humidity exceed approximately 100Â°F (37.8Â°C)[149,154,155,220,267,305] In times of heat waves, preventive public health programs should encourage visiting nurses, housekeepers, and community service programs, such as Meals-on-Wheels, to increase the awareness of the danger of heat and identify those individuals most at risk.[267] A decreased risk of death was found among people with contacts from these agencies during the Chicago heat wave.[267] The media must alert the public and provide information on avoiding heat illness, as well as encourage individuals to help others to stay cool by assuring access to cooling measures.

The number of deaths from exposure-related illness has increased 3-fold in foreign transients attempting to enter the United States from Mexico. Because urban areas are more tightly patrolled,

individuals attempting to cross into the United States illegally have turned to the harsh deserts and mountain ranges of the southwestern United States, increasing prolonged exposure and resulting in death from heat, cold and dehydration. Although many more bodies remain undiscovered, 99 individuals' deaths were attributed to environmental causes in the year 2000.[84]

From 1995â€“2002, 233 children died from heatstroke when left unattended in cars, 75% of whom were either forgotten or left by caretakers who did not expect the temperature to rise dangerously within the automobile. In 25% of the incidents, children were trapped inadvertently while playing. Most of these deaths occurred during the summer months.[113]

Infants may suffer heatstroke under environmental conditions that would not be expected to place the child in danger. Well-meaning parents sometimes overinsulate children with clothing and blankets, inhibiting their cutaneous heat loss and placing them at risk.[16,138,139]

During 2002, the United States military reported 1816 heat-related injuries of active duty soldiers.[14] During Operation Iraqi Freedom, 6 soldiers died from heat-related causes. There were 30 other cases of heatstroke and many other heat-related casualties. During the period 1997â€“2002, 8084 soldiers were treated as outpatients for heat injuries.[14] The United States military actively promotes heat illness prevention and exhorts its personnel to not repeat history.[289] In comparison, in 1917, 425 British soldiers on active duty in the area on the Persian Gulf formerly known as Mesopotamia, presently known as Iraq, died of heatstroke during 1 month, and 524 died in 1 year.[303]

There were 104 heatstroke deaths among football players from 1960 to 2004. In the past 10 years, 24 football players have died of heatstroke, 19 of these in high school, 3 in college, and 2 professional. Three heatstroke deaths occurred in high school football players in 2004.[160,213]

High ambient temperature is associated with an increase in mortality from cocaine overdose. The mean daily number of deaths from cocaine overdose was 33% higher when the ambient temperature exceeded 88Â°F (31Â°C).[195]

Thermoregulation and Heat Stress

The normal thermoregulatory response to heat stress is mediated primarily by heat-sensitive neurons in the hypothalamus. Increased body-core temperature results in active dilation of cutaneous vessels and skin blood flow increases.[128,252] Because increased skin blood flow is attained primarily by an increase in heart rate and stroke volume, the capacity to increase cardiac output is critical to cooling. Compensatory shifting of blood flow from the splanchnic and renal vessels to the skin further increases skin blood flow.[135,252] Sweat-gland function is activated by parasympathetic stimulation, and the combination of vasodilation, increased skin blood flow, and increased sweating results in heat loss through convection and

evaporation. Dehydration after profuse sweating increases plasma osmolarity. Heat-sensitive neurons in the preoptic anterior hypothalamus are inhibited by locally increased osmolarity and by input from distal hepatoportal osmoreceptors. The inhibition of heat-sensitive neurons results in decreased heat dissipation response.[52,230]

Types of Heatstroke

Heatstroke is commonly divided into two types: exertional and nonexertional. Nonexertional, or classic, heatstroke describes heatstroke occurring in the absence of extreme exertion. Nonexertional heatstroke is most commonly described during heat waves, and the victims are predominantly those persons least able to tolerate heat: infants,[16] the aged,[59] those with psychiatric

disorders, and the chronically ill.

Exertional heatstroke occurs as a result of increased motor activity. It may occur in young, healthy individuals who are exercising, or in individuals whose increased motor activity results from other causes, such as seizures or agitation. Often a period of significant heat stress in exercising individuals precedes the development of heatstroke. Military recruits who develop heatstroke may sometimes present to the camp infirmary with vague complaints prior to collapse.[270] Published studies of heatstroke in miners, athletes, and military recruits describe several precipitating factors in heatstroke: fatigue associated with a recent deficit in sleep; poor physical conditioning; a recent febrile illness; recent heat-related symptoms such as thirst or weakness; relative volume depletion; failure to allow for acclimatization; and obesity. Symptoms of nausea, weakness, headache, diarrhea, or irritability often precede the development of heatstroke. Although rapid onset of symptoms and acute loss of consciousness are frequently reported in exertional heatstroke, the preceding period of heat stress and insidious symptoms may go unrecognized. Although exertional heatstroke is more likely to occur during intense exertion in a hot, humid environment, it may also occur with moderately intense exercise early in the morning, when environmental conditions do not usually represent a thermoregulatory stress.[13]

Differential Diagnosis of Hyperthermia

In addition to exposure and exertion, conditions that predispose to severe hyperthermia include primary hypothalamic lesions; intracranial hemorrhage; agitation; alcohol and sedative-hypnotic withdrawal; seizures; and the use of therapeutic and illicit drugs (Table 16-5).[104,109,110 and 111,168,196,281] Included in the differential diagnosis of severe hyperthermia are the serotonin syndrome, malignant hyperthermia, and neuroleptic malignant

syndrome, all of which may result in high temperature, altered mental status, and increased muscle tone.

Serotonin Syndrome

The serotonin syndrome results from excess stimulation of the serotonin receptor, primarily the 5-HT_{1A} subtype.[278] Drug interactions are most commonly the cause of the syndrome. Monoamine oxidase inhibitors used in conjunction with tricyclic antidepressants,[18] selective serotonin reuptake inhibitors,[88] L-tryptophan,[88,282] meperidine,[120] dextromethorphan,[247] amphetamines,[168] and sumatriptan are reported to lead to serotonergic hyperstimulation and severe symptoms.[105,278] The clinical condition resulting from excess serotonin includes alterations in consciousness, restlessness, increased muscle tone, tremor, gastrointestinal disturbances, and hyperthermia. Treatment of the syndrome focuses on control of hyperthermia by using aggressive cooling; muscle relaxation primarily by using benzodiazepines; or, in severe cases, endotracheal intubation and paralysis (Chap. 70).

TABLE 16-5. Differential Diagnosis of Hyperthermia

I. Increased heat production
- *Increased muscle activity*
  - Agitation
  - Catatonia
  - Ethanol withdrawal
  - Exercise
  - Infectious diseases
  - Malignant hyperthermia
  - Monoamine oxidase inhibitor drug interactions
  - Neuroleptic malignant syndrome

Parkinson disease
Sedative-hypnotic withdrawal
Seizures
Serotonin syndrome
Xenobiotics
- *Increased metabolic rate*
  Hyperthyroidism
  Pheochromocytoma
  Sympathomimetics

II. Impaired heat loss
- *Environmental*
  Heat
  Humidity
  Lack of acclimatization
- *Social disadvantage*
  Isolation
  Poverty
  Lack of air conditioning
  Confinement to bed
- *Medical illness*
  Cardiac insufficiency
  Diabetes
  Hypertension
  Pulmonary
  CNS dysfunction
- *Dehydration*
- *Fatigue*
- *Limited behavioral response*
  Extremes of age
  Psychiatric impairment
  Mental retardation
  Xenobiotics

Malignant Hyperthermia

Malignant hyperthermia is a very rare disorder that is associated with a congenital disturbance of calcium regulation in striated muscle. Malignant hyperthermia was first reported in 1960. Ten deaths occurred in a single family following general anesthesia.[73] Exposure to anesthetics, depolarizing muscle relaxants, or, rarely, severe exertion, precipitates uncontrolled calcium influx into the sarcoplasmic reticulum, leading to severe muscle rigidity and hyperthermia.[112,140] The clinical setting of severe muscle rigidity and hyperthermia following general anesthesia usually is adequate to define the syndrome (Chap. 66).

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome, a severe extrapyramidal syndrome associated with muscle rigidity, autonomic dysfunction, and altered mental status, was first

described in 1968.[70] This disorder develops during the administration of antipsychotic drugs or the withdrawal of dopaminergic agents. Increased muscle tone, because of dopaminergic blockade of the striatum, as well as central altered hypothalamic thermoregulation, leads to hyperthermia.[126] Temperature elevation and alteration of mental status occur after the onset of â€œlead pipeâ€• muscle rigidity.[24,116] Laboratory findings are not specific and include marked elevation of creatine phosphokinase (CPK) in some patients and leukocytosis with a left shift. Neuroleptic malignant syndrome must be distinguished from the much more common cases of heatstroke in psychiatric patients that are caused by heat intolerance resulting from the anticholinergic effects of antipsychotic drugs or antihistamines prescribed to control extrapyramidal symptoms (Chap. 67).[257,310]

Acute Phase Response and Heat Shock

Proteins

The response to heat stress is a coordinated interplay between the mediators of inflammation, including endothelial cells, leukocytes, inflammatory cytokines, and endotoxins. These are important mediators of the systemic immune response. However, in heatstroke, they are responsible for systemic inflammation, similar to the sepsis syndrome. Many proinflammatory cytokines are identified in heatstroke, including tumor necrosis factor; interleukins-2, 6, 8, 10, and 12; interferon-Î± and -Î³; and granulocyte colony-stimulating factors.[31] Hypothermia delays the release of interleukin-1B, interleukin-6, and tumor necrosis factor in vitro.[158]

Heat stress causes increased gene transcription of heat shock proteins, which render the organism more resistant to heat injury, protecting cells from injury and increasing cell survival. Heat shock protein 72 is protective against injury, from heat stress, and the extent of protection correlates with the level of heat shock protein.[188]

During exercise, splanchnic hypoperfusion may increase translocation of bacteria from the gut into the bloodstream, establishing the cascade of inflammation and injury which perpetuate tissue injury after normothermia is established.[85]

Pathophysiologic Characteristics of Heatstroke

Hypotension and tachycardia in heatstroke are caused by a number of factors. The patient with heatstroke may have a reduced plasma volume secondary to dehydration. There is peripheral pooling of blood associated with an increase in cutaneous blood flow from 0.5 L/min to 7â€“8 L/min.[135,252] In addition, patients may manifest primary myocardial insufficiency.[161] Clinically, patients exhibit either a hypo- or

hyperdynamic circulatory response. The observed circulatory response to heat stress is a function of the patient's cardiac reserve, volume status, and degree of myocardial heat injury. The hyperdynamic condition is characterized by increased cardiac index and decreased systemic vascular resistance.[228] These hemodynamic characteristics occur in patients who are able to maintain a significantly increased cardiac output in response to the circulatory demand of heat stress.

Volume-depleted patients, or those patients with primary myocardial insufficiency, may exhibit a hypodynamic response. These patients have a decreased cardiac index and increased systemic vascular resistance.[228,277] Whether pulmonary vascular resistance is affected is unclear. High central venous pressures have been found in some patients, with evidence of right-heart failure and right-heart dilation on autopsy.[193] This has led to the suggestion that pulmonary vascular resistance may be elevated.[228] In 22 (64%) of 34 patients with heatstroke, central venous pressures (CVPs) were greater than 3 cm H_2O. Twelve patients had a CVP â‰¤ 0, and 10 had a CVP that exceeded 10 cm H_2O. These authors cautioned against injudicious infusion of large quantities of intravenous fluids that can result in complications of congestive heart failure and fluid overload. In the study, only 3 patients required more than 2 L of 0.9% sodium chloride solution during cooling. Crystalloid infusion ranged from 500 to 2500 mL, and none of the patients developed problems associated with fluid overload.[268]

A study of compromised elderly patients with heatstroke, using pulmonary artery catheters, showed that pulmonary vascular resistance was low or normal. Pulmonary capillary wedge pressures were not elevated.[276] A study of 13 cases of heatstroke in pilgrims to Mecca, Saudia Arabia, monitored with pulmonary artery catheters, demonstrated a good correlation of CVP with pulmonary capillary wedge pressures.[2] Serial electrocardiograms in 51 of these pilgrims suffering from heatstroke showed normal

sinus rhythm in 25%, sinus tachycardia in 52%, atrial fibrillation in 16%, and sinus bradycardia in 6%. ST segment depression and other ST-T wave changes were reported. The QTc interval showed no abnormality.[3] ST changes suggestive of acute coronary syndrome may occur and normal coronary arteries are noted upon coronary catherization.[214] In some patients, echocardiography showed pericardial effusions and regional wall motion abnormalities, asymmetric septal hypertrophy, right ventricular dilation, and left ventricular dilation with impaired function.[3]

Autopsy studies of the heart demonstrate right-heart dilation, pericardial effusions, interstitial edema, degeneration and necrosis of myocardial fibers, and subendocardial hemorrhages.[152,193] Postmortem examination of the lungs revealed vascular congestion, pleural effusions, and parenchymal hemorrhages.[193,228]

Gastrointestinal hemorrhage, vomiting, and diarrhea occur frequently.[270] At autopsy, edema and hemorrhage of the bowel wall occur.[49] These changes may be partly a result of to regional ischemia of splanchnic blood vessels and resultant hypoperfusion and hypoxia. Increased bowel wall edema and bleeding predispose to the release of bacteria into the bloodstream from the gut, causing focal microvascular changes in the intestinal villi, leading to bowel wall anoxia and further injury.[86] Liver injury occurs commonly and is not clinically manifest until the second or third day following the temperature increase.[151,270] Centrilobular changes, such as widening of central veins and adjacent sinusoids and pooling of blood, and varying degrees of hepatocellular degeneration, are demonstrated on liver biopsy. Repeat biopsies demonstrated that these changes resolve as the patient recovers.[151] In other cases, only congestion and fatty infiltration are reported.[49]

Neuropsychiatric impairment is, by definition, present in all cases of heatstroke. Length of coma correlates significantly with

mortality.[15,270] Autopsy studies demonstrate a variety of structural and microscopic CNS injuries. Edema and venous congestion are evident. The number of cortical neurons is reduced, with concomitant glial proliferation. Cerebellar Purkinje cell deterioration is marked. The hypothalamus appears to be relatively spared, with limited edema of the neuronal nuclei. Hemorrhages occur throughout the brain.[49,193,270] Carotid artery vasoconstriction occurs in response to heating, in an in vitro model using the carotid arteries of rabbits as a possible mechanism of ischemia and injury, in heatstroke.[218] Heatstroke-induced cerebral ischemia is associated with increased glutamate release, activation of cerebral dopaminergic neurons causing dopamine overload, and gliosis. These changes are attenuated by induction of hypothermia in an animal model.[51]

Reports of MRI of brains of patients recovering from heatstroke describe radiographic findings, including hemorrhagic and ischemic abnormalities of the cerebrum and cerebellum, delayed cerebellar atrophy, central pontine myelinolysis, vascular infarcts, and medial thalamic lesions, which correspond anatomically to the paraventricular nucleus.[23,201,202] The paraventricular nucleus is involved with core temperature regulation via the hypothalamicâ€“pituitaryâ€“adrenal axis.[22] The clinical symptoms of dysphagia, quadriparesis, wasting extrapyramidal syndrome, and pancerebellar syndrome have corresponding MRI findings.[4] Persistent cerebellar dysfunction occurs, as does lower motor neuron damage, manifested by areflexia and muscle wasting.[71,176] Abnormal nerve conduction studies are documented.[145] Higher cortical functions may be spared in survivors, or may be reversible when they occur.[85,179,204] Permanent neurologic sequelae are correlated with the degree and duration of hyperthermia.

Acute renal failure was the major cause of death in heatstroke victims before the advent of hemodialysis.[263,294] In addition to the direct effects of heat, volume depletion, and hypotension,

myoglobinuria secondary to rhabdomyolysis results in further renal tubular injury. This is especially common in the agitated or exercising patient.[56,104,238] The mechanism by which myoglobin contributes to renal failure remains controversial. At autopsy the kidneys are enlarged, with numerous petechial hemorrhages.[193] Acute tubular necrosis is seen on biopsy. In exertional heatstroke with acute renal failure, renal hemodynamics are compromised because of increased vasoconstrictive hormones, such as catecholamines, renin, aldosterone, and endothelin-1, and decreased vasodilatory hormones, such as prostaglandin E_2.[182]

Bleeding is associated with significant morbidity and mortality in many cases of heatstroke. Coagulation disturbances seen in patients with heatstroke appear to be multifactorial. Elevation of the prothrombin time may occur within 30 minutes of temperature elevation and is attributed to direct heat injury of clotting factors.[18] Liver damage may significantly contribute to the coagulation disturbances, although this does not manifest as rapidly.[18,219,241] Two patients with severe liver failure secondary to heatstroke received liver transplantation; both died after chronic rejection.[254] A third patient with extensive liver cell necrosis as a consequence of heatstroke was referred for consideration of liver transplantation but recovered completely with supportive therapy.[101] Evidence of diffuse capillary basement-membrane injury has been demonstrated by electron microscopy and is thought to precipitate consumptive coagulopathy in severe cases of heatstroke.[49,273] Thrombocytopenia is very common and occurs within 30 minutes of onset of heatstroke, frequently in the absence of other evidence of disseminated intravascular coagulation. Direct thermal injury leading to decreased platelet survival and megakaryocyte damage may play a role (Table 16-6).[193,219]

Clinical Findings in Heatstroke

Clinical evaluation of the hyperthermic patient begins with careful assessment of the vital signs. Vital sign abnormalities commonly include heart rates greater than 130 beats/min, hypotension, and an elevation of the respiratory rate, often above 30 breaths/min. Most importantly, temperature is elevated. After cooling, there is often a secondary rise in temperature that suggests persistent disturbances of thermoregulation.[193]

Neurologic examination reveals a confused, delirious, comatose, or seizing patient. Pupils may be normal, fixed and dilated, or pinpoint. Decerebrate or decorticate posturing may be evident. Muscle tone is increased, normal, or flaccid. The skin may be hot and dry or diaphoretic. Nasal and oropharyngeal bleeding may be present as a consequence of the acute coagulopathy. Examination of the lungs is often nonspecific, although heatstroke victims are at risk of pulmonary edema as a primary event associated with capillary endothelial damage or following overly aggressive fluid resuscitation. Cardiac auscultation may reveal a flow murmur secondary

to high cardiac output or a right ventricular gallop. Neck vein distension indicates increased central venous pressure. Jaundice suggests hepatic injury and occurs on the second or third day following the onset of heatstroke.[50] Nasogastric aspiration or rectal examination may demonstrate gross bleeding. A petechial rash develops, probably secondary to capillary endothelial damage.

TABLE 16-6. Physiologic and Clinical Manifestations of Heatstroke

Cardiovascular
Hypodynamic states in elderly

- Hyperdynamic states in young healthy individuals
- Electrocardiogram
  - Nonspecific
  - Widening of QRS because of an underlying abnormality (cocaine toxicity, hyperkalemia associated with rhabdomyolysis)

Central nervous system

- Altered mental status
  - Irritability, confusion, ataxia, seizures, coma
  - Weakness, dizziness, headache
  - Plantar extension, pupillary abnormalities, decorticate posturing
- EEG
  - Normal or diffuse slowing
- CSF
  - Normal or increased protein
  - Lymphocytosis

Gastrointestinal

- Vomiting, diarrhea, hematemesis

Hematologic

- Bleeding diathesis
  - Prolonged PT and PTT
  - Disseminated intravascular coagulation
  - Thrombocytopenia
  - Petechiae
  - Purpura
- Leukocytosis

Hepatic

- Hepatic insufficiency at 12â€“36 h
- Elevated AST, ALT, LDH

Metabolic

- Metabolic acidosis and respiratory alkalosis
- Electrolyte disturbance
  - Hypernatremia

- Hypokalemia
- Hypocalcemia
- Hypophosphatemia

Muscle
- Rhabdomyolysis
- Elevated CPK

Renal
- Decreased renal perfusion
- Myoglobinuria
- Proteinuria
- Oliguria
- Acute tubular necrosis
- Interstitial necrosis

Laboratory Findings of Heatstroke

Lactic acid dehydrogenase (LDH) rises as a consequence of diffuse tissue injury. Early rises in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which peak at 48 hours, are indicators of the liver damage that occurs during heatstroke.[151] Muscle enzymes were elevated in all patients in a study of exertional heatstroke,[270] and in 86% of patients in one study of nonexertional heatstroke.[108] Nonspecific ST- and T-wave changes on ECG are common. Myocardial enzyme elevation occurs and correlates with ECG changes.[152] Results of lumbar puncture are nonspecific, are often normal, or may demonstrate elevated cerebrospinal fluid (CSF) protein and lymphocytosis.[270]

Other laboratory parameters are affected by heatstroke. Dehydration leads to hemoconcentration in patients exposed to elevated temperatures for a period of time. Hypokalemia is common, with potassium deficits as great as 500 mEq occurring during the early period of heat exposure. Arterial blood-gas analysis may show a respiratory alkalosis secondary to direct

stimulation of the respiratory center by heat, or a metabolic acidosis secondary to lactic acid production.[63,277] Metabolic acidosis is the most frequent acidâ€“base disturbance, either alone or part of a mixed picture. The prevalence of metabolic acidosis correlates with the degree of hyperthermia; 95% of patients demonstrated metabolic acidosis when the body temperature exceeded 107.6Â°F (42Â°C).[30]

Hypophosphatemia is common and is attributed to respiratory alkalosis, which causes intracellular shifts of phosphate. However, 8 of 10 heatstroke patients developed hypophosphatemia and none were alkalemic.[29] The hypophosphatemia in these cases was associated with increased phosphaturia and decreased tubular reabsorption of phosphorus, a finding which reversed after cooling.[162] Renal tubular damage may also lead to phosphate depletion.[114] Phosphate and potassium are elevated when significant muscle injury has occurred. Calcium is normal or low, the latter secondary to binding to damaged muscle tissue. Later, hypercalcemia occurs, possibly as a result of release of this bound calcium.[97,184]

Significant alterations occur in lymphocyte subsets in heatstroke victims. One study reported an increased ratio of T-suppressor to T-cytotoxic cells, as well as increased natural killer cells. There was a significant decrease in the percentages of T and B cells and T-helper cells. These changes correlated with the degree of hyperthermia.[27] Catecholamines are increased in heatstroke,[1] and may affect the distribution of the lymphocyte subsets.[27] It is possible that the increased susceptibility to infection described in heatstroke and the alterations in lymphocyte populations are related.[27]

Effects of Drugs in Heatstroke

Drugs predispose the individual to heatstroke by two primary mechanisms: increased production of heat as a result of drug

action and interference with the body's ability to dissipate heat because of pharmacologic effects on thermoregulatory centers (see Table 16-5). Drugâ€“drug interactions may cause life-threatening increases in temperature, such as the combination of monoamine oxidase inhibitors with meperidine or dextromethorphan resulting in the serotonin syndrome. The uncoupling of oxidative phosphorylation by salicylate, pentachlorophenol, or dinitrophenol leads to the release of metabolic energy as heat, rather than trapping that energy in the form of high-energy phosphate bonds in ATP. Increased heat production occurs as a result of the stimulation of hepatic metabolism by sympathomimetic drugs and, of course, by the increased physical activity often associated with sympathomimetic drug use.

During heat stress, vasodilation leads to increased cutaneous blood flow, resulting in an increased cardiac output. Parasympathetic stimulation results in increased sweating. Drugs that impair these physiologic mechanisms for heat dissipation predispose the individual to heatstroke. Drugs with anticholinergic effects, such as antihistamines, cyclic antidepressants, and antipsychotics interfere with sweating. Sympathomimetic drugs stimulate Î±-adrenergic receptors, impairing vasodilation. Antihypertensives and antianginal drugs (most notably calcium channel blockers and Î²-adrenergic antagonists) with negative inotropic and chronotropic effects impair the ability of the heart to meet the output requirements of increased skin blood flow. Diuretic induced volume depletion also limits cardiac output. Antipsychotics cause hypothalamic depression, altering the normal CNS response to heat stress. Finally, drugs such as ethanol, opioids, and sedative-hypnotics impair normal behavioral responses, and heat-related discomfort may go unnoticed.[292]

Heatstroke and Subsequent Heat

Intolerance

Whether heatstroke victims are subsequently unable to adapt to exercise in a hot environment remains unclear. Is the heatstroke victim genetically predisposed to heat intolerance, or does heatstroke occur as a result of environmental and host factors? Several studies suggest that heatstroke leads to persistent heat intolerance. These studies often use a single heat intolerance test.[83,269,271,272] A study of 10 previous heatstroke victims showed no difference in acclimatization responses, thermoregulation, whole-body sodium and potassium balance, sweat-gland function, and blood values when compared with controls.[13] The rate of recovery from exertional heatstroke probably differs among individuals. In this study, 1 of 10 patients was found to have recurrent heat intolerance 12 months after the study.[13] Resolution of heat intolerance was delayed for 5 months in an individual who had experienced heatstroke twice.[150]

Treatment of Heatstroke

Management must focus on the early recognition of hyperthermia. Body temperatures > 106Â°F (>41.1Â°C) place the patient at great risk for end-organ injury. Rapid cooling is the first priority, and is associated with improved outcomes. Cooling that is delayed allowing body temperatures to remain above 102.2Â°F (38.9Â°C) for more than 30 minutes is associated with a high morbidity and mortality. In one report of the Chicago heat wave of 1995, only 1 patient of 58 victims was cooled within 30 minutes, resulting in an in-hospital mortality of 21% and an additional 28% mortality within 1 year.[72] Cooling by covering in ice water was twice as rapid in lowering the core temperature as was cooling by using evaporative spray.[12] Ice water immersion results in faster cooling when compared with all of the evaporative cooling methods.[62,91,98] A recent report of endovascular cooling using a heat exchange balloon catheter demonstrated dangerously lengthy

cooling times and inadequate cooling measures.[203]

Successful treatment requires adequate preparation. Equipment needed for rapid cooling should always be readily available in the emergency department, and includes fans, ice, and tubs for submersion. En route to the hospital, the patient's clothes should be removed and the patient should be covered with ice and water-soaked sheets. Respiration and cardiovascular status should be stabilized and monitored. Oxygen should be administered. The cause of the heatstroke should be determined and appropriate measures initiated immediately. Pharmacologic agents, such as antihistamines, butyrophenones, and phenothiazines, and physical restraints that interfere with heat dissipation, such as camisoles and strait jackets, should not be used.[111] Light hand and foot restraints should be used to protect the patient from self harm. If light restraints are used, the patient should be monitored continuously. The patient who is hyperthermic in the setting of ethanol or sedative-hypnotic withdrawal should be treated with a benzodiazepine.[110] The patient should never be confined to a small, unventilated seclusion room. Adequate cooling, hydration, sedation, and electrolytes and substrate repletion should be ensured.[108]

In the emergency department, appropriate laboratory studies should be performed and an IV line inserted. Administration of 0.5â€“1.0 g/kg dextrose as $D_{50}W$ and 100 mg of thiamine should be considered. A rectal probe should be placed for continuous temperature monitoring. The patient should be immersed in an ice bath with a fan blowing over the patient if possible. In addition to the ice bath, iced gastric lavage may be effective.

Agitation, seizures, and cardiac dysrhythmias must be managed while cooling is accomplished. Benzodiazepines are the treatment of choice for agitation and seizures. Heatstroke patients may have significant volume needs, depending on the amount of fluid lost

prior to the onset of heatstroke. Hypotension should be treated with fluids and cooling. Volume repletion should be monitored carefully by parameters such as blood pressure, pulse, central venous pressure, pulmonary wedge pressure, and urine output. As the temperature returns to normal, the hypotension may resolve if significant volume deficits are not present.[55,161,163] In patients with myoglobinuria, an attempt should be made to increase renal blood flow and urine output. The use of sodium bicarbonate and mannitol in the prevention of acute tubular necrosis in these cases is controversial.[82,97,251]

Phenothiazines should not be used in the treatment of heatstroke. Phenothiazines depress an already altered mental status, may produce hepatotoxicity in a compromised liver, lower the seizure threshold,[26] cause acute dystonic reactions, exacerbate hypotension, and interfere with thermoregulation and cooling by affecting the hypothalamus. However, although phenothiazines may theoretically reduce shivering and the possibility of rebound hyperthermia, their onset of action is slow.[227] When shivering occurs during cooling, we recommend the judicious use of a benzodiazepine. In addition, benzodiazepines treat ethanol and sedative-hypnotic withdrawal and cocaine intoxication, common causes of hyperthermia.

There is no role for antipyretic agents in the management of heatstroke. Aspirin and acetaminophen lower temperature by reducing the hypothalamic set point, which is only altered in a patient febrile from inflammation or endogenous pyrogens.[73,128] Heatstroke, however, occurs when cooling mechanisms are overwhelmed, and the hypothalamic thermoregulatory set point is not disturbed.[20]

Dantrolene sodium is the preferred drug in the treatment of malignant hyperthermia (see Antidotes in Depth: Dantrolene Sodium).[140,296] It acts directly on skeletal muscle and either inhibits the release of calcium or increases calcium uptake through

the sarcoplasmic reticulum.[34] Its usefulness has not been demonstrated in other conditions associated with hyperthermia, and there is no evidence to support its administration for other conditions.[9] In a prospective, randomized, double-blind, placebo-controlled study of 52 patients with heatstroke, IV dantrolene sodium at 2 mg/kg of body weight did not alter cooling time.[28] There was no significant difference in the mean number of hospital days necessitated by heatstroke victims who received dantrolene and cooling versus those who received cooling alone. Dantrolene may influence central dopaminergic metabolism in patients with neuroleptic malignant syndrome by affecting calcium-triggered neurotransmitter release in the central nervous system; however, further study is required.[225] Anecdotal reports of the efficacy of dopamine agonist agents such as bromocriptine and amantadine have appeared in descriptions of neuroleptic malignant syndrome.[199] No drug therapy should delay the institution of aggressive external cooling (Table 16-7).

Prevention of Heatstroke

In the young, active population, prophylaxis should be accomplished by gradual acclimatization. Active persons should select the coolest and least humid time of day to be outdoors. Exposure should be increased slowly, and work paced. Breaks should be frequent initially and later may be decreased in number and length. Overweight and underconditioned persons require even longer periods of acclimatization. Airy and cool clothing should be chosen. The practice of exercising in unventilated plastic clothing to increase weight loss leads to the loss of fluid, not fat, and defeats the body's cooling mechanisms, resulting in hyperthermia.

Athletes performing during hot, humid weather should increase their fluid intake, although excessive consumption of fluids

may cause hyponatremia.[6,212,261] All individuals who fatigue easily

or manifest nausea, vomiting, cramps, weakness, dizziness, or collapse should limit their activity and must be carefully observed.

TABLE 16-7. Management of Heatstroke

Preparation
- Ice and cooling fans available in emergency department
- Monitor weather reports
- Alert media

On Arrival
- Rapid cooling
  - Clear airway and administer oxygen
  - Cover with ice and water-soaked sheets
  - Stabilize respiratory and cardiovascular status
  - Cool as rapidly as possible
- Intravenous access
  - 0.9% NaCl or Ringer lactate based on CVP or pulmonary artery catheter
  - Administration of dextrose 0.5â€“1.0 g/kg, and thiamine 100 mg
  - Benzodiazepines for agitation, shivering, seizures
- Continous monitoring
  - Remove from ice bath at 101Â°F (38.3Â°C)
  - Watch for rebound hyperthermia
- Cautions
  - Antipsychotics may have serious adverse effects
  - Antipyretics do not work
  - Cooling blankets alone are inadequate

Anyone who takes illicit drugs, who takes medications, or who has a medical condition that may interfere with thermoregulation

should be monitored closely for signs of heat intolerance or hyperthermia.

Summary

The thermoregulatory processes responsible for the maintenance of normothermia are complex. Pharmacologic agents may disturb normal thermoregulation and result in the abnormal conditions of hyperthermia or hypothermia. These disturbances of homeostasis present significant clinical management challenges. In particular, recommendations for the treatment of hypothermia perpetuate themselves in the literature with little supportive scientific evidence. Although greater understanding is gained through research and thoughtful analysis, emphasis must be placed on prevention. Hypothermia and heatstroke are largely preventable conditions. During heat waves, many socioeconomically disadvantaged and elderly individuals are affected, and it is essential that cities be prepared and that the public be aware of the dangers of heat waves, to themselves and to others. Similarly, hypothermia is preventable by prudent preparation for harsh environmental conditions, and by policies that provide for shelter for those at greatest riskâ€”the poor, the homeless and those with underlying medical and psychiatric illnesses.

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Chapter 17

Fluid, Electrolyte, and Acidâ€“Base Principles

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A meaningful analysis of fluid, electrolyte, and acidâ€“base abnormalities must be based on the clinical characteristics of each patient. Although a rigorous appraisal of laboratory parameters often yields the correct differential diagnosis, essential information concerning extracellular fluid volume (ECFV), pathophysiology, and treatment may only be gained from the history and physical examination. Thus, the evaluation always begins with an overall assessment of the patient's status.

Initial Patient Assessment

History

The history should include clinical complaints associated with fluid

and electrolyte abnormalities. Common manifestations of xenobiotic exposure result in fluid losses through the respiratory system (hyperpnea and tachypnea), gastrointestinal tract (vomiting and diarrhea), skin (diaphoresis), and kidneys (polyuria). Patients with ECFV depletion may complain of dizziness, thirst, and occasionally polydipsia, and usually the patients can identify the source of fluid loss.

A history of exposures to nonprescription and prescription medications, alternative therapies and other xenobiotics may suggest the most likely electrolyte or acidâ€“base abnormality. In addition, premorbid conditions and the ambient temperature and humidity should always be considered.

Physical Examination

The vital signs are invariably affected by gross alterations in ECFV. Whereas hypotension and tachycardia may herald life-threatening ECFV depletion, an initial increase of the heart rate and a narrowing of the pulse pressure may be earlier findings. Abnormalities may be recognized through an ongoing dynamic evaluation, realizing that the measurement of a single set of supine vital signs offers useful information only when grossly abnormal. The addition of orthostatic pulse and blood pressure measurements provides a more meaningful determination of functional ECFV status (Chaps. 3 and 23).

The respiratory rate and pattern can give clues to the patient's metabolic status. Hyperventilation (manifested by tachypnea, hyperpnea, or both) may be caused by a primary respiratory stimulus (a respiratory alkalosis) or may be a response to the presence of metabolic acidosis. Although hypoventilation (bradypnea or hypopnea or both) is present in patients with metabolic alkalosis, it is rarely clinically significant except in the presence of chronic lung disease. More commonly, it is associated with a primary depression of consciousness and respiration, and

respiratory acidosis. Unless the clinical scenario (eg, nature of the overdose or poisoning, presence of renal or pulmonary disease, findings on physical examination or laboratory testing) is diagnostic, arterial blood gas analysis is required to determine the acidâ€“base disorder associated with a change in ventilation.

The skin should be evaluated for turgor, moisture, and the presence or absence of edema. The moisture of the mucous membranes can also provide valuable information. These are nonspecific parameters and may not correlate perfectly with the status of hydration. This dissociation is especially true with xenobiotic exposure, as many xenobiotics alter skin and mucous membrane moisture without necessarily altering ECFV status. For example, antihistamines and anticholinergics commonly dry mucous membranes and skin without producing ECFV depletion. Conversely, patients exposed to sympathomimetic agents (eg, cocaine) or cholinergic agents (eg, organic phosphorus insecticides) may have moist skin and mucous membranes even in the setting of significant fluid losses. These dissociative characteristics further reinforce the need to assess patients meticulously.

The physical findings associated with electrolyte abnormalities also are nonspecific. Hyponatremia, hypernatremia, hypercalcemia, and hypermagnesemia all may produce a depressed mental status. Neuromuscular excitability such as tremor and hyperreflexia may occur with hypocalcemia, hypomagnesemia, hyponatremia, and hyperkalemia. Multiple, concurrent electrolyte disorders can produce confusing clinical presentations, or patients may appear normal. Rarer diagnostic findings, such as Chvostek and Trousseau signs (primarily found in hypocalcemia), may be useful in assessing patients with potential xenobiotics exposures.

Rapid Diagnostic Tools

The electrocardiogram (ECG) is a useful tool for screening of some

common electrolyte abnormalities (Chap. 5). It is easy to perform, rapid, inexpensive, and routinely available. Unfortunately,

because poor sensitivity (0.43) and moderate specificity (0.86) were demonstrated when ECGs were used to diagnose hyperkalemia, in actuality, the test is of limited diagnostic value.[173] However, the ECG is valuable for the evaluation of changes in serum potassium and calcium concentrations ($[K^+]$ and $[Ca^{2+}]$) in a single patient.

In many patients, bedside assessment of urine specific gravity by dipstick analysis may provide valuable information about ECFV status. A high urine specific gravity (>1.015) signifies concentrated urine and is often associated with ECFV depletion. However, urine specific gravity may be similarly elevated in states of ECFV excess, such as congestive heart failure or third spacing. Furthermore, when renal impairment is the source of the volume loss, the specific gravity is usually â‰¤1.010 (known as isosthenuria). Patients with lithium-induced diabetes insipidus excrete dilute urine (specific gravity <1.010) despite ongoing water depletion, and patients with methylenedioxymethamphetamine (MDMA)-induced antidiuretic hormone secretion excrete concentrated urine (specific gravity >1.015) in the presence of a normal to high ECFV status.

The urine dipstick is particularly useful for rapidly determining the presence of ketones, which are often associated with specific toxicologic problems and common causes of metabolic acidosis (eg, diabetic ketoacidosis, salicylate poisoning, alcoholic ketoacidosis). The urine ferric chloride test rapidly detects exposure to salicylates with a high sensitivity and specificity (Chap. 35).

Laboratory Studies

A simultaneous determination of the venous serum electrolytes,

blood urea nitrogen (BUN), and glucose, and arterial or venous blood gases is adequate to determine the nature of the most common acidâ€“base, fluid, and electrolyte abnormalities. More complex clinical problems may require determinations of urine and serum osmolalities, urine electrolytes, serum ketones, serum lactate and other tests. A systematic approach to common problems is discussed in the following sections.

Acidâ€“Base Abnormalities

Definitions

The terminology of acidâ€“base disorders often leads to confusion and error. The following definitions provide the appropriate frame of reference for the remainder of the chapter.

The terms *acidosis* and *alkalosis* refer to processes that tend to change pH in a given direction. By definition a patient is said to have:

- A *metabolic acidosis* if the patient's arterial pH is <7.40 and serum bicarbonate concentration ($[HCO_3^-]$) is <24 mEq/L. Because acidemia stimulates ventilation (respiratory compensation), metabolic acidosis is usually accompanied by a PCO_2 <40 mm Hg.
- A *metabolic alkalosis* if the patient's arterial pH is >7.40 and serum $[HCO_3^-]$ is >24 mEq/L. Because alkalemia inhibits ventilation (respiratory compensation), metabolic alkalosis is usually accompanied by a PCO_2 >40 mm Hg.
- A *respiratory acidosis* if the patient's arterial pH is <7.40 and partial pressure of carbon dioxide (PCO_2) is >40 mm Hg. Because an elevated PCO_2 stimulates renal acid excretion and the generation of $[HCO_3^-]$ (renal compensation), respiratory acidosis is usually accompanied by a serum $[HCO_3^-]$ >24

mEq/L.

- A *respiratory alkalosis* if the patient's arterial pH is >7.40 and PCO_2 is <40 mm Hg. Because a decreased PCO_2 decreases renal net acid excretion and increases the excretion of [HCO_3^-] (renal compensation), respiratory alkalosis is usually accompanied by a serum [HCO_3^-] <24 mEq/L.

It is important to note that under most circumstances a venous pH permits an approximation of arterial pH (see Chap. 22 for a further discussion of the relationship between arterial and venous pH). Any combination of acidoses and alkaloses can be present in any one patient at any given time. The terms *acidemia* and *alkalemia* refer only to the resultant arterial pH of blood (acidemia referring to a pH <7.40 and alkalemia referring to a pH >7.40). These terms do not describe the processes that led to the alteration in pH. Thus, a patient with acidemia must have a primary metabolic and/or respiratory acidosis, but may have an alkalosis present at the same time. Clues to the presence of more than one acidâ€“base abnormality include the clinical presentation, an apparent excess or insufficient â€œcompensationâ€• for the primary acidâ€“base abnormality, a delta (Î”) anion gap-to-Î” [HCO_3^-] gap ratio that significantly deviates from 1, and/or an electrolyte abnormality that is uncharacteristic of the primary acidâ€“base disorder.

The following case discussion illustrates an organized approach to acidâ€“base disorders.

Patient 1 A 27-year-old man was found unconscious at home with a suicide note and some empty pill containers. A history of injection drug use was assumed by the paramedics because of the presence of track marks on his skin. The initial assessment was notable for a blood pressure of 140/90 mm Hg, a pulse of 120 beats/min, and a respiratory rate of 18 breaths/min. The patient was placed on high-flow oxygen and transported to the emergency

department (ED). En route to the ED, an IV line was inserted and blood samples were obtained for later analysis at the hospital.

On arrival at the ED the patient was intermittently agitated and stuporous with a blood pressure of 120/90 mm Hg, a pulse rate of 110 beats/min, labored respirations of 18 breaths/min, and a rectal temperature of 100.6Â°F (38.1Â°C). His skin was slightly diaphoretic and was notable for multiple track marks of various ages. There were no signs of head trauma. Pupils were 4 mm in size, equal and round, but sluggishly reactive to light. His neck was supple, without signs of meningeal irritation. His chest was clear to auscultation and percussion, and heart sounds were normal. His abdomen was soft, without organomegaly, and with normal bowel sounds. Rectal tone was normal, and stool was negative for occult blood. Neurologic assessment revealed good motor strength, intact corneal and oculocephalic reflexes, and brisk but symmetric deep tendon reflexes. Plantar flexion was present.

The blood specimens obtained by the paramedics were sent to the laboratory for electrolytes, glucose, BUN, complete blood cell count (CBC), and a serum acetaminophen concentration. Two serum tubes were placed aside for future studies. An arterial blood-gas analysis was obtained on room air, and an ECG showed sinus tachycardia with no evidence of PR, QRS, QTc abnormalities, or ectopy.

The arterial blood gas analysis showed a pH of 7.30, PCO_2 of 15 mm Hg, and PO_2 of 120 mm Hg. The calculated arterial bicarbonate concentration ($[HCO_3^-]$) was 12 mEq/L.

Determining the Primary Acidâ€“Base Abnormality

It is helpful to begin by determining whether the patient is acidemic or alkalemic. In patient 1, the arterial pH of 7.30

signifies acidemia, and the [HCO_3^-] of 12 mEq/L and PCO_2 of 15 mm Hg indicate the presence of metabolic acidosis with respiratory compensation. Of

note, concomitant reductions in the arterial [HCO_3^-] and PCO_2 also are observed in respiratory alkalosis. However, under those circumstances the patient would be alkalemic; that is, the arterial pH would be increased above 7.40.

Next it is important to determine whether the compensation of the primary acidâ€“base disorder is appropriate or excessive. It is generally assumed that overcompensation cannot occur.[118] That is, if the primary process is metabolic acidosis, respiratory compensation tends to raise the pH toward normal, but never to greater than 7.40. If the primary process is respiratory alkalosis, compensatory renal excretion of HCO_3^- tends to lower the pH toward normal, but not to less than 7.40. The same is true for primary metabolic alkalosis and primary respiratory acidosis. As a rule, compensation for a primary acidâ€“base disorder that is inadequate or excessive suggests the presence of a second primary acidâ€“base disorder.

The Winters equation,[8] based on patient data, predicts the degree of the respiratory compensation (the decrease in PCO_2) in metabolic acidosis. As Equation 17-1 illustrates:

$$P_{CO_2} = [1.5 \times HCO_3^-] + 8 \pm 2 \qquad \text{(Eq. 17–1)}$$

Thus, in this patient with an arterial [HCO_3^-] of 12 mEq/L, the predicted PCO_2 may be calculated as in Equation 17-2:

(1.5 Ã— 12) + 8 Â± 2

or

$$26 \pm 2 \text{ mm Hg} \qquad \text{(Eq. 17–2)}$$

Because the PCO_2 of patient 1 is substantially lower than is predicted by the Winters equation, it can be concluded that both a

primary metabolic acidosis and a primary respiratory alkalosis are present.

An alternative to the Winters equation is the observation by Narins and Emmett that in compensated metabolic acidosis, the arterial PCO_2 is usually the same as the last two digits of the arterial pH.[118] For example, a pH of 7.26 predicts a PCO_2 of 26 mm Hg. In this case, the PCO_2 of 15 mm Hg is much lower than would be predicted from the last two digits of the arterial pH of 7.30. As was deduced from the Winters equation, this method also suggests that a second primary process (respiratory alkalosis) is present in patient 1.

Guidelines are also available to predict the compensation for metabolic alkalosis,[69] respiratory acidosis, and respiratory alkalosis.[89] Patients with metabolic alkalosis compensate by hypoventilating and increasing their PCO_2 above 40 mm Hg. However, the concomitant development of hypoxemia limits this compensation so that respiratory compensation in metabolic alkalosis usually results in a PCO_2 no greater than 55 mm Hg. It is difficult to be more precise about the expected respiratory compensation for metabolic alkalosis although the compensation, as in metabolic acidosis, is nearly complete within hours of onset.

By contrast, the degree of compensation in primary respiratory disorders depends on the length of time the disorder has been present. In a matter of minutes, primary respiratory acidosis results in an increase in the serum $[HCO_3^-]$ of 0.1 times the increase (Î”) in the PCO_2. This is a result of the production and dissociation of H_2CO_3. Over a period days, respiratory acidosis causes the compensatory renal excretion of acid. This compensation increases the serum $[HCO_3^-]$ by 0.3 times the Î”PCO_2. Primary respiratory alkalosis acutely decreases the serum $[HCO_3^-]$ by 0.2 times the Î”PCO_2. If respiratory alkalosis persists for several days, renal compensation, by the urinary excretion of HCO_3^-, decreases the serum $[HCO_3^-]$ by 0.4 times the Î”PCO_2.

Further assessment of patient 1, including calculating the anion gap, requires an evaluation of the serum electrolytes. The laboratory studies of patient 1 were as follows: serum sodium concentration ($[Na^+]$) 133 mEq/L; potassium ($[K^+]$) 3.6 mEq/L; chloride ($[Cl^-]$) 99 mEq/L; bicarbonate ($[HCO_3^-]$) 12 mEq/L; BUN 12 mg/dL; creatinine (Cr) 0.9 mg/dL; and glucose (Glu) 120 mg/dL.

Calculating the Anion Gap

The concept of the anion gap is said to have arisen from the â€œGamblegramâ€• originally described in 1939;[53] however, its use was not popularized until the determination of serum electrolytes became routinely available. The law of electroneutrality states that the net positive and negative charges of the serum must be equal. Thus, all of the negative charges present in the serum must equal all of the positive charges, and the sum of the positive charges minus the sum of the negative charges must equal zero. The problem that immediately arose (and produced an â€œanion gapâ€•) was that all charged species are not routinely measured.

Normally present but not routinely measured cations consist of calcium and magnesium, whereas normally present but not routinely measured anions consist of phosphate, sulfate, albumin, and organic acids.[42,51,121] Sodium and K^+ normally account for 95% of extracellular cations, whereas Cl^- and HCO_3^- account for 85% of extracellular anions.[42] Thus, because more cations than anions are measured, subtracting the anions from the cations normally yields a positive number, known as the anion gap. The anion gap is therefore derived as shown in Equation 17-3:

$$\mathrm{Na^+ + K^+ + unmeasured\ cations\ (U_c) = Cl^- + HCO_3^-} \\ \mathrm{+ unmeasured\ anions\ (U_a)} \\ \mathrm{Anion\ gap = U_a - U_c}$$

or

$$\text{Anion gap} = (Na^+ + K^+) - (Cl^- + HCO_3^-) \quad \text{(Eq. 17–3)}$$

Because K^+ is largely an intracellular cation and rarely alters the anion gap, it is often deleted from the equation for simplicity. Most prefer this approach, yielding Equation 17-4:

$$\text{Anion gap} = (Na^+) - (Cl^- + HCO_3^-) \quad \text{(Eq. 17–4)}$$

Using Equation 17-4, the normal anion gap was initially determined to be 12 Â± 4 mEq/L.[42,170] More recent data suggest that as a result of a change in laboratory instrumentation and higher serum [Cl^-] values than previously reported, the range for a normal anion gap may be lower: 7 Â± 4 mEq/L.[169]

A variety of pathologic conditions may result in a rise or fall of the anion gap. High anion gaps result from increased presence of unmeasured anions or decreased presence of unmeasured cations (Table 17-1).[42,51,100,144] Similarly, a low anion gap results from an increase in unmeasured cations or a decrease in unmeasured anions (Table 17-2).[42,51,65,143,154]

Anion Gap Reliability

Several authors have considered the usefulness of the anion gap determination.[21,52,78] When 57 hospitalized patients were studied to determine the cause of elevated anion gaps, in those patients whose anion gap was greater than 30 mEq/L the cause was always lactic acidosis or ketoacidosis.[52] In patients with smaller elevations of the anion gap, the ability to define the cause of the elevation

diminished; in only 14% of patients with anion gaps of 17â€“19 mEq/L could the etiology be defined. It should be noted that because of the small size of this study, there were no patients with toxic alcohol ingestion. Another study determined that although the anion gap is often used as a screening test for hyperlactacidemia (as a sign of poor perfusion), only those

patients with the highest serum lactate concentrations had elevated anion gaps.[78] Finally, in a sample of 571 patients, those with higher anion gaps tended to have increased severity of illness. This resulted in higher admission rates, a greater percentage of admissions to intensive care units, and a higher mortality.[21] Thus, although the absence of an increased anion gap does not exclude significant illness, a very elevated anion gap can generally be attributed to a specific cause and usually indicates a relatively severe illness.

TABLE 17-1. Xenobiotic and Other Causes of a High Anion Gap

Increased unmeasured anions
- Metabolic acidosis (see Table 17-3)
- Dehydration
- Therapy with sodium salts of unmeasured anions
  - Sodium citrate
  - Sodium lactate
  - Sodium acetate
- Therapy with certain antibiotics
  - Carbenicillin
  - Sodium penicillin
- Alkalosis

Decrease in unmeasured cations
- Simultaneous hypomagnesemia, hypocalcemia, and hypokalemia

Metabolic Acidosis

Once the diagnosis of metabolic acidosis has been made by finding an arterial pH <7.40, a [HCO_3^-] <24 mEq/L, and a PCO_2 <40 mm Hg (as in patient 1), the serum anion gap should be analyzed. Indeed, the popularity of the anion gap is primarily based on its usefulness in categorizing metabolic acidosis as being of the high-anion-gap or normal-anion-gap type. This determination should be made after correcting the anion gap for the effect of hypoalbuminemia, a common and important confounding factor in such patients. The anion gap decreases approximately 3 mEq/L per 1 g/dL decrease in the serum albumin.[48] In general, the electrolyte abnormalities that frequently accompany metabolic acidosis usually have only small and insignificant effects on the anion gap.

TABLE 17-3. Xenobiotic and Other Causes of a High Anion Gap Metabolic Acidosis

Carbon monoxide
Cyanide
Ethylene glycol
Hydrogen sulfide
Isoniazid
Iron
Ketoacidoses (diabetic, alcoholic, and starvation)
Lactate
Metformin
Methanol
Paraldehyde
Phenformin
Salicylates
Sulfur (inorganic)
Theophylline
Toluene

Uremia (acute or chronic renal failure)

Note: Many clinicians rely on the mnemonic MUDPILES to help remember this differential diagnosis where M represents methanol, U (uremia), D (diabetic ketoacidosis), P (paraldehyde), I (iron), L (lactic acidosis), E (ethylene glycol), and S (salicylates).

TABLE 17-2. Xenobiotic and Other Causes of a Low Anion Gap

Increase in unmeasured cations
Hypercalcemia
Hypermagnesemia
Hyperkalemia
Lithium poisoning
Multiple myeloma
Decrease in unmeasured anions
Hypoalbuminemia
Dilution
Overestimation of the chloride
Bromism
Iodism
Nitrate excess

A high-anion-gap metabolic acidosis results from the absorption or generation of an acid that dissociates into an anion other than Cl^- that is neither excreted nor metabolized. The retention of this

â€œunmeasuredâ€• anion (eg, lactate in lactic acidosis) increases the anion gap. Normal-anion-gap metabolic acidosis results from the absorption or generation of an acid that dissociates into H^+ and Cl^-. In this case, the â€œmeasuredâ€• Cl^- is retained as HCO_3^- is titrated and reduced during the acidosis, and no anion gap is produced. Normal-anion-gap acidosis, also referred to as hyperchloremic metabolic acidosis, may be caused by intestinal or renal bicarbonate losses as in diarrhea or renal tubular acidosis, respectively. Other causes of high- and normal-anion-gap metabolic acidoses are described elsewhere[2] and shown in Tables 17-3 and 17-4. Patient 1, described above, has an anion gap of 22 mEq/L [133 mEq/L (99 mEq/L + 12 mEq/L)], and thus is said to have a high-anion-gap metabolic acidosis.

Narrowing the Differential Diagnosis of a High-Anion-Gap Metabolic Acidosis

The ability to diagnose the etiology of a high-anion-gap metabolic acidosis is an essential skill in clinical medicine. The following

discussion provides a rapid and cost-effective approach to the problem. As always, the clinical history and physical examination may provide essential clues to the diagnosis. For example, iron poisoning is virtually always associated with significant gastrointestinal symptoms, the absence of which essentially excludes the diagnosis of this poisoning (Chap. 40). Furthermore, when iron overdose is suspected, an abdominal radiograph may show the presence of tablets. The acidosis associated with isoniazid (INH) toxicity results from seizures, the absence of which excludes INH as the cause of a metabolic acidosis (Chap. 55). Methanol toxicity may be associated with visual complaints or an abnormal funduscopic examination (Chap. 103). Methyl salicylate has a characteristic odor (Chap. 21). When these findings are absent, the laboratory analysis must be relied on, as follows:

- *Begin with the electrolytes and glucose:* A rapid glucose reagent test should be performed to help confirm or exclude the possibility of hyperglycemia. While hyperglycemia should raise the possibility of diabetic ketoacidosis, the absence of an elevated serum glucose does not exclude the possibility of euglycemic diabetic ketoacidosis,[80] or alcoholic or starvation ketoacidosis, which are often associated with normal or even low serum glucose concentrations. An elevated BUN and creatinine are essential to diagnose acute or chronic renal failure.
- *Proceed to the urinalysis:* Do not wait for the laboratory results, as all of these urinary studies are easily accomplished. In addition, if there is a suspicion of a high-anion-gap metabolic acidosis, and only the arterial or venous blood-gas analysis is completed, the evaluation may begin here, while the electrolyte determination is pending. A urine dipstick for glucose and ketones helps with the diagnosis of diabetic ketoacidosis and other ketoacidoses. However, the absence of urinary ketones does not exclude a diagnosis of alcoholic ketoacidosis (Chap. 75), and ketones are often present in severe salicylism (Chap. 35), and biguanide-associated metabolic acidosis (Chap 48). The urine of a patient who has ingested fluorescein-containing antifreeze (ethylene glycol) does not reliably fluoresce when exposed to a Wood lamp. Also, because ethylene glycol is metabolized to oxalate, calcium oxalate crystals may be present in the urine of a poisoned patient. Both fluorescent and calcium oxalate-containing urine are useful findings if present, but their absence does not exclude ethylene glycol poisoning (Chap. 103). When clinically available, a urine ferric chloride test should be performed. Although highly sensitive and specific for the presence of salicylate, this test is not specific for the diagnosis of salicylism, as small amounts of salicylate will be detected in the urine even days after its last use (Chap. 35).

Thus, a serum salicylate level must be obtained to quantify the findings of a positive ferric chloride test. A negative ferric chloride test essentially excludes a diagnosis of salicylism.

- An arterial or venous blood lactate level can be helpful. In theory, if the lactate (measured in mEq/L) can entirely account for the fall in serum [HCO_3^-], then the cause of the increased anion gap can be attributed to lactic acidosis. However, it is important to remember that glycolate (a metabolite of ethylene glycol) can produce a significant false-positive elevation of lactate with many current laboratory techniques.[112,129,171]

TABLE 17-4. Xenobiotic Causes of a Normal Anion Gap Metabolic Acidosis

Acetazolamide
Acidifying agents
Ammonium chloride
Arginine hydrochloride
Hydrochloric acid
Lysine hydrochloride
Cholestyramine
Sulfamylon
Toluene
Topiramate

When the above analysis is unproductive, the diagnosis is usually toxic alcohol ingestion, starvation, alcoholic ketoacidosis (with minimal urine ketones), or a multifactorial process involving small amounts of lactate and other anions. One approach is to provide the patient with 1â€“2 hours of intravenous hydration, dextrose,

and thiamine. If the acidosis improves, the etiology is either ketoacidosis or lactic acidosis. Alternatively, a more detailed search for the toxic alcohols, involving either the osmol gap or specific levels, should be initiated (discussed below).

In patient 1, urinalysis revealed trace amounts of protein, small ketones, and large glucose (after dextrose administration). There were no crystals or fluorescence, but a ferric chloride test was positive. A lactate level was not obtained.

Diagnosis of Patient 1

There are many causes of a concomitant high-anion-gap metabolic acidosis and respiratory alkalosis (as was observed in patient 1). Examples include pneumonia in the presence of renal failure; diabetic ketoacidosis or lactic acidosis in the presence of sepsis; renal failure in a patient with cirrhosis of the liver; and salicylate poisoning (Chap. 35). In patient 1, with the positive ferric chloride test, the presence of urinary ketones, and the acidâ€“base abnormalities noted, salicylate toxicity is strongly suggested. In fact, the patient's serum salicylate level was later reported as 97 mg/dL, and he underwent hemodialysis with complete metabolic recovery.

The Î” Anion Gap-to-Î”[HCO_3^2] Gap Ratio

Like patient 1, many patients have mixed acidâ€“base disorders such as metabolic acidosis and respiratory alkalosis. Depending on their relative effects, the patient may have significant acidemia or alkalemia, minor alterations in pH, or even a normal pH. Although the clinical presentation, degree of compensation for the primary acidâ€“base disorder, and the presence of unexpected electrolyte abnormalities may suggest whether more than one primary acidâ€“base disorder is present, sometimes comparing the Î” anion

gap (Î”AG) with the Î”[HCO_3^-] gap may be useful.

A typical example is the patient with diabetic ketoacidosis (DKA) and vomiting. Although DKA would be expected to produce a classic high-anion-gap metabolic acidosis, the vomiting could raise the [HCO_3^-] and pH to normal. The toxicologic clinical correlate of the patient with a mixed acidâ€“base disorder might be the iron-poisoned patient with refractory vomiting and a multifactorial high-anion-gap metabolic acidosis (Chap. 40). Another example is the patient with alcoholic ketoacidosis and vomiting. In these cases with two clinically obvious disorders, the arterial blood gas analysis could yield values of pH 7.40, PCO_2 40 mm Hg, and [HCO_3^-] 24 mEq/L. In most circumstances, of course, one process predominates, although its significance may be minimized by the presence of the second, undiagnosed primary acidâ€“base disorder.

In the patient with a simple high-anion-gap metabolic acidosis, each 1 mEq/L decrease in the serum [HCO_3^-] should (at least initially) be associated with a 1 mEq/L rise in the anion gap.[118] This occurs because the unmeasured anion is paired with the acid that is titrating the HCO_3^-. Any deviation from this direct relationship may be an indication of a mixed acidâ€“base disorder.[66,118,125] Thus, the ratio of the change in the anion gap (Î”AG) to the deviation of the serum [HCO_3^-] from normal (Equation 17-5) evolved:

$$\text{Anion gap ratio} = \Delta AG/\Delta HCO_3^- \qquad \text{(Eq. 17–5)}$$

A ratio close to 1 would suggest a pure high-anion-gap metabolic acidosis. When the ratio is >1, there is a relative increase in [HCO_3^-] (suggesting a mixed disorder) that can result only from a concomitant metabolic alkalosis or renal compensation (ie, renal

generation of HCO_3^-) for a respiratory acidosis. Alternatively, when the ratio is <1, the additional presence of either hyperchloremic (normal-anion-gap) metabolic acidosis or

compensated respiratory alkalosis is suggested.

One author[172] suggested calculating the â€œdelta gapâ€• or gap of the gap as shown in Equation 17-6:

$$\text{Gap of the gap} = \Delta AG - \Delta HCO_3^- \qquad \text{(Eq. 17–6)}$$

where a delta gap >6 mEq/L would suggest concomitant metabolic alkalosis and a delta gap <6 mEq/L would suggest concomitant hyperchloremic acidosis.

The usefulness of this relationship between the change in the anion gap and the change in the serum [HCO_3^-] has been evaluated by many authors. Although supported strongly by some authors,[122,125] others suggest that it is often flawed and frequently misleading.[35,139] The next section summarizes the discussion.

For the fall in the serum [HCO_3^-] to be either proportionally or linearly related to the rise in the anion gap, the following criteria should be met:

- All of the acid formed should be titrated by HCO_3^-. In fact, there are many non-HCO_3^- buffer systems, and the duration of acidosis alters the relative contributions of these systems.[145]
- The volumes of distribution of H^+, its associated anion, and HCO_3^- should be the same. This is not always true. For example, in the case of lactic acidosis, lactate remains extracellular while some of the lactic acid is buffered intracellularly. Thus, the increase in the anion gap (because of lactate) is usually less than the decrease in [HCO_3^-].
- The rates of elimination of the anion and regeneration of HCO_3^- should be equal. For example, in the patient with ketoacidosis, acetone and the anions acetoacetate and Î²-hydroxybutyrate are often cleared quickly when renal function is normal and poorly when renal function is impaired.

- Acidosis and alkalosis should not alter the anion gap themselves. As pH changes, the charges on serum proteins change, such that acidemia tends to decrease the anion gap and alkalemia tends to increase the gap.[1] This change is related to the generation of lactate and a change in the charges on albumin (an unmeasured anion).
- There must be no concurrent process other than the metabolic acidosis that is affecting the anion gap.

For these reasons, the statements of one author[35] appear to be correct in concluding that â€œthe exact relationship between the Î”AG and Î”[HCO_3^-] in a high-anion-gap metabolic acidosis is not readily predictable and deviation of the Î”AG/Î”[HCO_3^-] ratio from unity does not necessarily imply the diagnosis of a second acidâ€“base disorder.â€• However, very large deviations from a value of 1 usually are associated with the presence of a second acidâ€“base disorder. Indeed, in the first patient discussed above, the Î”AG-to-Î”[HCO_3^-] ratio was very high, 1.8 (Î”AG 22 mEq/L-to-Î”[HCO_3^-] 12 mEq/L), strongly suggesting the presence of two primary acidâ€“base disorders.

The Osmol Gap

The osmol gap is defined as the difference between the values for the measured osmolality and the calculated osmolarity.[154] Osmolarity is a measure of the total number of particles in 1 L of solution. Osmolality differs from osmolarity in that the number of particles is expressed per kilogram of solution. Thus, osmolarity and osmolality represent molar and molal concentrations of solutes, respectively.[58] In clinical medicine, osmolarity is usually calculated, whereas osmolality is usually measured.

Calculating osmolarity requires a summing of the known particles in solution. Because molarity and milliequivalents are particle-based measurements, unlike weight or concentration, the known

constituents of serum have to be converted to molar values. Assumptions are required based on the extent of dissociation of polar compounds (such as NaCl), the water content of serum, and the contributions of various other solutes such as Ca^{2+} and Mg^{2+}. The nature and limitations of these assumptions is beyond the scope of this chapter. The reader is referred to several reviews for more details.[61,72,123] Many equations have been used and evaluated for calculating osmolarity. One investigation that used 13 different methods to evaluate sera from 715 hospitalized patients[37] concluded that Equation 17-7 provided the most accurate calculation:

$$1.86(Na^{+} \text{ in mEq/L}) + (\text{glucose in mg/dL})/18 + (\text{BUN in mg/dL})/2.8 \qquad \text{(Eq. 17–7)}$$

Obvious sources of potential error in this calculation include laboratory error in determining the measured parameters, and the failure to account for a number of osmotically active particles.

The measurement of serum osmolality has the potential for error as well, stemming from the use of different laboratory techniques. A 1989 survey of clinical laboratory methodology demonstrated that while more than 80% of facilities studied offered osmometry, 11% used the vapor pressure method exclusively (as opposed to the freezing-point method).[41] Furthermore, 50% of the laboratory supervisors questioned failed to recognize that the vapor pressure technique was likely to produce an erroneously low serum osmolality for sera containing methanol, ethanol, or isopropanol. This error results from the fact that these alcohols will boil out of solution before the boiling point of water is reached.

The mathematical and theoretical errors in determining osmolarity and osmolality are potentially additive when the two values are mathematically combined to determine the osmol gap. In addition, a conceptual error is present. In methanol poisoning, the methanol particle has osmotic activity that is measured but not calculated, and no increase in the anion gap is present until it is metabolized

to formate. Although the metabolite also has osmotic activity, its activity is accounted for by Na^+ in the osmolarity calculation because it is largely dissociated, existing as Na^+ formate. Thus, at least in theory, an early methanol ingestion is marked by an elevated osmol gap and a normal anion gap, whereas later, the anion gap increases and the osmol gap decreases. This effect is highlighted by several case reports.[10,31,157] Despite these limitations, a determination of the osmol gap is commonly proposed as a diagnostic adjunct when considering ingestions of toxic alcohols.

To qualify as a good screening test, the osmol gap should predict toxic alcohol ingestion with a low frequency of false-negative results (high sensitivity). To exclude a diagnosis of toxic alcohol ingestion, the determination of an osmol gap should have a low frequency of false-positive results (high specificity). As a first step, the range of normal values (and its variability) must be known. Using Equation 17-7 to calculate osmolarity, the previously mentioned study determined that the â€œnormalâ€• osmol gap was 10 Â± 6 mOsm.[37] However, when more than 300 adult samples were studied with a more commonly used equation (Equation 17-8):

$$2(Na^+ \text{ in mEq/L}) + (\text{glucose in mg/dL})/18 + (\text{BUN in mg/dL})/2.8 \qquad \text{(Eq. 17–8)}$$

normal values were -2 Â± 6 mOsm. Other commonly used equations yield normal values that range from -5 to +15 mOsm.[72] Almost identical results are reported in children.[107] While the concept of a negative osmol gap might be disconcerting, the numerous assumptions and approximations used to calculate osmolarity may not be valid. Also, although ethanol is the most common cause of elevated osmolality in varied groups of patients,[22,28,124,135] a serum ethanol measurement was not included for any of the patients used in the reference that serves

as the standard to define osmol gaps.[37] The relatively recent inclusion of ethanol in the osmolarity formula in a systematic evaluation of normal values predictably increased the calculated osmolarity in patients in whom ethanol was present, making the osmol gap smaller than previously suggested, or even negative.[72] Furthermore, a slight rise in measured serum [Na^+] has occurred.[169] If this is related to changes in laboratory determination, it will also lead to a lowering of the osmol gap. In fact, other investigations have concluded that the mean osmol gap in control (presumably ethanol-free) populations was a negative value.[61,79,142] Thus, the commonly used â€œnormalâ€• value of <10 mOsm, often attributed to two earlier works,[58,154] is clearly arbitrary and erroneous in the authors' own words, and should be abandoned.

The largest limitation of the osmol gap calculation comes from the documented large standard deviation around a small â€œnormalâ€• number.[37,72,79,142] This variability may result from the heterogeneity of the control population and/or the imprecision of laboratory measurements. For example, an error of 1 mEq/L (<1.0%) in the determination of the serum [Na^+] may result in an error of 2 mOsm in the calculation of the osmol gap. Considering this variability, the molecular weights and relatively modest blood concentrations of the xenobiotics in question (eg, ethylene glycol, MW 62 daltons, at a concentration of 50 mg/dL contributes only 7.8 mOsm/L), and the predicted fall in osmol gap as metabolism occurs, small or even negative osmol gaps can never be used to exclude toxic alcohol ingestion.[60,72] This overall concept is illustrated by the case of a patient with an osmol gap of 7.2 mOsm (well within the normal range) who ultimately required hemodialysis for severe ethylene glycol poisoning.[157]

Finally, although large osmol gaps may be suggestive of toxic alcohol ingestions, common conditions such as alcoholic ketoacidosis, lactic acidosis, renal failure, and shock are all associated with elevated osmol gaps.[79,142,151] Because lactate,

acetoacetate, and Î²-hydroxybutyrate should not account for any increase in the osmol gap because they are charged (and accounted for in the osmolarity calculation), these conditions are probably associated with the accumulation of small uncharged molecules in the serum.

The above discussion suggests that the negative and positive predictive values of the osmol gap are too poor to recommend this test to screen for xenobiotic ingestion. However, in the presence of very high osmol gaps (>50â€“70 mOsm), the diagnosis of toxic alcohol ingestion is usually confirmed (Chap. 103).

Differential Diagnosis of a Normal-Anion-Gap Metabolic Acidosis

Although the differential diagnosis for a normal-anion-gap metabolic acidosis is extensive (Table 17-4), most cases result from either urinary or gastrointestinal HCO_3^- losses: renal tubular acidosis (RTA) or diarrhea, respectively. A number of xenobiotics can cause this disorder, including toluene,[26] which also may cause a high-anion-gap metabolic acidosis. When the findings of the history and physical examination cannot be used to narrow the differential diagnosis, the use of a urinary anion gap is suggested.[15,133]

The urinary anion gap can be calculated as shown in Equation 17-9:

$$(Na^+ + K^+) - (Cl^-) \qquad \text{(Eq. 17–9)}$$

The size of this gap is inversely correlated with urinary ammonium (NH_4^+) excretion.[64] As NH_4^+ elimination increases, the urinary anion gap narrows and may become negative, because NH_4^+ serves as an unmeasured urinary cation and is accompanied predominately by Cl^-.

The normal-anion-gap metabolic acidosis associated with diarrhea

results from HCO_3^- loss. During this process, the kidney's ability to eliminate NH_4^+ is undisturbed; in fact, it increases as a normal response to the acidemia. Thus, with gastrointestinal HCO_3^- losses the urinary anion gap should decrease and may become negative. Alternatively, the patient with RTA has lost the ability to either reabsorb HCO_3^- (type 2 RTA) or increase NH_4^+ excretion (types 1 and 4 RTA) in response to metabolic acidosis, and the urinary anion gap should become more positive. Indeed, when the urinary anion gap was calculated in patients with diarrhea or RTA, it was found that those patients with diarrhea had a mean negative gap (-20 Â± 5.7 mEq/L), as compared to a positive gap (23 Â± 4.1 mEq/L) in those with RTA.[64] Therefore, when evaluating the patient with a normal-anion-gap metabolic acidosis, the determination of a urinary anion gap may help to determine the source of the disorder.

Adverse Effects of Metabolic Acidosis

The acuity and severity of metabolic acidosis determine the consequences of the disorder. Acute metabolic acidosis is usually characterized by obvious hyperventilation (due to respiratory compensation). At arterial pH values <7.20, cardiac and central nervous system abnormalities also become evident. These may include decreases in blood pressure and cardiac output, cardiac dysrhythmias, and progressive obtundation.[2] Chronic metabolic acidosis is often asymptomatic. The symptoms of anorexia and fatigue may be the only manifestations of chronic acidosis, and compensatory hyperventilation may be undetectable. Because the consequences of even severe metabolic acidosis are not specific, the presence of metabolic acidosis is most often suggested by the clinical setting and the underlying cause.

Management Principles in Patients with Metabolic Acidosis

The treatment of metabolic acidosis depends on its severity and cause. In most cases of severe poisoning, a serum [HCO_3^-] concentration <8 mEq/L and arterial pH values <7.20 should probably be treated with HCO_3^- to increase the pH to >7.20, as described in detail elsewhere.[2] As an example, to raise the serum [HCO_3^-] by 4 mEq/L in a 70-kg person with an estimated HCO_3^- distribution space of 50% of body weight, approximately 140 mEq must be administered. When ECFV overload (caused by heart failure, renal failure and/or the sodium bicarbonate therapy) cannot be prevented or managed by administering loop diuretics, hemofiltration or dialysis may be necessary.

In patients with arterial pH values >7.20, the cause of the acidosis should guide therapy. Metabolic acidosis primarily caused by the overproduction of acid (eg, ketoacidosis, lactic acidosis) will require very large quantities of HCO_3^- and may not respond well to HCO_3^- therapy. Treatment in these patients should be directed

at the cause of acidosis (eg, insulin in diabetic ketoacidosis; fomepizole in methanol and ethylene glycol poisonings [see Antidotes in Depth: Fomepizole]; fluids, glucose, and thiamine in alcoholic ketoacidosis; antibiotics in sepsis-induced lactic acidosis). Metabolic acidosis primarily caused by underexcretion of acid (eg, acute or chronic renal failure, RTA), should be treated with a low-protein diet (if feasible) and oral sodium bicarbonate or substances that generate HCO_3^- during metabolism. Such patients can usually be managed with an oral citrate solution (eg, Shohl solution yields 1 mEq base/mL). The goal of therapy is to increase the [HCO_3^-] to >20 mEq/L and pH >7.30.

Metabolic Alkalosis

Patient 2 A 2-week-old boy was brought to the ED by his parents because of a 36-hour history of fever, diarrhea, and lethargy. The child was born at 39 weeks gestation via normal spontaneous

vaginal delivery and had Apgar scores of 9 and 10. The baby and the mother were discharged from the hospital at the usual time, and the baby remained well until 36 hours prior to presentation in the ED. Physical examination was remarkable for an irritable child who was inconsolable, even by his parents. Vital signs on arrival were as follows: blood pressure, 60/40 mm Hg; irregular pulse, 160 beats/min; respiratory rate, 28 breaths/min; rectal temperature, 100.9Â°F (38.3Â°C). His skin was dry and without a rash. His anterior fontanel was depressed, and his capillary refill was delayed. The remainder of the physical assessment was unremarkable.

The child was attached to a cardiac monitor that showed frequent premature ventricular contractions (confirmed by 12-lead ECG). An intravenous catheter was inserted, and blood was drawn for culture, electrolytes, glucose, and CBC. An arterial blood-gas sample was obtained on room air and supplemental oxygen was administered. The child was given dextrose (1 g/kg) and a 20-mL/kg bolus of 0.9% sodium chloride solution intravenously. A lumbar puncture was performed and the child was started on broad-spectrum antibiotics.

The laboratory studies revealed arterial pH 7.76; PCO_2 40 mm Hg; PO_2 96 mm Hg. Electrolytes were [Na^+], 154 mEq/L; [K^+], 3.1 mEq/L; [Cl^-], 86 mEq/L; and [HCO_3^-], 43 mEq/L. BUN, Cr, and glucose were normal. The lumbar puncture revealed a normal cell count and chemistry, with a negative Gram stain.

Adverse Effects of Metabolic Alkalosis

Life-threatening metabolic alkalosis is rare but can result in tetany (from decreased ionized [Ca^{2+}]),[97] weakness (from decreased serum [K^+]),[108] altered mental status leading to coma,[92] seizures,[62] and cardiac dysrhythmias.[85] In addition, metabolic alkalosis shifts the oxyhemoglobin dissociation curve to the left, impairing tissue oxygenation (Chap. 22). The expected

compensation for a metabolic alkalosis is hypoventilation and increased PCO_2. As discussed above, respiratory compensation is irregular and inadequate at best, invoking the teleologic argument that hypoxia is more undesirable than alkalemia.[118] Several authors, however, have reported that severe hypoventilation and respiratory failure can occur in response to metabolic alkalosis, suggesting a real, although uncommon risk.[108,126]

Approach to the Patient with Metabolic Alkalosis

Metabolic alkalosis results from gastrointestinal or urinary loss of acid, administration of exogenous base, and/or renal HCO_3^- retention (ie, impaired renal HCO_3^- excretion). Table 17-5 lists the causes of metabolic alkalosis. As compared to metabolic acidosis, metabolic alkalosis is less common and less frequently a consequence of poisonings.

TABLE 17-5. Xenobiotic and Other Causes ot Metabolic Alkalosis

Gastrointestinal acid loss
Nasogastric suction (protracted)
Vomiting (protracted)
Urinary acid loss
Common
Diuretics
Glucocorticoids
Rare
Hypercalcemia
Licorice (glycyrrhizic acid)

Magnesium deficiency

Base administration
Acetate (dialysis or hyperalimentation)
Bicarbonate
Carbonate (antacids)
Citrate (posttransfusion)
Milk alkali syndrome

Renal bicarbonate retention
Hypercapnia (chronic)
Hypochloremia
Hypokalemia
Volume contraction

The etiologies of metabolic alkalosis can be characterized from a therapeutic standpoint as chloride-responsive or chloride-resistant. Chloride-responsive etiologies such as diuretic use, vomiting, and nasogastric suction, or Cl^- diarrhea, are usually associated with a low urinary [Cl^-] <10 mEq/L.[69,85] These disorders respond rapidly to infusion of 0.9% NaCl solution when concomitant therapy addresses the underlying problem.[3] Chloride-resistant disorders exemplified by hyperaldosteronism and severe K^+ depletion are characterized by urinary [Cl^-] >10 mEq/L and tend to be resistant to 0.9% NaCl solution therapy.[55,69] These disorders often require K^+ repletion or agents that reduce mineralocorticoid effects, such as spironolactone, before correction can occur.[55] When 0.9% NaCl solution repletion is ineffective, or emergent correction of the alkalosis is required, some authors have suggested infusions of lysine or arginine HCl, or dilute HCl.[3,108] However, this technique is rarely necessary.

Diagnosis of Patient 2

Further history revealed that patient 2 was being fed oral baking soda several times per day as part of a folk remedy. Urinary [Cl^-] was 6 mEq/L. He was treated with intravenous 0.9% NaCl solution with subsequent resolution of clinical and laboratory abnormalities. The parents were educated about the risks of prescription and nonprescription medications, and complementary therapies.

Xenobiotic-Induced and other Alterations of Water Balance

Significant fluid abnormalities commonly occur in the setting of xenobiotic exposure. Gastrointestinal losses in the form of vomiting,

diarrhea, gastrointestinal hemorrhage, and third spacing (such as from gastrointestinal burns) result from a variety of xenobiotic exposures and their management, such as emetics and cathartics. Renal fluid losses result from the ability of many toxins to increase the glomerular filtration rate (inotropes), impair absorption (diuretics), or enhance urine volume in response to an obligate solute load (salicylates). Fluid losses also may occur through the skin as a result of sweating (sympathomimetics, cholinergics, and uncouplers of oxidative phosphorylation) or the lung as a result of increased minute ventilation (salicylates and sympathomimetics) or bronchorrhea (cholinergics). To the extent that these lost fluids contain Na^+, various signs, symptoms, and laboratory evidence of ECFV depletion will be present.

The diagnosis and treatment of abnormal serum electrolyte concentrations are usually addressed after repletion of the ECFV deficit with isotonic, Na^+-containing fluids (eg, blood products, 0.9% NaCl solution, lactated Ringer solution). Other fluid balance issues are discussed in Chaps. 25 and 27 and in chapters relating to individual toxins. This section focuses on body water balance (abnormalities of which manifest as hypernatremia and

hyponatremia) and specifically on the toxicologically relevant syndromes of diabetes insipidus (DI) and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

Sodium concentration in the extracellular space is intrinsically related to and directly reflects total body water balance. This occurs because the sodium cation is largely restricted to the extracellular space, and its (serum) concentration is primarily, if indirectly, controlled by factors that control water balance. Thus, both the serum [Na^+] and plasma osmolality vary inversely with changes in the quantity of body water.

Plasma osmolality is maintained through a complex interaction between dietary water intake; the hypothalamus, pituitary gland, and kidney; and the effects of hormones such as antidiuretic hormone (ADH) and adrenal mineralocorticoids.[17,20,120,165] Briefly, changes in osmolality are caused by changes in water intake and insensible (dermal, respiratory, and stool) and sensible (urinary, sweat) water losses. Urinary water losses are controlled by the hormone arginine vasopressin (ADH). Increases in the osmolality in the extracellular fluid stimulate anterior hypothalamic osmoreceptors, thereby stimulating thirst and ADH synthesis and release by the posterior pituitary gland. ADH release reaches its maximum level at a serum osmolality of about 295 mOsm/kg. Antidiuretic hormone is transported to the kidney via the bloodstream, where it stimulates the synthesis of cyclic adenosine monophosphate (cAMP). cAMP increases the water permeability of the distal convoluted tubule and collecting duct (by stimulating the insertion of aquaporin channels in the apical membrane) increasing water reabsorption and urine concentration, and minimizing urinary water losses. Conversely, as plasma osmolality falls, thirst and ADH release are diminished. This results in decreased renal cAMP generation, decreased water permeability of the distal convoluted tubule and collecting duct, and the excretion of a relatively dilute urine that ultimately corrects the body water excess. Marked alterations in water intake combined with

perturbations of these various processes often lead to hypernatremia or hyponatremia.

Hypernatremia

Table 17-6 summarizes the xenobiotics that cause hypernatremia. Hypernatremia may be caused by the parenteral administration of sodium-containing drugs or rapid and excessive oral Na^+ intake.[4] Oral NaCl and oral sodium citrate have been used as emetics and antiemetics, respectively. As might be expected, both have produced severe hypernatremia.[20] One case of fatal hypernatremia resulted from gargling with a supersaturated salt solution.[111] Similarly, massive ingestion of sodium hypochlorite bleach was associated with hypernatremia.[70,137]

More commonly, xenobiotic induced hypernatremia results from relatively electrolyte-free (hypotonic) water losses, including xenobiotics or conditions that cause urinary, gastrointestinal, and dermal fluid losses.[4] Indeed, all fluid losses from the body, with the exceptions of bleeding and fistulous losses, are hypotonic (and have the potential to cause hypernatremia). The failure of patients to replace these losses is a key element in the development of hypernatremia because even the large losses caused by diabetes insipidus or cholera-induced diarrhea will not cause hypernatremia if the losses are adequately replaced. Thus, in patients with hypernatremia caused by fluid losses, the reason why the losses were not replaced by the patient should always be sought.

Agents that produce significant diarrhea, such as lactulose or cholestyramine, can cause hypernatremia through unreplaced stool water losses. A similar pathogenesis accounts for the hypernatremia caused by the polyethylene-containing solution used for bowel preparation for colonoscopy.[14] Of particular concern is the use of cathartics in the management of poisonings, especially when fluid losses are not anticipated. For example, multiple doses of sorbitol can produce severe hypernatremic

dehydration and death in both children and adults.[24,44,57,166]

TABLE 17-6. Xenobiotic Causes of Hypernatremia

Sodium gain
Antacids (baking soda)
Sodium salts (bicarbonate, chloride, citrate, hypochlorite)
Seawater

Water loss
Cholestyramine
Diuretics
Glycerol
Lactulose
Mannitol
Povidone-iodine
Sorbitol
Urea

Water loss: Diabetes Insipidus
Î±-Adrenergic antagonists
Amphotericin
Colchicine
Demeclocycline
Ethanol
Foscarnet
Glufosinate
Lithium
Lobenzarit disodium
Methoxyflurane
Mesalazine
Minocycline

Opioid antagonists
Propoxyphene
Rifampin
Streptozotocin
Vasopressin V_2-receptor antagonists

Significant water loss also can occur through the skin. Although diffuse diaphoresis resulting from cocaine or organic phosphorus agent toxicity has the potential to produce hypernatremia, this rarely, if ever, occurs. However, application of a burn remedy containing hyperosmolar povidone-iodine to the skin of burn patients has been reported to produce significant water losses and hypernatremia.[146]

Diagnosis and Treatment

The symptoms of significant hypernatremia consist largely of altered mental status ranging from confusion to coma, and neuromuscular weakness that occasionally results in respiratory paralysis. If hypernatremia is associated with Na^+ losses and marked ECFV depletion, cardiovascular symptoms, tachycardia, and orthostatic hypotension may be present. Treatment consists of replacing the Na^+ deficit first, if necessary (with isotonic fluids such as 0.9% NaCl solution), and then replacing the water deficit. The water deficit may be estimated by assuming that the fractional increase in serum [Na^+] is equal to the fractional decrease in total body water. Thus, a serum [Na^+] that has increased by 10% (from 144 mEq/L to 158 mEq/L) indicates that the water deficit is 10% (3.6 L in a 60-kg person with 36 L of body water).

When the hypernatremia develops over several hours, for example, as occurs after ingestion or administration of a sodium salt, rapid correction is indicated. However, when hypernatremia

develops over several days or when the duration is unknown, slow correction of hypernatremia (over several days) is recommended.[4] The adaptation of brain cells to the water deficit (including the loss of intracellular solute) makes cerebral edema a frequent result of rapid water replacement. Although some sources suggest that 0.9% NaCl solution infusion is an appropriate replacement fluid regardless of the magnitude of the water deficit, recent emphasis has been on the use of hypotonic fluids in the absence of a significant sodium deficit.[4]

Diabetes Insipidus

The greatest water losses and, therefore the potentially most severe cases of hypernatremia, occur during DI, which is always characterized by greater or lesser degrees of hypotonic polyuria. DI may be neurogenic (resulting from failure to sense a rising osmolality, or from a failure to release ADH), or nephrogenic (resulting from failure of the kidney to respond appropriately to ADH). Although there are many nontoxicologic causes of DI (eg, trauma, tumor, sarcoidosis, vascular and congenital), drug-induced DI is not uncommon, and may interfere with ADH effects through both central and peripheral mechanisms.

Ethanol, opioid antagonists, and Î±-adrenergic agonists all suppress ADH release.[10,115] Lithium,[99,150] demeclocycline,[149] methoxyflurane,[103] propoxyphene, foscarnet,[119] mesalazine,[101] streptozotocin, amphotericin,[74] glufosinate,[160] lobenzarit,[138] rifampin,[130] and colchicine,[165] are associated with nephrogenic DI (see Table 17-6). In addition, nephrogenic DI may be caused by severe hypokalemia from diuretic use, and hypercalcemia from vitamin D poisoning.[165] Of all these agents, lithium has been the most extensively evaluated. Although polyuria is a common finding with lithium therapy (occurring in 20â€“70% of patients on maintenance therapy), the exact incidence of DI and hypernatremia is unclear. Estimates range from 10â€“20% to as

high as 80%.

Diagnosis

Patients with DI complain of polyuria and polydipsia. Urine volumes typically exceed 30 mL/kg/d[165] and may be as high as 9 L/d with nephrogenic DI[99] and 12â€“14 L/d with neurogenic (central) DI.[116] Nocturia, fatigue, and decreased work performance are noted.[165] Neurogenic DI resulting from hypothalamic or pituitary damage is typically associated with other signs of neuroendocrine dysfunction.[116]

Once polyuria is confirmed (eg, in adults, by measuring a urine output >200 mL over 1 hour), the urine osmolality or specific gravity should be measured. The diagnosis of DI is established by the occurrence of dilute urine (urine osmolality <300 mOsm/kg, urine specific gravity <1.010) in the presence of increased serum [Na^+] and serum osmolality >295 mOsm/kg.[165] Following this determination, a trial of desmopressin (DDAVP), an arginine vasopressin analog, helps to differentiate between neurogenic and nephrogenic DI. If the etiology of the DI is neurogenic, the patient promptly responds to DDAVP with a decrease in urine output and increase in urine osmolality. In nephrogenic DI, DDAVP will have no significant effect.

Treatment

The initial approach to the hypernatremic patient with DI involves the repletion of the water deficit (as described above) and the restoration of electrolyte balance, if necessary. If a reversible cause for the DI can be established, it should be corrected. Specifically, drugs implicated as the cause of DI should be discontinued or their dose reduced. Patients with neurogenic DI should be maintained on either vasopressin or DDAVP. The latter is preferred because of the lack of vasopressor effects and ease of administration. In the past, patients were occasionally treated with

oral agents known to produce SIADH (see below). Patients with nephrogenic DI can be treated with thiazide diuretics,[38] prostaglandin inhibitors,[34,74,94] and/or amiloride.[16]

Hyponatremia

Hyponatremia may be associated with a high, normal, or low plasma osmolality. Patients with myeloma or severe hyperlipidemia may exhibit artifactual hyponatremia whenever the measurement technique requires dilution of the serum sample rather than direct measurement by a sodium electrode. These patients have a normal serum osmolality, no symptoms related to their artifactual hyponatremia, and require no therapy. Hyperglycemic patients develop hyponatremia because the increase in plasma osmolality caused by hyperglycemia results in a water shift from the intracellular to the extracellular space. The reduction in serum $[Na^+]$, which may cause symptoms, is an approximately 2 mEq/L per 100 mg/dL increase in serum glucose concentration. The contribution of hyperglycemia to the hyponatremia should be calculated to determine if other causes of hyponatremia should also be sought. All other causes of hyponatremia are associated with a low plasma osmolality. In fact, in the absence of myeloma, hyperlipidemia and hyperglycemia, the plasma osmolality need not be measured in hyponatremic patients and may be assumed to be low.

Hyponatremia associated with a low plasma osmolality usually results from water intake in excess of the renal capacity to excrete it. When renal water excretion is normal, very large quantities are required to cause hyponatremia. Usually such quantities are ingested over a short period of time by people with psychiatric or neurologic disorders.[63,134] Xenobiotic-induced water excess comparable to psychogenic polydipsia is quite uncommon. An example occurs during urologic procedures, such as transurethral resection of the prostate (TURP), where large volumes of irrigation

solution are required. Because the wounds are electrically

cauterized, these fluids cannot contain conductive electrolytes such as sodium. Sorbitol, dextrose, and mannitol were tried in an attempt to maintain a normal osmolality in these irrigating solutions, but their optical characteristics were undesirable. Thus, irrigation during TURP is performed with glycine-containing solutions. When 1.5% glycine (osmolality 220 mOsm/Kg) is absorbed through the prostatic venous plexus, a rapid reduction in serum [Na^+] results and will persist until the glycine is metabolized.[71,110] Symptoms in these patients are probably a result of several factors: hyponatremia, the glycine itself, and NH_3, a glycine metabolite. A similar complication is also described during hysteroscopy.[127,147]

Rarely, hyponatremia results from the loss of a body fluid with a [Na^+] greater than the extracellular fluid (ECF) [Na^+] (of 154 mEq/L). This may occur in patients with adrenal insufficiency through hypertonic urinary losses (although increased ADH secretion as a consequence of ECF sodium depletion is probably a more important mechanism; see below). In burn patients, Na^+ may be lost directly from the ECF. When treated with the topical applications of silver nitrate cream, hyponatremia may develop from the diffusion of sodium through permeable skin into the hypotonic dressing.[29] Ingestion of licorice, which contains glycyrrhizic acid, produces a syndrome of hyponatremia, hypokalemia, and hypertension that resembles mineralocorticoid excess. Although the exact mechanism of hyponatremia is debated, one report suggested that a glycyrrhizic acid-induced reduction in 11-Î²-hydroxysteroid dehydrogenase activity could account for the findings.[40,43] Lithium, which is usually associated with diabetes insipidus and hypernatremia, has been reported to cause renal sodium-wasting and hyponatremia that seems to be unrelated to ADH effects.[109]

Most cases of hyponatremia are caused by water intake in excess

of a reduced renal excretory capacity. This reduction in urinary water excretion may be physiologic (as during ECF sodium depletion) or pathologic (in association with renal failure, heart failure, or cirrhosis of the liver).[5,14] Because these conditions are accompanied by alterations in renal sodium handling, signs and symptoms of ECFV depletion (eg, postural hypotension) or excess (eg, edema) usually accompany the hyponatremia. Other patients cannot excrete water normally because malignancy or various brain or pulmonary diseases cause ADH secretion.[5] In fact, in some cases the tumors are associated with paraneoplastic disease and directly secrete ADH. Xenobiotics may cause ECFV depletion (eg, diuretics), but most directly stimulate ADH secretion or augment the renal effects of ADH. Drugs such as the thiazide diuretics cause hyponatremia by several mechanisms, including interference with maximal urinary dilution, and by ADH-induced water retention in response to decreased ECFV.[5,47] Patients with excess secretion and/or action of ADH who have near-normal ECFV are said to have SIADH. Table 17-7 summarizes these and other causes of hyponatremia.

SIADH

SIADH is characterized by hyponatremia and plasma hypotonicity in the absence of abnormalities of ECFV, adrenal, thyroid, or renal function. Early reviews claimed that SIADH was a disorder of volume overload, based largely on evidence of weight gain.[115] The consistent absence of edema, however, and the fact that the decrease in serum [Na^+] cannot be accounted for by the fluid gain (weight gain), suggest that water retention is only part of the mechanism.[88] Urinary Na^+ loss and Na^+ redistribution from the extracellular to the intracellular space are apparently important as well.

TABLE 17-7. Xenobiotic and Other Causes of Hyponatremia

Arginine
Captopril and other angiotensin-converting enzyme inhibitors
Diuretics
Glycine (transurethral prostatectomy syndrome)
Lithium
Nonsteroidal antiinflammatory drugs
Primary polydipsia
Silver nitrate

SIADH
- Amiloride
- Amitriptyline (and other tricyclic antidepressants)
- Biguanides
- Carbamazepine (and oxcarbamazepine)
- Cisplatin
- Clofibrate
- Cyclophosphamide
- Desmopressin (DDAVP)
- Diazoxide
- Indapamide
- Indomethacin
- MDMA (methylenedioxymethamphetamine)
- Metformin
- Nicotine
- Opioids
- Oxytocin
- Selective serotonin reuptake inhibitors
- Sulfonylureas
- Thioridazine
- Tranylcypromine

Vasopressin
Vincristine and vinblastine

There are many nontoxicologic etiologies of SIADH, most of which involve pulmonary or intracranial processes. These causes include infections, malignancies, and surgery.[5,88,115,116] Table 17-7 summarizes xenobiotics known to produce SIADH. The oral hypoglycemics, including agents from both the sulfonylurea (eg, chlorpropamide) and biguanide (eg, metformin) classes, produce hyponatremia more commonly than other agents.[114] Their actions are multifactorial and can include both the potentiation of endogenous ADH and the stimulation of ADH release.[114] Many psychiatric medications, including the selective serotonin reuptake inhibitors, cyclic antidepressants, and antipsychotics are implicated in causing SIADH.[27,86,96,156,163] The effects of these drugs may be mediated by the complex interactions between the dopaminergic and noradrenergic systems that control ADH release.[156] Additional evidence supports a role of serotonin in drug-induced SIADH. Serotonin (specifically $5\text{-}HT_2$ and/or $5\text{-}HT_{1C}$) directly stimulates ADH release[11] and water intake.[77] An important role of serotonin is supported by the occurrence of SIADH with (methylenedioxymethamphetamine) MDMA use.[76,168]

Diagnosis

The clinical presentation of patients with hyponatremia depends on the cause, the absolute serum $[Na^+]$ and the rate of decline in serum $[Na^+]$. Patients with associated ECFV excess or depletion will present with evidence of altered ECFV, as well as signs and symptoms of the disease that caused the abnormality in ECFV, such as adrenal insufficiency and heart failure.[5] Rarely will these patients exhibit findings caused by the hyponatremia and hyposmolality of body fluids per se. This may be because of the moderate degree of hyponatremia (>130 mEq/L), the

moderate rate of decline in serum [Na^+], and/or because the loss of Na^+ and water limits the development of cerebral edema.[91] It is important to note that patients with hyponatremia and a low plasma osmolality (excluding those with primary polydipsia) all have a urinary osmolality that is relatively high, regardless of whether they have excess, diminished, or normal ECFV. Consequently, these disorders can only be differentiated by the history, physical examination, and other laboratory tests.

Patients with SIADH, if symptomatic, usually present with signs and symptoms of hyponatremia. As noted above, the clinical manifestations of hyponatremia are dependent on both the absolute serum [Na^+] and its rate of decline.[12,91,116] Chronic, slow depression of the serum [Na^+] is usually well tolerated, whereas rapid decreases may be associated with symptoms and sometimes catastrophic events. Symptoms include headache, nausea, vomiting, restlessness, disorientation, depression, apathy, irritability, lethargy, weakness, and muscle cramps. In more severe cases, respiratory depression, coma, and seizures develop.

The diagnosis of SIADH is based on establishing the presence of hyponatremia, a low plasma osmolality, and impaired urinary dilution in the absence of edema, hypotension, hypovolemia, and renal, adrenal, or thyroid dysfunction.[88] As discussed above, the presence of any of these clinical findings suggests that another cause of hyponatremia may be present. A serum uric acid concentration may be helpful in differentiating SIADH from other causes of hyponatremia. In the presence of hyponatremia and impaired urinary dilution, patients with SIADH have hypouricemia, whereas patients exhibiting ECFV excess or depletion characteristically have hyperuricemia.[32,155]

Treatment

Treatment of patients with demonstrable ECFV excess or depletion

should be directed at the abnormal ECFV and its cause, rather than the hyponatremia. In almost all cases, the hyponatremia will improve with correction of the ECFV.[5,91] In a similar way, correction of the serum glucose in hyperglycemic patients and the removal of glycine by hemodialysis in patients with the TURP syndrome will correct the serum [Na^+]. The rate of correction of the serum [Na^+] in these patients is generally not of concern.

In patients with SIADH, treatment begins with fluid restriction. Because the goal of this therapy is to establish a negative fluid balance, careful attention to intake and output is required. If an offending agent can be identified, it should be eliminated. Although most cases resolve in 1â€“2 weeks,[88,116] SIADH caused by chronic cerebral or pulmonary conditions or by malignancy often persists. If this occurs, therapy with demeclocycline or lithium may be helpful, because severe fluid restriction is often intolerable. One author suggested that demeclocycline was more efficacious than lithium when the two agents were compared in a small series of patients with SIADH.[50]

In all asymptomatic or mildly symptomatic patients (usually patients with chronic hyponatremia of more than 2 days duration), correction should proceed slowly, and certainly at a rate less than 0.5 mEq/L/h during the first 24 hours. This is because too rapid correction of hyponatremia may increase the risk of irreversible CNS damage known as central pontine myelinolysis.[5,13,158] Water restriction is usually sufficient, but occasionally demeclocycline may be appropriate in these patients in whom the rate of correction represents a greater risk for brain damage than the absolute serum [Na^+]. The anticipated availability of oral vasopressin V_2- and $V_{1/2}$-receptor antagonists will make the management of these asymptomatic patients much easier.[5,68]

When hyponatremia is associated with life-threatening clinical presentations, careful infusion of hypertonic (3%) saline (eg, 0.5â€“1 mEq/kg/h), with or without furosemide, is indicated.[5,88]

In these symptomatic patients, the goal is to increase the serum [Na^+] by 1â€“2 mEq/L/h, or by 10% over 12â€“24 hours, or until the symptoms abate.[5,91] After this initial correction and amelioration of symptoms, the serum [Na^+] should be increased at a rate <0.5 mEq/L/h, preferably by water restriction alone. Formulae are available to help calculate the rate of correction of hyponatremia.[5] Equation 17-10 might be helpful.

When one liter of fluid is infused:

$$\text{The change in the serum } Na^+ = \frac{\text{infusate } Na^+ - \text{serum } Na^+}{\text{total body water} + 1 \text{ liter}}$$

Where infusate Na^+ concentrations in mEq/L equal:

3% sodium chloride	513
0.9% sodium chloride	154
Lactated Ringer solution	130
0.45% sodium chloride	77
0.33% sodium chloride	51

(Eq. 17–10)

Xenobiotic-Induced Electrolyte Abnormalities

Potassium

Xenobiotic-induced alterations in serum [K^+] are potentially more serious than alterations in other electrolyte concentrations because of potassium's critical role in a variety of homeostatic processes. Potassium balance is complex.[23,128,141] The total body potassium content of an average adult is about 54 mEq/kg, of which only 2% is located in the intravascular space. The large intracellular store of potassium is maintained by a variety of systems, the most important of which is membrane Na^+-K^+-adenosine triphosphatase (ATPase). The relationship between total body stores and serum [K^+] is not linear, and small changes in the total body potassium may result in dramatic alterations in serum concentrations, and, more importantly, in the ratio of extracellular

to intracellular [K^+].

People eating a western diet ingest 50â€“150 mEq/d of potassium, approximately 90% of which is subsequently eliminated in the urine. The body has two major defenses against a potassium load: acutely, potassium is transferred into cells; chronically, potassium is excreted in the urine by decreased proximal tubular reabsorption and increased distal tubular secretion (to a maximum of 600â€“700 mEq/d).[23] Intracellular [K^+] is maintained through insulin and catecholamine-mediated uptake of potassium in liver and muscle cells.[98,136] Renal potassium excretion is primarily modulated by the reninâ€“angiotensinâ€“aldosterone system. In addition, the gastrointestinal absorption of potassium decreases as the serum [K^+] increases.

Hypokalemia results from decreased oral intake, gastrointestinal losses caused by repeated vomiting or diarrhea, urinary losses through increased secretion or decreased reabsorption, and processes that shift potassium into the intracellular compartment.[20,23,148,167] Table 17-8 summarizes the xenobiotics commonly associated with hypokalemia.

The neuromuscular manifestations of hypokalemia are reviewed elsewhere.[87] Patients with hypokalemia are often asymptomatic when the decrease in serum [K^+] is mild (serum concentrations of

3.0â€“3.5 mEq/L). Occasionally, hypokalemia interferes with renal concentrating mechanisms and polyuria is noted. More significant potassium deficits (serum concentrations of 2.0â€“3.0 mEq/L) cause generalized malaise and weakness. As the [K^+] fall to less than 2 mEq/L, weakness becomes prominent and areflexic paralysis and respiratory failure may occur, often necessitating intubation and mechanical ventilation.[87] Rhabdomyolysis is also likely. These neuromuscular manifestations are so prominent that they may be erroneously attributed to a primary neuromuscular syndrome such as Guillain-BarrÃ©. Other clinical findings

associated with hypokalemia may include gastrointestinal hypoperistalsis (ileus), manifestations of cardioactive steroid toxicity, worsening hyperglycemia in diabetic patients, and symptoms and signs of metabolic abnormalities that often accompany hypokalemia such as hyponatremia, metabolic acidosis, or alkalosis.[167]

TABLE 17-8. Xenobiotic Causes of Altered Serum Potassium

Hypokalemia	Hyperkalemia
Aminoglycosides	Amiloride
Amphotericin	Angiotensin-converting enzyme inhibitors
Barium (soluble salts)	
Î²-Adrenergic agonists	Angiotensin receptor blockers
Bicarbonate	Î±-Adrenergic agonists (phenylephrine)
Caffeine	
Carbonic anhydrase inhibitors	Î²-Adrenergic antagonists
Cathartics	Arginine hydrochloride

Chloroquine	Cardioactive steroids
Cisplatin	Fluoride
Dextrose	Heparin
Hydroxychloroquine	Nonsteroidal antiinflammatory drugs
Insulin	
Licorice (glycyrrhizic acid)	Penicillin (potassium)
Loop diuretics	Potassium salts
Metabolic alkalosis	Spironolactone
Oral hypoglycemics	Succinylcholine
Osmotic diuretics	Triamterene
Quinine	Trimethoprim
Salicylates	
Sodium penicillin and its analogs	
Sodium polystyrene sulfate	

Sympathomimetics	
Theophylline	
Thiazide diuretics	
Toluene	

Electrocardiographic changes also are common, even with mild potassium depletion, although the absence of ECG changes should never be used to exclude significant hypokalemia. Common ECG findings of hypokalemia include depression of the ST segment, decreased T-wave amplitude, and increased U-wave amplitude (Chap. 5). These findings may herald life-threatening rhythm disturbances.[75,95,167]

Treatment of hypokalemia involves discontinuing or removing the offending xenobiotic and correcting the potassium deficit. Potassium supplementation may be given orally and/or intravenously. The choice of potassium salt should be based on the associated acidâ€“base abnormality, if present. Thus, KCl should be administered when metabolic alkalosis is present, and another salt of potassium (eg, potassium citrate or $KHCO_3$) should be administered when metabolic acidosis is present.[167] Potassium phosphate should be part of the K^+ supplement when hypophosphatemia is present (as in many hypokalemic patients with diabetic ketoacidosis). Hypomagnesemia, which may cause or accompany hypokalemia (eg, in diuretic-induced hypokalemia), must be corrected because this abnormality may prevent successful potassium replacement.

The debate over the maximum safe infusion rate for intravenous potassium is summarized elsewhere.[90,167] Based on experience

with more than 1300 infusions, one group concluded that under intensive care monitoring, intravenous administrations of 20 mEq/h (by central or peripheral vein) were well tolerated. They also found that each 20 mEq of potassium administered resulted in an average increase in serum [K^+] of 0.25 mEq/L. Others have used significantly larger doses (up to 100 mEq/h) in life-threatening circumstances.[33]

Hyperkalemia results from decreased urinary elimination (renal insufficiency, potassium-sparing diuretics, hypoaldosteronism), increased intake (either orally or intravenously), or redistribution from tissue stores.[20,23] The last mechanism is of major toxicologic importance. Overdoses of both cardioactive steroids (Chap. 62) and Î²-adrenergic antagonists (Chap. 59) cause hyperkalemia by promoting net potassium release from its intracellular reservoir. Presumably because of other protective mechanisms, overdose with a Î²-adrenergic antagonist produces only a moderate rise in serum [K^+] (usually to 5.0â€“5.5 mEq/L). By contrast, a similar rise in serum [K^+] as a consequence of blockade of the Na^+-K^+-ATPase pump during cardioactive steroid toxicity may be lethal. This suggests that hyperkalemia per se is not the cause of the lethality of cardioactive steroid overdose. Thus, the focus of therapy should involve efforts to neutralize or eliminate the cardioactive steroid rather than reduce the serum [K^+].[18] Table 17-8 lists xenobiotics that cause hyperkalemia.

After oral overdoses of potassium salts, patients usually complain of nausea and vomiting. Ileus, and intestinal irritation, bleeding and perforation may complicate the clinical course.[141] In the absence of potassium ingestion, gastrointestinal symptoms of hyperkalemia are usually very mild. Neuromuscular manifestations include weakness with an ascending flaccid paralysis and respiratory compromise, with intact sensation and cognition.[87,105,128] The similarity of these signs and symptoms to those associated with hypokalemia is striking, suggesting that hyperkalemia may be diagnosed with certainty only by laboratory

measurement.

The cardiac manifestations of hyperkalemia are distinct, prominent and life-threatening. Electrocardiographic patterns progress through characteristic changes.[140,141] Although the progression of ECG changes is very reproducible, there is tremendous individual variation with respect to the serum $[K^+]$ at which these ECG findings occur. Initially, the only ECG finding may be the presence of tall, peaked T waves. As the serum $[K^+]$ concentration increases, the QRS complex tends to blend into the T waves, the P-wave amplitude decreases, and the PR interval becomes prolonged. Next, the P wave is lost and ST-segment depression occurs. Finally, the distinction between the S and T waves becomes blurred and the ECG takes on a sine wave configuration (Chap. 5). Hemodynamic instability and cardiac arrest can result. As the patient's serum $[K^+]$ falls with therapy, these ECG changes resolve in a reverse fashion.

The treatment of severe hyperkalemia includes standard airway management, methods to reverse the ECG effects, methods to transfer K^+ to the intracellular space, and methods to enhance K^+ elimination. Pharmacologic interventions, extensively discussed elsewhere,[141] are summarized here. Calcium (eg, $CaCl_2$ 10â€“20 mEq administered intravenously) works almost immediately to protect the myocardium against the effects of hyperkalemia although it does

not reduce the serum $[K^+]$. However, a potentially life-threatening interaction occurs when the patient with cardioactive steroid toxicity is given Ca^{2+} (Chap. 62); thus, this therapeutic modality is relatively contraindicated in such circumstances.

The administration of insulin (and dextrose to prevent hypoglycemia), sodium bicarbonate, and/or inhalation of a Î²-adrenergic agonist all stimulate potassium entry into cells.[9] They reduce the serum $[K^+]$ over approximately 30 minutes, but

potassium begins to reenter the extracellular space over the next several hours. Cationic exchange resins, such as Na^+ polystyrene sulfonate, take somewhat longer (about 45 minutes), but they enhance gastrointestinal potassium loss. Hemodialysis or peritoneal dialysis may be useful, especially when significant renal impairment is present.

Calcium

Calcium is the most abundant mineral in the body and 98â€“99% is located in bone. Approximately half of the remaining 1â€“2% of the body's calcium is bound to plasma proteins (mostly albumin) and most of the rest is complexed to various anions, with free, ionized calcium representing a very small fraction of extraosseous stores. The serum [Ca^{2+}] is maintained through interactions between dietary intake and renal elimination, modulated by vitamin D activity, parathyroid hormone, and calcitonin. More extensive discussions of calcium physiology are found elsewhere.[7,117]

Xenobiotic-induced hypercalcemia is uncommon and usually caused by an increased dietary calcium as a result of milk or antacid usage, or a decrease in its renal excretion such as occurs with thiazide use.[7,20] Cholecalciferol, available as a rodenticide, can increase the serum [Ca^{2+}] by increasing its release from bone, increasing gastrointestinal absorption, and decreasing renal elimination (Chap. 104). Vitamin D toxicity from excessive vitamin intake or supplementation of milk also can cause hypercalcemia.[49,82] Table 17-9 lists other causes of hypercalcemia.

Symptoms of hypercalcemia consist of lethargy, muscle weakness, nausea, vomiting, and constipation. Life-threatening manifestations include complications from altered mental status such as aspiration pneumonia and cardiac dysrhythmias (Chap. 5). Treatment of clinically significant hypercalcemia focuses on

removing the offending agent when possible, decreasing gastrointestinal absorption, increasing distribution into bone, and enhancing renal excretion through forced diuresis with intravenous 0.9% NaCl solution and furosemide.[7,159] Hemodialysis may be required when significant renal impairment is present.

TABLE 17-9. Xenobiotic Causes of Altered Serum Calcium

Hypocalcemia	Hypercalcemia
Aminoglycosides	Aluminum
Bicarbonate	Androgens
Bisphosphonates	Antacids (calcium containing)
Calcitonin	Antacids (magnesium containing)
Citrate	Cholecalciferol and other Vitamin D analogs
Ethanol	Glucocorticoids
Ethylene glycol	Lithium
Fluoride	Milkâ€“alkali syndrome
Furosemide	Tamoxifen

Mithramycin	Thiazide diuretics
Neomycin	Vitamin A
Phenobarbital	
Phenytoin	
Phosphate	
Theophylline	
Valproate	

Xenobiotic-induced hypocalcemia is more common than hypercalcemia. Minor, usually clinically insignificant decreases in serum [Ca^{2+}] can occur in association with anticonvulsant[93] and aminoglycoside therapy.[20] Severe, life-threatening hypocalcemia can occur, however, from ethylene glycol poisoning (Chap. 103) or as a manifestation of fluoride toxicity from either fluoride salts or hydrofluoric acid (Chap. 101).[39,161] Complex formation with fluoride or oxalate ions is responsible for the rapid development of hypocalcemia in these settings. Similar effects occur with excess phosphate[164] or citrate[104,162] intake or administration. This mechanism (calcium complex formation) decreases the ionized [Ca^{2+}], but may or may not reduce the measured total serum [Ca^{2+}]. Other drugs and toxins that produce hypocalcemia decrease absorption, enhance renal loss, and/or stimulate calcium entry into cells (Table 17-9).

Symptoms of hypocalcemia consist largely of neuromuscular

findings, including paresthesias, cramps, carpopedal spasm, tetany, and seizures. Although ECG abnormalities are common (Chap. 5), life-threatening dysrhythmias are rare. Treatment strategies focus on calcium replacement. When hypomagnesemia or hyperphosphatemia is present, these abnormalities should be corrected or calcium replacement may fail.

Magnesium

Magnesium is the fourth most abundant cation in the body (after Ca^{2+}, Na^{+}, and K^{+}), with a normal total body store of about 2000 mEq in a 70-kg human.[131] Approximately 50% of magnesium is stored in bone, with most of the remainder distributed in the soft tissues. Because only approximately 1â€“2% of magnesium is located in the extracellular fluid, serum concentrations correlate poorly with total body stores.[132] Magnesium homeostasis is maintained through dietary intake, and renal and gastrointestinal losses, modulated by hormonal effects.[7]

Clinically significant hypermagnesemia is uncommon in the absence of renal failure, except when massive parenteral infusions of magnesium salts overwhelm renal excretory mechanisms. This has been reported with inadvertent intravenous infusion,[19,25,73,113] urologic procedures involving irrigation with magnesium salts,[45,83] and ingestion of large quantities of magnesium-containing antacids[106] and cathartics.[46,54,59] Of concern is iatrogenic overdose from the use of magnesium-containing cathartics as part of routine poison management.[56,84,152] In a series of poisoned patients, a single-dose of a magnesium-containing cathartic failed to produce any demonstrable rise in serum $[Mg^{2+}]$.[153] However, patients who received three doses of magnesium sulfate over 8 hours had a statistically significant increase in their serum $[Mg^{2+}]$.[153] Thus, as with the cathartic sorbitol, the potential for iatrogenic toxicity exists, mandating cautious use of magnesium-containing

cathartics, especially in patients with renal insufficiency. Table 17-10 lists the causes of hypermagnesemia.

The symptoms of hypermagnesemia correlate roughly with serum concentrations but depend somewhat on the rate of increase and host factors. At serum [Mg^{2+}] of about 3â€“10 mEq/L, patients feel weak, nauseated, flushed, and thirsty. Bradycardia, a widened QRS complex on ECG, hypotension, and decreased deep tendon reflexes may be noted. As concentration increases, hypoventilation, muscle paralysis, and ventricular dysrhythmias occur. Serum [Mg^{2+}] greater than

10 mEq/L, and especially those greater than 15 mEq/L, often cause death.

TABLE 17-10. Xenobiotic Causes of Altered Serum Magnesium

Hypomagnesemia	Hypermagnesemia
Aminoglycosides	Antacids (magnesium containing)
Amphotericin	Cathartics (magnesium containing)
Cisplatin	Lithium
Citrate	Magnesium sulfate
Cyclosporine	
DDT	

Ethanol	
Fluoride	
Foscarnet	
Insulin	
Laxatives	
Loop diuretics	
Methylxanthines	
Osmotic diuretics	
Phosphates	
Strychnine	
Thiazide diuretics	

Hypermagnesemia should be considered a life-threatening disorder. When significant neuromuscular or ECG manifestations are noted, administration of $CaCl_2$ 5â€“20 mEq intravenously will reverse some of the toxicity.[7,67] Further therapy should focus on enhancing renal excretion by administering fluids and loop diuretics such as furosemide.[67] In the presence of renal failure or inadequate renal excretion, hemodialysis will rapidly correct hypermagnesemia.

Xenobiotic-induced hypomagnesemia is common, but rarely life-threatening. Renal losses (caused by diuretics), gastrointestinal losses (caused by ethanol), intracellular shifts from insulin[102] or Î²-adrenergic agonists, and complex formation (by fluoride or phosphate) are common.[7] Table 17-10 lists these and other causes of hypomagnesemia. Of note, many causes of hypomagnesemia also cause hypokalemia and hypocalcemia.[6] Therefore, when hypomagnesemia is suspected or discovered, the presence of other electrolyte abnormalities should be sought.

The symptoms of hypomagnesemia are lethargy, weakness, fatigue, neuromuscular excitation (tremor and hyperreflexia), nausea, and vomiting.[30,36] Dysrhythmias may occur, especially during therapy with cardioactive steroids. Signs and symptoms consistent with hypocalcemia and hypokalemia also may be present.

Treatment involves removing the offending agent (if it can be identified) and restoring magnesium balance. Although either oral or parenteral supplementation is usually acceptable for mild hypomagnesemia, parenteral therapy is required when significant clinical effects are present. When oral therapy is indicated, a normal diet or magnesium oxide, magnesium chloride, or magnesium lactate in divided doses (magnesium 20â€“100 mEq/d) will often correct the hypomagnesemia.[6,7] When hypomagnesemia is severe or symptomatic, several authors suggest that in the absence of renal insufficiency, the administration of magnesium sulfate 16 mEq (2 g) intravenously over several minutes to a maximum of 1 mEq/kg of magnesium in a 24-hour period.[7,30,81] During any substantial magnesium infusion, frequent serum [Mg^{2+}] determinations should be obtained and the presence of reflexes documented. If hyporeflexia occurs, the magnesium infusion should be discontinued.

Summary

The management of poisoned or overdosed patients must include an evaluation of their fluid, electrolyte, and acidâ€“base status. Abnormalities in acidâ€“base and water balance, and alterations in potassium, calcium, and magnesium metabolism are common in such patients, and often are life-threatening. Conversely, the possibility of xenobiotic ingestion or administration must always be considered when patients present with abnormalities of water, electrolyte, or acidâ€“base balance. This is because these abnormalities are frequently caused by therapeutic doses of many drugs. Clearly, an appreciation of the pathophysiology of these abnormalities and a rational approach to their correction are essential for reducing morbidity and mortality. Finally, fluid and electrolyte abnormalities may result from the therapy of poisoned patients. Thus, the poisoned or overdosed patient must be monitored and reevaluated as treatment progresses to insure that iatrogenic fluid, electrolyte, or acidâ€“base disorders do not complicate the clinical course.

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Chapter 18
Psychiatric Principles

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Psychiatric problems may be the cause or the effect of many toxicologic presentations. Suicide attempts and aggressive behaviors are commonly associated with intoxications and can be uniquely difficult to assess and manage. These patients are often viewed as either totally voluntary and deliberate or totally â€œout of controlâ€• and irrational. The truth is usually more complex, with some aspects occurring within the patient's awareness and control and other aspects either unknown or overwhelming to the patient. This chapter presents schemas for understanding suicide and violence, in order to enable the physician to adopt the appropriate role of both diagnostician and medical decision maker.

Suicide and Self-Injurious Behavior

Suicide and self-injurious behavior are among the most common and challenging emergency department (ED) presentations. It is estimated that there are 790,000 annual suicide attempts in the

United States; more than 30,000 people complete suicide every year.[15] Suicide is the 11th leading cause of death in America and third leading killer of young people. In 2002, for example, more than 124,000 visits to US emergency departments were made after attempted suicides or other self-harm incidents among persons between 10 and 24 years of age.[15] A recent population-based estimate of the 12-month prevalence of suicide attempts was 0.7%, suggesting that perhaps 10 times more attempts occur than present to EDs.[22] These statistics reveal that suicide is significantly underreported. One survey estimated a 12-month incidence of suicidal ideation at 5.6%, representing some 10.5 million people.[25] According to the latest available data males are 4 times more likely to die from suicide than females and of the 24,672 suicides reported among men in 2001, more than 60% involved the use of a firearm.[6] In contrast, women are 3 times more likely to attempt suicide than men and often use xenobiotics in their attempt.

Suicidal crises are heterogeneous, with suicide the final outcome of many possible psychiatric conditions and social circumstances. This distinction is rendered even more complex by the possibility or probability that suicidal ideation may be deliberately concealed, making it critical for healthcare providers to address this issue with all patients as part of their medical history. Consequently, early identification of the acutely suicidal patient places an extreme burden on the emergency physician to detect and intervene to prevent death.

Suicide is usually discussed in terms of attempts and completions. When the term *suicide* is used alone, it refers to completed suicide. The two are considered separately because those who attempt and those who complete suicide appear to constitute somewhat different groups.

Patients with self-inflicted injury are also common ED presentations. In 2000, for example, there were more than 40

million ED visits because of injuries. Of these, 3 million were the result of intentional injuries, and of this group, approximately 25â€“30% were intentionally self-inflicted.[48] A common method of injurious behavior takes the form of self-poisoning. A recent British study found that approximately 50% of patients who present to the ED with 2 or more episodes of self-poisoning were at increased risk of death by suicide in the future.[14] These investigators found that the factors associated with an increased risk of suicide from one self-poisoning episode to the next included an increase in the number of drugs ingested, an increase in the dose ingested, an increase in coma score and an increase in subsequent drug or alcohol abuse.[14] Additional factors associated with future death included patient consumption of 70 or more tablets or capsules, patients who had an increase of 2 or more in the number of different agents ingested from prior visits, and patients' who had an increase of 50 or more in the number of defined daily doses ingested. Self-poisoned males older than age 45 years who had a delay to toxicology consultation were also at increased risk for death.[11] In addition, Israeli investigators found that the large majority of self-poisoning patients were 15- to 20-year-old women who used pharmaceuticals and had neurologic impairment.[11] A group of Finnish investigators followed a cohort of 100 consecutive self-poisoned patients in Helsinki for 37 years.[70] They found suicides in this group continued to accrue throughout the 37 years after the initial suicide attempt. The authors' concluded that a history of a self-poisoning suicide attempt represents a high suicide risk throughout the adult life span.[70] These recent studies reveal that patients who attempted suicide by self-poisoning represent a group of people with persistent suicidality.[11 , 70]

However, it is difficult for the emergency physician to assess the patient's intention for self-injurious behavior. Self-injurious behavior may be caused by factors other than suicidal intent. The challenge for emergency physicians is determining which of those

among the patients presenting with self-injurious behaviors are seriously suicidal. Failure to do so is associated with some of the largest

damage awards in emergency medicine. Intentional self-poisoning is a common method of attempting suicide, but this must be differentiated from unintentional overdoses, particularly in the young, the developmentally challenged, those with dementia, and those who chronically abuse drugs.[30] In addition, self-injurious behavior may be the result of a patient's attempt to manipulate others or their environment, to cope with emotional lability, or as a reaction to delusions or hallucinations.

Self-poisoning to attempt suicide is also more common in younger women with depression or personality disorders. But the methods preferred by women have shifted over time. While self-poisoning remains common, since the 1960s and 1970s use of this method has decreased, perhaps in part because of changing prescription practices and, in part, because of other social changes. In 1970, 47.9% of suicides committed by women were by poisoning compared to 34.6% in 1993. In 2002 both women and men were most frequently the victims of self-inflicted gunshot wounds (54%), while self-poisoning accounted for only 17.3% of all suicides.[41]

The tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) are the most common drugs implicated in suicide because of their toxicity and frequent use in the populations at risk. The decline in self-poisoning may be related to decreased use of these potentially more lethal medications.[21, 37] Data from the Drug Abuse Warning Network suggest that newer antidepressants are significantly safer in overdose. Although the risk of an attempt is roughly similar, the risk of death is 8.5 times greater with desipramine than fluoxetine.[40]

Psychiatric Management of Self-Poisoning

Table 18-1 depicts a case of suspected self-poisoning from the starting point of prehospital care through the completion of a comprehensive assessment and treatment planning.

Focused Psychiatric Assessment

At a relatively early point in the patient's course, when the patient can be cooperative, a focused psychiatric assessment is critical to address specific clinical concerns. A thorough psychiatric consultation is warranted, once the patient is medically stable. The determination that the patient is stable is not solely established on the basis of blood concentrations of a xenobiotic or ancillary medical tests, but rather when the emergency physician or medical toxicologist with an understanding of pharmacokinetics deems it appropriate. Psychiatric examination is warranted when the altered mental status has cleared. There are several reasons for this approach.

Patient course
Patient found in the community unresponsive
Patient monitored in the ED; vital signs stable; still unresponsive
Patient lethargic but cooperative; answers simple questions
Patient fully awake and alert
Evaluation complete
Treatment course
Prehospital
Triage
Medical assessment
Observation and monitoring
Formal psychiatric evaluation
Treatment planning
Physician course

Patient identification
Search for prescription drugs, drug paraphernalia
Assessment of cardiac and respiratory functions
Orogastric lavage(?)
Activated charcoal
Diagnostic testing (blood studies, ECG, toxicology)
Contact collateral sources for history
Prior records
Focused psychiatric assessment: elopement, aggressive behavior, decisional capacity, addressing confidentiality, and immediate suicide risk
Comprehensive psychiatric assessment: diagnostic interviewing, risk factors, future risk
Treatments: medication, hospitalization, substance abuse, crisis intervention family therapy

Case Evolution Disposition

TABLE 18-1. Case Presentation: Suspected Self-Poisoning

The physician should not unequivocally attribute altered mental status to poisoning or intoxication until the signs of altered consciousness have resolved and cognitive functions have returned to normal. Until that time, other toxic metabolic and structural conditions that might coexist with, or masquerade as, intoxication cannot be excluded. If the patient's cognitive functioning is impaired by xenobiotics critical historical details may be unreliable. It should be understood that much of what the patient reports may be ephemeral, caused by the predictable temporary and reversible effects on mood of these xenobiotics.

A focused assessment is necessary to ascertain elopement risk or decisional capacity. Subacute residual CNS effects of ingestions such as confusion, fatigue, and fear can dispose patients to wander or elope. Additionally, the patient's intentions remain

unclear at this point, and the question of unintentional versus intentional exposure to a xenobiotic cannot be completely resolved. For these reasons, a high level of supervision should be maintained, and a patient should not be allowed to leave until an adequate assessment of the patient's mental status is completed. Depending on the architecture and organization of the ED and personnel, it may be sufficient to place the patient in an open area in the direct line of sight of nursing staff. If such an arrangement is not possible, or if the patient is agitated and disruptive, it may be necessary to separate the patient from the general population. Under these circumstances, an individual aide should be assigned to observe the patient on a â€œone-to-oneâ€• basis. Safe physical and/or chemical restraints may be necessary to prevent further injury both to patient and staff.

In general, patients are presumed competent and must consent to treatment, but the issue of decisional capacity frequently arises. Patients may request their discharge, refuse care, or become aggressive. Aggression may arise from lingering effects of a toxic ingestion, severe anxiety, fear, anger at the loss of autonomy, or the discomfort associated with unpleasant procedures. Although patients may respond to verbal limit setting and repeated explanations of

their care, they may also require chemical (pharmacologic) or physical restraint and involuntary treatment. Patients are not allowed to make poor healthcare decisions if their ability to weigh the risks and benefits of the proposed care is limited by cognitive deficits or mental illness. In the setting of intoxication, appropriate care may be provided under the doctrine of implied consent.

The emergency exception to the doctrine of informed consent may also apply in circumstances where self-injury is suspected. The emergency exception permits forcible detention, restraint, medication over objection, and necessary medical care until

psychiatric assessment can be accomplished. After the management of the immediate medical emergency and resolution of intoxication, suspected self-injury is sufficient evidence of impaired decisional capacity for the emergency physician to hold a patient for further psychiatric assessment. The emergency physician should note the patient's objections in the patient's medical record and indicate the basis for the determination of diminished capacity.

After the intentionally self-poisoned patient is stabilized, there may be a need for a more thorough assessment of decisional capacity. Psychiatric consultation is appropriate at this stage to help document the degree of impairment, determine the etiology, and predict the likely course.

Immediate Risk

After these safety considerations have been addressed, the aim of the focused psychiatric assessment moves toward a determination of immediate suicide risk. This examination should answer the following questions:

- What is the patient's attitude toward lifesaving care?
- What are the patient's current wishes with regard to living or dying?
- What are the patient's thoughts about his or her rescue and likely recovery?

These questions can only be answered in the course of a frank discussion between the patient and the emergency physician. The physician should not be concerned about â€œprovokingâ€• further self-injurious impulses by having this vital discussion; many patients will be relieved that the healthcare provider is speaking directly about their distress.

Reliability and Confidentiality

Mention should be made here about the difficult issues of reliability and confidentiality with regard to gathering history. Evasiveness, lack of detail, inconsistency, and improbability may lead to an unreliable history. It is appropriate to confront the patient with the implausible aspects of this history and offer an opportunity for the patient to rethink his or her history. This is often successful, although subsequent reports are, of course, equally suspect.

The most important step from the standpoint of both clinical care and risk management is to locate other sources of information to clarify the patient's situation. A careful review of any previous medical and psychiatric records is critical. Any pattern to a patient's presentations such as increasing frequency, more aggravated behavior, or disheveled appearance should be noted.

Collateral contacts are another important source of information, although the level of involvement, sophistication, and reliability of the collaterals must also be taken into account. In the interest of providing necessary medical and psychiatric care for a patient, the ED staff may make contacts that are limited to soliciting information without specific consent. An effort should be made to obtain consent for any broader discussion with family, friends, or other physicians. The patient may express concern about the ED staff contacting a family member or counselor. Any information to be imparted to third parties can be negotiated in advance with the patient. The patient may restrict consent to receiving information only and may withhold consent to impart certain information. More caution is indicated in contacting an employer. Although disclosing information about the patient without the patient's consent is a breach of confidentiality, a physician may do so in the interest of protecting the patient.[5]

Comprehensive Psychiatric Assessment

The comprehensive psychiatric assessment includes a characterization of the suicidal ideation present, exploration of certain so-called risk factors, and the formulation of a diagnostic impression. These three elements help to determine the attendant risk and guide treatment planning.

Stress Vulnerability Model

The best understanding of suicide at this time is that it results from intrinsic vulnerability factors interacting with extrinsic circumstances. Intrinsic vulnerability may be conferred by a variety of traits such as impulsivity or conditions such as depression, anxiety, and hopelessness. Extrinsic factors include stressful life events, access to lethal means, and a host of other factors, positive and negative.

Characterization of Suicidal Ideation

The core of the suicide risk assessment is a detailed discussion of the patient's suicidal thoughts and urges. This must be included in every mental status examination. It is important to establish rapport and introduce the topic in an appropriate context in order to improve the patient's candor. This evaluation requires significant time and skillful interviewing, for which there is no substitute. This approach will enhance the therapeutic quality of the interview as well as its reliability. For example, almost everyone has had some period in life when he or she was discouraged. The clinician may spend a few moments talking with the patient about the point in life when the patient was most disheartened. This is done by asking the patient if he or she has been feeling â€œdownâ€• lately; and if the patient has, by asking if this is the worst the patient has ever felt. If the patient denies recent depression altogether, or indicates that this is not the

worst, it is helpful, for several reasons, to ask the patient to describe the point in his or her life when the patient felt worst. Depression may fluctuate markedly, and characterizing the worst period assures that a prior history of major depression will not be overlooked.

At some point, the physician should ask if, during that worst period in the patient's life, the patient ever felt that perhaps things would never get better (hopelessness), that he or she could not go on (helplessness), or perhaps that he or she would be better off dead (passive suicidal ideation). If failing others was involved in the patient's demoralization (guilt), the physician should ask if the patient had ever felt that others would be better off without him or her. These are common thoughts that most people can endorse without much difficulty and lay the groundwork for discussing more troublesome ideas in the suicidal spectrum. Ultimately, the patient must be asked directly if he or she has ever felt like â€œkillingâ€• himself or herself (active suicidal ideation). Nothing else

will do. The more generic form, â€œhurtingâ€• himself or herself, which might seem to cover more, is in fact confusing to patientsâ€”even those who wish to die do not usually consciously intend to be hurt in the process. The latter is more typical of multiple suicide attempters than suicide completers.

For those patients who have felt like killing themselves at some point, the next step in this scenario might be to establish how the patient is currently and to compare this to a prior episode(s). One dimension to assess is the progression from passive to active suicidal ideation. Suicidal feelings may take the form of a relatively inchoate wish to die, perhaps from a fatal disease or injury, and then proceed to consideration of various active means of hastening death. Planning might range from fleeting thoughts or images of a variety of methods from which the patient recoils, to a more detailed consideration of a particular, realistic method of

choice, to serious planning concerning acquisition of the means, and so-called last acts. At some point the patient goes beyond thinking to acting by hoarding pills or completing his or her will. An astute family member may observe a series of odd conversations including phone calls to distant friends and family members as the suicidal individual begins to implement the plan with a series of vague farewells. In psychological autopsy studies, approximately 50â€“70% of those who completed suicides gave some warning of their intention and 30â€“40% of individuals who completed suicides disclosed a direct and specific intent to kill themselves.[8,63]

Other dimensions to assess include frequency, urgency, chronicity, reactivity to positive and negative external events, and subjective distress. Table 18-2 presents a schema for the detailed characterization of suicidal ideation.

The communication of suicidal ideas either directly or indirectly should not be misconstrued as a â€œcry for helpâ€• and hence evidence of lower risk. Communication is probably related to the degree of preoccupation with morbid thoughts and to personality characteristics that dispose individuals to revealing their thoughts to various degrees.[42]

The risk of suicide increases 50 to 100 times within the first 12 months after an episode of self-harm, compared to the general population risk. About half of all people who commit suicide have a history of self-harm and this ratio increases by 60% in juvenile age groups.[6]

Onset
None, acute
Chronic, stable
New or fluctuating
Frequency
Occasional

Daily
Constant
Pesistence
Fleeting thoughts
Persistent thoughts
Preoccupation
Urgency
Disinterested
Engaged
Intense
Complexity
Simple
Some detail
Elaborate
Activity
Passive ideas
Plans without action
Action
Emotional response
Death repellent
Ambivalent
Death desirable
Circumstances
Victim identifies one clear precipitant
Several complex contributory stressors
Either noncontributory or overwhelming stressors
Alternatives
Some, realistic
Few, problematic
Seems hopeless
Insight
Recognizes remediable psychological problem
Overvalued ideas present, temporarily reassured
Morbid delusions present, reassurance impossible

Intent
Opposed to suicide
Suicide acceptable but prefers to live
Resolutely suicidal

Dimension Benign Intermediate Malignant

TABLE 18-2. Characterization of Suicidal Ideation

While much is known about the risk of suicide for various groups over time, little can be said with certainty about an individual patient at a particular point in time. There is no one type of â€œtypicalâ€• suicidal patient or clinically useful test or rating scale at this time. Albeit, while one investigator was able to prospectively identify almost all of those who ultimately died by suicide (97% sensitivity), the investigator overpredicted suicide by almost half (56% specificity).[60] However, there is also no patient in distress for whom the risk of suicide is so remote that it need not be considered. Assessment of the potentially suicidal patient begins with a screen for psychiatric illness, substance abuse and history of self-harm.

Psychiatric Illness and Suicide

One major consideration in suicide risk assessment is the occurrence of severe mental illness. Suicide risk for individuals with severe mental illness is 20â€“40 times higher than it is for the general population.[41] Psychological autopsy studies in the United States and Europe over the years have consistently revealed major psychiatric illness to be a factor in suicide, present in 93% of adult suicide cases.[39, 41, 61, 64] This is also true of those who make medically serious suicide attempts.[10, 39] In particular, prospective cohort studies and retrospective case control investigations have revealed clinical depression and bipolar disorder to dramatically increase suicide risk.[16, 42, 75] For mood

disorders, factors correlated with acute suicidality have included current depression, severe anxiety, anhedonia, panic, insomnia, ambivalence, and acute alcohol abuse.[42] After mood disorders, chronic alcoholism is the most commonly reported disorder; it is present in approximately 20% of cases. Moreover, alcoholic patients who also suffer from periodic episodes of depression are at more risk for suicide than patients who present with either disorder separately. As a result, any assessment conducted on a patient with a substance abuse history must include an examination of symptoms of major depression or bipolar illness.[26, 76]

Schizophrenic patients are at risk for suicide at rates comparable to major depression and are 20 times more likely to attempt suicide than the general population.[74] Approximately 50% of schizophrenic patients will attempt suicide and 13% of schizophrenic patients will complete suicide.[13, 74] Additionally, between 5 and 18% of patients with severe borderline personality disorder (especially patients who are comorbid for depression) ultimately

kill themselves.[28, 69] Figure 18-1 shows the odds of suicide attendant to various conditions.[39]

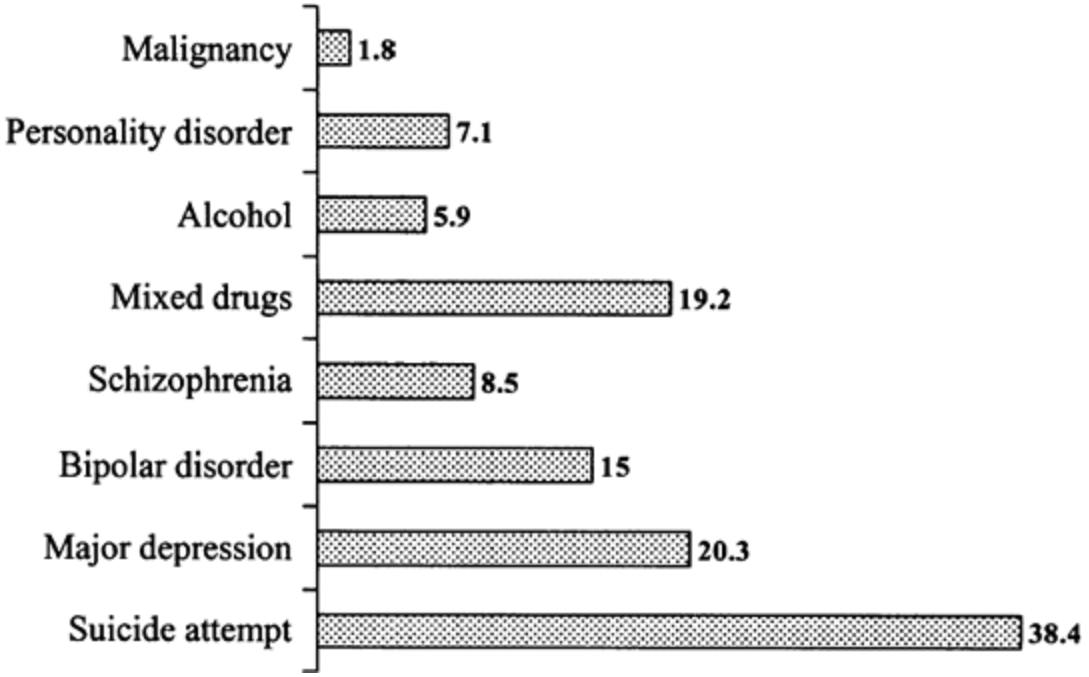

Figure 18-1. Increased likelihood of suicide for various conditions. *(Data adapted from Inskip HM, Harris EC, Barraclough B: Lifetime risk of suicide for affective disorder, alcoholism and schizophrenia. Br J Psychiatry 1998;172:35â€“37.)*

The ability to treat psychiatric disorders such as mood disorders, schizophrenia, and alcoholism suggests that most suicides are preventable. Intentional self-injury, consequently, represents a major, but preventable, US public health problem.

Indeed, a suicide prevention program directed at general practitioners in Sweden was able to demonstrate prevention based on the detection and treatment of depression.[62] The possibility of preventing suicide necessitates a comprehensive psychiatric assessment to identify contributory psychiatric disorders.

The Centers for Disease Control and Prevention (CDC) reported that psychiatric problems in US emergency departments represented approximately 3% of the visits, which is significantly lower than the national psychiatric rate of 20â€“28%.[15] This suggests significant psychiatric underdiagnosis is occurring in the

ED. Emergency physicians, consequently, must enhance the comprehensive nature of their psychiatric screens in order to pick up suicidality and concomitant mental disorders in presenting self-injurious patients.

Demographic Risk Factors

A complete assessment should also include an examination of demographic risk factors. Factors have been identified empirically that place groups of individuals at high risk for suicide. Although this level of prediction is actuarial and reflective of groups rather than individuals, knowledge of these risk factors is important.[50] Although not specifically predictive, suicide is statistically more common in men than women and in whites than in nonwhites. Younger black men, however, have approximately the same suicide rate as white men of the same age. Suicide rates for both black and white adolescents (15 to 19 years of age) have been increasing. In contrast, suicide rates in the those over 65 years of age have decreased 3-fold since 1940, but still occur in disproportionately high numbers.[41, 75]

Previous suicide attempts are an obvious risk factor. However, those who attempt suicide appear to be a somewhat different group demographically and diagnostically. Parasuicidal behavior is more common in 25- to 44-year-olds than in the elderly, and more common in women than men. Existing data also indicate that nonfatal suicide attempters are equally prevalent across racial and ethnic groups.[25, 54] Most individuals who kill themselves seem to do so on the first attempt. Although that suicide attempt is still the strongest predictor of suicidal outcome, only about 1 in 10 attempters is ultimately successful.[35, 60] Multiple attempters also appear to have higher risk than those who make a single attempt.[32, 70] Medically serious attempts may be a better marker of risk. Those who make serious attempts tend to share with completers a higher rate of serious mental illness.[9]

A number of avenues of inquiry suggest that violent suicide attempts are associated with a persistent deficiency in brain serotonin levels. Impulsive types of aggression and impulsive suicidal behavior have been linked to serotonergic dysfunction in prefrontal cortical regions of the brain.[23] This deficiency has been measured in postmortem brains and spinal fluid of suicide victims and survivors of violent attempts compared to nonviolent attempts and to other patients. Serotonergic deficiencies persist during periods of acute psychiatric illness as well as remission. Hopelessness has also received a significant amount of study as a potential predictor of suicide. However, hopelessness appears to have high sensitivity but low specificity.[10] Identifying hopelessness as a problem also suggests possible interventions.

Ultimately, most persons belonging to a high-risk group do not commit suicide, and some individuals with no apparent risk factors do. Many risk factors are not modifiable. This type of information, then, weighs most heavily in the assessment in the absence of other more specific data, early in the hospital course, or in the case of the uncooperative or hostile patient. The best foundation for treatment planning and clinical decision making is direct examination and clinical diagnosis.

Treatment

Following the comprehensive psychiatric assessment, the next step is deciding on treatment alternatives. Any patient who has made a suicide attempt must be considered to be at risk, and some further intervention is warranted. The risk of a subsequent lethal attempt is approximately 1% per year over the first 10 years. The risk is highest in the first 1 month to 1 year.

The treatment alternatives available will depend on the psychiatric sophistication of the staff available to the ED at any given time. This section describes the commonly used interventions in the ED; they can be used singly or in combination.

Medications can be used acutely in the treatment of severe anxiety or psychosis; however, in the case of antidepressants, a period of weeks is required for therapeutic effect, so their immediate use is not indicated in the ED. In fact, there are concerns about prescribing medications with relatively high potential for lethality in overdose, such as the cyclic antidepressants and nonselective monoamine oxidase inhibitors, to persons who have recently attempted suicide. However, newer antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs), can be used as first-line drugs for treatment of most depressions and are relatively safe in overdose. A marked drop in the number of deaths per million antidepressant prescriptions was observed between 1970 and 1974 in Europe.[37] Nonetheless, the initiation of antidepressant therapy by the nonpsychiatric physician is not recommended unless a tight linkage can be made between discharge and immediate (within days) aftercare by either a community outreach team or a crisis clinic.

Patients with depressive disorders may suffer from significant anxiety, as may patients with overwhelming situational stressors such as job loss, new financial hardship, bereavement, or divorce.

The prescription of a short course of a benzodiazepine may provide significant relief to the patient in crisis.

After the patient's immediate symptoms have been treated in the emergency department, the next treatment decision is determining the setting in which further treatment may safely be provided. Not all patients with suicidal ideation or even significant attempts necessarily require hospitalization, and there is still a substantial stigma attached to psychiatric hospitalization. In general, it should be the treatment used if less restrictive measures cannot insure the patient's safety. If significant doubt exists about the safety of outpatient treatment, the patient should be held in the ED for further evaluation, admitted to a general hospital with close

nursing supervision, or admitted to a psychiatric unit. â€œHolding bedsâ€• now available in some larger psychiatric emergency departments are ideal for this purpose. Some localities may also have crisis outreach services that follow the patient after discharge from the ED and improve appropriate monitoring and continuity of care.

Patients most likely to respond to interventions in the ED are individuals who until recently have been stable but who, as a result of some external event, find their way of life threatened. This acute change results in a painful state of anxiety and the mobilization of some combination of adaptive and maladaptive coping strategies. Finally, a second event, the precipitant, intensifies the anxiety to the point that the patient cannot tolerate the instability and is thrown into crisis. The patient then feels desperate and may be completely immobilized or vulnerable to various strong impulses including the impulse to run away, strike out at someone else, or kill himself or herself. Reality testing is preserved, and no major psychiatric syndrome is present. The patient accurately perceives his or her situation, understands that the current reaction is a psychological problem, and is highly motivated to obtain help. The crisis may last for a matter of hours or weeks prior to the ED presentation and will ultimately resolve. Such patients respond well to crisis intervention and may actually undergo some positive development in the course of treatment.

By contrast, patients whose condition has been deteriorating for some time in the absence of significant stressors, and who appear on examination to be suffering from severe depressive symptoms, are unlikely to benefit rapidly from supportive techniques. If such patients present with suicidal ideation or attempts, it will be difficult, though not impossible, to manage them outside the hospital.

Outpatient settings have the advantage of maintaining the patient's functioning as much as possible. Work and child care

responsibilities, financial obligations, and social relationships are not disrupted. Unnecessary regression is halted. The patient is able to assume more responsibility for his or her outcome, and independence helps preserve self-esteem. These individuals remain closer to and more engaged with the people and situations with whom and with which they must learn to cope. Their morale may be rapidly improved by the combination of support, planning, and modest early treatment successes.

In some cases, though, these same factors may be disadvantageous. Routine tasks may seem overwhelming. High levels of conflict may render major relationships at least temporarily unworkable. Inpatient settings offer the advantage of respite, high levels of structure, more intensive professional and peer support, constant supervision, and, usually, more rapid pharmacologic and psychosocial intervention. The physical plant also reduces, although it cannot eliminate, the possible means of suicide.

The choice of inpatient or outpatient setting will depend on the balance of strengths and weaknesses of the patient, the involvement and competence of family or friends, the availability of a therapist in the community, and the ongoing stresses in the patient's life and this decision is best made by a psychiatrist. Because a psychiatrist is not always present in many facilities, a trained mental health professional should be on call to every emergency department. This may be a psychiatric social worker, nurse clinician, or psychologist. When such services are not available, it is appropriate to detain patients in the ED until a practitioner with specific competence is available or to transfer the patient to another facility for evaluation. Every state has laws that provide for the involuntary commitment of the mentally ill under circumstances that vary from state to state. Any acute, deliberate self-injurious behavior would generally qualify. Chronic, repetitive dangerous behavior that is not â€œdeliberate,â€• such as frequent unintentional opioid, alcohol, sedative-hypnotic, or illicit

â€œrecreationalâ€• psychoactive drug overdoses warrant careful evaluation. In the absence of psychiatric illness, involuntary treatment is usually not necessary. The practitioner should be familiar with the criteria for commitment and the classes of healthcare providers so empowered under state law.

There are other treatment interventions that can be provided in the emergency setting, including crisis intervention, substance abuse counseling, and family therapy. A single session in the ED may be sufficient to defuse a crisis or to spur the drug-abusing patient to seek help. Alternatively, the intervention may be initiated in the ED and continued as an outpatient.

Crisis intervention is a brief, highly focused therapy that seeks to deconstruct how a crisis occurred, with an the intent of examining the patient's role. Often, patients have distorted perceptions of the crisis, and a gentle â€œcorrectionâ€• of catastrophic thinking can be extremely helpful. An example follows:

- Patient: â€œI'm going to be broke and unemployed the rest of my life.â€•
- Physician: â€œHow did you get your last job?â€•
- Patient: â€œWell, I interviewed a couple of times.â€•
- Physician: â€œSo people have hired you in the past, right?â€•

The crisis is presented to the patient as an unfortunate and perhaps tragic experience that the patient can overcome. Ideally, the patient should have a relief of symptoms and learn how crises may be avoided in the future. This insight intervention will likely fail for patients with severe depression because of the presence of profound hopelessness. It is best used for patients who give a history of high functioning just prior to the crisis.

Substance abuse treatment is ultimately an intermediate (weeks to months) to long-term (months to years) intervention. However,

there are powerful initial steps that the emergency physician can take. Chief among these is confronting the patient about the medical consequences of substance use. This can take the form of discussion only, or the physician can invite the patient to examine clinical laboratory results or view remarkable clinician/diagnostic findings (hepatomegaly, repeated fractures from falls, increased liver enzymes or evidence of â€œsilentâ€• past myocardial infarction). There is little to be lost from a respectful but blunt confrontation of the patient's deterioration, and he or she may listen to a physician rather than family or friends. Peer counseling is particularly useful in addictive disorders; if possible, patients should be referred to community 12-step programs such as Narcotics Anonymous and Alcoholics Anonymous. Family therapy can occur as a series of sessions over the long-term or can be useful in the emergency setting to defuse a crisis, reinstate social supports for the patient, or

educate families about mental illness. It is most important to respect a patient's request as to the level of family involvement, because in the emergency setting, a patient may be either too angry or ashamed to confront his or her family. It is prudent to defer to the patient's wishes, and to assure the family that the patient is safe and that you will keep them as informed as confidentiality and discretion allow at a later date.

Violence

Aggression also presents unique challenges to the emergency physician. Moreover, aggression is intimately related to suicidal behavior. Chronic aggression and impulsivity are risk factors for suicidal behavior. Also like suicidal patients, aggressive patients are difficult to treat and they tend to elicit strong negative reactions in ED personnel.[66] In one study of violence in the ED, directors of residency programs in emergency medicine were surveyed as to the frequency of verbal threats, physical attacks,

and the presence of weaponry in the area. Of the 127 institutions surveyed, 74.7% of the residency directors responded; 41 (32%) reported receiving at least one verbal threat each day; moreover, 23 (18%) reported that weapons were displayed as a threat at least once each month. Fifty-five program directors (43%) noted that a physical attack on medical staff occurred at least once a month.[45] In a second study, the authors conducted a retrospective review of university police log records and ED staff incident reports to examine the problem of violence in the ED setting. Almost 75% of the incidents occurred during the evening or night. Of the 686 episodes of violence in this study, more than 25% required physical restraint or removal from the premises. In addition, it was found that the police responded to the ED nearly twice daily.[59] These studies underscore the need for timely identification of the violent patient, as well as appropriate management for this diagnostically heterogeneous group. The assessment and management of the violent patient should include provisions for patient and staff safety as well as a thorough search for the cause of violent behavior.[66] This section addresses the differential diagnosis of violent behavior, the pharmacotherapy of aggressive and/or agitated behavior, and the use of seclusion and restraint. It also provides an overview of potential risk factors for violent behavior.

Stress-Vulnerability Model of Aggression

As in the case of suicide, there are many and varied causes of violent behavior, some more social and some more medical in nature. It is most helpful to think of violence as the outcome of a dynamic interaction among numerous factors both intrinsic and extrinsic to the individual, some of which promote and some of which ameliorate the potential for violent behavior at any given moment. This is the stress-vulnerability model. Education may

provide alternatives to violence, but delirium may cause an otherwise nonviolent person to misinterpret healthcare efforts, in which case, education is of no benefit at that time. Hence, the individual becomes violent under circumstances that would not normally be sufficient to provoke a violent outburst. Some patients, on the other hand, come from cultures in which aggressive behavior is more acceptable, and these patients require little stress or provocation before responding in what can be perceived as aggression by western cultural standards.

In the ED, likely medical sources of vulnerability include metabolic derangements, exposure to xenobioticsâ€”both licit and illicit, withdrawal syndromes, seizure disorders, head trauma, psychotic states, and personality disorders. Additionally, patients with severe pain, delirium, or extreme anxiety can respond to the efforts of emergency personnel with resistance, hostility, or frank aggression.

Prediction

Research on risk factors for community violence may not apply to the prediction of inpatient violence. Some researchers have postulated that violence committed outside the hospital may not be predictive of inpatient violence and that hospital violence may result from the interaction of patients with specific factors found in the hospital environment.[36 , 66] Other studies are contradictory.[58 , 68] Consequently, prior violence is not a perfect predictor of future violence. Other factors, such as mental illness and substance abuse, need to be examined in order to make meaningful predictions of inpatient violence for each individual case.[66] One study found that the most common types of hospital violence were incidents of aggression against objects in the hospital (56.7%), violence directed against the hospital staff (27.8%), and violence directed against other patients (14.4%).[67] In this study, men were not found to be committing significantly

greater incidents of violence than women. Other studies concur that male patients are not necessarily more of a risk for inpatient violence than female inpatients. For example, researchers examining inpatient violence found that close to half of the violent incidents were committed by female patients,[43, 61] and the number of violence-related injuries committed by male and female inpatients were almost proportional to the ratio of male and female inpatients on the unit. The conclusion was that gender should not be considered a risk factor for inpatient violence. Long hospitalization was not considered a factor predictive of violence for the majority of inpatients. As with outpatient violence, the correlation of violence with younger age appears to hold true in the inpatient setting.[53, 61, 62]

Substance Use

The association between substance use and violence is well established. Alcohol is found in the offender, the victim, or both in one-half to two-thirds of homicides and serious assaults.[17, 61] Substance abuse is seldom the sole cause, but it may contribute to violence in a number of ways. The direct pharmacologic effects include disinhibition and misinterpretation, suspiciousness, or paranoia. Psychological effects of substance use include cultural expectations of appropriate behavior under the influence and the ability to excuse or disavow inappropriate behavior that occurs while intoxicated. Substance use then interacts with other physiologic, cognitive, psychological, situational, and cultural factors including any underlying mental illness. A tripartite model has been described: (a) systemic violence related to drug distribution, (b) economic compulsive violence associated with the criminal activity necessary to sustain a drug habit, and (c) psychopharmacologic violence resulting from the direct effects of the particular xenobiotic.[30, 31]

Mental Illness

The relationship between mental illness and violence is also complex. Efforts made to destigmatize mental illness have confused the issue, but it seems clear that mental illness is associated with a greater risk for violence.[61] In one large epidemiologic study, the prevalence of violence for those with no disorder was 2%. Schizophrenia was associated with an 8% rate of violent behavior, and other mental disorders all had similar prevalences of approximately

12%. But of all respondents reporting violent behaviors, 42% had a substance use disorder. Substance use more than tripled the rate of violence for individuals with schizophrenia. Mental illness appears to reduce the threshold for aggression, and the more comorbid conditions present, the greater the risk.[71, 72]

Researchers are consistently finding a greater prevalence of personality disorders among violent inpatients than among nonviolent inpatients.[55] However, antisocial personality is the condition most strongly associated with both substance use and aggression. In one study, when the history of juvenile deviance was controlled, alcohol, the drug most commonly associated with violence, accounted for only 2% of the violent behavior.

In conclusion, some aggressive behavior is attributable to the direct pharmacologic effects of xenobiotics, but probably represents only a modest fraction. Substance use is also a part of the setting of violent behavior in the community, a coincidental part of the lifestyle of violent individuals and both substance use and violence are related to common underlying characteristics such as a character disorder.

Medication Noncompliance

Many research studies currently list medication noncompliance as

a risk factor for violence that is as serious as substance use or mental illness. One such study associated medication noncompliance and substance use with increased violence risk in the mentally ill.[73] It suggested that medication noncompliance may lead to self-medicating through the use of illicit xenobiotics, and substance use may lead to further medication noncompliance. These two factors together may then have the effect of increasing violence for the mentally ill. This study also suggested that low insight into their illness can be associated with greater violence. However, they found that poor insight was correlated with substance use and medication noncompliance, so it is unclear if poor insight is truly predictive. Other studies have replicated these findings.[72]

Patients entering the ED who did not adhere to their medications as outpatients may be more of a risk for inpatient violence. Furthermore, inpatients who refuse to adhere to medication prescribed in the hospital also are more of a risk for violence, especially when comorbid with substance abuse disorders.

Additional Factors in Aggressive Behavior

Many of the factors correlated with aggression are easy to observe and monitor in the hospital. However, some additional factors that influence violent behavior may not be as easy to detect. For example, one study examining violent behavior found that most violent incidents in the hospital occur on Mondays and Fridays, with very few incidents on weekends.[44] These violence research investigators suggested that the analysis was comparable in the general population as Mondays and Fridays have special significance in the workweek and weekends are usually less stressful. This finding illustrates the point that seemingly minor social stressors can be as conducive to violent behavior as any other factor.

Furthermore, researchers have postulated a seasonal variation of violence.[19] They reported finding an increase in the frequency of assaults by inpatients during the winter months and hypothesized that increased population density, cold temperature, and less sunlight during the day could account for the increased violence. This finding is in contrast to the literature on outpatient violence, which has reported greater incidence of violence during the warmer months.[7] However, this same review conceded that any extreme temperature could evoke aggressive feelings and frustration. Yet another study examined the relationship between temperature and violence and found that more aggressive acts occur during the summer months, both in the hospital and in the community.[27] They cited several explanations, one of which was that the high rate of staff turnover, as vacations are taken, disrupts the social networks that the patients have established, evoking aggressive feelings.

Although it is unclear whether the cold can provoke aggression as much as it has been established that heat can, it does seem clear that overcrowding and social stressors can lead to violent behavior. If the effects of temperature and social stressors (eg, holidays) correlate so drastically with violence in the community, it is likely that such effects would have even more impact when comorbid with severe mental illness, substance use, or any of the other risk factors of aggression.

Assessment

The comprehensive evaluation of the violent patient should include a complete physical examination. The examination may reveal the underlying cause of the violent behavior as well as insuring the treatment of any secondary patient injuries. Laboratory analysis may include blood chemistries (thyroid-stimulating hormone, glucose, electrolytes including calcium and liver enzymes), a complete blood count, lumbar puncture and neuroimaging as

guided by the examination and clinical history.

Illicit xenobiotic and alcohol use often present with symptoms of violence. Acute intoxication with cocaine can produce extreme psychomotor agitation, delirium, and transient psychosis characterized by paranoia and hallucinations; a clinically indistinguishable syndrome can be seen following the ingestion of amphetamines. Phencyclidine intoxication is manifested by assaultiveness, muscle rigidity, dysarthria, nystagmus, autonomic instability, and ataxia. Alcohol intoxication is characterized by typical signs of cerebellar dysfunction such as slurred speech, gait ataxia, and incoordination; however, patients who are intoxicated are also at risk for violent behavior. Cannabis does not typically produce violent or aggressive behavior but paranoia can occur with intoxication and can secondarily promote reactions of extreme fear associated with distorted perception, as can occur with lysergic acid diethylamide (LSD) and psilocybin, particularly in the naive user.

Withdrawal syndromes from specific xenobiotics can also promote aggressive behavior as a consequence of physical discomfort or anticipatory anxiety. Opioid withdrawal is characterized by myalgias, rhinorrhea, and piloerection with a clear sensorium, whereas alcohol, benzodiazepines, and barbiturates share a common syndrome of autonomic hyperreactivity, seizures, and subsequent delirium. Patients suffering from any of these signs and symptoms may become aggressive, verbally abusive, or threatening. Prompt recognition of these syndromes and immediate treatment can prevent some aggressive outbursts. Because drug use is often concealed, is difficult to ascertain on clinical grounds, and frequently contributes to violent behavior, urine and blood toxicologic studies may be useful to enhance the understanding and long-range treatment of some patients.[61]

Delirium can be a cause of aggression. Patients are often suddenly confused, frightened, or frankly psychotic as a result of impaired

perception. Patients may require sedation or physical restraint in order to prevent injury to themselves as well as staff.

Although persons suffering from psychotic disorders are not generally aggressive, there are aspects of the psychotic state that

place patients at risk for aggressive behavior. Paranoid ideation can serve to promote misperceptions of impending bodily harm (â€œThey're trying to kill meâ€•), sexual victimization (â€œMen and women are raping meâ€•), and humiliation (â€œEveryone is laughing at meâ€•). It follows that these fearful perceptions might provoke violent reactions in a patient. Hallucinations can cause aggression, either as a result of command hallucinations or in reaction to the anxiety and irritation that patients experience with loud or persistent auditory hallucinations (â€œhearing voicesâ€•). Patients with either borderline or antisocial personality disorder are at risk for violent acting out as a result of poor impulse control.

Violence risk has also been associated with cognitive dysfunction. Both acute mental illness and chronic substance use can result in neurologic impairment. Psychiatric patients with compromised cognitive abilities such as impaired attention, memory, or executive functioning such as reasoning and planning have been found to be at increased risk for violence.[61] Patients presenting with cognitive impairment may also be at increased risk for committing acts of violence in the ED.

Treatment

The acute pharmacotherapy of violent behavior is directed simply at reducing the level of arousal. A recent review of this issue proposed a model for the efficient use of medication for the control of episodic, as opposed to chronic, agitation and aggression.[3] In this model, agitation and violent outbursts are viewed as transient disturbances of the usual treatment

relationship between the physician and patient. Pharmacotherapy and seclusion or restraint are to be used only as needed to restore that relationship, for the benefit of the patient as well as other members in the environment. The restoration of the treatment relationship is necessary in order to take measures to understand and address the cause of the agitation, with the input and consent of the patient, thus preventing future incidents. For this reason, sleep is considered an undesirable use of medication. Sleep delays, rather than promotes, assessment, may further frighten or anger the patient, and does not even guarantee elimination of the agitated state on awakening.

As aggression derives from varied and multiple etiologies, it follows that there is much debate about the specific sedative that should be used, the route of administration, and the dosing interval. Studies examining the treatment of aggression and/or agitation have included such diverse populations as schizophrenics, acutely intoxicated patients (alcohol), trauma patients, postoperative patients, patients in alcohol withdrawal, and patients with presumed personality disorders. Treatment settings for these studies included psychiatric inpatient units, intensive care units, and the ED.[1,12,14,42,43 and 44] An excellent review examined a number of these studies, finding that both benzodiazepines and antipsychotics resulted in rapid control of agitation and aggression.[24]

It seems, however, that there are specific clinical situations when benzodiazepines and antipsychotic agents might be preferentially used. Haloperidol has been safely used in the treatment of agitation and aggression in patients with psychoses, acute alcohol intoxication, and delirium.[2,14,42,43] The drug can be administered orally, intravenously, or intramuscularly. Dosing intervals range from 30 minutes to 2 hours, with a usual regimen of haloperidol 5 mg given every 30 to 60 minutes; most patients respond after 1 to 3 doses. The dose of haloperidol needed to achieve sedation rarely exceeds a total of 50 mg in acute

management.

Benzodiazepines are also quite effective for sedation; their use has been examined in patients with psychoses, stimulant intoxication, sedative-hypnotic and alcohol withdrawal, and postoperative agitation.[1,29,52] Lorazepam 1 to 2 mg may be given orally or parenterally and repeated at 30- or 60-minute intervals, respectively, until the patient is calm. Because diazepam is poorly absorbed from intramuscular sites, its route of administration is either intravenous or oral. Diazepam may be given as 5 to 10 mg IV, with repeat dosing titrated to desired effect. Concerns regarding respiratory depression mandate careful observation of patients receiving sedation with these agents. Benzodiazepines may have a unique role in the treatment of agitation secondary to cocaine intoxication, as seizures may develop in this syndrome (Chap. 74). Antipsychotics, particularly low-potency antipsychotics, are known to lower the seizure threshold in animals, so their use for patients with cocaine intoxication should be avoided. Studies have examined the use of combinations of lorazepam with antipsychotics in patients with psychiatric illness and delirium and it appears that the combination of benzodiazepines and antipsychotics afforded relief of psychotic symptoms while allowing for a reduced dose of antipsychotic medications.[2,18,65]

Physical Restraint

Isolation and restraint are also used in the treatment of violent behavior. Isolation or seclusion can help to diminish environmental stimuli and thereby reduce hyperreactivity. However, a few aspects are worth mentioning: Because seclusion is defined by a condition of very limited interactive and environmental cues, it is not indicated for patients with unstable medical conditions, delirium, dementia, self-injurious behavior (cutting, head banging), or who are suffering extrapyramidal reactions as a

consequence of antipsychotic medication.[4] Restraint is used to prevent patient and staff injury. All facilities should have clear, written policy guidelines for restraint that address monitoring, provisions for patient comfort, and documentation.

Training

Finally, training in the management of aggression helps to reduce violence and injuries through the early identification of impending episodes of violence, use of verbal techniques to defuse incidents, and appropriate physical techniques to minimize injuries in those that occur. It is necessary for healthcare providers to maintain their skills through training and to advocate for continuing medical education on this topic at the workplace.[13]

Summary

Both violent and suicidal behavior in the ED may be the cause or the effect of many toxicologic presentations. Patients presenting with suicidal or aggressive behavior pose unique problems for the clinician who must make appropriate assessment and management decisions. It is incumbent on all emergency physicians to screen patients for psychiatric emergency presentations as part of a comprehensive screening for self-harm.

Identifying risk factors for suicide and aggression can aid the clinician in employing preventive or early intervention strategies in the ED. Important risk factors for both suicidal and violent behavior include past history of the behavior, comorbid mental illness,

drug and alcohol intoxication, and young age. Mental status examination for suicidality should focus on extrinsic factors such as current ideation, intent, lethality of plan, current life stressors, as well as intrinsic vulnerability factors such as comorbid mental

illness, feelings of hopelessness, and impulsivity. In terms of violence risk assessment, drug and alcohol intoxication, mental illness, and psychiatric medication noncompliance (alone or in combination) are robust predictors of aggressive behavior in the ED and other inpatient settings. Early detection and rapid intervention for patients at risk for suicide or violence is, to date, the best means for preventing injury or death.

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Chapter 19
Neurologic Principles

Rama B. Rao

The central nervous system (CNS) coordinates responses to the fluctuating metabolic requirements of the body and modulates behavior, memory and higher levels of thinking. These functions require a diversity of cells: astrocytes, neurons, ependymal cells, and vascular endothelial cells. Disruption or death of any one cell type can cause critical changes in the function or viability of another. This cellular interdependence along with the high metabolic demands of the central nervous system, make neurons especially vulnerable to injury from both endogenous neurotoxins and xenobiotics. Endogenous neurotoxins like the metals iron, copper and manganese, are substances which may be critical to CNS function, but are harmful when their penetration into the CNS is poorly controlled.

The understanding of the normal chemical and molecular functions of the CNS is limited at best. Interestingly normal cellular mechanisms have sometimes been revealed by investigating xenobiotic induced neuronal injuries.[167] For example, the

pathophysiology of Parkinson disease, which affects movement and motor tone, was elucidated by the inadvertent exposure of individuals to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The mechanisms of axonal transport were elucidated by investigations of the effects of acrylamide exposures in human and animal models.[141] The neurodegenerative changes of amyotrophic lateral sclerosis has a promising xenobiotic model in Î²-methylamino-L-alanine (BMAA), a neurotoxin found in the cyanobacteria associated with cycad plants ingested by the Chamorro people of Guam.[69]

There are few minimally invasive methods available to investigate xenobiotic-induced CNS injury. Biomarkers are usually nonspecific and not readily available. Xenobiotic concentrations in blood and urine rarely reflect tissue concentrations of the central nervous system.[145] Cerebrospinal fluid may be useful in excluding CNS injury from infection, hemorrhage, and inflammatory processes, but is, with few exceptions, poorly reflective of the mechanisms of neuronal injuries.[224] Similarly, electroencephalograms and electromyelograms are useful in only a few types of xenobiotic exposures, and neuroimaging, while progressively evolving,[132] is a poor substitute for neuroanatomic evaluations that are usually only available on autopsy. Much of the current study to elucidate the mechanisms of CNS injury uses animal models, cultured astrocytes and other tissue, or postmortem investigations. Less commonly, occupational evaluations, such as the enzyme activity of cholinesterases in pesticide workers, are employed.

This is not a comprehensive chapter on all neurotoxic compounds and the status of their associated investigations. Instead, the concept of excitotoxicity is introduced, as are the common mechanisms by which xenobiotics exploit the functional and protective components of the CNS, with a few relevant examples. The multiple factors determining the clinical expression of neurotoxicity are reviewed. Finally, a special section on the delivery and complications of intrathecal xenobiotics is included.

Chap. 14 offers a detailed review of neurotransmitters.

Neurons: Classification, Infrastructure, and Functional Pathways

Neurons are the major route of cellular communication in the CNS. Having one of the highest metabolic rates in the body, these cells are especially sensitive to changes in the microenvironment and are dependent on astrocytes, choroidal epithelium, and capillary endothelium to confer protection and deliver glucose and other sources of energy.

Although each neuron is capable of receiving information through different neurotransmitters and receptor subtypes at the dendrite, neurons typically produce and release a single type of neurotransmitter at the axonal terminal. This specificity allows for cellular classification of neurons based on the neurotransmitter released, for example, serotonergic, cholinergic, and dopaminergic neurons (Chap. 14). Other substances that are less specific to the neuron type, such as adenosine, may also be produced and released.

The anatomic structure of neurons facilitates their function. Dendrites located on the cell body are lined with receptors that bind neurotransmitters and affect cellular changes via several mechanisms. The soma, or cell body is responsible for coordination and production of multiple proteins required to carry out normal physiologic functions. This synthesis occurs at a rate several times greater than the liver or kidney. These proteins, organelles, and substrates must then be transported across long distances to the terminal axon. This energy-dependent function is supported by a cytoskeleton comprised of neurofilaments, microfilaments, microtubules, and complex transport proteins. Fast anterograde transport of membrane-bound organelles occurs through kinesin at a rate of 200â€“400 mm per day. Channel proteins, synaptic

vesicles, mitochondria, Na^+ -K^+ -adenosine triphosphatase (ATPase), glycolipids, and other substances are transported by kinesin. Slow anterograde transport also occurs at a substantially slower rate (0.5â€“4 mm/d). The retrograde transport protein dynein is produced in the soma

and delivered to the nerve terminal for the movement of larger vesicles and reusable proteins back to the cell body.

In the CNS, groups of neurons are organized into complex functional pathways, with a single class of neuron regulating different functions and clinical effects depending on the brain region affected. As an example, dopaminergic neurons regulate cravings, movement, and resting muscle tone, each of which is determined not only by dopaminergic neurons and receptor subtype, but the part of the cortex or basal ganglia specifically affected (Chap. 14).

Neurons must be able to respond to changes in the local environment and alter the expression of different receptors in response to signaling from neurotrophic factors, variations in metabolic requirements, and xenobiotic interactions. This â€œneuroplasticityâ€• accounts for the diversity of clinical responses to substances that induce tolerance to xenobiotics such as ethanol (Chap. 15).

Glial Cells

Astrocytes, Oligodendrocytes, Microglia

Astrocytes comprise between 25% and 50% of the brain volume.[159] In addition to the anatomic contribution to the bloodâ€“brain barrier (BBB), astrocytes play a critical role in maintaining neuronal function.[4 , 5 , 209] They contribute to three

major areas: homeostasis of the extraneuronal environment, provision of energy substrates, and limitation in oxidative stress. In addition, astrocytes contribute to the â€œplasticityâ€• of cells and receptor expression in the CNS.

For cells of all types to function in the CNS, membrane potentials must be adequately maintained. Astrocytes contribute to this by closely regulating the extracellular pH, free water, and, like brain capillaries, the extracellular potassium concentration. Metallothioneins, which control the entry of heavy metals necessary for CNS function, are produced by astrocytes.[62 , 239] To further support CNS functions, astrocytes release energy substrates such as lactate, citrate, alanine, glutathione and Î±-ketoglutarate for use by neurons.[25]

Astrocytes metabolize glutamate, the main excitatory neurotransmitter in the CNS, and ammonia. These cells also produce superoxide dismutase and glutathione peroxidase to reduce free radical propagation. Glutathione, the major antioxidant for the brain, is predominantly located in the astrocytes. It can be released into the extracellular space or cleaved for neuronal uptake and intracellular reformulation.[25]

Through the release of complex trophic factors, astrocytes control the expression of endothelial transporters of the BBB and the production of tight junctions in both the bloodâ€“cerebrospinal fluid barrier (B-CSFB) and BBB. Angiogenesis is similarly astrocyte regulated, as is detection of neuronal injury, immune mediation, and neurotransmitter production. The growth of neurites, the branches of neuronal cell bodies that eventually become dendrites or axons, are similarly modulated by astrocytes.

Oligodendrocytes are a type of glial cell that provide anatomic support, protective insulation, and facilitate rapid neuronal depolarization by the production of myelin. Myelin is the primary constituent of white matter in the CNS. The production of myelin in the peripheral nervous system is performed by the Schwann

cells.

Finally, microglial cells, another type of glial cell, modulate immune response, inflammation, and tissue repair from a variety of CNS injuries. Like neurons, microglia are dependent on signaling from astrocytes.

Neuroprotective Mechanisms

The nervous system has multiple neuroprotective mechanisms. Xenobiotics are prevented from accessing the CNS by the bloodâ€“brain and bloodâ€“CSF barriers. For xenobiotics that enter the CNS, there are multiple cellular specializations to limit oxidant stress. These protective mechanisms are reviewed in the following sections.

Bloodâ€“Brain Barrier

The BBB confers an anatomic and enzymatic barrier to xenobiotic entry into the CNS. Brain capillaries are surrounded by the foot processes of adjacent astrocytes. The potential spaces between endothelial cells are limited by tight junctions, or zonulae occludens, which are between 50 and 100 times tighter than those found on peripheral capillaries.[3 , 4 and 5 , 126] This anatomic barrier prevents movement of substances between cells, also known as the paracellular aqueous pathway, as a result of osmotic and oncotic forces.[3 , 4 and 5 , 126 , 156]

Trans-endothelial movement of critical substrates and, potentially, xenobiotics, occurs through three major mechanisms: diffusion, transport proteins, and endocytosis.[3 , 4] These routes allow carefully controlled entry of critical substrates and cofactors while limiting the potential for injury from either endogenous or exogenous neurotoxins.

Lipophilic substances may move directly across the luminal and abluminal endothelial membranes abutting the central nervous

system. Other substances may enter the endothelium through bidirectional transport proteins on the luminal surface. These proteins may be specific, such as the GLUT-1 protein for uptake of glucose, or less-specific large neutral amino acid transporters (LNAAs) which move amino acids and xenobiotics, such as baclofen, intracellularly. These transporters also line the abluminal surface of the endothelial cell for movement of substrates and xenobiotics into the CNS. The third line of entry for larger proteins is via endocytosis. This can be either adsorptive or mediated through specific receptors such as insulin or transferrin.[3 , 4 and 5 , 126 , 156 , 239]

Endothelial cells have other protective properties including intracellular enzymes to metabolize xenobiotics, and efflux proteins to transport certain xenobiotics back into the capillary lumen. These efflux proteins include energy dependent P-glycoproteins which are adenosine triphosphate (ATP)-binding cassette transporters and are sometimes referred to as multidrug-resistant (MDR) proteins. Several hydrophobic xenobiotics are prevented from accumulating in the CNS through these transporters, including vinca alkaloids, digoxin, cyclosporine, and protease inhibitors. Nonsedating antihistamines may have limited sedative properties due, in part, to efflux though P-glyproteins.[58] Another type of saturable transporter, know as organic acid transport (OAT) protein, facilitates the efflux of hydrophilic xenobiotics such as valproic acid and baclofen. The expression of each of these transporters may be upregulated under certain conditions such as intermittent disruptions in the BBB from seizures. This expression upregulation is theorized to account for the resistance of anticonvulsant medications in patients with epilepsy. Comprehensive lists of xenobiotics that are substrates for these transporters are available elsewhere.[3 , 126]

Bloodâ€“CSF Barrier

The ventricles of the brain are lined by the epithelial cells of the choroid. These cells also have tight junctions, but they are not as extensive as those of the BBB. They are, however, rich in glutathione peroxidase and other xenobiotic

metabolizing enzymes in concentrations approximating that of the liver. Similar to brain capillary cells, the choroid contains efflux transporters for organic anions and cations, as well as MDR efflux proteins to limit entry of xenobiotics into the CSF.[3, 5, 126, 239]

Excitotoxicity

Neuronal function is strictly dependent on aerobic metabolism with an adequate supply of substrates and functioning mitochondria for the production of ATP. When energy expenditure exceeds production, cellular dysfunction and ultimately, cell death or apoptosis, results. The specific cascade of molecular events relating to this process is termed *excitoxicity*.[24, 187]

The initial event is traced to an oxidant stress and excessive stimulation of *N*-methyl-D-aspartate (NMDA) receptors by glutamate, an excitatory amino acid neurotransmitter. An influx of intracellular calcium changes membrane potentials across the cellular and mitochondrial membranes. The mitochondria become progressively more inefficient at ATP production and handling the resulting reactive oxygen species. As membrane damage is propagated, calcium further depolarizes the mitochondria, activating a permeability transition pore across the mitochondrial membrane. Gradients are further disrupted, precipitating more injury, energy failure, and ultimately, cell death.

Excitotoxicity is considered a common mechanism of cell death as a consequence of xenobiotic, ischemic, traumatic, infectious, neoplastic, or neurodegenerative injury. It is the subject of study for many therapeutic interventions in central nervous system injury.

Determinants of Neurotoxicity

The clinical expression of neurotoxicity is related to many factors, including the chemical properties of the xenobiotic; the dose and route of administration; xenobiotic interactions; and underlying patient characteristics including age, gender, and comorbid conditions (Table 19-1).

Chemical Properties of Xenobiotics

An important determinant of neurotoxicity is the capability of a xenobiotic to penetrate the BBB. Water-soluble molecules larger than M_r 200â€“400 (molecular weight ratio, or mass of a molecule relative to the mass of an atom) are unable to bypass the tight junctions.[3] Xenobiotics with a high octanol-to-water partition coefficient are more likely to passively penetrate the capillary endothelium, and potentially the BBB, whereas those with a low partition coefficient may require energy-dependent facilitated transport.[156] Xenobiotics that are substrates for capillary endothelial efflux mechanisms will have limited penetration regardless of the coefficient.[3 , 5 , 126 , 239]

Chemical properties of xenobiotics
Route of administration
Xenobiotic interactions
  Altered CNS penetration
  Clinical synergy
  Enhanced concentration
  Excessive neurotransmitter availability
Patient characteristics
  Age and gender
  Comorbidities
    Alterations in receptor function or expression
    Conditions affecting BBB integrity

Nutritional status
Extraaxial organ dysfunction
Enhanced sensitivity to xenobiotics
Production of endogenous neurotoxins
Undiagnosed diseases

TABLE 19-1. Determinants of Neurotoxicity

Route of Administration

The route of xenobiotic administration may also be consequential. Whereas most xenobiotics gain access to the nervous system through the circulatory system, aerosolized solvent and heavy metals in industrial and occupational exposures gain CNS access through inhalation, traveling via olfactory and circulatory routes. Alternatively, some agents may move from the peripheral nervous system via retrograde axonal transport to the CNS. Naturally occurring proteins such as tetanospasmin, rabies, polio, and herpes viruses use this mechanism to access the peripheral and central nervous system.[29 , 35 , 112] The toxalbumins ricin and abrin, as well as bismuth salts may also use this mechanism to a limited extent.[208 , 230] This understanding may prove beneficial from a therapeutic perspective. For example in one small series of patients experiencing severe pain, doxorubicin was injected into the involved peripheral nerves. Therapeutically, a chemical ganglionectomy occurred through retrograde â€œsuicideâ€• transport of doxorubicin, providing substantial relief in these patients in this experimental therapy.[122]

Some xenobiotics may be delivered directly into the CSF (intrathecally), the consequences of which are variable. See Special Considerations: Intrathecal Xenobiotic Administration.

Xenobiotic Interactions

Coadministration of xenobiotics may precipitate neurotoxicity by several mechanisms.[110] Extraaxially (outside of the CNS), xenobiotic interactions that increase the blood concentration of one or both agents may overwhelm the protective mechanisms of the BBB.[46] Similar effects may occur in the peripheral nervous system (PNS), where elevated blood concentrations may have enhanced clinical effects, resulting in peripheral neuropathies.[23]

Xenobiotic interactions can be synergistic, acting on the same neuroreceptor with additive effects. Benzodiazepines and ethanol, for example, both stimulate the Î³-aminobutyric acid type A ($GABA_A$) receptor.[31] The excessive neuroinhibition can result in deep coma and even respiratory depression when these agents are administered together.

In some circumstances, xenobiotic interactions result in excessive neurotransmitter availability. This is demonstrated in patients with the serotonin syndrome, the result, for example, of coadministration of a monoamine oxidase inhibitor and a serotonin reuptake inhibitor or other serotonergic agent (Chap. 70).

Access to the CNS may be altered by one of the xenobiotics, allowing the other to bypass the BBB. For example, mannitol causes transient opening of the BBB; as a result,[127] therapeutic use of mannitol is under investigation for the delivery of antineoplastic agents that might otherwise be unable to access the nervous system.[127] Similarly, some xenobiotics, such as verapamil, cyclosporine, and probenecid, are blockers of capillary endothelium efflux.[3 , 239] These theoretically limit efflux of other substrates of P-glycoprotein or OAT. The clinical usefulness of employing such efflux blockers

is under investigation as was done in a study in which primates received intrathecal methotrexate. The CSF clearance was reduced in animals administered intrathecal probenecid.[27 , 192]

Patient Characteristics

Age

Patient-specific variables may affect either the ability of a xenobiotic to penetrate the BBB and/or the clinical effects of a given exposure. For example, age of the patient at the time of exposure is critical, especially in the fetus and neonates.[194] The structural and enzymatic development of the bloodâ€“brain barrier is incomplete and synaptogenesis, or formation of intercellular relationships, is especially sensitive to impaired protein synthesis or other excitotoxic events. This is demonstrated classically by maternal exposure to methylmercury. The mother may be minimally affected, but the developing fetus suffers profound neurologic and developmental consequences (Chaps. 30 and 92).

In neonates, immature liver function may lead to the accumulation of circulating bilirubin. Because of incomplete formation of the bloodâ€“brain barrier, the bilirubin may access the central nervous system and produce a form of encephalopathy known as kernicterus.

Elderly patients may also have increased susceptibility to neurotoxins as a result of relatively impaired circulation or age-related changes in mitochondrial function that predispose to excitotoxicity.[201] Xenobiotic-induced parkinsonism, or the unmasking of subclinical idiopathic Parkinson disease may occur more readily in older than in younger patients. Animal models also suggest age-related sensitivity, with one study noting increased toxicity to manganese as the animals age.[83]

Gender

The role of gender in expression of xenobiotic-induced neurologic injury is potentially contributory. In animal models, the presence of estrogen- and progesterone-related compounds may be

neuroprotective for some xenobiotic injuries.[159, 179] In humans, females are more susceptible to some movement disorders, such as drug-induced parkinsonism and tardive dyskinesia, whereas dystonias and bruxism are more prevalent in young male patients.[188] The etiologies of these gender-related differences are incompletely understood.

Comorbidities

Conditions affecting the integrity of the bloodâ€“brain barrier can affect CNS penetration of xenobiotics and endogenous neurotoxins. For example, glutamate concentrations are normally higher in the circulatory system than the CNS.[140] Patients with trauma, ischemia, or lupus vasculitis[2] may experience neuropsychiatric disorders as a result of increased penetration of glutamate or sensitivity to additional xenobiotics. Similarly, meningitis and encephalitis cause openings in the BBB, which can be exploited to enhance therapy. Intravenous penicillin achieves a higher CSF concentration in animals with meningeal inflammation than in animals without meningitis.[193]

In some patients, previously undiagnosed diseases become evident on exposure to xenobiotics. This is especially true in patients with peripheral neuropathies. For example, patients being treated with therapeutic doses of vincristine suffered a severe polyneuropathy as a result of unmasking of a previously undiagnosed Charcot-Marie-Tooth disease.[54] Similarly, patients with diabetes mellitus, which is the most common cause of peripheral neuropathy, or HIV disease may have exacerbation of symptoms in the presence of antiretroviral agents.[56, 181] Patients with myasthenia gravis may have exacerbation of weakness with aminoglycoside administration, which can affect transmission at the neuromuscular junction.[235]

Chronic exposures to some neuroinhibitory xenobiotics such as ethanol may alter neuronal receptor expression and

â€œupregulateâ€• or increase the amount of receptors for excitatory amino acids. In addition to receptor augmentation, neurotransmitter concentrations of the excitatory neurotransmitters glutamate and aspartate are increased, as is homocysteine. These changes induce a tolerance to neuroinhibitory xenobiotics acting on the same receptor, and patients require escalating doses to achieve the same clinical effect. In such patients, cessation of ethanol intake results in a relative deficiency of exogenous inhibitory tone. The patient experiences neuroexcitability and the clinical syndrome of withdrawal (Chap. 15).[38 , 39]

Adequate nutritional status is important for the maintenance of normal neurologic function. The BBB may not be adequately maintained in patients with malnutrition. Deficiencies of heavy metal cofactors such as manganese, copper, zinc, and iron can affect neurologic function. In some cases, the deficiencies enhance absorption of other xenobiotics. For example, iron deficiency enhances lead and manganese absorption in the gastrointestinal tract, which can ultimately overwhelm neuroprotective mechanisms. Vitamins serve as enzymatic cofactors in modulating the production of glutamate, homocysteine, and other amino acids. Specific vitamin deficiencies can precipitate neurologic syndromes such as Wernicke encephalopathy in thiamine-depleted patients (see Antidotes in Depth: Thiamine Hydrochloride and Chap. 41). The toxicity of xenobiotics may also be enhanced. For example, a relative pyridoxine deficiency in patients with acute isoniazid overdose may result in seizures as a result of a relative excess of excitatory amino acids (see Antidotes in Depth: Pyridoxine and Chap. 55). Glucose is a critical energy substrate that can cause profound neurologic impairment when delivery is inadequate (see Antidotes in Depth: Dextrose and Chap. 48).

Extraaxial Organ Dysfunction

Renal failure may impair metabolism of xenobiotics or endogenous neurotoxins such as urea, rendering it more available to the central nervous system. Hyperglycemia in patients with diabetes mellitus may also increase formation of CNS-reactive oxygen species. Similarly, patients with liver failure may have elevations in CNS manganese.

Hepatic encephalopathy illustrates the concept of excitotoxicity from endogenous neurotoxins. Hyperammonemia increases oxidative stress and free radical formation in astrocytes. Ammonia potentially decreases critical metabolic enzymes such as catalases, superoxide dismutase, and glutathione peroxidase. Nitric oxide (NO) production is increased as a result of elevations in NO synthetase. Under these conditions, astrocytes upregulate the expression of the peripheral benzodiazepine receptor (PBR) on the outer mitochondrial membrane. The PBR modulates the production of neurosteroids and, in turn, the $GABA_A$ receptor. Continued CNS exposure to ammonia and other endogenous solutes propagates this oxidative and nitrosative stress to the mitochondrial membrane, potentially opening the mitochondrial permeability transition pore (channel). Osmotic swelling of the mitochondrial membrane followed by excitotoxicity results in cerebral edema, which produces hepatic encephalopathy.[160 , 161]

Mechanisms of Neurotoxicity

Alteration of Endogenous Neurotransmission

Xenobiotics can induce neurotoxicity by triggering changes in neurotransmission in either the central or peripheral nervous systems. In some cases, xenobiotics enhance neurotransmission through a specific receptor subtype. This enhanced transmission

can occur through inhibition of presynaptic metabolism (monoamine oxidase inhibitors), stimulation of neurotransmitter release (amphetamines), impairment of neurotransmitter reuptake (cocaine), or inhibition of synaptic degradation (acetylcholinesterase inhibitors).

Alternatively, synaptic neurotransmission may be impaired.[198] Xenobiotics may inhibit the presynaptic release of neurotransmitters (botulinum toxin), block receptors (antimuscarinics) or alter membrane potentials at the postsynaptic membrane (tetrodotoxin).[75, 78] Patients may present with a clinical syndrome of toxicity associated with altered neurotransmission of the specific receptor (Chap. 3).

Direct Receptor Interaction

Some xenobiotics are able to directly stimulate receptors. Both kainate and AMPA (Î±-amino-3-hydroxy-5-methyl-4-isoxazole propionate) are subclasses of the glutamate receptors that are targeted by some naturally occurring xenobiotics.[101] An example is Î²-*N* -oxalylamino-L-alanine (BOAA) found in the grass pea, *Lathyrus sativus.* BOAA stimulates the AMPA and inhibits specific mitochondrial enzymes resulting in the spastic paraparesis of lathyrism.[169] Domoic acid stimulates the kainate receptor and causes the neuroexcitation associated with neurotoxic shellfish poisoning.

Direct inhibition is also possible, as exemplified by phencyclidine, an NMDA (*N* -methyl-D-aspartate) receptor antagonist.

Enzyme and Transporter Exploitation

The classic example of xenobiotics that exploit endogenous enzymes and/or transporters is MPTP.[92] Once MPTP crosses the BBB, it is converted by monoamine oxidase to the neurotoxic compound MPP^+ (1-methyl-4-phenylpyridine) in astrocytes. MPP^+

is taken up by dopamine transporters into the neurons of the substantia nigra pars compacta. MPP^+ inhibits complex I of the mitochondrial electron transport chain resulting in dopaminergic excitotoxicity and the clinical syndrome similar to Parkinson disease (see Disorders of Movement and Tone below and Chap. 38).

Altered Conduction Along Membranes: Demyelinating Neurotoxins

Aside from xenobiotics that affect neurotransmission at the postsynaptic membrane, some affect the production or maintenance of myelin by oligodendrocytes and Schwann cells.[55, 79, 90, 115] In the central nervous system, these are often associated with white matter abnormalities and a leukoencephalopathy.[79] Agents such as hexachlorophene, arsenic, inhibitors of tumor necrosis factor-Î±, neural tissue-derived rabies vaccine, and the act of â€œchasing the dragonâ€• or inhaling volatilized heroin are associated with a demyelinating neurotoxicity.[55] In the peripheral nervous system, nitrous oxide, suramin, and tacrolimus are associated with peripheral demyelination (Table 19-2).[111]

Inhibition of Intracellular Functions

Some xenobiotics are nonspecific inhibitors of cellular function.[64] The neurotoxicity of substances such as carbon monoxide (CO) or cyanide can result in diffuse dysfunction or, depending upon the dose and specific vulnerabilities of an exposed patient, be more focal. For example, patients surviving CO exposure may experience delayed neurologic sequelae that is a diffuse impairment of neuropsychiatric function, or more focally, present with a xenobiotic induced Parkinson syndrome (see below and Chap. 120).

Alterations in endogenous neurotransmission
Alterations in membrane conduction
Direct receptor interactions
Exploitation of enzymes and transporters
Inhibition of intracellular function
  Inhibition of neuronal transport
  Inhibitors of protein production
  Mitochondrial inhibitors

TABLE 19-2. Mechanisms of Neurotoxicity

Chemotherapeutic agents can affect the production of critical proteins required for cellular maintenance. These can be very specific, such as the ability of vincristine to impair cytoskeletal transport in the peripheral nervous system (Chap. 52).

Clinically Relevant Xenobiotic Mediated Conditions

Alterations in Consciousness

The toxicologic differential diagnosis of xenobiotics that induce alterations in mental status or consciousness is expansive. These xenobiotics can be broadly divided into those agents that produce some form of neuroexcitation, and those that produce neuroinhibition. While some agents, such as phencyclidine, have elements of both, depending on dose, this categorization facilitates a general clinical understanding of neurotoxic alterations in mental status.

Xenobiotics resulting in neuroexcitation are agents that enhance neurotransmission of excitatory amino acids (EAAs), or diminish inhibitory input from GABAergic neurons. The clinical presentation of the patient can vary, therefore some patients may be alert and

confused, suffering from an agitated delirium, hallucinations or a seizure.

Neuroinhibitory xenobiotics typically enhance GABA-mediated neurotransmission. These patients may be somnolent or in deep coma. Benzodiazepines hyperpolarize cells by increasing inward movement of Cl^- ions through the chloride channel of the $GABA_A$ receptor complex. This hyperpolarization limits subsequent neurotransmission. Less commonly, neuroinhibition is a result of diminution of EAAs. Patients presenting the day after bingeing on cocaine may be sleepy but arousable and oriented in what is termed cocaine â€œwashout,â€• theoretically related to depletion of EAAs and dopamine. Xenobiotics that cause diffuse cortical dysfunction through impairment in the delivery or use of oxygen or glucose can also present with depressed or altered consciousness.

Clinical evaluation of patients with altered consciousness includes obtaining a complete history, including medications, comorbid conditions, occupation, and suicidal intent, when relevant or available. Patients should have a complete physical examination, with particular attention to vital sign abnormalities or findings that may indicate a toxic syndrome. Assessment and correction of hypoxia or hypoglycemia should be performed. An electrocardiogram may be useful in some circumstances (Chaps. 5 and 23).

Xenobiotic-Induced Seizures

Seizures are the most extreme form of neuroexcitation. As with alterations of consciousness, this may be a result of enhanced excitatory amino acid neurotransmission (domoic acid, sympathomimetics) or of inhibition of GABAergic tone (isoniazid). Unlike patients with traumatic or idiopathic seizure disorders who have an identifiable seizure focus, the initiation and propagation of xenobiotic-induced seizures is diffuse. It is for this reason that

most nonâ€“sedative-hypnotic anticonvulsants such as phenytoin, are unlikely to be effective in seizure termination.

Status epilepticus is variably defined, but involves 2 or more seizures without a lucid interval, or continuous seizure activity for greater than 15 minutes. True xenobiotic-induced status epilepticus is rare. Cicutoxin, the toxin in water hemlock (*Cicuta maculata*), is a potent inhibitor of $GABA_A$ neurotransmission and may cause status epilepticus.

Analgesics and nonprescription (OTC) preparations
- Antihistamines
- Caffeine
- Mefenamic acid
- Phenylbutazone
- Salicylates

Prescription medications
- Antihistamines
- Bupropion
- Carbamazepine
- Chlorambucil
- Chloroquine
- Clonidine
- Digoxin
- Ergotamines
- Fenfluramine
- Isoniazid
- Lidocaine
- Methotrexate
- Phenytoin
- Procarbazine
- Quinine (cinchonism)
- Sulfonylureas
- Theophylline

Tramadol

Psychopharmacologic medications

Antiemetics

Antipsychotics

Cyclic antidepressants

Lithium

Methylphenidate

Monoamine oxidase inhibitors (esp w/food or drug reaction)

Opioids (propoxyphene, meperidine)

Pemoline

Sedative-hypnotic withdrawal

Alcohols and drugs of abuse

Amphetamines

Cocaine

Disulfiram reaction

Ethanol withdrawal

Ethylene glycol

MDMA (methylenedioxymethamphetamine)

Methanol

Phencyclidine

Botanicals

Ackee fruit

Cicutoxin

Coprinus spp (disulfiramlike reaction w/alcohol)

Daphne

Herbal preparations (Lobelia, jimson weed, *Galega* , mandrake, passion flower, periwinkle, wormwood) (see Chaps. 43 , 77 , 114)

Nicotine

Rhododendron

Heavy metals
- Arsenic
- Copper
- Lead
- Manganese
- Nickel

Household toxins
- Boric acid (chronic)
- Camphor
- Fluoride
- Hexachlorophene
- Phenol

Pesticides
- Organochlorines (lindane)
- Organic phosphorous compounds
- Pyrethrins
- Rodenticides (thallium, sodium monofluoroacetate, strychnine, zinc phosphide, arsenic)
- Tetramethylenedisulfotetramine (TETS)

Occupational and environmental toxins
- Carbon disulfide
- Carbon monoxide
- Chlorphenoxy herbicides
- Cyanide
- Hydrocarbons
  - Simple asphyxiants (methane, ethane, propane, butane, natural gas)
  - High volatility (benzene, toluene, gasoline, naphtha, mineral spirits, light gas oil)
  - Halogenated (carbon tetrachloride, trichloroethane)
- Hydrogen sulfide

Methyl bromide
Toxic inhalants (simple asphyxiants producing hypoxiaâ€”helium, nitrogen, nitrous oxide)
Triazine

Toxic envenomation and marine animal ingestion
Marine animals (Gymnothorax, saxitoxin [shellfish])
Pit viper
Scorpion
Tick bite (*Rickettsia rickettsii*)

TABLE 19-3. Xenobiotic-Induced Seizures

Theophylline toxicity precipitates seizures and status epilepticus through a different mechanism. Normally, endogenous termination of seizures is mediated through presynaptic release of adenosine during the release of the primary neurotransmitter at the terminal axon. Adenosine functions as a feedback inhibitor of the presynaptic neuron, disrupting propagation of excitatory neurotransmission. Theophylline is an adenosine antagonist. Adenosine administration is not a useful therapy for theophylline-induced seizures as adenosine is unable to cross the BBB. Generally high-dose sedative hypnotics, affecting $GABA_A$ receptors, are required for seizure control.

Some clinical conditions appear to be centrally mediated tonicâ€“clonic movements, but are caused by glycine inhibition in the spinal cord. Glycine is the major inhibitory neurotransmitter of motor neurons of the spinal cord. Under normal conditions glycine contributes to termination of reflex arcs. Glycine inhibition results in myoclonus, hyperreflexia and opisthotonos, often without alteration in consciousness. Presynaptic glycine inhibition is caused by tetanospasmin, the major neurotoxin from *Clostridium tetani.* Postsynaptic glycine inhibition is caused by strychnine, the

toxin in *Strychnos nux-vomica.* Patients with exposures to these agents are often treated in quiet environments where the stimuli to propagate hyperreflexia are minimized (Chap. 108 and Table 19-3).

Xenobiotic-Induced Mood Disorders

Certain xenobiotics are inconsistently associated with alterations in mood.[6 , 40] What predisposes individuals to xenobiotic-induced mood alterations is unclear. In some circumstances, patients with previously undiagnosed bipolar disorder are given a xenobiotic that unmasks their disease. Interestingly antibiotic-induced mania is found in some patients without a previous psychiatric history. The symptoms of mania are usually evident within the first week of therapy, and unlike the mania of purely psychiatric origin, readily abate within 48â€“72 hours of the last antibiotic dose. Some patients with clarithromycin-induced mania have documented reoccurrence on rechallenge of the antibiotic (Table 19-4).[6]

Disorders of Movement and Tone

Most movement disorders, including akathisia, bradykinesia, tics, dystonias, and chorea, are mediated by the complex dopaminergic pathways of the basal ganglia. Different dopamine receptor subtypes, modulated by GABAergic, glutaminergic, and cholinergic neurons are involved (Chap. 14).

Depression

Î²-Adrenergic antagonists

Amiodarone

Interferon

Isotretinoic acid

Ribavirin

Mania

- Acyclovir
- Amantadine
- Caffeine
- Chloroquine
- Clarithromycin
- Corticosteroids
- Dextromethorphan
- Dehydroepiandrosterone
- Efavirenz
- Fenfluramine
- Fluoroquinolones
- Gabapentin
- Ginseng
- Interferon-Î±
- Isophosphamide
- Isoniazid
- L-Dopa
- Mefloquine
- Phentermine
- Phenylpropanolamine
- Pseudoephedrine
- Quetiapine
- St. John's wort
- Testosterone
- Tramadol

TABLE 19-4. Xenobiotic-Induced Mood Disorders[6,10,15,17,40,44,53,81,93,102,124,125,138,157,158,162,163,168,172,173,180,183,185,199,223,225,227,228,231]

Anticholinergics

Anticonvulsants

- Carbamazepine
- Phenobarbital
- Phenytoin

Antiparkinsonians

- Amantadine
- Bromocriptine
- Levodopa
- Pergolide

Antipsychotics

Carbon monoxide

Corticosteroids

Ethanol

Lithium

Manganese

Metoclopramide

Oral contraceptives

Sympathomimetics

Thallium

Toluene

Anticonvulsants

Antiemetics

- Metoclopramide
- Prochlorperazine

Antipsychotics

Fluvoxamine

Levodopa

Antipsychotics

Calcium channel blockers

- Flunarizine
- Cinnarizine

Fluvoxamine

Orthopramides and substituted benzamides

- Clebopride
- Metoclopramide

Sulpride
Veralipride
Antidepressants
Selective serotonin reuptake inhibitors
Cyclic antidepressants
Phenelzine
Antiemetics
Metoclopramide
Prochlorperazine
Antipsychotics
Calcium channel blockers
Flunarizine
Cinnarizine
Dopamine storage and transport inhibitors
Î±-Methyltyrosine
Reserpine
Tetrabenzine

Chorea Dystonia Dyskinesia Akathisia

TABLE 19-5. Xenobiotic-Induced Movement Disorders

Dopamine receptor antagonists can precipitate acute dystonic reactions. The D_2 -receptor antagonists, in conjunction with alterations in muscarinic cholinergic tone, are usually implicated. Animal models suggest possible mediation through Ïƒ receptors, the craniofacial distribution of which corresponds to the common clinical manifestations of acute dystonias.[116]

Chorea occurs in some cases of carbamazepine overdose, therapeutic oral contraceptive use,[74] and after cocaine use when the stimulant effects have subsided.[188]

Other centrally mediated disorders of tone include serotonin syndrome and neuroleptic malignant syndrome (NMS). Both of

these potentially life-threatening syndromes consist of altered consciousness, hyperthermia, rigidity, and autonomic insufficiency. NMS may occur in patients on dopamine-receptor antagonists such as antipsychotic medications, or in patients with idiopathic Parkinson disease who abruptly stop their dopaminergic therapy. Dopamine receptor agonists such as bromocriptine or restoration of antiparkinson medications are used therapeutically in these circumstances (Chap. 67).

Flaccid paralysis usually occurs as a result of impaired transmission at the neuromuscular junction (NMJ)[31 , 34] or from xenobiotics causing demyelination. Rarely, toxins can enhance transmission at the NMJ. Latrotoxin, the toxic compound in black widow spider (*Latrodectus* spp), causes enhanced release of acetylcholine at the NMJ with severe, painful muscle contractions (Tables 19-5 , 19-6 , and 19-7).

Xenobiotic-Induced Parkinson Syndrome

Similar to idiopathic Parkinson syndrome, xenobiotic-induced Parkinson syndrome is defined by the clinical syndrome of unstable posture, rigidity, gait disturbance, loss of facial expression and hypokinesis.[18] The common neuroanatomic target involves the dopaminergic neurons of the basal ganglia, specifically the substantia nigra.[60 , 214]

Metabolic
- Hepatic failure
- Hyperosmolarity
- Hypoosmolarity
- Postanoxic encephalopathy
- Renal failure
- Ventilatory failure

Toxic
Anticholinergics
Anticonvulsants
Benzodiazepines
Bismuth
Crotaline venom
Cyclic antidepressants
DDT
Ethanol
Lead
Levodopa
Mercury
Methylbromide
Sedative-hypnotics

Modified, with permission, from Fahn S. Marsden CD, Van Woert MH: Definition and classification of myoclonus. Adv Neurol 1986;43:1â€“5.

TABLE 19-6. Toxic-Metabolic Causes of Asterixis and Multifocal Myoclonus

Antidiabetics
Amiodarone
Amiodarone
Calcium-channel blockers
Amphetamine
Antidiabetics
Carbon disulfide
Antidiabetics
Barbiturates
Carbon monoxide
Arsenic
Benzodiazepines
Captopril

Î²-Adrenergic agonists
Carbamazepine
Chlorpromazine
Caffeine
Chloral hydrate
Chlorprothixene
Carbon disulfide
Colistin
Clozapine
Carbon monoxide
Ethanol (chronic)
Cyanide
Chlorpromazine
Glutethimide
Droperidol
Chlorprothixene
Lithium
Ethanol (withdrawal)
Clozapine
Methaqualone
Fluphenazine
Cocaine
Methyl mercury
Haloperidol
Corticosteroids
Phenytoin
Lithium
Cyclic antidepressants
Piperazine
Loxapine
Droperidol
Valproic acid
Manganese
Ergotamine

Methanol
Ethanol
Methyldopa
Fluphenazine
Metoclopramide
Haloperidol
Mesoridazine
Lead
Molindone
Levodopa
MPTP[a]
Lithium
Perphenazine
Loxapine
Phenytoin
Pimozide
MAOIs (food interaction or drug)
Prochlorperazine
Mesoridazine
Reserpine
Methylbromide
Tetrabenazine
Molindone
Thioridazine
Monosodium glutamate
Thiothixene
Perphenazine
Trifluoperazine
Phencyclidine
Phenytoin
Pimozide
Sedative-hypnotics
Theophylline
Thioridazine

Thiothixene
Trifluoperazine
Valproic acid

[a] 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

Modified with permission from Weiner WJ, Lang AE: Movement Disorders: A Comprehensive Survey. Mt. Kisco, NY, Futura, 1989.

Resting Tremor Sustension Tremor Kinetic Tremor

TABLE 19-7. Xenobiotic-Induced Tremor

In some circumstances, the toxicity is transient and the mechanism inadequately understood. Some xenobiotics, such as MPTP, carbon disulfide, manganese, and the endogenous neurotoxin copper in patients with Wilson disease, produce predictable mitochondrial impairment of the basal ganglia neurons. Viscose rayon workers exposed to carbon disulfide may present with a Parkinson syndrome refractory to L-dopa administration.[106, 107] Manganese is a critical substrate for production and metabolism of several neurotransmitters including glutamate. Excessive manganese interferes with normal uptake of glutamate and is critical to the function of superoxide dismutase and glutamine synthetase.[72, 82] Patients with liver failure may accumulate manganese.[82] Although copper accumulation in the basal ganglia can produce parkinsonism, sometimes the syndrome is clinically silent until a xenobiotic with antidopaminergic properties is administered. Another example of subclinical Parkinson disease being unmasked occurs in patients with both AIDS and psychosis who are administered antipsychotic agents therapeutically.[59]

Amlodipine
Carbon disulfide
Cyclosporine
Carbon monoxide

Calcium channel blockers
Copper
Dopaminergic withdrawal
Cyanide
Kava kava (with manganese)
Heroin
Chemotherapeutics (numerous)
Manganese
Progesterone
MPTP
Sertraline
Valproate
Trazodone

[a] Improved with removal of xenobiotic, sometimes requiring persistent administration of dopaminergic therapy.

Reversible[a]	Irreversible

TABLE 19-8. Xenobiotic-Induced Parkinsonism [18,60,70,94,109,151,153,214]

Other xenobiotics, such as carbon monoxide and heroin, produce more diffuse tissue hypoxia, which occasionally results in xenobiotic-induced Parkinson syndrome. One study of patients with occupational exposure to pesticides suggested an increased risk of Parkinson disorder with long-term exposure. Specific agents were not clearly causative (Table 19-8).[80]

Cranial Neuropathies

Xenobiotics are a relatively rare cause of cranial nerve impairment. Some neuropathies are a result of direct delivery of the xenobiotic to the affected cranial nerve. For example, some patients may have optic nerve impairment from intraorbital

installation of silicone oil[9] or inadvertent deep space injection of a local anesthetic during dental anesthesia with a resultant abducens palsy.[146] In some cases, a xenobiotic is converted into a toxic substance such as formic acid in the retina.

The neuromuscular junction of the cranial nerves is sensitive to disruptions in neurotransmission and clinically noticed by the patient during disruptions of conjugate gaze. Botulinum toxin, elapid snake venom, and the cranial neuropathy associated with the organic phosphorus insecticide-induced intermediate syndrome are some examples.

Absence of critical substrates such as glucose or thiamine can result in an ophthalmoplegia. In most cases, however, the mechanisms underlying the cranial neuropathy are poorly understood, such as chemotherapeutic agents. Similarly, some patients who survive ethylene glycol poisoning experience transient ophthalmoplegia days after the initial exposure (Table 19-9 and Chaps. 20 and 21).[134 , 216]

Peripheral Neuropathies

Patients may complain of pain, paresthesias, numbness, or weakness of their extremities. This condition is clinically termed a neuropathy, but the mechanisms of its evolution are variable. Common to most xenobiotic-induced neuropathies is early bilateral involvement of the lower extremities. This may be partly a result of the patient's rapid recognition of impairment during an attempt to ambulate. Additionally, the axons serving the lower extremities are longer. Maintenance and transportation of substrates is more energy dependent and sensitive to xenobiotic-induced disruptions (Fig. 19-1).

In some cases, the anatomic structure of the nerve is maintained, but the xenobiotic affects neurotransmission. This may be a consequence of direct impairment of specific enzymes at the NMJ,

such as cholinesterase inhibitors.[61] Triorthocresyl phosphate (TOCP) is an inhibitor of neuropathic target esterase. Contamination of food and beverages with TOCP resulted in irreversible lower extremity paralysis in several epidemic exposures.[171, 217] Indirectly, the extracellular environment may be altered as in the case of hypermagnesemia, or hypokalemia which can be induced by multiple agents (Chap. 17). Ciguatoxin, a sodium channel opener, affects neurotransmission causing paresthesias and the unusual symptom of sensory reversal in which the perception of temperature is reversed to the stimulus.

Amiodarone
II, III
Ammonia
II
Antidiabetics (hypoglycemia)
I
Antiretrovirals

Barbiturates

Botulinum toxin
III, IV, V
Cadmium

Carboplatin

Cisplatin

Clioquinol

Contrast agents (intrathecal water soluble)
VI
Deferoxamine
II

Dichloroacetylene

Diiodohydroxyquin

Domoic acid

Ethambutol

Ethylene glycol
V, VIII
Hypothalamic-releasing hormone

Î ±$_2$ -Interferon
II, III
Lithium
VI
Local anesthetics
VI
MDMA
VI
Methotrexate/radiation

Nitroglycerin
VI
OKT3 (ornithine-ketoacid transaminase)
VI
Organic phosphorus compounds

Oxaliplatin

Oxalosis
V, VIII
Silicone oil

Solvents
II, IV, VIII
Stibanate
IX, X
Stilbamidine

Thallium
III, IV, VI
Thiamine deficiency

Trichloroethylene

Venoms
III, IV, VI
Elapid

Scorpion

Vincristine

Vitamin A
VI
[a] These are reported associations and not intended to be exclusive. Many xenobiotics have unpredictable effects on particular cranial nerves, whereas others appear more selective.

Substance Cranial Nerve

TABLE 19-9. Xenobiotic-Induced Cranial Neuropathies[a 14, 16, 20, 26, 30, 36, 48, 51, 77, 88, 96, 133, 154, 178, 182, 196, 209, 212, 216, 232]

Xenobiotics such as amiodarone and tacrolimus induce peripheral demyelination. Patients present with weakness and flaccidity.

Nitrous oxide impairs the production of *S* -adenosyl-L-methionine essential to the production of myelin and is additive to the nitrous

oxide disruptions of vitamin B_{12} , which further impair axonal function.[222]

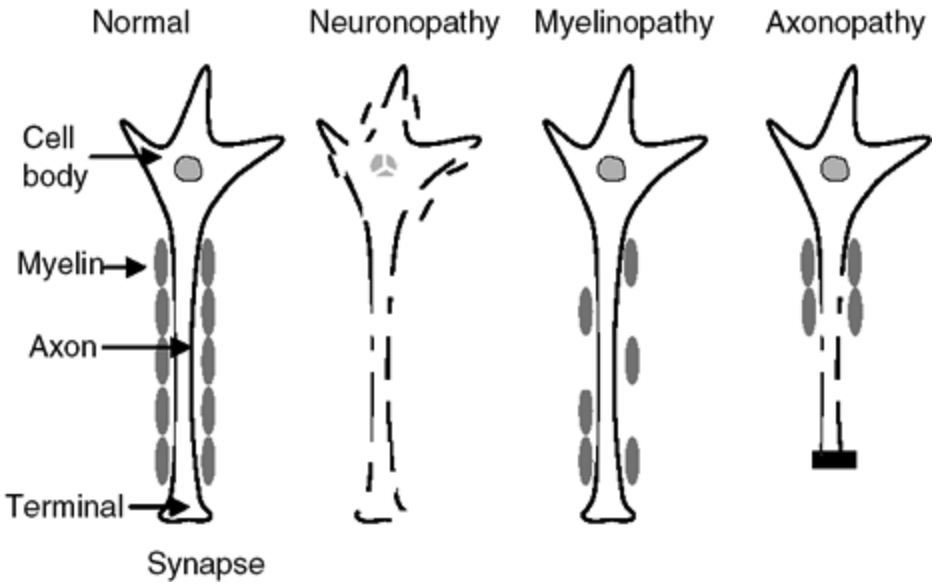

Figure 19-1. Schematic of a peripheral neuron and its three prototypic pathologic responses to toxic insults. Neuronopathies produce secondary axonopathic and myelinopathic changes, leading to degeneration of the entire peripheral nerve. Myelinopathies and axonopathies may occur separately or together. When the axon is involved, the prognosis is worse than with demyelination alone. Neuronopathies have the poorest prognosis of the three. *(Adapted from Chaudhry V: Multifocal motor neuropathy. Semin Neurol 1998;18:74; and Anthony DC, Montine TJ, Graham DG: Toxic responses of the nervous system. In: Klaassen CD, ed. Casarett and Doull's Toxicology, The Basic Science of Poisons, 5th ed. New York, McGraw Hill, 1996.)*

Other xenobiotics affect the structure or intracellular function of the peripheral nerves. Those that induce death of the cell body are termed *neuronopathies* and they may be clinically indistinguishable

from those that affect the axon, or *axonopathies* .

Peripheral nerve cell death is usually linked to injury at the spinal cord as was demonstrated by the doxorubicin injection of the peripheral nerves.[122] Pyridoxine overdose is another cause of neuronopathy. However, neuronopathies are an unusual mechanism of peripheral nerve toxicity.

Unlike neuronopathies, axonopathies are potentially reversible and are the most common mechanism of xenobiotic induced peripheral neuropathy. Xenobiotic-induced axonal injuries to the peripheral nerves are usually diffuse and bilateral, with preservation of the proximal cell body. These often target the cytoskeleton and impair the capacity for the microtubule system to deliver functional substrates.[52 , 100] Patients with occupational exposure to 2,5-hexanedione, a Î³ diketone metabolite of *n* -hexane present in certain glues, suffer from a sensorimotor axonopathy because of cross-linking of neurofilaments and impaired substrate transport.[164] Progressive neuropathy may occur long after the initial exposure. Vincristine similarly effects axonal transport. Acrylamide impairs fast anterograde and retrograde transport with animal models, suggesting effects on both kinesin and dynein.

Nucleoside reverse transcriptase inhibitors cause peripheral neuropathy by decreasing the production of mitochondrial DNA (Tables 19-10 , 19-11 , and 19-12).

Presynaptic action

Adrenocorticotropic hormone (ACTH), corticosteroids

Azathioprine

Botulinum toxins

Crotaline venom

Elapidae Î²-neurotoxins

Lactrodectus mactans venom

Magnesium

Tick paralysis

Verapamil

Postsynaptic action
D-Penicillamine
Neuromuscular blockers
Nicotine alkaloids
Organic phosphorous compounds, carbamates
Phenothiazines
Trimethaphan

Pre- and postsynaptic action
Antibiotics
Aminoglycosides
Clindamycin
Polymyxins
Î²-Adrenergic antagonists
Chloroquine
Lithium
Phenytoin
Procainamide
Quinidine

TABLE 19-10. Xenobiotics that Alter Transmission at the Neuromuscular Junction (Transmission Neuropathy)

5-Fluorouracil
Amiodarone
Amphotericin B methyl ester
Arsenic
Cyclosporine
Diethylene glycol
Fludarabine
Hexachlorophene
Interferon-Î±

Levamisole
Methotrexate
Neural tissue-derived rabies
Nitrous oxide
Podophyllin
Procainamide
Tacrolimus
Tumor necrosis factor-Î± inhibitors
L-Tryptophan
Trovafloxacin
Vincristine
Zinc

TABLE 19-11. Xenobiotics Associated with Demyelination

Myopathies

Some patients experience local muscle damage as a result of direct injury from extravasation of tissue toxic substances or enzymatic degradation associated with crotalid snake envenomations.

Acute toxic neuropathies
Pyridoxine (S)
Hexacarbons (SMA)
Thallium (SM)
Triorthocresyl phosphate (SM)
Vacor (MA)
Arsenic (SM)
Diphtheria (SM)
Black widow spider
Botulism
Ciguatoxin
Elapid and crotaline venoms

Gymnothoratoxin
Nicotine
Saxitoxin
Scorpion venom
Tetrodotoxin
Tick paralysis
Subacute/chronic toxic neuropathies
None convincingly demonstrated
Acrylamide (SM)
Allyl chloride (SM)
Arsenic (SM)
Buckthorn (M)
Carbon disulfide (SM)
Colchicine (S)
Disulfiram (SM)
Dapsone (M)
2â€²-3â€²-Dideoxycytidine (ddC), ddI
Ethanol (M)
Ethambutol (S)
Ethionamide (S)
Ethylene oxide (SM)
Glutethimide (S)
Gold (SM)
Hexacarbons (SM)
Hydralazine (SM)
Hydroxycholoquine
Interferon-Î±
Isoniazid (SM)
Linezolid
Methyl bromide (SM)
Mercury (M)
Methanol
Metronidazole (SM)
Misonidazole (SM)

Nucleoside analogs
Nitrofurantoin (SM)
Nitrous oxide (S)
Nucleosides (S)
Organic phosphorus compounds (SM)
Oxaliplatin
Polychlorinated biphenyls (SM)
Phenytoin (SM)
Platinum (S)
Podophylin (SM)
Taxol (S)
Thallium (SM)
Vincristine (SM)
5-Fluorouracil
Amiodarone (SM)
Amphotericin B methyl ester
Amygdalin
Buckthorn
Cyclosporine
Diethylene glycol
Diphtheria (SM)
Fludarabine
Gold (SM)
Hexachlorophene
Interferon
Levamisole
Methotrexate
Nitrous oxide
Podophyllin
Procainamide
Tacrolimus
Trichlorethylene (SM)
Trovafloxacin
L-Tryptophan

Tumor necrosis factor-Î±
Vacor (PNU)
Vincristine
Zinc

A = autonomic; M = motor; S = sensory.

Neuronopathy	Axonopathy	Myelinopathy	Transmission Neuropathy

TABLE 19-12. Classification of Selected Xenobiotic-Induced Peripheral Neuropathies

Most xenobiotic-induced muscle injuries or myopathies are more diffuse.[97,190,202,215] Î²-Hydroxy-Î²-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors can cause myalgias, cramping, myositis, or rhabdomyolysis. The incidence appears to be higher in patients taking other medications that share the same liver metabolic enzymes. The mechanism underlying the myopathy may be related to impaired cholesterol synthesis in myocytes, or diminished production of regulatory proteins such as ubiquinone and guanosine triphosphate (GTP)-binding proteins required for mitochondrial function.

Another myopathy that presents predominantly with weakness is the acute quadriplegic myopathy of intensive care patients. This syndrome was originally described in ventilated patients with asthma who received glucocorticoids and nondepolarizing neuromuscular blockers, but is also reported in other critically ill patients

(Chap. 66).[21] The mechanisms underlying quadriplegic myopathy, eosinophilia myalgia syndrome, and toxic oil syndrome are poorly described. Table 19-13 lists xenobiotics associated with muscle

injury.

Amiodarone
Azidothymidine
Bothrops asper, Agkistrodon, Acanthophis
Chloroquine
Cimetidine
Clofibrate
Clostridium toxin
Colchicine
Crotaline and other tissue-toxic snake venoms
Cyclosporine
Doxylamine
Epsilon aminocaproic acid
Ethanol
Ethchlorvynol
Glucocorticoids
Heroin
HMG-CoA reductase inhibitors
Hydroxychloroquine
Ipecac
Loxosceles spider envenomation
Niacin
Organic phosphorus compounds
Penicillin
D-Penicillamine
Phencyclidine
Procainamide
Propylthiouracil
Rifampin
Sulfonamides
Suxamethonium
Toxic oil syndrome
L-Tryptophan
Vincristine

Zidovudine

TABLE 19-13. Xenobiotics Associated with Muscle Toxicity[19, 21, 43, 131]

Special Considerations: Cerebrospinal Fluid Administration of Xenobiotics

Cerebrospinal fluid (CSF) is produced by the choroid plexus lining the ventricles at a rate of between 15 and 30 mL/h, or roughly 500 mL/d in adults.[108] Cerebrospinal fluid flows in a rostral to caudal direction and is resorbed through the arachnoid villi directly into the venous circulation. The estimated total volume of CSF in a healthy adult is between 130 and 150 mL, and 35 mL in infants.[108, 142, 186]

For more than 100 years, a variety of experimental and therapeutic agents have been delivered directly into the CSF.[121, 223, 233] The most common current indications for intrathecal xenobiotic administration include analgesia, anesthesia, and treatment of spasticity or CNS neoplasms. The clinical advantages of this route of administration include targeted delivery and lower medication dosages with fewer systemic effects. Medications are usually administered via a spinal needle or an indwelling intrathecal catheter. Catheters may be attached to either an external or subcutaneous pump. Less commonly, substances are administered into a reservoir of an intraventricular shunt (Table 19-14).

The distribution of intrathecal xenobiotics is determined by a variety of factors. Baricity is the ratio of the specific gravity of the xenobiotic to the specific gravity of CSF at 98.6Â°F (37Â°C). Hyperbaric agents typically distribute in accordance with gravitational forces.[104] Patient position, baricity, and interindividual variations in lumbosacral CSF fluid volume may

affect xenobiotic distribution and may account for the differences in the level of spinal anesthesia among patients administered the same local anesthetic dosages.[104] In overdose or administration of agents unintended for intrathecal administration, however, distribution, resorption, and clinical effects might not follow predictable models.

Complications can occur from preparation and dosing errors or inadvertent puncture of the CSF during epidural anesthesia or analgesia.[67, 103] Medications intended for intrathecal delivery might

be administered into the wrong port of a pump delivery system, resulting in a massive overdose. Another potentially fatal error involves inadvertent administration of the wrong medication into the CSF.[117] This occurs with misidentification or mislabeling of medications during pharmacy preparation, or at the bedside. For patients with indwelling devices, medications intended for intravenous delivery can be misconnected to the intrathecal catheter, which also operates via the Luer-Lock system.

Adjuvants
- Dextrose
- Elliot B solution

Analgesics/anesthetics
- Anesthetics (local)
- Clonidine
- Ketamine
- Midazolam
- Neostigmine
- Octreotide
- Opioids
- Ziconotide

Antibiotics
- Amikacin
- Amphotericin B
- Cefotetan
- Ceftriaxone
- Gentamicin
- Penicillin
- Polymyxin E
- Vancomycin

Antiinflammatory
- Corticosteroids

Antispasmodic
- Baclofen

Chemotherapeutics
- Cytarabine
- Methotrexate

Vasoactive
- Epinephrine
- Papaverine
- Phenylephrine

Other Agents
- Bethanechol
- Colistin
- Leucovorin[b]
- Somatostatin
- Tetanus immunoglobulin

[a] very few of these are FDA approved and many are controversial applications at best.

[b] Intrathecal leucovorin is potentially fatal.

TABLE 19-14. Intrathecal Xenobiotics Administered Inadvertently or Therapeutically[a] [1,7,32,33,41,42,50,57,68,91,99,117,135,147,148,155,170,175,176,177,197,204,211,221,226,236]

Several factors affect the clinical toxicity of intrathecal medication errors. The properties of the xenobiotic are important. Ionized xenobiotics are likely to disrupt normal neurotransmission and cause toxicity, as may hyperosmolar or lipophilic substances. The site of administration also might be important. Patients administered the wrong xenobiotic into an Ommaya CSF reservoir may suffer more immediate alterations in mental status depending on the agent administered. Although intrathecal administration of preservatives and excipients are investigated in animal models, the characteristics of these adjuvants in medication errors is unlikely to be of value in predicting clinical effect.[105]

Patients may present with exaggerated symptoms that are typically associated with the xenobiotic. For example, patients with intrathecal morphine overdose may present with symptoms of opioid toxicity.[119] Other manifestations of intrathecal errors, regardless of the substance, include pain and paresthesias, often ascending in nature, autonomic instability, especially with extremes of blood pressure, and hyperreflexic myoclonic spasms similar to those seen in patients with tetanus. Seizures or depressed mental status may also occur. The time of onset of these life-threatening symptoms may be determined by the dose, and characteristics of the xenobiotic. For example, a woman inadvertently administered intrathecal potassium chloride complained immediately of severe back pain.[149] Myoclonic spasms, seizures, and coma followed, and the patient expired within 3 hours despite a normal serum potassium concentration. Patients with inadvertent vincristine exposures can be asymptomatic for many hours and expire within a few days to a few weeks.

Once a medication delivery error is identified, rapid intervention is mandatory, especially for ionic agents, chemotherapeutics, or iodinated water-soluble contrast agents. In cases in which outcome is uncertain or not previously described, the exposure should be treated as potentially fatal. Any existing access to the CSF, ideally of the lumbosacral area, should be maintained.[219] Immediate drainage by gravity of CSF, in volumes as high as 75 mL in adults, is indicated. This can be replaced with lactated Ringer solution or 0.9% sodium chloride solution. Some authors recommend that the initial large volume drainage be performed in 20â€“30-mL aliquots. For children, multiple aliquots of between 5 and 10 mL can be drained and replaced with isotonic fluid. If the patient can tolerate an upright position, cephalad movement of xenobiotics may be limited, but positioning for any critical life support measures should take precedence.

Delays to initial CSF drainage should be minimized as the interval between the exposure and CSF drainage may affect xenobiotic recovery. In the interim, a neurosurgical consultation should be obtained to consider the placement of ventricular access for the performance of continuous CSF lavage. This procedure, also known as ventriculolumbar perfusion, involves continuous ventricular instillation of an isotonic solution with CSF drainage through a lumbar site. Another intervention involves placement of an epidural catheter into the intrathecal space at a space above the lumbar drainage site. An isotonic solution can be perfused through the catheter and drained caudally. This serves as a readily available, rapid intervention for patients awaiting placement of an emergent ventriculostomy.[152]

The CSF replacement fluid is isotonic. Lactated Ringer solution, 0.9% sodium chloride solution, Plasma-Lyte, or a combination of those have been used. Some older cases used Elliot B solution. For ventriculolumbar perfusion, lavage flow rates can be as high as 150 mL/h. Fresh-frozen plasma can be added to the lavage fluid to increase the CSF protein content in accordance with intracranial

pressure monitoring. The ideal lavage fluid, protein components, and infusion rates are not known.[98] Table 19-15 describes some previously used protocols. Although artificial CSF formulations exist, their role in such medication errors has not been evaluated.[165]

Depending on the xenobiotic exposure, specific antidotes or rescue agents can be employed. With most intrathecal exposures, these rescue agents are administered via oral, intramuscular, or intravenous routes. Extreme caution should be used to avoid delivery of antidotes directly into the CSF, unless specific data supports their use.

Xenobiotic Recovery from CSF

Immediate, aggressive CSF removal and lavage resulted in nearly 95% recovery of vincristine in the lavage fluid of a patient with inadvertent exposure. Of the published cases in which xenobiotic recovery is reported, percentages relate to the both the lavage method and quantity of CSF drained. For example, drainage of 10 mL of CSF 45 minutes after a methotrexate overdose in a 4-year-old patient recovered 20% of the initial dose.[8] Drainage of 200 mL of CSF in aliquots, 45 minutes after methotrexate overdose in a 9-year-old recovered 78% of the initial dose.[85] Interestingly, the specific xenobiotic may affect recovery as well. For example a patient underwent drainage of 30 mL of CSF at 18 minutes after an overdose of simultaneously administered lidocaine, epinephrine, and fentanyl. Approximately 39% of lidocaine was recovered, whereas the recovery of fentanyl was only 7%.[205]

Specific Exposures

Ionic Contrast Media

Several different agents have been used historically for contrast

myelography. Many of these agents were abandoned because of their capacity to cause an adhesive arachnoiditis and chronic pain syndromes or other complications (eg, Thorotrast). Low osmolar, nonionic contrast media are currently used, but, unfortunately, other hyperosmolar ionic media are readily available in radiographic suites and sometimes inadvertently administered. Exposed patients become symptomatic between 30 minutes and 6 hours with hyperreflexia and myoclonic spasms on minimal stimulation.[189, 191, 213] Clinical symptoms typically begin in the lower extremities and move in a cephalad direction, sometimes progressing to opisthotonos. This is likely caused by alterations in inhibitory neurotransmission as seen in patients with tetanus, and has been termed ascending tonicâ€“clonic syndrome (ATCS). In one review, nearly one-third of patients died as a result of their exposures.[220] Immediate, large-volume CSF drainage should be performed in 20-mL aliquots with isotonic fluid replacement. Ventriculolumbar perfusion should be considered in severe cases.

Chemotherapeutics

Methotrexate is administered intrathecally for the prevention and treatment of leukemic meningitis and other CNS neoplasms. Errors are generally dose related.[8, 84, 85, 113] In most reported cases, aggressive drainage of CSF up to 250 mL in aliquots with isotonic fluid replacement was used without ventriculolumbar

perfusion. Experimental treatment of patients with intrathecal carboxypeptidase G2 without obvious adverse events has been described.[166, 229] Leucovorin can be administered intravenously, but intrathecal leucovorin is absolutely contraindicated because it can be fatal.[114, 130, 218]

TABLE 19-15. Table of Adverse Intrathecal Exposures

Vincristine is typically administered intravenously and does not cross the bloodâ€“brain barrier. There are no therapeutic indications for intrathecal vincristine, and such errors are almost always fatal.[11, 12, 13, 37, 71, 95, 128] As soon as the exposure is identified, immediate CSF drainage should be instituted and rapid neurosurgical consultation obtained. The few known survivors with cognitive function underwent early neurosurgical intervention for ventriculolumbar perfusion.[12, 152] One of these patients had an epidural catheter placed intrathecally above the drainage site for lumbolumbar perfusion while awaiting ventriculostomy. This method of intrathecal perfusion should be considered in all patients with intrathecal vincristine exposures until definitive ventriculolumbar perfusion can be established. Other rescue medications are covered in Chap. 52 .

Pump Malfunctions and Errors

Some implantable pumps contain two access sites, one of which is contiguous with the intrathecal space and allows for CSF withdrawal or injection of nonionic contrast media for imaging. The other is a depot port that is intermittently filled with concentrated amounts of drug (usually an opioid analgesic or baclofen) to be delivered through a programmable pump. In some cases, a template must be placed on the skin overlying subcutaneous pumps to ascertain the proper medication port. Errors occur when a concentrated bolus is inadvertently injected into the wrong port resulting in a massive, sometimes fatal, overdose.[117, 175, 234] Massive intrathecal morphine overdose can have severe rapid symptoms, including hypertensive crises. Either reaccessing the CSF port immediately or placing a spinal needle into the intrathecal space at another site is critical for the withdrawal of CSF. Large-volume drainage with isotonic fluid replacement is

required, along with other supportive measures, such as intravenous naloxone. These patients usually require intubation and care in an intensive care unit. The clinical service which placed the pump should be consulted to assist in further CSF access and perform interrogation of the pump in cases where malfunction is suspected.[73] If the consultant is not readily available, then emptying the deport port will automatically cause the pump motor to stop.

The other pump problem encountered is sudden, insufficient delivery of either baclofen or opioid pain medication.[184] This may occur because of pump malfunction. Alternatively, the intrathecal catheter may kink, migrate, or become obstructed by an inflammatory mass.[65, 66, 117, 174] Patients with chronic use of baclofen or morphine may suffer severe withdrawal symptoms when intrathecal delivery is disrupted. Intrathecal doses are between 100 and 1000 times more potent than the equivalent dose administered intravenously.[120] Consequently, these patients may require very high oral or intravenous doses to treat withdrawal until intrathecal delivery can be reestablished. The clinical service that implanted the pump should be consulted, and a thorough neurologic examination to evaluate for spinal cord compression symptoms should be performed.[117] An anteroposterior and lateral radiograph can be obtained to assess for kinking or fracture of the catheter.

Conclusions

The principles involving xenobiotic-induced neurologic injury are an area of ongoing intensive investigation. With improved understanding of these neurotoxic principles, therapeutic medications can be better delivered to the central nervous system while limiting the entry of potentially toxic substances. Toxicologic models for the investigation of neurodegenerative disorders can be

further developed as can new and creative therapies for mood disorders, hepatic encephalopathy, and injuries from infections, trauma, and ischemia. Elucidation of neurotoxicologic principles shows promise for the treatment of many nervous system disorders, and is an evolving field of investigation. The chemical properties of the xenobiotic and the characteristics of the patient exposed are critical to the clinical expression of neurotoxicity.

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Chapter 20
Ophthalmic Principles

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Xenobiotics can affect the eyes in diverse manners. The eyes may be injured by direct contact with a number of xenobiotics, may provide a portal of entry for systemic toxicity, and may themselves be adversely affected by systemic exposures. The clinician must perform a thorough ophthalmic examination. Examination of the eye not only provides clues to the diagnosis of certain direct toxic exposures, but may also lead to timely detection of life-threatening indirect effects, such as intracranial hemorrhage. In addition to providing diagnostic clues, the visual system is the target of many xenobiotics that threaten normal vision. Understanding these principles can be lifesaving or sightsaving, and is essential to efficient, systematic patient care.

Ophthalmic Examination

As a matter of convention, the routine eye examination is

performed in the following sequence: visual acuity, pupillary response, extraocular muscle function, funduscopy, and when indicated, a slit-lamp examination. Examination of the pupillary size and response to light can help determine the presence of a toxic syndrome. Opioid and cholinergic agents may produce miosis, whereas anticholinergic agents may produce mydriasis. Assessment of the extraocular muscles can reveal xenobiotic-induced nystagmus. Funduscopy can reveal pink discs characteristic of poisoning by methanol or carbon monoxide. The slit-lamp examination allows for evaluation of toxic exposure to the lids, lacrimal systems, conjunctiva, sclera, cornea and anterior chamber. However, before considering specific toxic exposures in detail, it is important to review the anatomy and physiology of the visual pathways and how alteration of the normal physiology and anatomy correlate with clinical signs and symptoms.

Ocular Anatomy

The eye is a roughly spherical structure referred to as a globe. The globe is divided into anterior and posterior structures (Fig. 20-1). The most anterior structures are the cornea, conjunctiva, and sclera. Posterior to the cornea are the iris, the lens, and the ciliary body. The space between the cornea and the iris is the anterior chamber, and the space between the iris and the lens is the posterior chamber. Both chambers contain aqueous humor, which is produced by the ciliary bodies. The fundus is the most posterior structure and includes the retina, retinal vessels, and the head of the optic nerve or disc. The fundus is surrounded by gelatinous vitreous fluid, an important body fluid in forensic toxicology (Chap. 33). Xenobiotic-mediated injury to any of these structures can lead to symptoms as mild as chemical conjunctivitis or as severe as permanent blindness.

Visual Acuity and Color Perception

Normal vision is dependent on light transmission to intact neural elements. Appropriate light transmission requires a clear cornea and aqueous humor, proper pupil size, an unclouded lens and clear vitreous. The neural elements include the retina, optic nerve, and the optic cortex; all of these structures require intact blood circulation for proper function. Decreased acuity can result from abnormalities anywhere in the visual system that affect either light transmission or neural elements.[4,16,30] Corneal injury or edema may result in blurring of vision, characteristically described as â€œhalosâ€• around lights. Toxicologic causes of corneal abnormalities include direct exposure to chemicals, failure of corneal protective reflexes because of local anesthetic effects or a profoundly decreased level of consciousness, and incomplete eyelid closure during coma. Mydriasis, secondary to various xenobiotics (Table 20-1), may interfere with the pupillary constriction necessary for accommodation, thereby resulting in decreased acuity for near objects. Lens clouding or cataract formation causes blurred vision and decreased light perception, as does blood (hyphema) or other deposits in the aqueous humor or vitreous humors. Xenobiotic-induced lens abnormalities caused by chronic exposures are well described (Table 20-2),[23,30,39] but are unimportant in the evaluation of an acute toxicologic emergency. Even if light reaches the retina without distortion, abnormal reception or transmission can result from ischemia or injury to any neural element from the retina to the optic cortex. Direct, acute, visual neurotoxic injury is rare and is caused almost exclusively by methanol or quinine. Indirect injury following xenobiotic-induced central nervous system (CNS) ischemia or hypoxia is far more common. Alterations in color perception generally result from abnormalities in retinal or optic nerve function. Color-vision abnormalities are attributed to hundreds of agents, but unlike those caused by chronic xenobiotic exposure such abnormalities are rare and inconsistent features of acute toxicity.[23,30]

Pupil Size and Reactivity

Generally, pupils are round and symmetric with an average diameter of 3â€“4 mm under typical light conditions. Physiologic anisocoria (unequal pupils) is a normal variant and is defined as a difference in pupil size of 1 mm or less. However, in the absence

of a history of physiologic anisocoria, any asymmetry in pupil size should be considered an abnormal finding. Pupils react directly and consensually to light intensity by either constricting or dilating. Constriction is also a component of the near reflex (accommodation) that occurs when the eye focuses on near objects. The iris controls pupil size through a balance of cholinergic innervation of the sphincter (constrictor) muscle by cranial nerve III and sympathetic innervation of the radial (dilator) muscle.[16]

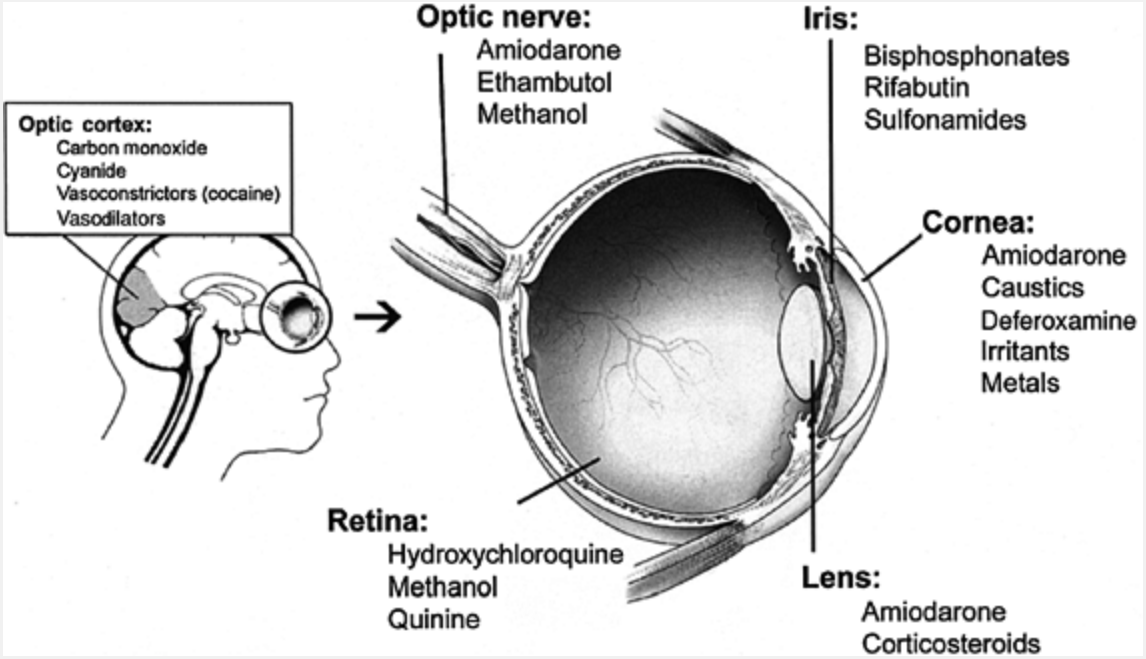

Figure 20-1. The major xenobiotics and their areas of ophthalmic injury. *(Courtesy of the National Eye Institute,*

National Institutes of Health, adapted by Joseph Lewey.)

Pupillary dilation (mydriasis) can result from increased sympathetic stimulation by endogenous catecholamines or, from xenobiotics such as cocaine, amphetamines, and other sympathomimetics as well as ophthalmic instillation of sympathomimetic agents such as phenylephrine. Mydriasis can also result from inhibition of muscarinic cholinergic-mediated pupillary constriction secondary to systemic or ophthalmic exposure to anticholinergic agents (Chap. 50). Because pupillary constriction in response to light is a major determinant of normal pupil size, blindness from ocular, retinal, or optic nerve disorders also leads to mydriasis as exemplified by methanol and quinine toxicity. Reactivity of mydriatic pupils to light varies with the etiology of the mydriasis.[30] Although often difficult to appreciate, constriction to light can usually be elicited after sympathomimetic exposures because constrictor function is preserved, whereas this is often not the case when mydriasis results from anticholinergic excess. Light reactivity is absent in cases of complete blindness caused by retinal or optic nerve damage, but may be preserved if there is some remaining light perception.

Miosis can result from increased cholinergic stimulation such as opioids, pilocarpine, and cholinesterase inhibitors such as organic phosphorus compounds, or inhibition of sympathetic dilation caused by clonidine. There are conflicting reports regarding the pupillary reactions to many xenobiotics. Depending on the stage and severity of toxicity, the presence of coingestants or coexistent hypoxemia, and numerous other factors, many individual substances (eg, phencyclidine and barbiturates) are reported to cause either mydriasis, miosis, or hippus, the fluctuation between miosis and mydriasis.[30,40] For some xenobiotics, the pupillary examination provides consistent information (Table 20-1), but many factors are involved and the significance of the pupil size

and reactivity must always be considered in the context of the remainder of the patient evaluation.

Extraocular Movement, Diplopia, and Nystagmus

Maintenance of normal eye position and movement requires a coordinated function of a complex circuit involving bilateral frontal and occipital cortices, multiple brainstem nuclei, cranial nerves, extraocular muscles, and connecting fibers between each.[2,16] Because of the many elements necessary for normal function, abnormalities of eye movement can result from several causes and are extremely common.[30] Probably the most common abnormality is reversible nystagmus or rhythmic oscillations of the globes (Table 20-1). Xenobiotic-induced nystagmus can take many forms, but is most commonly jerk nystagmus, as opposed to pendular, or horizontal and symmetric. The nystagmus may be evident at rest but is accentuated by visual pursuit and extreme lateral gaze. Although nystagmus with extreme lateral gaze is a normal finding, it extinguishes within 2â€“5 beats; if nystagmus persists, it is evidence of underlying pathology. Xenobiotic-induced vertical nystagmus occurs with phencyclidine, ketamine, dextromethorphan, or phenytoin toxicity; vertical nystagmus, however, is usually associated with a structural lesion of the CNS. Loss of conjugate gaze commonly results from CNS depression of any cause, typically after a sedative-hypnotic or ethanol overdose. Except after extremely rare exposures to neurotoxins (Table 20-1), diplopia without a decreased level of consciousness should not be attributed to an acute toxicologic etiology. In addition to the transient effects of some xenobiotics thallium, carbon disulfide, and carbon monoxide, may cause sustained gaze disorders as a consequence of residual cranial nerve and CNS injury.[30] Nystagmus and ophthalmoplegia caused by thiamine deficiency usually improves after therapy, but the nystagmus may not

completely resolve.[63]

Systemic Absorption and Toxicity from Ocular Exposures

Systemic absorption from ocular exposures has caused serious toxicity, morbidity, or death.[20,33] Although the patterns of toxicity are characteristic of the xenobiotics involved, recognition may be

delayed as a result of a failure to appreciate the eye as a significant route of absorption. Although transcorneal diffusion of xenobiotics are limited, there is substantial nasal mucosal absorption after nasolacrimal drainage, and absorption via conjunctival capillaries and lymphatics, which is markedly increased during conjunctival inflammation. Unlike the gastrointestinal route of absorption, there is no significant first-pass hepatic removal after ocular absorption; consequently, bioavailability is much greater.[20,33,57] If nasolacrimal outflow is normal, up to 80% of instilled drug may be absorbed systemically.[20] By the time toxicity is apparent, there is no role for ocular decontamination to prevent further absorption. After instillation of eye drops, absorption is generally complete within 7 minutes.

TABLE 20-1. Ophthalmic Findings Caused by Acute Xenobiotic Exposures

Miosis
Increased cholinergic tone
Carbachol
Cholinesterase inhibitors (carbamates, organic phosphorus compounds)

Muscarine
Nicotine
Pilocarpine
Decreased sympathetic tone (clonidine, guanabenz, methyldopa, opioids)
Coma from sedative-hypnotics (barbiturates, benzodiazepines, ethanol)
Mydriasis
Decreased cholinergic tone
Antihistamines
Belladonna alkaloids
Cyclic antidepressants (inconsistent finding)
Postanoxic encephalopathy
Increased sympathetic tone (amphetamines, cocaine, phenylephrine and other sympathomimetics, ethanol and sedative-hypnotic withdrawal)

Nystagmus
Carbamazepine
Dextromethorphan
Ethanol
Ketamine
Lithium
Monoamine oxidase inhibitors
Phencyclidine
Phenytoin
Sedative-hypnotics
Thiamine deficiency

Disconjugate gaze
Botulism
Elapid envenomation
Neuromuscular blockers
Paralytic shellfish poisoning

Tetrodotoxin
Thiamine deficiency
Secondary to decreased level of consciousness (many causes)

Funduscopic abnormalities
Carbon monoxide (red)
Cocaine (vasoconstriction)
Cyanide (retinal vein arteriolization)
Ergot alkaloids (vasoconstriction)
IV drug use (embolic)
Methanol (disc and retinal pallor or hyperemia)
Methemoglobin (cyanotic)

Papilledema
See causes of pseudotumor cerebri (Table 41-2)

Children appear to be at greatest risk, possibly because of the higher relative drug dose they experience when systemic absorption does occur.[20,47,57] Diligent attempts to comply with prescribed dosing in a struggling, crying infant may also result in excessive dosing. As eyedrop size (40â€“50 ÂµL) exceeds ocular cul-de-sac capacity (30 ÂµL), overflow often occurs and is assumed to represent a failed instillation, which leads to unnecessary reinstillation. Also, as doses of ocular medications are typically not adjusted based on patient weight, the consequences of equivalent degrees of systemic absorption are much greater for an infant than for an adult. Toxicity from eye drops is also a problem among the compromised, probably because of the combination of greater use of potentially toxic ophthalmic medications and the presence of comorbid conditions.

Prevention of systemic toxicity from topical ophthalmic medications requires recognition of the risk, a careful history, use

of the lowest effective concentration and dose, and patient education including proper administration instructions. To minimize inadvertent absorption, no more than one drop of any eyedrop solution should be instilled at one time in the superolateral corner of the eye while using gentle finger compression of the medial canthus to limit nasolacrimal drainage.[20,33]

Mydriatics

Mydriatics are used almost exclusively to dilate the pupils prior to diagnostic evaluation of the eyes. This common practice is not generally considered to be potentially dangerous; however, the risk may be substantial if the precautions outlined are not considered. Anticholinergic poisoning (Chap. 50), including substantial morbidity and mortality, is well described after ocular use of atropine, cyclopentolate, or scopolamine eyedrops, especially in infants.

The use of the Î±-adrenergic agonist phenylephrine eyedrops in a 10% solution may cause severe hypertension, subarachnoid hemorrhage, ventricular dysrhythmias, and myocardial infarction.[22] Fortunately, these effects are rare if the 2.5% ocular phenylephrine is used. Mydriatics can also precipitate acute angle closure glaucoma in susceptible individuals.

Miotics and Other Antiglaucoma Drugs

Maintaining miosis to prevent angle closure is an important part of glaucoma therapy. Cholinesterase inhibitors used for this purpose, such as echothiophate, can exacerbate asthma, parkinsonism, and cardiac disease. If neuromuscular blockade is required for patients using ocular cholinesterase inhibitors, an agent not metabolized by plasma cholinesterase (eg, atracurium, pancuronium, vecuronium, or tubocurarine) must be used. Succinylcholine and mivacurium

are cleared by plasma cholinesterase and have profoundly prolonged effects when a cholinesterase inhibitor is present.[33] Because of their long duration of action and resultant risk of accumulation after repeated dosing, cholinesterase inhibitors are associated with the highest incidence of adverse reactions among susceptible patients.

Miosis can also be produced by use of direct cholinergic agonists, such as pilocarpine, which have a much shorter duration of action. Although absorption is limited, nausea and abdominal cramps can occur at recommended doses. After excessive dosing, salivation, diaphoresis, bradycardia, and hypotension may occur.

Î²-Adrenergic antagonists, such as timolol, levobunolol, metipranolol, carteolol, and betaxolol, are used to lower intraocular pressure but cause a variety of adverse effects, including bradycardia, hypotension, myocardial infarction, syncope, transient ischemic attacks, congestive heart failure, exacerbation of asthma, status asthmaticus, and respiratory arrest. Timolol has exacerbated symptoms in patients with myasthenia gravis and is implicated in both causing and masking symptoms of hypoglycemia in diabetics.[61,62] Nonspecific complaints of anorexia, anxiety, depression, fatigue, hallucinations, headache, and nausea are also described after use of timolol eyedrops. Despite the cardioselectivity of betaxolol, respiratory toxicity has been reported.[20]

Dipivefrin, an esterified epinephrine derivative sometimes used to treat glaucoma, can cause adrenergic systemic effects, although much fewer than those caused by epinephrine. Ophthalmic formulations of highly selective $\hat{I}\pm_2$-adrenergic agonists, brimonidine (Alphagan) and apraclonidine (Iopidine) have been introduced to treat glaucoma.[20,65] Apraclonidine is expected to have a lower potential for toxicity because of limited CNS absorption. Systemic absorption of brimonidine eye drops in a

child has led to bradycardia, hypotension, and a decreased level of consciousness, similar to the central effects of other Î±$_2$-adrenoceptor agonists (eg, clonidine),[7] apparently mediated through both Î±$_2$-adrenoceptors and imidazoline receptors.[11]

Antimicrobials

Life-threatening reactions to ophthalmic antimicrobials are unusual but do occur. Episodes of aplastic anemia have occurred after prolonged use of chloramphenicol eye preparations,[21] and Stevens-Johnson syndrome was reported after short-term use of ophthalmic sulfacetamide in a patient with a history of allergy to sulfa drugs.[29]

Ocular Caustic Exposures: First AID and Initial Approach

The initial approach to all patients with ocular caustic exposures should be immediate decontamination by irrigating with copious amounts of fluids, water being the most often used.[12,64] Water, normal saline, lactated Ringer solution, and balanced salt solution (BSS) are all appropriate choices.[54] In theory, BSS is ideal, because it is both isotonic and buffered to physiologic pH. Lactated Ringer solution (pH 6â€“7.5) and 0.9% sodium chloride solution (pH 4.5â€“7) are also isotonic and therefore theoretically preferable to water.[32] The use of an ocular anesthetic is usually required to perform irrigation properly. Irrigation is intended to accomplish at least 4 objectives: immediate dilution of the offending agent; removal of the agent; removal of any foreign body; and in some cases, normalization of anterior chamber pH. As delays of even seconds can dramatically affect outcome,[30] there is no justification for waiting for any specific solution if water is the first available agent. Irrigation must include the external and internal palpebral surfaces, as well as the cornea and

bulbar conjunctiva and its recesses. Effective irrigation includes lid retraction and eversion or use of a scleral shell or other irrigating device. After irrigation, visual acuity testing, inspection of the eye, and slit-lamp examination should be performed.

Exposure-Specific Irrigating Solutions

Despite theoretical concern, there is probably no toxic exposure for which standard aqueous solutions are contraindicated. Of greatest concern are agents such as white or yellow phosphorus, metallic sodium, metallic potassium, and calcium oxide (cement) that may theoretically react violently in the presence of water, leading to heat or mechanical injury, or resulting in the generation of sodium hydroxide, potassium hydroxide, and calcium hydroxide.[30] Although not well-studied, irrigation with large amounts of water probably dissipates the heat of the initial hydration reaction with conjunctival moisture more than it initiates a thermochemical reaction. In addition to removing the offending material, irrigation serves to dilute and remove the alkaline byproducts formed by reaction with conjunctival water.

The use of special irrigating solutions for more uncommon exposures, including hydrofluoric acid and phenols, is also debated. A recent animal model of alkaline injury suggests irrigation with amphoteric or buffered solutions rapidly restores anterior chamber pH.[55] However, the majority of the published human data have been case reports. Therefore, at this time these solutions are probably best suited for first aid treatment at worksite eyewash stations and are neither practical nor proven in the emergency department setting for prolonged irrigation.

Hydrofluoric Acid

For hydrofluoric acid exposures (Chap. 101), experimental irrigation with calcium salt solutions was too irritating to the eye, but isotonic magnesium chloride solutions appear effective and not

irritating.[41,42] From a practical standpoint, however, 0.9% sodium chloride solution remains readily available, well studied and effective.

Phenol

For phenol exposure, topical low-molecular-weight polyethylene glycol (PEG) solutions are effective for treatment of experimental skin exposure; for eyes, copious water irrigation appears to be as effective as PEG.[10] There is, however, a report of superior efficacy of PEG-400 over water in treatment of actual phenol eye burns.[35] Although PEG-400 may be readily available at worksites where phenols are used, it is not a realistic option in the emergency department, and there should be no hesitation to use water, 0.9% sodium chloride solution, lactated Ringer solution, or BSS as lavage solutions.

Cyanoacrylate Adhesives

Ocular exposures to cyanoacrylate adhesives such as Dermabond and Krazy Glue occasionally result in rapid adherence between upper and lower eyelids that may persist for days. Such occurrences may be associated with corneal abrasions,[17] but are otherwise relatively harmless. In fact, cyanoacrylate has been safely used for decades to treat corneal perforations.[66] Solvents such as acetone or ethanol, which are often effective treatment for dermal-to-dermal adhesions caused by cyanoacrylates, should never be used in or around the eyes. Expectant management is the safest approach as spontaneous rejection of the glue will occur over time. Application of gauze pads soaked with antibiotic ophthalmic ointment may speed recovery.[34] A thorough eye examination should be performed once the eyelids can be fully opened.

Other xenobiotic-specific treatments have been tried experimentally or clinically,[32] but none should be considered prior

to or instead of copious irrigation, most are not advocated, and consideration of such agents should be vanishingly rare.

Duration of Irrigation

To accomplish the desired goals of irrigation, the appropriate duration varies with the exposure. Most solvents, for example, do not penetrate deeper than the superficial

cornea, and brief (10â€“20 minutes) irrigation is generally sufficient.[30] After exposure to acids or alkalis, normalization of the conjunctival pH is often suggested as a useful end point. Testing of pH should be done in every case of acid or alkali exposure, but the limitations of testing must be understood. When measured by sensitive experimental methods, normal pH of the conjunctival surface is 6.5â€“7.6.[1] This is highly method-dependent, however, and normal values in the literature range from 5.2 to 8.6.[14] When measured by touching pH-sensitive paper to the moist surface of the conjunctival cul-de-sac, normal pH is most often near 8.[3] Therefore, after irrigation following alkali burns, pH should not be expected to reach 7 and is more likely to stabilize near 8.[30] In this setting, lower pH values may indicate the pH of the irrigant rather than of the ocular surface. Waiting for an interval of several minutes between irrigation and pH testing allows washout of any residual irrigant.[15] Choice of testing paper is important, as some are intended for use at extremes of pH and lack sensitivity in the clinically useful range.

Despite these limitations, a logical role for pH assessment can be described: Probably a minimum of 500â€“1000 mL of irrigant should be used for each affected eye before any assessment of pH, and after 7â€“10 minutes, the pH of the lower fornix conjunctiva should be checked. Thereafter, cycles of 10â€“15 minutes of irrigation followed by rechecks should be continued until the pH is 7.5â€“8. This is certainly adequate for exposures to weak acids,

which do not penetrate well, and for alkaline exposures where the pH is less than 12.

For strong alkaline, concentrated acid, or for hydrofluoric acid exposures with apparent eye abnormalities, normal surface pH is not an adequate end point (see Alkalis below). After these burns, irrigation should be continued for at least 2â€“3 hours, regardless of surface pH, in an attempt to correct anterior chamber pH;[30,53,64] in addition, immediate ophthalmologic consultation is mandatory. Following this lengthy irrigation, it is important to verify that conjunctival pH has normalized. If not, irrigation must be continued, sometimes for 24â€“48 hours.

Other General Measures

There is a wide array of options for adjunctive therapy of chemical burns of the eye. In all cases in which serious injury is evident, the treatment plan must include consultation with an ophthalmologist. Generally, patients with corneal injury should be treated with an ocular topical antibiotic providing antistaphylococcal and antipseudomonal coverage. Cycloplegics not only reduce pain from ciliary spasm, but also decrease the likelihood of posterior synechiae (scar) formation. Topical NSAIDs and systemic analgesics also improve patient comfort. It is never appropriate to dispense topical ophthalmic anesthetic agents, because repeated use of these agents leads to further corneal disruption both by direct chemical effects and by eliminating corneal protective reflex sensation.

Ocular Caustic Exposures: specific xenobiotics

The effect of any xenobiotic on the eye depends on the inherent properties as a solvent or detergent; the amount, concentration, and pH of the xenobiotic; and the duration of exposure. The end

result of ocular exposure to these agents depends on the extent of damage to the cornea, particularly the integrity and function of the stroma; penetration into the anterior chamber and the resulting injury to its structures; and resultant inflammatory reaction.[30,64] Because similar xenobiotics tend to produce similar reactions, they can be conveniently grouped for discussion into acids, alkalis, and others.

Acids

Fortunately, weak acids do not penetrate the cornea well.[30,64] The hydrogen ion causes damage by lowering ocular pH, while the anion denatures ocular proteins on contact, causing precipitation and coagulation that actually limits the extent of penetration. The dehydrating effect of some acids, the heat of hydration, and the affinity of each anion for corneal tissues all affect the extent of injury. Intense pain usually results from stimulation of exposed nerve endings in the corneal epithelium. Corneal defects are common, but in many cases the damaged epithelium is swept away, revealing a healthy Bowman layer, over which epithelium resurfaces the cornea. Strong acids can penetrate the stroma, damage deeper tissue and structures of the anterior chamber, and lead to the more serious sequelae, such as those that often occur after alkali burns.[30,64] Prolonged exposure to weaker acids may result in significant extension of the injury, making immediate irrigation mandatory.

Hydrofluoric acid may cause unexpectedly severe injury because of its ability to penetrate deep into the eye.[41,42,52] Damage is generally concentration dependent, with severe injury expected after exposure to 20% solutions or higher, but even dilute formulations have led to persistent abnormalities. On the basis of anecdotal reports, some authors[60] advocate repeated instillation of calcium gluconate eye drops to bind free fluoride, but there is no evidence that this is beneficial.[5] At this time, we do not

advocate the use of calcium or magnesium solutions for irrigation or instillation after hydrofluoric acid eye exposure.

Alkalis

Alkali burns of the eye represent an ophthalmic emergency. A rational approach to care is based on an understanding of the complex pathophysiology of these injuries.[64] The hydroxyl ion saponifies lipid membranes, directly disrupting cells, whereas the penetration of the alkali is determined by the cation. Cations react with and hydrate stromal collagen and glycosaminoglycans, causing loss of clarity. For this reason, once the damaged epithelium is swept away, any haziness of the underlying stroma is evidence of alkali penetration and potential serious sequelae. If injury is limited only to destruction and lysis of corneal epithelium, with clear stroma, rapid and complete resolution is expected. Large amounts of concentrated strong bases such as sodium hydroxide, xenobiotics that penetrate rapidly such as ammonium hydroxide, and prolonged exposure all promote deeper injury.[30,51,64] Penetration into corneal stroma may destroy keratocytes, alter collagen structure, and damage the endothelium.[62] Paradoxically, more extensive burns may be less painful, because of destruction of corneal nerve endings and resultant anesthesia. In addition to indicating an increased depth of the burn, stromal and endothelial injuries often impair the ability of the cornea to regenerate later and to maintain an adequate epithelium. Further penetration can cause the pH of the anterior chamber to rise significantly within 2â€“3 minutes.[48,64] Ammonium hydroxide is especially destructive by this mechanism, as it penetrates far more rapidly than other alkalis. Experimentally, 8.5% ammonium hydroxide increases anterior chamber

pH within 15 seconds.[30] As a result, the sequelae of these exposures are severe and may be out of proportion to both pH and

the degree of surface injury.

The increase in intraocular pH is injurious to the trabecular meshwork, iris, lens, and ciliary body, and also triggers a sudden contraction of corneal and scleral collagen, leading to increased intraocular pressure and exacerbation of pain. A less dramatic but more sustained increase in intraocular pressure ensues, resulting from intraocular prostaglandin release.[64]

In addition to these direct effects, further injury results from the inflammatory response to the initial injury. Dysfunction of the normal bloodâ€“aqueous humor barrier results in exudation of protein and inflammatory cells into the anterior chamber, leading to a severe fibrinous reaction. Fibrosis, in turn, can lead to permanent angle closure with resultant glaucoma. At the opposite extreme, permanent dysfunction of the ciliary body, which produces the aqueous humor, can result in visual loss as a consequence of collapse of the eye (phthisis bulbi).[30,64]

The full extent of injury may not be evident for 48â€“72 hours. In the ensuing days to weeks, outcome is determined by the balance between degradation and repair of the stromal matrix, the quantity and quality of corneal reepithelialization, and the extent of inflammatory cell infiltration. After severe burns, normal repair is distinctly rare and extensive scarring is the rule. The goal of therapy is to prevent corneal ulceration, ocular perforation, and glaucoma while preserving the eye for possible secondary surgical revision or repair.

The mainstay of treatment is immediate and copious irrigation following the guidelines discussed. After exposures to calcium hydroxide (lime) from mortar or cement splashes, any adherent material must be found and removed. A sterile cotton-tipped applicator soaked in 0.05 mol/L edetate disodium (Na_2 EDTA) may aid this process.[30,51,64] Follow up is essential in all cases of alkali eye burns. Emergent consultation with an ophthalmologist should be obtained for all suspected severe burns. For isolated, very

superficial corneal defects this is not necessary; however, if there is pain unrelieved by topical anesthetics, evident corneal opacification, increased intraocular pressure, or any slit-lamp examination evidence of deep corneal burn, corneal edema, or anterior chamber cell or flare, immediate consultation is essential.

Not only is comprehensive early evaluation important, but the advisability of several adjunctive treatments should be determined in conjunction with the ophthalmologist. Emergent needle paracentesis and lavage of the anterior chamber removes alkali and returns pH to normal and also decreases intraocular pressure.[30,48,64] Animal studies suggest that this technique is useful if performed within minutes, but its benefit is not proven in human exposures, possibly because of delay in patient presentation and limited availability of expertise in the technique. In addition to topical antibiotics, cycloplegics, topical steroids, topical and systemic tetracyclines, and antiglaucoma medications may all be indicated. Early steroid treatment may decrease the inflammatory response, but continued use inhibits fibroblast function and healing.[18,64] Ophthalmologists therefore suggest steroids only for the first 7 days. Although well-controlled research in animal models of ocular alkali injury suggest that topical citrate and ascorbate improve healing, a recent long-term study showed no significant benefit in humans and demonstrated delayed healing when used in patients with mild to moderate injury.[9,49,50]

Tetracyclines, particularly doxycycline, inhibit collagenase activity by chelating zinc, and reduce corneal ulceration.[13,56] In addition, they also inhibit leukocyte activity. These treatments have supplanted less-effective earlier collagenase inhibitors (cysteine, acetylcysteine, penicillamine, EDTA), and many other previously used approaches. Investigational agents include fibronectin, epidermal growth factor, hyaluronate, and retinoic acid to promote regrowth of epithelium; and medroxyprogesterone and NSAIDs to limit inflammation without inhibiting stromal repair and collagen formation. Many surgical interventions are investigational and may

be indicated, including limbal stem cell and amniotic membrane transplantation.[58,65]

Others

Most solvents cause immediate pain and superficial injury because of dissolution of corneal epithelial lipid membranes, but do not penetrate or react significantly with deeper tissue.[30] The epithelial defect may be large or complete, but the limited depth of injury usually allows rapid regeneration of normal epithelium. Detergents and surfactants cause variable injury, ranging from minor irritation from soaps to extensive injury from cationic agents such as concentrated benzalkonium chloride.[30] Ocular exposure to A-200 Pyrinate pediculicide shampoo causes typical detergent-surfactant injury, leading to extensive loss of corneal epithelium but with normal underlying stroma, and therefore complete healing within days. Lacrimators (tear gases), such as chloroacetophenone, stimulate corneal nerve endings and cause pain, burning, and tearing, but produce no structural injury at low concentrations. At high concentrations, these agents can produce significant corneal injury.

Pepper spray, often used for self-protection by civilians or law enforcement agents, contains the active ingredient oleoresin capsicum (OC). OC results in rapid depolarization of nociceptors containing substance P, resulting in immediate pain, blepharospasm, tearing, and blurred vision. In general, ocular injury is uncommon, although corneal erosions can occur. The solvent used for the spray can be more injurious to the eye than the OC itself. Although most sprays use a water- or oil-based solvent, some use alcohol, which can result in significant corneal damage.[67] Management of pepper spray exposure consist of rapid irrigation and pain control. Corneal erosions can be treated with artificial tears but corneal abrasions should be treated with topical antistaphylococcal antibiotics. Specific information on thousands of

agents is readily available if needed.[30]

Disposition

Disposition of patients with chemical burns of the cornea can be challenging. Patients with extensive burns to other parts of the body should be evaluated for transfer to a burn center. Grading the degree of injury in patients with isolated ocular injury can guide disposition. The most commonly used grading system is the Roper-Hall modification of the Ballen classification system. Injury is graded on a 4-tier scale: Patients with mild conjunctival injection with corneal epithelial loss and minimal corneal haziness are classified as grades 1 and 2 (mild to moderate). These patients can be safely discharged from the emergency department with ophthalmology followup within 24â€“48 hours. Patients with severe corneal haziness or opacification with significant limbal ischemia are classified as grades 3 or 4 (moderate to severe) and should receive immediate consultation with an ophthalmologist and transfer to a burn unit should be considered.

Toxicity to Ocular Structures from Nonocular Exposures

Ocular toxicity from systemic xenobiotics is almost always the result of chronic exposure, and the manifestations develop over a prolonged period of time. Thousands of substances are implicated, affecting every element of the visual system from the cornea to the optic cortex. Thorough discussion of this topic is beyond the scope of this text, but Table 20-2 lists examples of causative xenobiotics.[23,30] Many topical and systemic medications are associated with inflammation of the eye, as well as uveitis.[24] Unlike many other ocular abnormalities caused by xenobiotics, uveitis should prompt immediate ophthalmologic consultation.

Because many etiologies are commonly prescribed medications, adverse drug effects should always be considered when patients present with visual abnormalities or unusual ocular findings on examination.

TABLE 20-2. Examples of Ocular Abnormalities Caused by Chronic Systemic Xenobiotic Exposures[a]

Corneal/conjunctival inflammation	Retrobulbar and optic neuropathy
Cytosine arabinoside (Ara-C)	Carbon disulfide[d]
Isotretinoin[b]	Chloramphenicol[d]
Mercury (acrodynia)	Dinitrobenzene[d]
Practolol[c]	Dinitrochlorobenzene[d]
	Dinitrotoluene[d]
Retinal injury	Disulfiram
Carmustine[c]	Ethambutol[b]
Carbon disulfide[d]	Isoniazid[c]
Chloramphenicol[c]	Lead[c]

Chloroquine	Thallium
Cinchona alkaloids (quinine)	Vincristine[c]
Deferoxamine[c]	
Digitalis[c]	Cataracts
Ethambutol	Busulfan[c]
Thallium	Corticosteroids[b]
Vigabatrin	Deferoxamine
Vincristine[c]	Dinitrophenol (internal use)[d]
	Trinitrotoluene[d]
Uveitis	
Bisphosphonates	Cortical blindness
Pamidronate	Cisplatin
Rifabutin	Cyclosporine
Sulfonamides	Interleukin[c]

	Tacrolimus
Corneal deposits	Methylmercury compounds[d]
Amiodarone[b]	
Chloroquine	Lens deposits
Chlorpromazine	Amiodarone[b]
Copper[d]	Chlorpromazine
Gold	Copper[d]
Mercury[d]	Iron
Retinoids	Mercury[d]
Silver (argyria)[d]	Silver[d]
Vitamin D	
	Myopia[c]
	Acetazolamide
	Diuretics (chlorthalidone, thiazides, spironolactone)

	Retinoids
	Sulfonamides

[a] This list includes only selected examples and is not intended to be comprehensive.
[b] Particularly important example.
[c] Reported, but extremely rare from this exposure.
[d] Mostly of historical interest; associated with patterns of use that are no longer common.

TABLE 20-3. Xenobiotics Reported to Cause Visual Loss After Acute Exposures

Direct causes
- Caustics
- Methanol
- Quinine
- Lead[a]
- Mercuric chloride[a]

Indirect causes[b]
- Amphetamines
- Cocaine
- Embolization of foreign material (parenteral injection)
- Cisplatinum
- Combined endocrine agents (thyrotropin-releasing hormone with gonadotropin-releasing hormone and glucagon)
- Ergot alkaloids

Hypotension (eg, calcium channel blockers)

[a] Distinctly rare with these poisonings.
[b] Distinctly rare with use of these agents; visual loss often instantaneous, secondary to sudden hypotension, vascular spasm, or embolization.
Adapted, with permission, from Smilkstein MJ, Kulig KW, Rumack BH: Acute toxic blindness: Unrecognized quinine poisoning. Ann Emerg Med 1987;16:98â€“101.

In the setting of emergency care, xenobiotic-induced disturbances of normal vision from systemic exposures take many forms. Impaired near-vision from mydriasis, and diplopia or nystagmus from interference with normal control of extraocular movements, are examples of common, usually harmless, visual effects. Serious effects generally result from injury or dysfunction of the neural elements from the retina to the cortex. Such toxicity can be direct (neurotoxic) or indirect (hypoxia, ischemia). Many xenobiotics historically reported to cause acute visual loss directly are no longer available.[30] Methanol and quinine are currently the most important xenobiotics that cause direct visual toxicity after acute oral poisoning. Many xenobiotics capable of causing vasospasm, hypotension, or embolization also cause acute visual loss (Table 20-3).[59] Blindness and other visual defects are described following recovery from severe toxicity with barbiturates and other sedative-hypnotics, opioids, carbon monoxide, and many others.[30]

Methanol

Formate, the byproduct of methanol metabolism (Chap. 103), is the cause of visual toxicity from methanol poisoning. Although interspecies differences complicate the analysis, it appears that the primary event in ocular toxicity is the metabolism of methanol

by retinal glial cells, which results in local elevation of formate concentration.[19,27,28,38,46] The exact effects of formate remain to be defined, but formate is postulated to interfere with mitochondrial cytochrome oxidase and succinate-cytochrome c reductase, and possibly with the Na^+-K^+-adenosine triphosphatase (ATPase) system in the fibers of the optic nerve head.[37] Although the retina is the likely primary site of toxicity,[19,27,28,38,45,46] injury to the retinal ganglion cells and the retrobulbar optic nerve are also described, possibly as secondary effects. The visual signs and symptoms of methanol-induced visual disturbance include blurred or misty vision, â€œsnowfieldâ€• vision, spots, central and peripheral scotomata, decreased light perception, and complete blindness.[6] The physical examination is consistent with the mechanism described: Although

in many patients with only mild visual impairment the examination may be normal, the most consistent finding in severe cases is initial hyperemia of the optic nerve head, which later becomes edematous. The extension of the edema to the surrounding retina correlates with central scotomata, which are common. In severe cases, the edema may extend to large areas of the retina. In the most severe cases, when light perception is lost, the pupils may be widely dilated and unreactive.

In severe cases, histopathologic examination reveals injury to the retinal ganglion cell layer and extension of the optic nerve injury to the retrobulbar nerve fibers.[28] Optic atrophy often follows, and although central scotomata and peripheral visual field constriction are common, more complete visual loss may then occur. Patients with prolonged metabolic acidosis show a tendency towards developing residual visual impairment.[36] Additionally, the constellation of severe initial impairment, dilated and unreactive pupils, and widespread retinal edema also implies a particularly poor visual prognosis.

The concentration and duration of formate exposure also appears

to be critical to the development of retinal toxicity, but there are not yet reliable estimates or practical methods of determining these variables after human poisoning. Therefore, any patient with acidemia after methanol poisoning is assumed to be at risk for retinal damage. As discussed in Chap. 103, the risk can be reduced by the administration of folate or folinic acid to enhance the elimination of formate and to prevent retinal folate depletion[27,28] (see Antidotes in Depth: Leucovorin [Folinic Acid] and Folic Acid and Antidotes in Depth: Sodium Bicarbonate).

Quinine

The mechanism of quinine-induced visual impairment is less-well understood, but it is known to involve neurotoxic injury to the optic nerve and perhaps retinal ganglion cells.[31] Visual symptoms can include blurred vision, central and peripheral scotomata, and complete blindness.[8] The onset of visual impairment varies, but sudden visual loss can occur as late as 14 hours or more after overdose.[59] Physical examination reveals pupils that are dilated and unreactive in proportion to the degree of visual impairment. Funduscopic examination is often completely normal but may show edema of the optic nerve, retina, or both, and retinal arteriolar constriction.[30] Retinal vasoconstriction was previously thought to be the cause of visual injury, and therapies such as vasodilators and stellate ganglion block were used in an attempt to reverse the vasospasm. Further study clearly shows both complete blindness with normal vessels, and recovery in patients with vasospasm.[26,59] Thus, retinal vasoconstriction is no longer thought to be of primary importance, although there is still speculation that vasospasm may have a modifying effect on outcome. Currently, there is no role for vasodilator therapy in these cases.

Recovery is often very rapid, but residual impairment is common in severe cases. In a study of 225 cases of quinine poisoning, 70 patients developed visual impairment. Of 31 patients whose worst

ocular manifestation was blurred vision, all had complete visual recovery. However, of 39 patients who developed complete blindness, only 17 had full recovery.[8] The most common residual effects are peripheral field defects and central scotomata. Impaired color vision and complete blindness may also persist, but this is less common. Varying degrees of visual impairment (quinine amblyopia) have resulted from diverse forms of quinine exposure, but complete blindness is reported only after oral ingestion of large amounts of quinine. It is difficult to predict which patients will develop quinine amblyopia, but it does appear to be dose related. Although it certainly occurs at lower levels, permanent blindness should be expected if quinine serum levels exceed 20 mg/mL in the first 10 hours after ingestion (Chap. 56).[8]

Ocular Complications of Drug Abuse

In addition to the well-known ocular pupillary signs of opioid, cocaine, amphetamine, and phencyclidine toxicity, a number of complications may result from short- or long-term use of these and other agents.[43] Quinine amblyopia (see Quinine above) caused by intravenous use of quinine-containing heroin is one of many ocular complications caused by injection of contaminants. Talc retinopathy was first described after prolonged intravenous use of adulterated methylphenidate,[25] but has subsequently been noted after intravenous use of heroin, methadone,[44] codeine, meperidine, and pentazocine. Talc retinopathy develops only after extensive intravenous drug use. In one study of intravenous methadone abusers, only patients who had injected more than 9000 tablets developed this complication.[44] Infectious complications, such as fungal (*Candida, Aspergillus*) or bacterial (*Staphylococcus* spp, *Bacillus cereus*) endophthalmitis, are well known as both direct effects of intravenous drug use and secondary complications of AIDS. In addition to AIDS-related ophthalmic infections such as cytomegalovirus, cryptococcus, toxoplasmosis retinitis, and choroidal *Mycobacterium avium-*

intracellulare complex (MAC), other disorders include retinal cotton-wool spots, conjunctival Kaposi sarcoma, and ocular motility disorders caused by infectious or neoplastic meningitis. Corneal defects have been noted after smoking cocaine alkaloid (â€œcrack eyeâ€•).[54] Cocaine that is either volatilized or inadvertently introduced by direct contact, probably results in corneal anesthesia and loss of corneal protective reflex sensation. Minor trauma, such as eye rubbing, then leads to corneal epithelial defects. In addition, there appears to be an increased incidence of infectious keratitis and corneal ulceration in these patients. The ability of local anesthetics to interfere with corneal epithelial adhesion may also play a role.

Summary

Both systemic and local toxicologic emergencies occur in the ophthalmic system. This discussion has focused on the research in the treatment of damage to the eye caused by xenobiotics. Although the obvious physical injuries are apparent to the clinician, the more subtle clues to toxicologic mechanisms that involve the ophthalmic and neurologic systems are only made by a meticulous examination of the eye. A careful ophthalmic examination often leads to early recognition of a toxicologic emergency.

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Chapter 21
Otolaryngologic Principles

William K. Chiang

Many xenobiotics adversely affect the special senses of olfaction, gustation, and cochlear-vestibular functions. These toxic effects are not life-threatening and frequently are not considered to be important. Because of the lack of standardized diagnostic techniques and normal parameters, particularly for olfactory and gustatory functions, it is likely that such adverse effects will be overlooked and dismissed by healthcare providers, despite significant patient distress and dysfunction. This chapter reviews the anatomy and physiology related to these senses; delineates the effects of xenobiotics on these senses; and examines the significant diagnostic information these senses contribute to the detection of xenobiotics. Understanding the effects of xenobiotics on the senses may allow for early detection, which occasionally can be lifesaving.

Olfaction

Anatomy and Physiology

Olfactory receptors are bipolar neurons located in the superior nasal turbinates and the adjacent septum. There are 10â€“20 million cells per nasal chamber, and the receptor portion of the cell undergoes continuous renewal from the olfactory epithelium.[111 , 114] Renewed olfactory receptors regenerate neural connections to the olfactory bulb. Olfactory receptor neurons are distinctive in their ability to regenerate.[25] The axons of these cells form small bundles that traverse the fenestrations of the cribriform plate of the ethmoid bone to the dura. Within the dura, these bundles form connections with the olfactory bulb. Neural projections then connect to the olfactory cortex. There are extensive central interconnections to other parts of the brain, such as the hippocampus, thalamus, hypothalamus, and frontal lobe, suggesting effects on other biologic functions.[111] Although primary odor detection is a function of the olfactory cranial nerve (CN I), some irritant odors, such as ammonia and acetone, are transmitted through the trigeminal cranial nerve (CN V) and its receptors.[44 , 150]

The actual olfactory receptor sites are structurally similar to taste receptors of the mouth and photoreceptors of the retina. The receptor is a single polypeptide chain consisting of approximately 350 amino acids, which folds back and forth on itself to transverse the cellular membrane 7 times. The outer end of the polypeptide contains an amine group (N-terminal) and the cytosol end contains a carboxyl group (C-terminal). The transmembranous portions determine the receptor shape and characteristics of the binding site. When a molecule binds to a specific receptor site, the resultant conformational change leads to the activation of the G-protein system, and calcium and/or sodium channel activation and neurotransmission.[77]

Smelling is an extremely sensitive detector of certain substances. Olfactory receptors can detect as little as a few molecules of

certain xenobiotics with a sensitivity that is superior to some of the most sophisticated laboratory detection instruments.[69]

Limitations of the Olfactory Senses

A number of problems present the greatest utility of smell as a toxicologic warning system. Human olfaction is a variable trait.[5, 122, 179] For example, 40â€“45% of people have specific anosmia (inability or loss of smell) for the bitter almond odor of cyanide.[45, 91, 122] There are limited data on the inheritance characteristics or genetic basis of these specific forms of anosmia. While some studies suggest that the ability to detect the odor of cyanide is a sex-linked recessive trait,[59] other studies yield conflicting results.[5, 20, 93] Females have a greater ability to detect androsterone, which is also prominent in human underarm secretion.[69] Human olfaction usually can distinguish a mixture of no more than 4 xenobiotics,[97] and therefore specific odors may be masked by other stimuli.

Olfactory fatigue is the process of olfactory adaptation following exposure to a stimulus for a variable period of time. This leads to a temporal diminution of the smell. Unfortunately, this adaptation may lead to a false sense of security with continued exposure to a xenobiotic. For example, hydrogen sulfide, which inhibits cytochrome oxidase, is readily detectable as distinct and offensive at the very low concentration of 0.025 ppm. At the higher and potentially toxic concentration of 50 ppm, the odor is less offensive, and recognition may disappear after 2â€“15 minutes of exposure.[8, 154] At an even higher concentration, when toxicity is likely, the onset of olfactory fatigue is even more rapid. The combination of the rapid onset of olfactory fatigue and toxicity at high concentrations of hydrogen sulfide exposure has contributed to numerous fatalities (Chap. 121).[1, 27]

In industrial settings, it is important to be aware of impaired olfactory function in any worker who may be exposed to chemical

vapors or gases.[75, 159] Such workers are at increased risk for toxic injury. The National Institute for Occupational Safety and Health (NIOSH) requires that an individual using an air-purifying respirator be capable of detecting the odor of a xenobiotic at levels below those producing toxicity.[6, 159] Sensory perception at this level ensures that the individual can detect filter cartridge â€œbreakthroughâ€• or failure at a safe level.[159] The odor safety factor refers to the ratio of the time-weighted average (TWA) threshold limit value (TLV)

to the odor threshold for a given xenobiotic. A xenobiotic with a high odor safety factor can be detected despite prolonged exposure.[6] Nontoxic xenobiotics, such as ethyl mercaptan, with a very high odor safety factor, can be added to xenobiotics that are odorless with lower safety factors, so that olfactory detection is predictable. This enhanced sensory awareness is the basis for the addition of mercaptans to the odorless natural gases used in the home so as to limit the potential for unrecognized hazardous exposure.

Clinical Use of Odor Recognition

The recognition of odors has traditionally been considered an important diagnostic skill in clinical medicine. Diseases can be diagnosed solely by recognizable associated odors: diabetic ketoacidosis as fruity; diphtheria as sweet; scurvy as putrid; typhoid fever as fresh-baked brown bread; and scrofula as stale beer.[38] Odors are also described for disorders of amino acid and fatty acid metabolism, such as phenylketonuria, maple syrup urine disease, hypermethioninemia, and isovaleric acidemia.[38]

The recognition of odors continues to be an important diagnostic skill for the rapid detection of xenobiotics (Table 21-1). To increase the awareness of odors of toxic xenobiotics, a â€œsniffing barâ€• of commonly available odors may be prepared (Table 21-2

).[64] Nontoxic xenobiotics that simulate the odors of toxic xenobiotics are placed in test tubes, numbered, and inserted in a test tube rack for circulation among staff. The sniffing bar, brief descriptions of clinical presentations, and a table of diagnostic odors (Table 21-1), may be used to teach the recognition of odors in medical toxicology.[64]

Etiology of Olfactory Impairment

There are different types of olfactory dysfunction. Anosmia, the inability to detect certain odors, and hyposmia, a decrease in the perception of certain odors, are the most common forms of olfactory impairment. The etiology of olfactory impairment may be classified as conductive, from anatomic obstruction of inspired air, or perceptive, from dysfunction of the olfactory receptors or signal transmission. Most conductive olfactory dysfunction results in hyposmia, because the obstruction is usually incomplete.[111 , 147]

Acetone (sweet, fruity)
Lacquer, ethanol, isopropanol, chloroform, trichloroethane, paraldehyde, chloral hydrate, methylbromide
Bitter almond
Cyanide
Carrots
Cicutoxin (water hemlock)
Disinfectants
Phenol, creosote
Eggs (rotten)
Hydrogen sulfide, carbon disulfide, mercaptans, disulfiram, *N* -acetylcysteine
Fish or raw liver (musty)
Zinc phosphide, aluminum phosphide
Fruit
Nitrites (amyl, butyl)
Garlic

Phosphorus, tellurium, arsenic, organic phosphorus compounds, selenium, thallium, dimethyl sulfoxide (DMSO)
Hay
Phosgene
Mothballs
Naphthalene, *p* -dichlorobenzene, camphor
Pepper
0 -chlorobenzylidene malonitrile
Rope (burnt)
Marijuana, opium
Shoe polish
Nitrobenzene
Tobacco
Nicotine
Vinegar
Acetic acid
Vinyl
Ethchlorvynol (Placidyl)
Violets
Turpentine (metabolites excreted in urine)
Wintergreen
Methyl salicylate

Characteristic Odor Potentially Responsible Xenobiotic

TABLE 21-1. Diagnostic Odors

The most common causes of anosmia and hyposmia are viral infections, trauma, xenobiotics, tumors, and congenital and psychiatric disorders (Table 21-3).[44 , 133 , 139 , 147 , 150] Viral infections may result in olfactory impairment either by obstructing nasal airflow or by causing damage to the olfactory epithelium.[78] Trauma to the head or nose can shear fragile olfactory nerves crossing the cribriform plate. In fact, as many as 5% of patients

with head trauma have subsequent olfactory dysfunction.[150, 169]

Chronic exposures to numerous xenobiotics are associated with olfactory dysfunction (Table 21-3). The most common toxic mechanism related is perceptive olfactory dysfunction. This may be a result of a direct injury or of a structural alteration of the receptor, or its components such as G proteins, adenylate cyclase, or receptor kinase.[76, 77] Anosmia or hyposmia from hydrocarbons, formaldehyde, heavy metals such as cadmium, and antineoplastic agents such as cytarabine result from direct effects on the receptor sites.[48, 77, 82] Local effects on the epithelium and the receptors from antibiotic nose drops may lead to temporary anosmia and hyposmia.[88, 178] Inhaled corticosteroids may have local effects on the epithelium, as well as direct effects on both G proteins and adenylate cyclase.[79] Cocaine insufflation causes direct local effects, as well as effects on receptor functions.[65, 73] Because of local effects of most xenobiotics and the regenerative ability of the olfactory receptor neurons, most xenobiotic-induced olfactory dysfunction is reversible.

Most people with anosmia have congenital anosmia to selected individual molecules, such as hydrogen cyanide, *N* -butyl mercaptan, trimethylamine, and isovaleric acid.[7, 44] Some extreme forms of congenital anosmia are associated with other abnormalities, such as Kallmann syndrome, a hereditary form of anosmia associated with hypogonadotropic hypogonadism. Agenesis of the olfactory bulbs and incomplete development of the hypothalamus causes this form of anosmia.[44, 150]

Dysosmia or parosmia is the distorted perception of smell (Table 21-3). Subclassifications of dysosmia include the perception of foul smell or cacosmia, the sensation of smell without a stimulus or phantosmia, and the sensation of the smell of a burnt or metallic material, torqosmia.[147] The etiologies are classified as peripheral or central. Peripheral etiologies include abnormalities of the nose, sinuses, and upper respiratory tract. Central etiologies

may be related to disorders such as Addison disease, hypothyroidism, temporal lobe epilepsy, and psychosis, or to conditions such as pregnancy.[44, 111, 148] How these conditions actually alter the perception of smell is unclear. A number of xenobiotics with similar effects are listed in Table 21-3. Bromocriptine alters dopaminergic transmission and inhibits adenylate cyclase. Levodopa also affects the dopaminergic transmission and chelates zinc, which is important in the maintenance of normal receptor functions.[77, 79]

Evaluation of Olfactory Impairment

General evaluation of olfactory function should include a detailed history, focusing on types, duration, and progression of symptoms, recent illnesses, head and nose trauma, sinus problems, family history, occupational history, hobbies, medications, and drug history.[39, 68] A complete physical examination and detailed examination

of the nasopharynx and sinuses should be performed to assess the potential for inflammation or structural abnormality. A simple set of olfactory stimulants, such as ground coffee, almond extract, peppermint extract, and musk, should be used to test each nostril individually with the patient's eyes closed.[68, 150] Standardized smell tests such as the UPSIT (University of Pennsylvania Smell Identification Test) and the CCCRC (Connecticut Chemosensory Clinical Research Center) tests are now commercially available; a composite score based on a panel of tests can determine the degree of olfactory dysfunction.[103] Pungent odors or stimulation associated with ammonia, capsaicin, acetone, and menthol are dependent on the trigeminal nerve (CN V) olfactory function, which is mainly

responsible for tactile pressure, pain, and temperature sensation in the mouth and nasal cavity. A patient who has olfactory nerve

damage should be able to detect these substances; conversely, a person with hysteria may deny detection of these substances that should physiologically be recognized.[68 , 150 , 178] If a xenobiotic-mediated mechanism is suspected, the offending agent should be discontinued. A coronal CT of the sinuses and nose or a CT or a MRI of the brain may be required if structural abnormalities are suspected.[150 , 178] Gas chromatographic analysis of the urine may be useful in patients with fish odor syndrome associated with trimethylaminuria.[98 , 156] Complicated cases and patients with significant impairment should be referred to an otolaryngologist or neurologist.

Tube 1
Tube 7
Case history:
A lethargic 28-year-old woman was brought to emergency department with an altered mental status.
Case history:
A 4-year-old boy was brought to the emergency department with a temperature of 103.5Â°F (39.7Â°C), a respiratory rate of 32 breaths/min, and markedly altered mental status. Laboratory tests on admission showed a high-anion-gap metabolic acidosis. The patient smelled like a â€œwintergreen candy.â€•
Odor:
Toxin:
Vinyl smell
Ethchlorvynol
Contents of tube:
Liquid contents of Placidyl capsule
Tube 2

Case history:
A 34-year-old man in cardiopulmonary arrest found in a chemical plant near several gas cylinders.
Odor:

Wintergreen

Toxin:

Methyl salicylate

Odor:

Bitter almond

Contents of tube:

Oil of wintergreen or wintergreen candy

Toxin:

Cyanide

Contents of tube:

Macerated seeds from inside of peach pit or almond extract.

Tube 8

Case history:

A 3-year-old boy was brought to the emergency department in considerable pain. On examination the department in considerable pain. On examination the child exhibited dysphagia and dysphonia, the oral mucosa appeared blistered and erythematous. The child's mother stated that he must have gotten into cleaning supplies.

Tube 3

Case history:

A 27-year-old man was brought to the emergency department with necrotic burns on his oral mucosa after gargling with an unknown liquid germicide.

The patient thought it would help his sore throat. The pH of the germicide was 5.

Odor:

Toxin:

Ammonia

Ammonia

Odor:

White paste (glue)

Contents of tube:
Ammonia (diluted household)
Toxin:
Phenol

Contents of tube:
Phenol (liquefied) (<1% concentration)
Tube 9

Case history:
A 2-year-old girl was brought to the emergency department after vomiting and having what was described as a grand mal seizure. The child had been playing several minutes earlier in a storage closet.
Tube 4

Case history:
A comatose 35-year-old man employed as a sanitary engineer was pulled out of the sewer by a fellow worker. CPR was initiated. When he was brought to the emergency department, the patient smelled like rotten eggs.

Odor:
Toxin:
Moth balls
Camphor
Odor:
Rotten eggs
Contents of tube:
Camphor
Toxin:
Hydrogen sulfide

Contents of tube:

Sulfurated potash or *N* -acetylcysteine

Tube 5

Case history:
A photographer was brought to the emergency department after unintentionally ingesting a chemical used in developing film. On presentation, patient was drooling and grasping his throat in considerable distress. On examination the patient's mouth and throat were erythematous and he smelled â€œlike a salad.â€•

Odor:
Vinegar

Toxin:
Glacial acetic acid

Contents of tube:
Vinegar

Tube 6

Case history:
A crop duster was brought to the emergency department in acute respiratory distress. The patient had hypersalivation, miotic pupils (2 mm), a very unpleasant breath odor, and coarse rhonchi in both lung fields.

Odor:
Garlic

Toxin:
Organic phosphorus insecticide

Contents of tube:
Garlic

Modified with permission from Goldfrank LR, Weisman R, Flomenbaum N: Teaching the recognition of odors. Ann Emerg Med 1982:11:685.

TABLE 21-2. Case Studies for â€œSniffing Barâ€•

Acrylic acid
Amebicides/antihelminthics:
Antihyperlipidemics: cholestyramine,
metronidazole
clofibrate, gemfibrozil, HMG-CoA
Anesthetics, local: varied
reductase inhibitors
Anticonvulsants: carbamazepine,
Cadmium
phenytoin
Chlorhexidine
Antihistamines
Cocaine
Formaldehyde
Antihypertensives: ACE inhibitors, diazoxide
Gentamicin nose drops
Antimicrobials
Hereditary
Antiinflammatory/antirheumatics:
Hydrocyanic acid
allopurinol, colchicine, gold,
Hydrocarbons (volatile)
D-penicillamine
Hydrogen sulfide
Antiparkinson agents: levodopa,

Methylbromide
bromocriptine
Nutritional
Antithyroid agents: methimazole,
Vitamin B_{12} deficiency
methylthiouracil, propylthiouracil
Zinc deficiency
Î²-Adrenergic antagonists
Pentamidine
Calcium channel blockers
Sulfur dioxide
Dental: tooth pastes
Diuretics: ethacrynic acid
DMSO (dimethylsulfoxide)
Insecticides
Lithium
Nicotine
Opioids: varied
Sympathomimetics: varied
Vitamin D

Definitions: Anosmia = the loss of smell; Cacosmia = sensation of a foul smell; Dysosmia = a distorted perception of smell; Hyposmia = a decreased perception of smell; Phantosmia = sensation of smell without stimulus.

Hyposmia/Anosmia Dysosmia/Cacosmia/Phantosmia

TABLE 21-3. Differential Diagnosis of Xenobiotics Responsible for Disorders of Smell

Gustation

Anatomy and Physiology

Taste, the sensory interpretation of orally ingested materials, is determined by taste buds on the tongue, palate, throat, and upper third of the esophagus. The cells in the taste buds are constantly renewed, and have a life span of 10 days.[11, 147] The taste buds on the anterior two-thirds of the tongue and the palate are innervated by the facial (CN VII) nerve, those on the posterior one-third of the tongue by the glossopharyngeal (CN IX) nerve, and those on the laryngeal and epiglottal regions by the vagus (CN X) nerve. There are at least 13 known chemical taste receptors responsible for the four primary taste sensations, sweet, sour, bitter, and salty: 2 sodium receptor types; 2 potassium receptor types; 1 chloride receptor; 1 adenosine receptor; two inosine receptor; 2 sweet receptor types; 2 bitter receptor types; 1 glutamate receptor; and 1 hydrogen ion receptor.[70] One substrate will typically activate multiple taste receptors, the combined effects of these stimulated receptors determine the taste of the substance.[57]

The structure of the taste receptors is similar to that of the olfactory receptors, in that they are coupled to G proteins and sodium and calcium channels permitting neural stimulation. The pH of the xenobiotic determines sour or acid taste, whereas sodium or potassium concentrations determine salty taste. Many xenobiotics such as sugars, glycols, aldehydes, ketones, amides, amino acids, inorganic salts of lead, and bretylium, activate the sweet receptors. Bitter taste may be the result of long-chain organic substances containing nitrogen, or alkaloids, including quinine, strychnine, caffeine, and nicotine.[70] Salivary proteins, such as zinc-containing gustin and ebnerin, are important in the regulation of taste sensation.[77, 81, 100, 155] These molecules may serve as binding proteins and growth factors for the regeneration of taste receptors. Taste is also affected significantly by the appreciation of aromas or odors and, to a lesser extent, by visual perception.[148]

Etiology of Gustatory Impairment

Types of gustatory dysfunction include ageusia, the inability to perceive taste; hypogeusia, the diminished sensitivity of taste; and dysgeusia, the distortion of normal taste. There are several variations of dysgeusia, such as cacogeusia, which is a perceived foul, perverted, or metallic taste.[68, 108] Taste impairment is commonly related to direct damage to the taste receptors, adverse effects on their regeneration, or effects on receptor mechanisms.[77] These effects can result from various xenobiotics, diseases, aging, and nutritional disorders (Table 21-4).[63, 70, 138, 165] Any abnormality that interferes with either the direct contact of a xenobiotic with the gustatory cells of the tongue or cranial nerves VII, IX, or X dramatically affects taste.[147] Most common forms of xenobiotic-induced dysgeusia are related to direct effects on the taste receptor site or effects related to receptor mechanisms such as G proteins, adenylate cyclase, and calcium channels.[96] Other forms of dysgeusia may result from direct stimulation of chemical receptors by xenobiotics.[70, 77]

Angiotensin-converting enzyme (ACE) inhibitors commonly cause gustatory impairment, usually hypogeusia and dysgeusia.[19, 65, 110, 180] ACE inhibitors work by inhibiting zinc-dependent ACE, and chelating zinc from taste receptors and salivary proteins resulting in taste dysfunction. Calcium channel blockers act by inhibiting calcium channels of the taste receptor mechanisms.[70] Many diuretics cause zinc depletion by enhancing zinc elimination in the urine.[77] In addition, furosemide and spironolactone may also chelate zinc. Numerous other xenobiotics also cause gustatory dysfunction through variable degrees of zinc chelation, such as amrinone, ethambutol, hydralazine, methyldopa, the nonsteroidal antiinflammatory drugs (NSAIDs), the antithyroid agents, penicillamine, and phenytoin.[70, 77, 181] Metals, such as arsenic, mercury, chromium, and lead, may either chelate zinc or replace zinc in salivary proteins because of a higher level of affinity.

Antineoplastic agents and antimicrotubular agents such as colchicine inhibit cellular division and taste-receptor regeneration.[74] The oral antiseptic agent chlorhexidine directly alters taste-receptor function.[56] Acetazolamide causes cacogeusia when carbonated beverages are consumed. The exact mechanism is unclear, but is

postulated to be a result of the inhibition of carbonic anhydrase causing carbon dioxide accumulation and an increased tissue bicarbonate.[77, 89, 112]

Hypogeusia/ageusia
- Local
  - Chemical burn
  - Radiation therapy
- Systemic
  - ACE inhibitors
  - DMSO (dimethylsulfoxide)
  - Propranolol
  - Amiloride
  - Pyrethrins
  - Amrinone
  - Gasoline
  - Smoking
    - Carbon monoxide
  - Hydrochlorothiazide
  - Spironolactone
  - Cocaine
  - Methylthiouracil
  - Nitroglycerin
  - NSAIDs
  - Penicillamine
  - Triazolam

Dysgeusia
- Local

Chemical burn
Radiation therapy
Systemic
ACE inhibitors
DMSO (dimethylsulfoxide)
NSAIDs
Adriamycin
Nicotine
Amphotericin B
5-Fluorouracil
Nifedipine
Botulism (in recovery)
Griseofulvin
Phenylthiourea
Bretylium
Isotretinoin
(hereditary)
Carbamazepine
Levodopa
Quinine
Zinc deficiency
Metallic taste
ACE inhibitors
Ethambutol
Metronidazole
Acetaldehyde
Ferrous salts
Pentamidine
Allopurinol
Flurazepam
Procaine penicillin
Arsenicals
Iodine
Propafenone

Cadmium
Lead
Snake envenomation
Ciguatoxin
Levamisole
Tetracycline
Copper
Lithium
Coprinus spp
Mercury
Dipyridamole
Methotrexate
Disulfiram
Metoclopramide

TABLE 21-4. Xenobiotics Responsible for Alterations of Taste

Taste-Aversive Agents and Poison Prevention

Nontoxic taste-aversive agents are frequently added to products such as shampoo, cosmetics, cleaning products, automotive products, and rubbing alcohol to discourage ingestion.[70] Except in the case of rubbing alcohol, this is done primarily to prevent poisoning in children. The most common taste-aversive agents are the denatonium salts, particularly denatonium benzoate (Bitrex, benzyldiethyl[(2,6-xylylcarbamoyl)methyl] ammonium benzoate), one of the most bitter-tasting substances known.[26 , 42] The bitter taste of denatonium benzoate can be detected at 50 parts per billion (ppb). This agent is used in concentrations of 6â€“50 parts per million (ppm), typically 6 ppm in cosmetic products and ethanol and 30â€“50 ppm in methanol and ethylene glycol.[16 , 123]

Only limited data are available on the usefulness of taste-aversive agents for prevention of poisoning. Studies using denatonium benzoate added to liquid detergent and orange juice can decrease the amount ingested by children.[13,160] However, the degree of taste aversion is not universal; in one study, some children were noted to take more than one sip of denatonium benzoate-laced orange juice.[160] Taste aversion is partially a learned response; frequently young children do not find a bitter taste as offensive as do adults.[14] It seems unlikely that taste-aversive agents will eliminate unintentional ingestions in children, because oral ingestion is required for aversive effects to occur. Taste-aversive agents may be most beneficial in the prevention of poisoning by toxic and nonaversive xenobiotics, such as ethylene glycol, methanol, paraquat, certain pesticides, acetonitrile, and bromate-containing cosmetics, where more than one or two sips of the product must be ingested to cause toxicity. In 1995, Oregon became the first state to mandate the addition of an aversive agent to ethylene glycol- or methanol-containing car products (the 1995 Toxic Household Products statute). Analysis on the incidence and severity of ethylene glycol and methanol exposures before and after the mandate could not demonstrate any difference.[119] Taste-aversive agents are not and cannot be substitutes for other poison prevention modalities (Chap. 129).

Hearing

Anatomy and Physiology

Normal hearing begins when sound waves are captured by the external auricle, traverse the external auditory canal, and are conducted to the tympanic membrane, the three auditory ossicles of the middle ear, and through the oval window to the perilymph in the scala vestibuli of the cochlea (Figs. 21-1 and 21-2). The sound wave is then transferred through the Reissner membrane at

the roof of the cochlear duct, to the endolymph and the organ of Corti.[52 , 161] The specialized hair cells of the organ of Corti convert mechanical waves into neurologic signals. The hair cells contain cross-linked stereocilia projections that detect transmitted shear forces, which lead to the influx of potassium from the endolymph through opened potassium channels.[41 , 101] Depolarization of the hair cells result in calcium influx and neurotransmitter release to the cochlear nerve. Neurologic signals from the cochlear nerve are conducted to the cochlear nucleus of the pons; bilateral projections are then sent to the superior olivary nucleus of the midbrain, nuclei of lateral lemnisci, inferior colliculus, medial geniculate body of the thalamus, and then to the auditory cortex of the temporal lobe.[161] Interruption or damage to any part of the hearing mechanism may lead to auditory impairment.

The anatomy and physiology of the cochlea and its importance in the biomechanics of hearing are reviewed to understand the potential for xenobiotic injury. The word *cochlea* is derived from the Greek word *kochlias* , meaning snail, and describes its general structureâ€”a 2.5-turn, spirally wound tube. The cochlea is further divided into 3 inner tubular structures: the upper tube or scala vestibuli, the middle tube or cochlear duct, and the lower tube or scala tympani. The scala vestibuli and the scala tympani contain the perilymph fluid. The cochlear duct contains endolymph fluid, the Reissner membrane at the roof, and the organ of Corti.[161] The cochlear fluids serve multiple functions: to conduct sound waves to the hair cells; to provide nutrients for and remove waste from the cells lining the cochlear duct; to control pressure distribution in the cochlea; and to maintain an electrochemical gradient for the function of the hair cells. The sodium concentration of the perilymph is similar to that of the extracellular fluid, and the potassium concentration of the endolymph is similar to that of the intracellular

fluid.[54] Any significant alterations of the sodium or potassium concentrations will depress the cochlear potential and function. The stria vascularis controls the production of the cochlear fluids and the repolarization of the hair cells, and maintains the electrochemical gradient between the endolymph and the perilymph. The stria vascularis contains a high concentration of the oxidative enzymes, Na^+ -K^+ -adenosine triphosphatase (ATPase), adenylate cyclase, and carbonic anhydrase, which are highly susceptible to xenobiotics.[21 , 82 , 145]

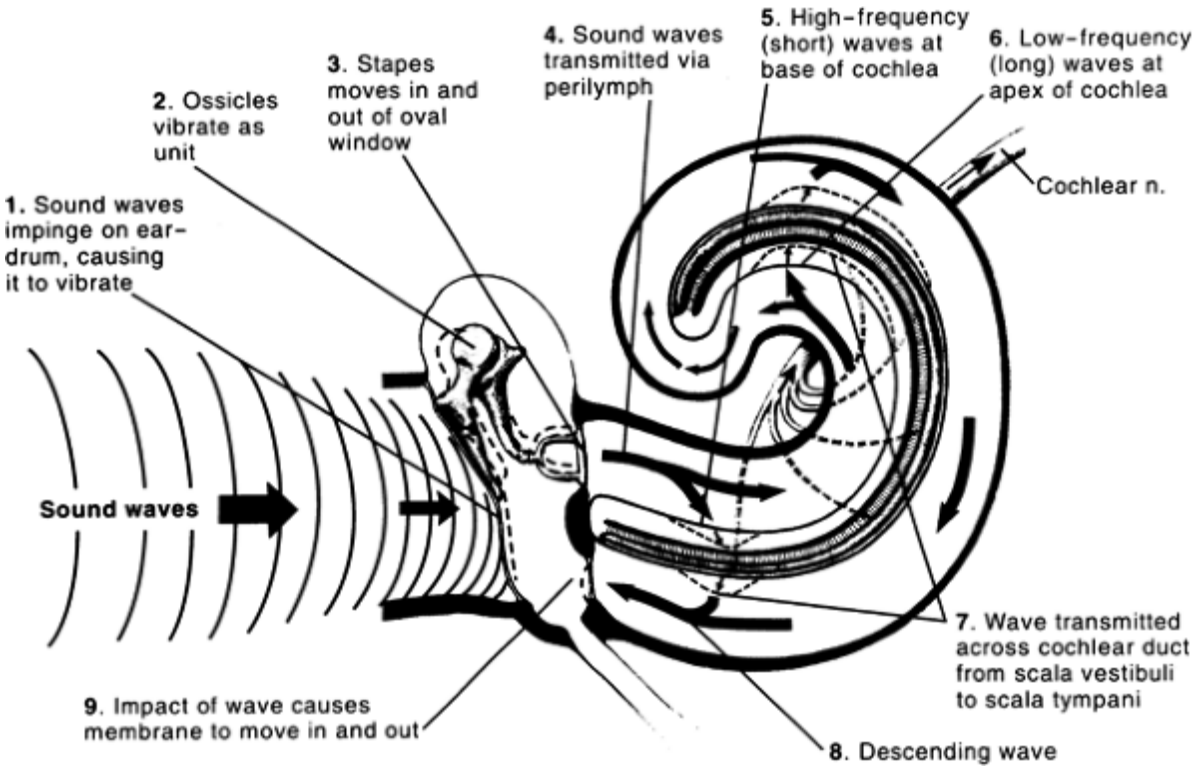

Figure 21-1. Pathways of sound conduction in the ear. *(Reproduced with permission from Silverstein H, Wolfson RJ, Rosenberg S: Diagnosis and management of hearing loss. Clin Symposia 1994;44:3.)*

Although human speech is composed of sounds in the frequency of 250â€“3000 Hz, humans can normally detect sounds in the frequency range of 20â€“20,000 Hz.[121] The cochlea is a

â€œtunedâ€• structure with varying width and stiffness, such that different regions can receive different sound waves. The stiffer and wider base of the cochlea serves as a receptacle for higher-frequency sounds, whereas the apex is responsible for receiving the lower-frequency sounds.[52] Because various regions of the cochlea are susceptible to different forms of injury, appropriate audiologic testing should be tailored specifically to each patient.[29]

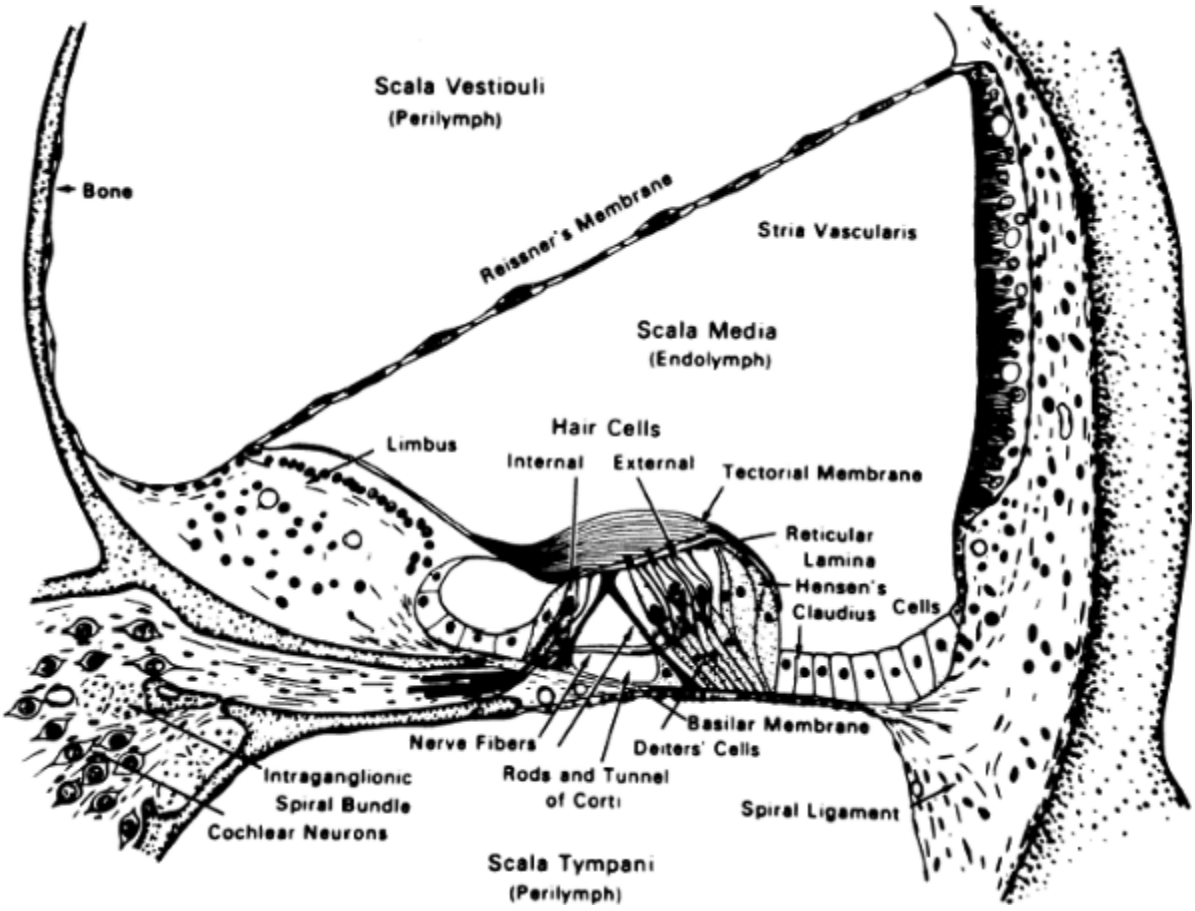

Figure 21-2. Cross-section of the organ of Corti. *(Reproduced with permission from Davis H: Advances in the neurophysiology and neuroanatomy of the cochlea. J Acoust Soc Am 1962;34:1379.)*

Xenobiotic-Induced Ototoxicity

Ototoxicity includes effects on the cochlear and vestibular system. This chapter focuses on cochlear toxicity. Quinine and salicylates were widely recognized in the 1800s and streptomycin in the 1940s as etiologies of ototoxicity.[83,140] Several hundred xenobiotics have been implicated as ototoxins, some of which cause reversible ototoxicity, and others, irreversible toxicity (Table 21-5).[24,87,94,117] Ototoxic agents primarily affect two different sites in the cochlea: the organ of Corti, specifically the outer hair cells and the stria vascularis. Because of the limited regenerative capacity of the

sensory hair cells and other supporting cells, when significant cellular damage occurs, the loss is often permanent.[46,52,83,158] Although cell death of the outer hair cells from inflammation and necrosis is expected when sufficient insults occurred, apoptotic cell death is now postulated to be a major mechanism of ototoxicity from certain xenobiotics such as cisplatin and aminoglycosides.[43,137] Inhibition of caspases and calpain associated with apoptosis of the hair cells is demonstrated to decrease ototoxicity from cisplatin and aminoglycosides in animals.[137,157] Evidence supports the concept that xenobiotic-related injury can be potentiated by loud noises and other ototoxic agents.[21,24,83,87] Although the actual cellular mechanisms for many forms of ototoxicity remain unclear,[177] some of the mechanisms are known.[60] Loop diuretics, such as furosemide, bumetanide, and ethacrynic acid, cause physiologic dysfunction and edema at the stria vascularis, resulting in reversible hearing loss.[83,106] The underlying mechanisms appear to be the inhibition of potassium pumps and G proteins associated with adenyl cyclase.[9] Physiologic studies of loop diuretics demonstrate decreased potassium activity in the endolymph and a decreased endocochlear potential.[142] Permanent hearing loss associated with furosemide and ethacrynic acid is also reported, and may be related to direct interference with oxidative metabolism in the

outer hair cells.[95, 106, 142]

Reversible
Antimicrobials: chloroquine, erythromycin, quinine
Carbon monoxide
Diuretics: acetazolamide, bumetanide, ethacrynic acid, furosemide, mannitol
NSAIDs
Salicylates

Irreversible
Aminoglycosides
Antineoplastics: bleomycin, cisplatin, nitrogen mustard, vincristine, vinblastine
Bromates
Hydrocarbons: styrene, toluene, xylene
Metals: arsenic, lead, mercury

TABLE 21-5. Etiologies of Xenobiotic-Induced Hearing Loss

Salicylates are a well-known cause of ototoxicity. Aspirin (acetylsalicylic acid)-induced hearing impairment was first reported in 1877.[90] Salicylate-induced hearing loss is generally mild to moderate (a 20â€“40 dB loss) and reversible.[18, 85] Animal studies demonstrate immediate hearing impairment with the use of high doses of salicylates.[17, 108, 129] The mechanism of salicylate-induced ototoxicity is unclear, although multiple factors are postulated. Salicylates and other NSAIDs inhibit cyclooxygenase, which converts arachidonic acid to prostaglandin G_2 and prostaglandin H_2. These effects may interfere with Na^+-K^+-ATPase pump function at the stria vascularis, and also decrease cochlear blood flow.[31, 49, 90] A reversible decrease in outer hair cell turgor secondary to membrane permeability changes may

impair otoacoustic emissions.[128, 132] In support of these theories, pretreatment of animals with leukotriene antagonists and Î±-adrenergic receptor antagonists attenuates or prevents salicylate-induced ototoxicity.[90]

NSAIDs and the cinchona alkaloid quinine also cause reversible hearing loss, particularly at the higher frequencies.[33, 83] Occasionally, quinine-induced hearing loss may be permanent.[83, 146] The primary mechanism is related to prostaglandin inhibition.[90] Quinine inhibits phospholipase A_2 enzyme, which converts phospholipids to arachidonic acid. Quinine also inhibits calcium channels that interact with prostaglandins.[90]

Antineoplastic agents, such as cisplatin, vinblastine, and vincristine, can cause permanent ototoxicity.[83] Cisplatin is the most toxic of the group, with clinically apparent hearing loss noted in 30â€“70% of the patients receiving doses of 50â€“100 mg/m^2. Children may be even more susceptible to ototoxicity. These agents typically damage the outer hair cells but may also affect the stria vascularis.[83] The underlying mechanisms may be related to the inhibition of adenyl cyclase in the stria vascularis, the inhibition of protein synthesis, and the formation of oxygen free radicals.[9, 83, 151] The generation of oxygen free radicals and the depletion of antioxidants is a significant mechanism in the irreversible damage to the hair cells.[51] Furthermore, cranial radiation will cause synergistic toxicity if radiation precedes cisplatin therapy. Various antioxidants and free radical scavengers prevent cisplatin-induced ototoxicity in animals.[115, 134, 141, 163, 176] Neurotrophic agents also prevent cisplatin-induced toxicity in animals, perhaps preventing oxidative injury induced apoptosis to hair cells.[137] Amifostine (WR-2721), a precursor to a thiol free radical scavenger, is available to prevent cisplatin-induced nephrotoxicity. However, amifostine does not appear to prevent cisplatin-induced ototoxicity.[144]

The aminoglycosides are the best known group of drugs associated

with irreversible ototoxicity.[127] Aminoglycosides are not concentrated in the cochlea. The endolymph concentration of gentamicin is approximately 10% of that in the serum. Neomycin and kanamycin are the most ototoxic of these antibiotics, although all aminoglycosides are potentially toxic.[95] With the development of newer aminoglycosides and therapeutic drug monitoring, the incidence of aminoglycoside-related ototoxicity appears to be decreasing. The reported rates of ototoxicity for the more commonly used aminoglycosides gentamicin and tobramycin are between 5 and 8%.[105] In China, where aminoglycosides are readily available as nonprescription medications, as much as 66% of deaf-mutism may be directly related to aminoglycoside toxicity.[58 , 102] A genetic predisposition to aminoglycoside-induced ototoxicity has been identified. The genetic transmission appears to be maternal via mitochondrial DNA.[55] Chinese patients with this genetic defect may suffer rapid and severe hearing loss compared to whites with a similar aminoglycoside exposure.[137]

Several mechanisms of ototoxicity have been postulated. Aminoglycosides antagonize calcium channels of the outer hair cells of the cochlea, blocking transduction of the hair cells and resulting in acute, reversible hearing deficits. Aminoglycosides also bind to polyphosphoinositides of cell membranes and alter their functions. Polyphosphoinositides are essential for the generation of the second messengers diacylglycerol and inositol triphosphate and their ultimate cellular function, for the maintenance of lipid membrane structure and permeability, and as a source for arachidonic acid.[171] Aminoglycosides interact with the transition metals iron and copper to generate free radicals, damaging the hair cells. Aminoglycosides also inhibit ornithine decarboxylase. The inhibition of this enzyme, important for cellular recovery following an injury, makes the cell more susceptible to toxicity.[145] It is postulated that toxicity is related to the metabolites of aminoglycosides and not the parent compounds because toxicity can be reproduced in in vivo models, but not in in vitro models.[145]

The outer hair cells of the cochlea are increasingly susceptible to aminoglycosides and damage progresses from the inner row of the outer hair cells to the basal turn of the cochlea, and, ultimately, to the apex.[4,7,95,136]

The risks of ototoxicity are increased with a duration of therapy of greater than 10 days, concomitant use of other ototoxic agents, and the development of elevated serum levels.[7,53,143] There is no evidence that single daily dosing of aminoglycosides alters the risk of ototoxicity.[124,172] Loop diuretics increase aminoglycoside toxicity by increasing aminoglycoside penetration into the endolymph. In animal models, certain free radical scavengers, such as glutathione, amifostine, and deferoxamine, decrease aminoglycoside-induced ototoxicity.[61,146,164,170,173] Fosfomycin, a phosphonic antibiotic, has limited efficacy in reducing aminoglycoside-induced ototoxicity and salicylates are also suggested to reduce ototoxicity.[120,154] Salicylates may act as free radical scavengers in low doses. Leupeptin and Z-DEVD-FNK, a calpain and caspase inhibitor respectively that affects the apoptotic pathway, is demonstrated in animal models to decrease ototoxicity.[157] Further studies are required to determine their applicability to humans.

Other antibiotics are also implicated as causing ototoxicity, particularly erythromycin, vancomycin, and their respective analogs.

There are a number of reports of hearing loss following erythromycin therapy in humans and an animal study supporting the ototoxic potential. Most deficits in humans are transient, although several cases of permanent hearing loss are reported.[22,23] The mechanisms of toxicity remain unclear, although the proposed effects are on the central auditory pathways. Erythromycin-induced hearing loss occurs at both lower and higher frequencies for speech, allowing for recognition in the early stages of ototoxicity.[22] Ototoxicity from the newer macrolide antibiotics

has also been reported.

The evidence for vancomycin-induced ototoxicity is less convincing. Although numerous cases of presumed vancomycin-related ototoxicity are reported, concomitant use of other ototoxic antibiotics was common or audiometric studies were not performed. In limited animal studies, vancomycin alone did not induce ototoxicity, but the agent increased ototoxicity when administered concomitantly with an aminoglycoside. Vancomycin analogs such as teicoplanin and daptomycin probably have similar ototoxic potentials.

Bromates are among the most extensively studied ototoxic agents.[36, 104, 130] Bromates are used in hair neutralizers, bread preservatives, and as fuses in explosive devices.[84, 130, 166] The stria vascularis and hair cells of the organ of Corti can be irreversibly damaged with significant exposure.[130] Bromates may also cause renal failure with substantial exposure, perhaps increasing the ototoxic potential.[84, 130]

It is intriguing that agents such as the bromates and aminoglycosides primarily affect both the cochlea and the kidneys. One possible explanation is that the stria vascularis and the renal tubules have similar functions in maintaining electrochemical gradients.[130, 131] However, renal tubules may regenerate while damage to the hair cells and the stria vascularis of the cochlea is more likely to be permanent.

Other xenobiotics implicated as ototoxins are carbon monoxide, lead, arsenic, mercury, toluene, xylene, and styrene.[80, 159] However, both human and animal data are quite limited. Carbon disulfide, carbon tetrachloride, and trichloroethylene, are also suspected of being ototoxic, but toxicity has not been demonstrated in humans.[80, 159] Because exposures to xenobiotics are frequently occupational, they are of great concern as they may potentiate or be additive to other types of occupational hearing impairments.[92, 135]

High-frequency hearing is most vulnerable, and early or limited impairment may not be noticeable unless audiometry, especially at 8 kHz and above, is performed.[171] These hearing tests can be performed in infants using the measurement of auditory brainstem response.[12]

Noise-Induced Hearing Impairment

Noise-induced hearing impairment was recognized for hundreds of years, but became of great concern and prevalence with the discovery of gunpowder and the industrial revolution.[52] Some of the anatomic changes in the organ of Corti and the audiometric features of noise-induced hearing impairment were well described by 1900.[2,3,109] Unfortunately, few longitudinal studies on noise-induced hearing impairment have been performed.

Although noises of sufficient magnitude may cause hearing impairment with limited exposure, most noise-induced hearing losses result from preventable prolonged cumulative occupational exposure. NIOSH has estimated that up to 1.7 million workers in the United States between 50 and 59 years of age have significant occupation-related hearing loss.[121] Noise can be defined as any unwanted sound, which can be further characterized by duration, time pattern (continuous, intermittent, or impulsive), frequency, and intensity. The intensity is measured in sound pressure levels (SPLs) and expressed in a logarithmic scale in decibels (dB). The intensity of a normal conversation is approximately 65 dB (Table 21-6).[121] The risk of noise-induced hearing loss is related to cumulative duration of exposure, intensity, and individual susceptibility.[118,125,175] Much of the risk assessment of noise-induced hearing loss is inexact. Most authorities agree that sounds with maximal intensity below 75â€“80 dB will not cause hearing impairment, regardless of the duration of exposure.[118] At higher intensity, the risk of hearing impairment increases with increased duration of exposure. Continued occupational exposure at 90â€“94

dB typically causes some high-frequency hearing loss in approximately 10 years.[2,125] Further exposure results in hearing loss in the lower-frequency range. The Occupational Safety and Health Administration (OSHA) established guidelines for permissible occupational noise exposure based on an analysis of the average intensity and duration of exposure (Table 21-7).[2,175]

Weakest sound that humans can detect
10
Quiet bedroom, soft whisper
20
Broadcast studio
25â€“30
Insulated lounge
50
Normal conversation
65
Television-audio
70
Vacuum cleaner
80
Machine press, subway car (35 mph)
95
Spray painting, snowmobile
105
Power saw
110
Car horn
115
Armored personnel carrier; ear pain begins
120
Jet plane engine, gunshot
145
Highest sound level that can occur

194

Sound Decibels

TABLE 21-6. Typical Sound Levels on the Decibel Scale

The pathophysiology of noise-induced hearing impairment is related to an excessive energy impact on the cochlea, but the exact biochemical changes are unclear. Apoptotic death of the hair cells have now been demonstrated and inhibition of apoptosis pathways mitigate noise-induced toxicity in animal models. A limited exposure to excessive noise results in a temporary hearing impairment or temporary threshold shift with a duration of hours to weeks. However, prolonged exposure results in a permanent threshold

shift or hearing impairment.[3, 52, 175] Initially, outer hair cells are lost, but more significant exposures result in damage to both inner and outer hair cells and all supporting structures in the organ of Corti. Cochlear nerve fibers degenerate after hair cell damage.[52, 175] The section of the cochlea most at risk from loud noises is at the 9â€“13 mm region (the total length is 32 mm).[109] This region is responsible for hearing at the 3â€“6 kHz range, corresponding to the typical noise-induced hearing loss pattern.

85
16
90
8
92
6
95
4
97
3

100
2
102
1.5
105
1
110
0.5
115
â ‰ ¤0.25
[a] Decibels using the A-scale filter.

dBA[a]	Duration of Exposure Per Day in Hours

TABLE 21-7. OSHA Standard for Permissible Noise Exposure

Much of the clinical assessment and monitoring of noise-induced hearing loss is based on pure tone hearing loss, demonstrating an audiometric deficit at 3â€“6 kHz.[121 , 175] This typical pattern occurs in other conditions and becomes less typical with aging.[125] Although human speech is composed mainly of low frequency sounds, the ability to perceive the higher frequency sounds is extremely important in speech recognition. For this reason, the major impairment in patients with noise-induced hearing loss is an inability to discriminate speech, particularly from background noise.[2 , 40] Currently, the science of the investigation of speech discrimination is limited with extensive areas for research.

Blast injury to the ear results from exposure of extremely short duration, but very high-intensity sound waves, usually greater than 140 dB. Military personnel are particularly at risk.[32 , 126 , 171] Hearing loss from blast injury may be related to rupture of the tympanic membrane, disruption of the ossicles, temporary cochlear dysfunction, and permanent cochlear dysfunction from

labyrinthine fistulae and basilar membrane rupture.[30] When a large tympanic membrane rupture or disruption of the ossicles occurs, surgical intervention may be required to treat hearing impairment.[30]

Prevention of any type of noise-induced hearing loss remains the best solution. Various hearing-protection devices are available, if the noise exposure cannot be reduced. Better monitoring and more longitudinal studies are required on noise-induced hearing loss. Exposure to xenobiotics that can impair hearing may have synergistic effects with noise-induced hearing loss.[92, 94] These factors should be considered when noise exposure is evaluated. Furthermore, noise exposure is not limited to the workplace. Significant noise exposure may occur at home or from leisure activities, such as power tools, stereo, and ambient exposure.[15, 37, 71, 125] The impact of noise exposure outside of the workplace has only recently attracted the attention of investigators.

Etiology of Tinnitus

Tinnitus is the sensation of sound not resulting from mechanoacoustic or electric signals. Virtually all humans experience tinnitus during their lives. The exact mechanism or mechanisms resulting in tinnitus are largely unknown.[149] Tinnitus may or may not be associated with hearing loss. Several theories are proposed, but none is completely satisfactory. Tinnitus may result from spontaneous neurologic discharges when the hair cells and/or cochlear nerve are injured. Altered sound perception may result from local or central effects when feedback mechanisms are interrupted.[47, 50, 86, 108] Severing the cochlear nerve terminates tinnitus in less than half of affected patients, suggesting important central mechanisms.[10] Furthermore, certain etiologies of tinnitus, such as migraine headache and temporal lobe seizures, do not affect hearing directly. *N* -methyl-D-aspartate (NMDA) glutamate receptor activation (and enhanced

cochlear signal transmission) has been implicated as a mechanism for tinnitus in animal models; NMDA receptor activation may result from cyclooxygenase inhibition or neurologic injuries. Xenobiotics, including salicylate, may cause hair cell dysfunction and may modify neurotransmission centrally in both the cochlear nucleus and the inferior colliculis.[62, 174] For salicylate and NSAIDs, cyclooxygenase inhibition and resulting NMDA receptor activation is the likely mechanism for tinnitus. Although the probable sites involved in tinnitus may be classified as peripheral (external ear, middle ear, or cochlear [CN VIII]), central, or extraauditory (vascular, nasopharyngeal), some etiologies may affect peripheral and central sites, and many etiologies remain unknown.[35, 50, 108]

Tinnitus may result from trauma or disease or as a manifestation of xenobiotic toxicity. Tinnitus is most commonly related to any mechanism that affects hearing. Excessive cerumen, fluid, or a foreign body in the external canal, perforated tympanic membrane, acoustic trauma resulting from exposure to excessive noise, otosclerosis, acoustic neuroma, and otitis media may produce tinnitus. However, the only otologic problem that always results in tinnitus is MÃ©niÃ¨re disease, a triad of tinnitus, vertigo, and diminished hearing. Other etiologies for tinnitus include diabetes, hypertension, autoimmune disease, hypothyroidism, and arteriovenous aneurysms.[34, 35, 108]

Numerous xenobiotics are associated with tinnitus (Table 21-8), but the incidence is probably low and the implied relationships have usually been supported only by case reports.[34, 152, 153] Tinnitus may or may not be associated with transient or permanent hearing loss. It is probable that the agents associated with hearing loss affect cochlear function, while those that produce tinnitus without hearing loss probably act on signal transmission at the cochlear and the central nervous system. Xenobiotics that frequently produce tinnitus are streptomycin, neomycin, indomethacin, doxycycline, ethacrynic acid, furosemide, heavy

metals, and high doses of caffeine.[66 , 152 , 153] Only a few drugs, such as quinine and salicylates, consistently cause tinnitus at toxic doses.[17 , 50] These two drugs also serve as examples of how the presence of tinnitus may be an indicator of drug toxicity.

Tinnitus associated with salicylates usually begins when serum levels are in the high therapeutic or low toxic range of approximately 20â€“40 mg/dL.[113] Before the wide availability of salicylate serum measurements, physicians treating gout or rheumatoid

arthritis often titrated the salicylate dosage until tinnitus developed.[37] Tinnitus and other signs and symptoms of salicylism (Chap. 35) should be sufficient for physicians to diagnose salicylate toxicity before serum salicylate levels are available. However, tinnitus may not be evident in patients with hearing impairment despite significantly elevated salicylate concentrations.[113] The classic constellation of symptoms of quinine and salicylate toxicity, called cinchonism, includes nausea, vomiting, tinnitus, and visual disturbances.[4 , 28 , 116] Because serum quinine levels are not readily available, symptoms of quinine toxicity define the clinical diagnosis (Chap. 56).[162]

Antifungal agents: amphotericin B
Anticonvulsants: carbamazepine
Antidepressants: cyclic antidepressants, amoxapine, lithium, trancylcypromine
Antihistamines
Antimicrobials: Aminoglycosides, vancomycin, dapsone, tetracyclines, sulpha drugs, metronidazole, thiabendazole, clindamycin
Antineoplastics: cisplatin, nitrogen mustard, 6-aminonicotinamide, methotrexate, vinblastine
Antiparasitics: chloroquine, hydroxychloroquine
Antipsychotics: haloperidol, molindone

Î²-Adrenergic antagonists
Bromates
Cinchona alkaloids: quinine, quinidine, salicylates
Diuretics: furosemide, ethacrynic acid, bumetanide
Hydrocarbons: benzene
Local anesthetics: mepivacaine, bupivacaine, lidocaine
Nonsteriodal antiinflammatory drugs
Oral contraceptives
Sympathomimetics: caffeine, theophylline, metaproterenol, albuterol, methylphenidate

TABLE 21-8. Xenobiotics That Cause Tinnitus

Summary

Numerous xenobiotics commonly affect the sense of smell, taste, and hearing. They may cause significant patient morbidity. Some of the events may be foreseeable, whereas others will require monitoring and appropriate testing. Significant patient risk and discomfort may be avoided by an understanding of the basic pathophysiology of the otolaryngologic organs and by a heightened suspicion on the part of healthcare providers. Current knowledge about the pathophysiology of xenobiotics and these special organs at the molecular level is expanding rapidly. It is particularly encouraging and exciting to understand and witness the development of potential therapeutic agents.

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Chapter 22
Respiratory Principles

Robert S. Hoffman

Essential Abbreviations

PO_2

Partial pressure of oxygen (in mm Hg; 1 mm Hg = 1 torr)

PAO_2

Alveolar PO_2

PaO_2

Arterial PO_2

PCO_2

Partial pressure of carbon dioxide (in mm Hg)

O_2 Sat

Hemoglobin oxygen saturation (in percent)

FiO_2

Percent oxygen in inspired air

CO

Carbon monoxide

COHb

Carboxyhemoglobin

MetHb

Methemoglobin

The primary function of the lungs is to exchange gases. Specifically, this role can be divided into the transport of oxygen (O_2) into the blood, and the elimination of carbon dioxide (CO_2) from the blood. In addition, the lungs serve as minor organs of metabolism and elimination for a number of xenobiotics, a source of insensible water loss, and a means of temperature regulation.

Cellular oxygen use is dependent on many factors, including respiratory drive; percent of oxygen in inspired air; airway patency; chest wall and pulmonary compliance; diffusing capacity; ventilationâ€“perfusion mismatch; hemoglobin content; hemoglobin oxygen loading and unloading; cellular oxygen uptake; and cardiac output. Xenobiotics have the unique ability to inhibit or impair each of these factors necessary for oxygen use and result in respiratory dysfunction. This chapter illustrates how xenobiotics acutely interact with the mechanisms of gas exchange and oxygen use. Discussion of chronic occupational lung injury is beyond the scope of this text; the reader is referred to a number of reviews for further information.[15, 80] The final section of this chapter provides a practical approach to assessing the poisoned patient.

Pulmonary Manifestations of Xenobiotic Exposures

Respiratory Drive

Respiratory rate and depth are regulated by the need to maintain a normal PCO_2 and pH. Most of the control for ventilation occurs at the level of the medulla, although this is modulated both by involuntary input from the pons and voluntary input from the higher cortices. Changes in PCO_2 are measured primarily by a central chemoreceptor, located near the exit for cranial nerves IX and X, which measures cerebral spinal fluid (CSF) pH, and secondarily by peripheral chemoreceptors in the carotid and aortic bodies, which actually measure PCO_2 . Input with regard to PO_2 is obtained from carotid and aortic chemoreceptors. Stretch receptors in the chest relay information about pulmonary dynamics, such as the volume and pressure.

Xenobiotics can affect respiratory drive in one of several ways: direct suppression of the respiratory center; alteration in the response of chemoreceptors to changes in PCO_2 ; direct stimulation of the respiratory center; increase in metabolic demands as a result of agitation or fever, which, in turn, increases total body oxygen consumption; or indirectly, as a result of the creation of acidâ€“base disorders. For example, opioids (Chap. 38) depress respiration by decreasing the responsiveness of chemoreceptors to CO_2 and by direct suppression of the pontine and medullary respiratory centers.[29 , 68 , 91] Any xenobiotic that causes a decreased respiratory drive or a decreased level of consciousness can produce bradypnea (a decreased respiratory rate), hypopnea (a decreased tidal volume), or both, resulting in hypoventilation (Chap. 3).

Methylxanthines, cocaine, and other sympathomimetics may cause an increase in respiratory drive as well as an increase in oxygen consumption. Salicylates produce hyperventilation by both central and peripheral effects (ie, respiratory alkalosis and acidemia). The net consequence of increased respiratory drive, increased oxygen consumption, or metabolic acidosis is the generation of either tachypnea (an elevated respiratory rate), hyperpnea (an increased tidal volume), or both. Whether alone or in combination,

tachypnea and hyperpnea produce hyperventilation. Tables 22-1 and 22-2 list xenobiotics that commonly produce hypo- and hyperventilation.

Baclofen
Barbiturates
Electrolyte abnormalities
Organic phosphorus compounds
Botulinum toxin
Ethanol
Poison hemlock (coniine)
Carbamates
Ethylene glycol
Clonidine
Î³-Hydroxybutyrate
Sedative-hypnotics
Colchicine
Isopropanol
Strychnine
Cyclic antidepressants
Methanol
Neuromuscular blockers
Tetanus toxin
Tetrodotoxin
Elapid envenomation
Nicotine
Opioids

TABLE 22-1. Xenobiotics that Produce Hypoventilation

Decreased Inspired FiO_2

Barometric pressure at sea level ranges near 760 mm Hg. At this pressure, 21% of ambient air is comprised of oxygen (FiO_2 = 21%), and after subtracting for the water vapor normally present in the lungs, PAO_2 (the alveolar partial pressure of oxygen) is about 150 mm Hg. Any reduction in FiO_2 decreases the PAO_2 , thereby producing signs and symptoms of hypoxemia (a low PaO_2 [the arterial partial pressure of oxygen]). At an FiO_2 of 12â€“16%, patients experience tachypnea, tachycardia, headache, mild confusion, and impaired coordination. A further decrease to an FiO_2 of 10â€“14% produces severe fatigue, cognitive impairment and decreases to between 6 and 10% are associated with nausea, vomiting, and lethargy. An FiO_2 of less than 6% is incompatible with life.[54]

This effect on FiO_2 is typically observed as elevation increases above sea level, because barometric pressure falls. By 18,000 feet, barometric pressure is only 380 mm Hg, and the PAO_2 falls to below 70 mm Hg. At 63,000 feet, the barometric pressure falls to 47 mm Hg, a level where the PAO_2 equals 0 mm Hg. Although it is important to remember this relationship, altitude-induced decreases in FiO_2 are rarely important in clinical medicine, even in commercial airline flights, where the cabins are pressurized to a maximum of several thousand feet above sea level. However, in closed or low-lying spaces, oxygen may be replaced or displaced by other gases that have no intrinsic toxicity. Common examples of these gases, referred to as simple asphyxiants (Table 22-3), are found alone or in combination with more toxic gases. Because they have little or no toxicity other than their ability to replace oxygen, removal of the victim from exposure and administration of supplemental oxygen are curative if permanent injury as a consequence of hypoxia has not already developed (Chap. 119).

The potential magnitude of toxicity from simple asphyxiants was best exemplified by the disasters in Cameroon near the Lakes of Monoun and Nyos, in 1984 and 1986, respectively. For unclear reasons, Lake Nyos, a volcanic lake, released a cloud of carbon

dioxide (CO_2) gas of approximately a quarter million tons. Because CO_2 is 1.5 times heavier than air, the gas cloud flowed into the surrounding low-lying valleys, killing by asphyxia more than 1700 people, and affecting countless more people because of hypoxia. Most survivors recovered without complications.[7, 33] Smaller scale, but equally serious, toxicity from CO_2 results from improper handling of dry ice or release into a closed space.[34, 38]

Amphetamines
Gyromitra mushrooms
Paraldehyde
Anticholinergics
Hydrogen sulfide
Pentachlorophenol
Camphor
Iron
Phenformin
Carbon monoxide
Isoniazid
Progesterone
Cocaine
Isopropanol
Salicylates
Cyanide
Methanol
Sodium monofluoroacetate
Dinitrophenol
Metformin
Ethanol (ketoacidosis)
Methemoglobin inducers
Ethylene glycol
Methylxanthines

TABLE 22-2. Xenobiotics that Produce Hyperventilation

Argon
Hydrogen
Carbon dioxide
Methane
Ethane
Nitrogen
Helium
Propane

TABLE 22-3. Simple Asphyxiants

Chest Wall

Hypoventilation can occur as a result of a decrease in either respiratory rate or tidal volume. Thus, even when the stimulus to breathe is normal, adequate ventilation is dependent on the coordination and function of the muscles of the diaphragm and chest wall. Changes in this function can result in hypoventilation by two separate mechanisms; both muscle weakness and muscle rigidity may impair the patient's ability to expand the chest wall. Toxicologic causes of muscle weakness include botulinum toxin,[76] electrolyte abnormalities such as hypokalemia,[49, 92] or hypermagnesemia,[27] organic phosphorus compounds,[59, 77] and neuromuscular blockers.[11, 43] Patients with hypoventilation caused by muscle weakness respond well to assisted ventilation and correction of the underlying problem (Chaps. 17, 46, 66, and 109). Chest-wall rigidity impairing ventilation can occur in strychnine poisoning,[12, 47, 53] tetanus,[19, 47, 82] and fentanyl use[18, 20] (Chaps. 38 and 108). Often these patients are difficult to ventilate despite intubation and may require muscle relaxants, neuromuscular blocking agents, or naloxone (for fentanyl).

Airway Patency

The airway itself may be compromised in several ways. As a patient's mental status becomes impaired, the airway is often obstructed by the tongue.[35] Alternatively, vomitus, or either aspiration of activated charcoal or a foreign body, can directly obstruct the trachea or major bronchi with resultant hypoxia.[35, 44, 56, 60, 71, 75] Obstruction may also result from increased secretions produced during organic phosphorus compound poisoning. Laryngospasm may occur either as a manifestation of systemic reactions, such as anaphylaxis, as a result of edema from thermal or caustic injury (Chaps. 100 and 123), or as a direct response to an irritant gas (Chap. 119). Similarly, the tongue can become swollen in response to thermal or caustic injury or toxic exposure to plants such as *Dieffenbachia* spp, or as a result of angioedema from drugs such as angiotensin-converting enzyme inhibitors (Chaps. 60, 100, 114, and 123).[29] Regardless of the mechanism, upper airway obstruction results in hypoventilation, hypoxemia, and hypercapnia (hypercarbia) with the persistence of a normal A-a gradient (see discussion of A-a gradients). Upper airway obstruction is often acute and severe and requires immediate therapy to prevent further clinical compromise.

Bronchospasm may be a manifestation of anaphylaxis, as well as exposure to pyrolyzed cocaine,[74, 83, 84] smoke, irritant gases[37, 41, 66] (Table 22-4), or dust (eg, cotton in byssinosis), or as a result of occupational asthma[52, 80] and hypersensitivity pneumonitis[96] (Chaps. 119 and 123).

Ammonia
Isocyanates
Chloramine
Nitrogen dioxide
Chlorine
Ozone
Chloracetophenone (CN)
Phosgene
Chlorobenzylidene-malonitrile (CS)

Phosphine
Fluorine
Sulfur dioxide
Hydrogen chloride

TABLE 22-4. Irritant Gases

Airway collapse may result from pneumothorax caused by barotrauma, which more commonly results from the manner of administration of illicit drugs than from actual drug overdose. Barotrauma may also result from nasal insufflation or inhalation of drugs. This form of barotrauma occurs most often in cocaine (particularly in the form of â€œcrackâ€•) and marijuana users, who either smoke or insufflate these drugs and then perform prolonged Valsalva maneuvers in an attempt to enhance the drug's effects (Chaps. 74 and 81).[9 , 16 , 64 , 78 , 93] The increased airway pressure leads to rupture of an alveolar bleb, and free air dissects along the peribronchial paths into the mediastinum and pleural cavities. Nitrous oxide abuse also causes barotrauma.[45] People who have access to nitrous oxide in the hospital or laboratory may siphon and abuse the agent from low-pressure tanks meant for inhalation. In contrast, at parties they inhale nitrous oxide that is used as a propellant in whipped cream cans. Tremendous pressure generated by the escaping gas from this high-pressure system is then transmitted to the airways, sometimes resulting in severe barotrauma (Chap. 65).

Ventilationâ€“Perfusion Mismatch

Ventilationâ€“perfusion (V/Q) mismatch is manifested at the extremes by aeration of the lung without arterial blood supply (as in pulmonary embolism from injected contaminants), and by a normal blood supply to the lung without any ventilation. Impaired blood supply to a normal lung and normal blood supply to an

inadequately ventilated lung constitute an infinite number of gradations that exist between the extremes. The normal response to regional variations in ventilation is to shunt blood away from an area of lung that is poorly ventilated, thereby preferentially delivering blood to an area of the lung where gas exchange is more efficient. An hypoxia-induced reduction in local nitric oxide production appears to be responsible for the regional vasoconstriction that occurs.[1] This effect, commonly known as hypoxic pulmonary vasoconstriction, is best described in patients with chronic obstructive lung disease and facilitates compensation for the V/Q mismatch associated with that disorder. It is unclear whether xenobiotic-induced alterations in pulmonary nitric oxide production are significant determinants in the V/Q mismatch that occurs in poisoning.

In toxicology, V/Q mismatch most commonly results from perfusion of an abnormally ventilated lung, as may occur following aspiration of gastric contents, a frequent complication of many types of poisoning.[44, 60] Although alterations in consciousness and loss of protective airway reflexes are predisposing factors, certain xenobiotics, such as hydrocarbons, directly result in aspiration pneumonitis because of their specific characteristics of volatility, viscosity, and surface tension (Chap. 102).

The diagnosis of aspiration pneumonitis often relies on the chest radiograph for confirmation. The location of the infiltrate depends significantly on the patient's position when the aspiration occurred. Most commonly, aspiration occurs in the right mainstem bronchus, because the angle with the carina is not as acute as it is for entry into the left mainstem bronchus. When aspiration occurs in the supine position, the subsequent infiltrate is usually manifest in the posterior segments of the upper lobe and superior segments of the lower lobe. Aspiration typically involves vomitus; but secretions, activated charcoal, teeth, dentures, food, and other foreign bodies are also frequently aspirated.

Diffusing Capacity Abnormalities

Severe impairment in diffusing capacity commonly results from local injury to the lungs in disorders such as interstitial pneumonia, aspiration, toxic inhalations, and near drowning, and from systemic effects of sepsis, trauma, and various other medical disorders.[8] When this process is acute and associated with clinical criteria including rales, hypoxemia (unspecified degree), and bilateral involvement on a chest radiograph demonstrating a normal heart size, it has been traditionally referred to as *noncardiogenic pulmonary edema* ; throughout this chapter and text, however, the term *acute lung injury* (ALI) is used instead, which reflects current nomenclature.[8] ALI is the presence of increased intraalveolar fluid in the lungs with a normal cardiac output. More rigid criteria, such as a PaO_2 /FiO_2 ratio <300 mm Hg (regardless of positive end-expiratory pressure [PEEP]), bilateral infiltrates on the chest radiograph, and either a pulmonary artery wedge pressure that is less than or equal to 18 mm Hg or no clinical evidence of left atrial hypertension, are used to further define the ALI.[8] When these same criteria are met, but the patient's PaO_2 /FiO_2 ratio is <200 mm Hg (regardless of PEEP), the term *acute respiratory distress syndrome* (ARDS) is used.[8 , 50] Approximately 150,000 Americans develop ARDS annually, many as a result of xenobiotics; ARDS has a fatality rate of almost 50%.[4]

Commonly, patients are chronically exposed to xenobiotics associated with reduced diffusing capacity by smoking tobacco and other xenobiotics or working with asbestos, silica, and coal, which cause slow pulmonary fibrosis or promote emphysema. More recent work emphasizes the ability of chronically smoked cocaine to alter pulmonary function.[84] Acutely, ALI from opioids, salicylates, or phosgene and delayed severe fibrosis from paraquat can cause profound alterations in diffusion (Chaps. 35 , 38 , 111 , and 119).[62 , 72 , 98] Associated parenchymal damage is almost

always present and causes both reduction in lung volumes and V/Q mismatch. Intravenous injection of talc, a common contaminant found in drugs of abuse,[65] and septic emboli from right-sided endocarditis[63 , 81] may result in isolated vascular defects with reduction in diffusion capacity. Similarly, cocaine-induced pulmonary spasm can obstruct vascular channels and alter pulmonary function, creating V/Q mismatch.[23]

ALI with or without progression to ARDS is a common occurrence from poisoning. The edema fluid (and the resulting hypoxia, pulmonary rales, and radiographic abnormalities) may develop in part because of increased permeability of the alveolar and capillary basement membrane.[17 , 21 , 55 , 72] Proteinaceous fluid leaks from the capillaries into the alveoli and interstitium of the lung. Several mechanisms are proposed as the cause for ALI, although there is no single unifying mechanism for all of the toxins that have been implicated. Acute lung injury may result from exposure to xenobiotics that produce hypoventilation by at least three different mechanisms: hypoxia may injure the vascular endothelial cells; autoregulatory vascular redistribution may cause localized capillary hypertension; or alveolar microtrauma may occur as alveolar units collapse, only to be reopened suddenly during reventilation.[72] These and other events may activate neutrophils and release inflammatory cytokines.[3 , 90] Other xenobiotics may be directly toxic to the capillary epithelial cells or may be partly responsible for the release of vasoactive substances.[3] The effects of salicylates and other nonsteroidal antiinflammatory agents may be mediated via effects on prostaglandin synthesis. Finally, sympathomimetic stimulants may cause â€œneurogenicâ€• pulmonary edema, which is thought to be mediated by massive catecholamine discharge. Elevated catecholamine levels are also noted in experimental opioid overdose, possibly supplying a link between hypoxia, hypercarbia, and the catecholamine hypothesis of ALI.[58]

In the 1880s, William Osler described â€œpulmonary edemaâ€• in an opium user. The opioids are still among the most common causes of ALI (Chap. 38), but it is now recognized that there are many types of xenobiotics that can cause ALI, such as the sedative-hypnotic agents, salicylates, cocaine, carbon monoxide, diuretics, and calcium channel blockers, all of which are associated with this entity (Table 22-5).[25 , 26 , 28 , 31 , 32 , 36 , 39 , 42 , 48 , 67 , 69 , 79 , 81 , 98] The route of xenobiotic administration is not usually the determining factor; ALI can result from oral, intravenous, and inhalational exposure. Because the source of the problem is increased pulmonary capillary permeability, patients with ALI have a normal pulmonary-capillary wedge pressure, unlike patients with cardiogenic pulmonary edema.

Cardiogenic pulmonary edema may also occur as the result of poisoning. Etiologies for this phenomenon include the ingestion of large amounts of a xenobiotic with negative inotropy (eg, Î²-adrenergic antagonists, type IA antidysrhythmics) or myocardial infarction (from cocaine). Because many overdoses are mixed overdoses, the distinction between cardiogenic pulmonary edema and ALI is often difficult to establish by physical examination and requires invasive monitoring techniques.

Although the treatments for cardiogenic pulmonary edema and ALI have many similarities, critical aspects of the therapy differ, and therefore an accurate diagnosis must be established. Most diagnostic tests are not helpful in differentiating between these two diseases. Physical examination reveals the presence of rales with both entities. An S_3 gallop, if present, suggests a cardiac cause of pulmonary edema, but its absence does not establish the diagnosis of ALI. In both entities, the arterial blood-gas analysis demonstrates hypoxia and the chest radiograph shows perihilar, basilar, or diffuse alveolar infiltrates. The presence of â€œvascular redistributionâ€• on the chest radiograph, however, is suggestive of a cardiogenic etiology; a normal-sized heart is more commonly associated with ALI, whereas an enlarged heart is more typical of

cardiogenic pulmonary edema. The diagnostic tests that may be useful in establishing the correct diagnosis include echocardiography, transcutaneous bioimpedance, pulmonary artery catheter pressure measurements, and radionucleotide ventriculography (â€œgated-poolâ€• scan). Although the radionucleotide scan accurately measures cardiac output, it is not routinely available in the emergency department (ED) or intensive care unit (ICU) and usually requires the transport of a critically ill patient to the nuclear medicine suite. Although echocardiography can be performed as a portable â€œbedsideâ€• technique, it is less sensitive and less specific for determinations of cardiac output. Therefore, the most definitive diagnostic procedure in the emergency setting is the insertion of a pulmonary artery catheter for hemodynamic monitoring. Although not specifically well-investigated in poisoning, recent experiences with transcutaneous bioimpedance measurements of cardiac output show promise for this portable noninvasive technique.[6 , 22 , 61] Cardiogenic pulmonary edema results from an elevated left-atrial filling pressure (elevated pulmonary-capillary wedge pressure) and a decreased cardiac output. In patients with ALI, the pulmonary artery wedge pressure and the cardiac output are normal (Table 22-6).

Amiodarone
Ethchlorvynol
Amphetamines
Irritant gases
Amphotericin
Lidocaine
Bleomycin
Opioids
Calcium channel blockers
Protamine
Carbon monoxide
Salicylates

Cocaine
Sedative-hypnotics
Colchicine
Smoke inhalation
Cyclic antidepressants
Streptokinase
Cytosine arabinoside
Vinca alkaloids

TABLE 22-5. Common Xenobiotic Causes of Acute Lung Injury

The basic treatment for ALI and ARDS is supportive care while the xenobiotic is eliminated and healing occurs in the pulmonary capillaries.[3,50] The most important specific therapeutic maneuver in patients with ALI/ARDS involves the use of low tidal-volume ventilation.[84,90] This results in reduced airway pressures which seem to â€œrestâ€• the lung and allow healing to occur. The efficacy of jet ventilators or membrane oxygenators is inadequately studied. Some studies suggested a potential role for extracorporeal membrane oxygenation in the treatment of ALI and ARDS.[46] PEEP may be particularly beneficial. The PEEP should be maintained as low as possible, in the range of 5â€“15 cm H_2O, to maintain a PO_2 of at least 55 mm Hg, or an oxygen saturation of 88%, with an inspired oxygen concentration of 40% or less. Higher PEEP settings are not always beneficial and can cause an increased incidence of pneumothorax or hypotension. An increase in PEEP may result in a modest increase in PO_2, but a larger decrease in venous return and decreased cardiac output. Therefore, with each change in PEEP, the resulting actual increase (or perhaps decrease) in oxygen delivery to the body should be determined.[4]

Hemoglobin and the Chemical

Asphyxiants

Disorders of hemoglobin oxygen content, as well as of hemoglobin loading and unloading, result in cellular hypoxia, which, in turn,

results in hyperventilation. Anemia is a common complication of the infectious diseases associated with parenteral drug use. In addition, many xenobiotics result in hemolysis or direct bone marrow suppression. Among the latter group are the heavy metals, lead, benzene, and ethanol. Hemolysis may occur in individuals exposed to lead, copper, or arsine gas, and in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency exposed to oxidants (Chap. 24).

Normal
5
20/5
20/10
16
4â€“12
2.5â€“4.0
Cardiogenic pulmonary edema
N-H
N-H/H
H/H
H
H
L
ALI and ARDS
N
N/N
N/N
N
N
N

CI = cardiac index; D = diastolic; H = high; L = low; N = normal; PA = pulmonary artery; PAW = pulmonary capillary wedge; RA = right atrium; RV = right ventricle; S = systolic.

RA Mean (mm Hg)	RV S/D (mm Hg)	PA S/D (mm Hg)	PA Mean (mm Hg)	PAW (mm Hg)	CI ($L/min/m^2$)

TABLE 22-6. Pulmonary Artery Catheter Values

The oxygen-carrying capacity of blood declines in almost direct proportion to hemoglobin content,[85] as seen in Figure 22-1 . As shown in Figure 22-1A , under most normal conditions the dissolved oxygen content of the blood contributes little, and thus the last portion of the equation can be eliminated. Anemia resulting in a decrease of the hemoglobin content to 7.5 g/dL (a hematocrit of approximately 22%) decreases the oxygen content of the blood to about 10.2 mL O_2 /dL (Fig. 22-1B). Because central cyanosis is only visible with a concentration of reduced deoxyhemoglobin of at least 5 g/dL, unless an abnormal hemoglobin is present, anemia can significantly impair oxygen-carrying capacity without the development of this common physical manifestation (Chap. 122).

In contrast, as the PO_2 reaches higher values (as in hyperbaric oxygen [HBO] chambers), the dissolved oxygen content becomes significant and may be of therapeutic value, particularly when the oxygen-carrying content of hemoglobin is compromised. The PO_2 corresponding to an FiO_2 of 100% is approximately 575 mm Hg. In HBO at 3 atm and 100% oxygen, PO_2 values in excess of 1500 mm Hg can be achieved.[54] Under these conditions, the dissolved oxygen content of the blood rises dramatically (to as much as 4.5 mL O_2 /dL) and may be adequate to sustain life, even in the absence of any contribution from hemoglobin (Fig. 22-1C).

Oxygen content (O_2 content) = hemoglobin bound oxygen + dissolved oxygen

A. Normal conditions: hemoglobin (Hb) = 15 g/dL; PO_2 = 100 mm Hg, oxygen saturation (O_2 Sat) = 95%

O_2 content = [(Hb)(O_2 sat) (constant) + (another constant)(PO_2)]

= [(Hb)(O_2 sat)(1.39 mL O_2/g%) + (0.003 mL O_2 /dL/mm Hg)(PO_2)]

= [(15 g/dL)(95%)(1.39 mL O_2/g%) + (0.003 mL O_2/dL/mm Hg)(100 mm Hg)]

= [(19.8 mL O_2/dL) + (0.3 mL O_2/dL)]

= 20.1 mL O_2/dL = 20.1 vol%

B. Anemia: Hb = 7.5 g/dL; PO_2 = 100 mm Hg, O_2 Sat = 95%

O_2 content = [(Hb)(O_2 sat)(1.39 mL O_2/g%) + (0.003 mL O_2/dL/mm Hg)(PO_2)]

= [(7.5 g/dL)(95%)(1.39 mL O_2/g%) + (0.003 mL O_2/dL/mm Hg)(100 mm Hg)]

= [(9.9 mL O_2/dL) + (0.3 mL O_2/dL)]

= 10.2 mL O_2/dL = 10.2 vol%

C. Hyperbaric oxygen: Hb = 15 g/dL; PO_2 = 1500 mm Hg, O_2 Sat = 100%

O_2 content = [(Hb)(O_2 sat)(1.39 mL O_2/g%) + (0.003 mL O_2dL/mm Hg)(PO_2)]

= [(15 g/dL)(100%)(1.39 mL O_2/g%) + (0.003 mL O_2/dL/mm Hg)(1500 mm Hg)]

= [(20.9 mL O_2/dL) + (4.5 mL O_2/dL)]

= 25.4 mL O_2/dL = 25.4 vol%

Figure 22-1. Oxygen content of the blood.

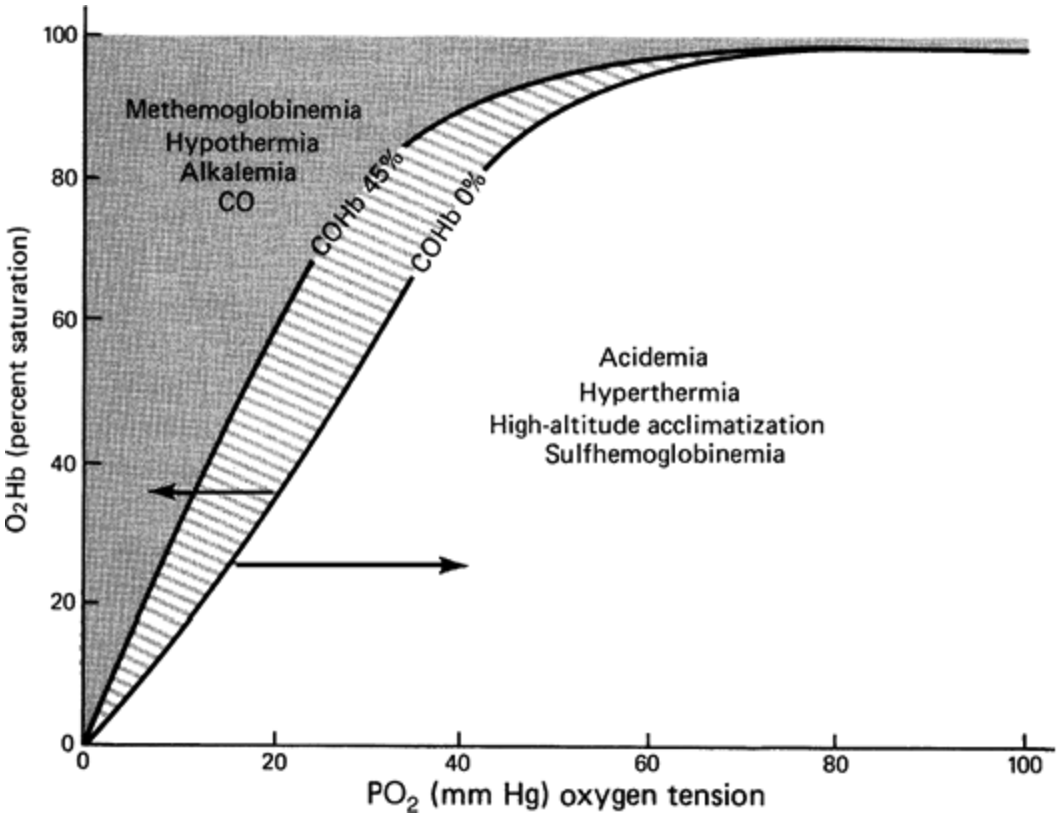

Figure 22-2. Oxyhemoglobin dissociation curve at 98.6Â°F (37Â°C) and pH 7.40. (Hematocrit does not alter this relationship.

The chemical asphyxiants that produce methemoglobin, carboxyhemoglobin, and sulfhemoglobin all interfere with oxygen loading and/or unloading to various degrees. Methemoglobin inhibits oxygen loading, producing cyanosis that is unresponsive to supplemental oxygen (Chap. 122). In addition, the oxyhemoglobin saturation curve is shifted to the left, interfering with unloading (Fig. 22-2). Carboxyhemoglobin has similar effects on oxygen loading and unloading, but carboxyhemoglobin is not associated with cyanosis (Chap. 120). Sulfhemoglobin has similar effects on oxygen loading, but actually shifts the oxyhemoglobin saturation curve to the right, favoring unloading. Cyanide, hydrogen sulfide, and sodium azide primarily affect oxygen use by interfering with the cytochrome oxidase system (Chap. 121).

Cardiac Output

Any xenobiotic that causes a decreased cardiac output or hypotension may result in tissue hypoxia and tachypnea. This occurs most frequently with overdoses of Î²-adrenergic antagonists and calcium channel blockers, antidysrhythmics, cyclic antidepressants, and phenothiazines (Chap. 23).

Approach to the Poisoned Patient

The initial assessment of every patient must involve the evaluation of upper airway patency. Adequacy of ventilation should then be determined. If concomitant injury is suspected, care must be taken to protect the cervical spine. When airway patency is in question, maneuvers to establish and protect the airway are of prime importance. Often this may simply involve repositioning the chin, jaw, or head, or suctioning secretions or vomitus from the airway. However, insertion of an oral or nasopharyngeal

airway, or nasopharyngeal or endotracheal intubation, or surgical cricothyroidotomy may be required as clinically indicated. After the airway is secured, high-flow supplemental oxygen should be provided and the depth, rate, and rhythm of respirations evaluated. An acceptable tidal breath is one that transports 10â€“15 mL of air/kg of body weight.[4]

Hypoventilation resulting from an inadequate respiratory rate or tidal volume is arbitrarily defined as PCO_2 greater than 44 mm Hg and leads to hypoxia and ventilatory failure if uncorrected.[94] The symptoms of hypoxia and or hypercarbia are nonspecific and resemble toxicity from many xenobiotics. Initially, patients appear restless and confused. Signs of sympathetic discharge, such as tachycardia and diaphoresis, may be noted. Later, patients may complain of headache, only to become sedated and subsequently comatose, as further deterioration occurs. Because these signs

and symptoms are nonspecific, arterial blood-gas analysis must be used early in the assessment of patients who present with xenobiotic overdose and possible ventilatory failure.

A trial of naloxone, hypertonic dextrose, and thiamine may be indicated for the patient with an altered mental status and or respiratory compromise (Chap. 4). Because opioid overdose and hypoglycemia are rapidly reversible, potential causes of respiratory failure, these diagnoses should be addressed before most other interventions are considered. Failure to identify and reverse these conditions may result in unnecessary diagnostic and therapeutic interventions in addition to irreversible neurologic sequelae.

Having assured an acceptable airway, the remainder of the evaluation can proceed. A rapid assessment of the remainder of the vital signs (Chap. 3) should then occur. Obtaining a history and physical examination, pulse oximetry, arterial blood-gas analysis, measured oxygen saturation, and a chest radiograph are sufficient to determine the diagnosis of pulmonary pathology in most cases. However, adjuncts, such as measurement of negative inspiratory force (NIF), invasive hemodynamic monitoring, evaluation of the arterialâ€“venous oxygen difference, xenon ventilation and technetium scanning, and CT scanning may be required.

History

A directed history must include questions on the nature, onset, and duration of symptoms; substance use and abuse; home and occupational exposures; and underlying pulmonary pathology. If the patient is suffering from a significant degree of respiratory compromise, most or all of the history may have to be obtained from friends, relatives, paramedics, coworkers, or others.

Physical Examination

The physical evaluation must include a detailed assessment of depth, rate, and rhythm of respirations, use of accessory muscles, direct evaluation of the oropharynx, position of the trachea, and presence and quality of breath sounds. Skin, nail bed, and conjunctival color must be observed for pallor or cyanosis. Funduscopic examination is a useful adjunct to the examination. Papilledema may be noted in the presence of acute hypercapnia. Additionally, because cyanide poisoning interferes with oxygen delivery to tissue, the venous oxygen saturation remains high. During the funduscopic examination, this may appear as arteriolization of the retinal veins, where the veins take on a color more characteristic of arteries (Chap. 121). A general assessment of muscle tone, with a specific emphasis on ocular and neck muscles may give clues to flaccidity or rigidity syndromes that interfere with respiration. When in doubt, a determination of the NIF will provide a rapid, objective, quantifiable bedside assessment of respiratory strength.

Pulse Oximetry

Pulse oximeters have gained widespread acceptance as rapid, noninvasive indicators of hemoglobin oxygen saturation. As defined, hemoglobin oxygen saturation is the ratio of oxyhemoglobin to total hemoglobin. By using two light-emitting diodes, the pulse oximeter is able to measure absorbance at the peak wavelengths for oxy- and deoxyhemoglobin (typically at 940 and 660 nm, respectively). Thus, the ratio of oxyhemoglobin to oxyhemoglobin plus deoxyhemoglobin (total hemoglobin) can be calculated. The clinician may then estimate the PO_2 from the oxygen saturation.

Some of the limitations of this approach require elaboration. Because the oxyhemoglobin saturation curve becomes quite flat above 90% saturation (Fig. 22-2), small changes in saturation

over 90% may represent very large changes in PO_2 . Thus, a decrease from 97% saturation to 95% saturation may represent a substantial decrease in PO_2 . Although a low saturation is an early indicator of hypoxic hypoxia, this is only one of many causes of tissue hypoxia. If total hemoglobin is low, oxygen-carrying capacity is inadequate even with excellent saturation (Fig. 22-1). Dyshemoglobinemias, such as carboxyhemoglobin, methemoglobin, and possibly sulfhemoglobin, interfere with the accuracy of pulse oximeter determinations and are of particular concern in the poisoned patient. Specifically, using a standard pulse oximeter, the presence of elevated concentrations of methemoglobin will tend to make the saturation approach 84â€“86% (Chap. 122).[5] , [73] Carboxyhemoglobin is falsely interpreted by the pulse oximeter as mostly oxyhemoglobin, thus readings tend to appear normal even with significant carbon monoxide poisoning,[86] as Table 22-7 illustrates.

Accurate response by the pulse oximeter also requires adequate blood pressure, lack of strong venous pulsations (as might occur in a patient with tricuspid regurgitation), translucent nails (some shades of nail polish may interfere), absence of circulating dyes (methylene blue), and a near-normal temperature. Finally, we are often more interested in PCO_2 than PO_2 because it is a better measure of ventilation. The pulse oximeter gives no information

with regard to PCO_2 . Although the pulse oximeter may give early clues to the presence of hypoxic hypoxia, extrapolation of oxygen saturation to standard arterial blood-gas values may be difficult because of the many possible sources of error. Pulse oximetry is therefore best used as an initial screening tool for hypoxic hypoxia and later in combination with the initial arterial blood-gas measurement, as a determination of the patient's response to therapy.

Normal

95
95
95
95
Anemia
95
95
95
95*
Methemoglobinemia (30%)
95
95
85
70
Carboxyhemoglobinemia (30%)
95
95
95
70
Hypoxemia
60
90
90
90

The table demonstrates limitations of the various methods for determining oxygen saturation (O_2 saturation). The arterial blood gas (ABG) calculates the O_2 saturation from the dissolved oxygen content (PO_2) and becomes abnormal only when the PO_2 falls. The pulse oximeter uses only two wavelengths of light and produces substantial errors in the presence of a dyshemoglobinemia. Because the cooximeter uses more wavelengths of light than the pulse oximeter, it can correctly identify the presence of carboxyhemoglobin and methemoglobin. The cooximeter has the additional advantage (*) of calculating the total hemoglobin and

oxygen content, so that it is useful in the setting of anemia. All techniques are acceptable for the assessment of hypoxemia.

		% Oxygen Saturation		
Condition	PO_2 (mm Hg)	ABG	Pulse oximeter	Cooximeter

TABLE 22-7. Sample Interpretations of Oxygen Saturations Reported from Various Sources

Blood-Gas Analysis

Arterial blood-gas analysis is an easy and rapid means of evaluating both acidâ€“base status and gas exchange. Attention must be paid to the method for determining oxygen saturation, specifically whether it is measured or calculated from PO_2 . If the measured O_2 saturation is lower than would be predicted from the PO_2 (the calculated O_2 saturation), the presence of an abnormal hemoglobin (such as carboxyhemoglobin or methemoglobin) must be suspected. A normal calculated O_2 saturation does not exclude these disorders (see Use of the Cooximeter below).

Because it is easier to obtain, venous blood-gas analysis is often used as a substitute for arterial blood-gas analysis.[13] When compared to arterial values, venous pH and PO_2 are lower, whereas PCO_2 is higher. Errors can be introduced by increased muscle activity of the extremity being tested (eg, seizures) or the prolonged placement of a tourniquet while attempting phlebotomy. Although a venous blood gas is generally acceptable for assessment of the blood pH, it cannot provide a good evaluation of gas exchange.

Mixed venous blood (defined as right-heart blood), however, is required for accurate determination of the arterialâ€“venous

oxygen extraction and is an excellent indicator of acidâ€“base status, cardiovascular function, and oxygen use. Unfortunately, a central venous catheter is required for sampling. When performing a peripheral venous blood-gas analysis, it is usually assumed that this is only an approximation of mixed venous blood.

The arterial PO_2 is generally considered adequate only if it lies within the flat portion at the upper right of the sigmoidal-shaped oxyhemoglobin dissociation curve (Fig. 22-2). That portion of the curve includes the PO_2 range from 60 to 100 mm Hg, which corresponds to oxygen saturations greater than 90%. As mentioned earlier, within this flat portion there can be discernible changes in PO_2 with little change in oxygen saturation. For instance, an arterial PO_2 of 80 mm Hg corresponds roughly to an oxygen saturation of 95%. If the PO_2 falls to 60 mm Hg, the oxygen saturation falls to 90%. This insignificant decrease in the oxygen-carrying capacity of the blood is of minimal clinical concern. If the PO_2 falls another 20 mm Hg, however, there is a more significant reduction in oxygen saturation, to approximately 70%. Thus, changes in PO_2 above 60 mm Hg are usually not of acute therapeutic significance, because the O_2 saturation is above 90%. These changes are, however, frequently of diagnostic significance.

An exception to this concept applies to the patient who is under metabolic stress, as might result from low cardiac output, impaired vascular flow, anemia, or dyshemoglobinemia. Under these circumstances even the modest gain achieved by increasing both dissolved oxygen content and hemoglobin saturation above 90% may be desirable, as discussed earlier (see Hemoglobin and Chemical Asphyxiants). Also, even if a PO_2 greater than 60 mm Hg or an O_2 saturation greater than 90% is considered acceptable in most acute settings, it is still desirable to achieve greater values, when feasible, to create a safety zone in case of clinical deterioration.

Significance of a Decreased PO_2

In a patient with a diminished PO_2 , five clinically relevant mechanisms for the hypoxemia should be considered: (a) alveolar hypoventilation; (b) V/Q mismatch; (c) shunting; (d) diffusion abnormality; and, rarely, (e) a decrease in FiO_2 . In most clinical circumstances, diffusion defects cannot be distinguished from V/Q mismatch. Usually, the responsible mechanism can be identified by calculating the alveolar-arterial (A-a) oxygen gradient. In patients with alveolar hypoventilation, the A-a gradient is completely normal (15 mm Hg or less when breathing room air). Patients with V/Q mismatch have an A-a gradient that is increased but which normalizes when 100% oxygen is administered for at least 20 minutes. A normal A-a gradient is defined as less than 100 mm Hg on 100% oxygen. The arterial PO_2 on 100% oxygen reaches approximately 575 mm Hg. In contrast, a patient with a shunt will also have an increased A-a gradient while breathing room air, but when 100% oxygen is administered, the arterial PO_2 falls substantially below 575 mm Hg and the A-a gradient does not normalize. Finally, in the case of a patient with hypoxia resulting from breathing in an environment in which the FiO_2 is less than 21%, the PO_2 should correct rapidly when the patient is removed from the environment or supplemental oxygen is delivered.

In general, a low PO_2 can be improved by supplying supplemental oxygen. Although in this instance the patient's laboratory values may be corrected, the underlying process persists. It is important to remember that the laboratory correlate of hypoventilation is hypercapnia on the arterial blood-gas analysis. If hypercapnia is associated with a low arterial pH (less than 7.35), assisted ventilation should be considered, regardless of whether the PO_2 corrects with supplemental oxygen.

Use of the Cooximeter

Routine analysis of an arterial blood-gas yields a measured pH,

measured PO_2 , and measured PCO_2 . Ordinarily, the serum bicarbonate, base excess, and percent oxygen saturation of hemoglobin are all calculated values. The oxygen saturation is of clinical significance because it usually correlates with the oxygen content of the blood, and thus the oxygen available to the tissues. However, implied in this relationship is a normal amount of functional hemoglobin. Because the oxygen saturation is calculated from the measured PO_2 using the oxyhemoglobin dissociation curve, it represents only the saturation of normal hemoglobin. Thus, in the presence of even a small percentage of abnormal hemoglobin, the calculated oxygen saturation overestimates the total oxygen content of the blood. For example, a patient with PO_2 of 95 mm Hg has a calculated oxygen saturation of 95%. If this patient also has a 30% methemoglobinemia, only 70% of the total hemoglobin is saturated to 95% and the actual saturation is only 67%. This gap is clinically important because hemoglobin saturations of less than 90% do not provide adequate oxygen delivery to the tissues. Most cooximeters spectrophotometrically measure total hemoglobin, oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and methemoglobin (Fig. 22-3). The resultant saturation is a measured oxygen saturation of the total hemoglobin by including four common hemoglobin variants, and thus correlates with the total oxygen content of the blood.

The difference between measured and calculated oxygen saturation represents the percentage of abnormal hemoglobin present. This gap is helpful in the diagnosis of methemoglobin and

carboxyhemoglobin, and is useful in assessing the adequacy of therapy for these disorders. Common indications for cooximetry include cyanosis that is unresponsive to oxygen (methemoglobin and sulfhemoglobin), known use of methemoglobin-forming xenobiotics (such as dapsone), smoke inhalation (carboxyhemoglobin and possibly methemoglobin), and evaluation of therapy for cyanide toxicity (methemoglobin).

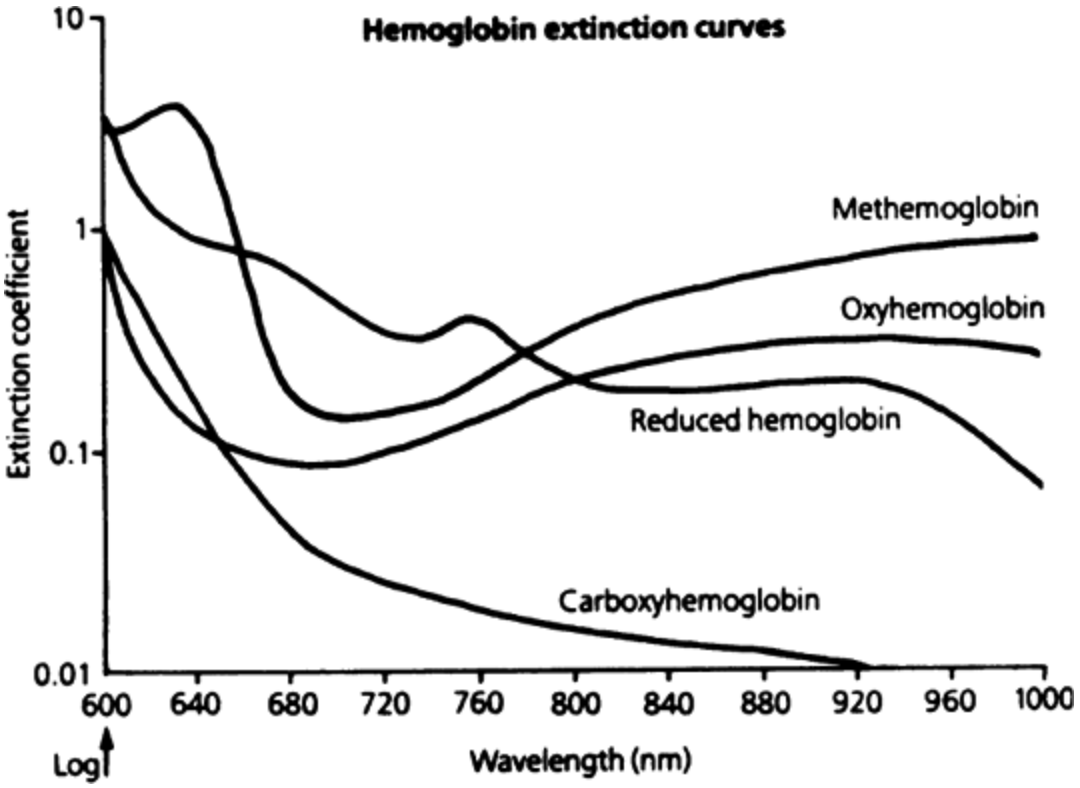

Figure 22-3. Cooximetry curves for normal and abnormal hemoglobin variants. Transmitted light absorbance spectra are shown for four hemoglobin species: oxyhemoglobin, reduced (deoxy) hemoglobin, carboxyhemoglobin, and methemoglobin. *(Adapted with permission from International Anesthesiology Clinics. Boston, Little Brown & Co., 1987;25(3):138. Tremper KK, Barker SJ: Using pulse oximetry when dyshemoglobin levels are high. J Crit Illness 1998;3:103â€“107.)*

Like so many other tools, the cooximeter is not perfect. Its biggest limitation occurs when dealing with uncommon hemoglobins. Because only four wavelengths of light are used by most cooximeters, they have the ability to define only four hemoglobin variants. Consequently, rare dyshemoglobinemias, such as sulfhemoglobin, are interpreted as one or a combination of the four common hemoglobin variants, giving erroneous results. This phenomenon is commonly noted in neonates, where fetal

hemoglobin may be interpreted as carboxyhemoglobin.[88, 95] Although this error rarely adds more than 10% to the true carboxyhemoglobin value, this amount can be significant because of the difficulties in assessing the neuropsychiatric status of infants possibly exposed to carbon monoxide. Some newer cooximeters are unaffected by fetal hemoglobin, and should be used in neonatal cases of suspected carbon monoxide poisoning.[89, 99] Similarly, these newer models are now beginning to provide measurements of sulfhemoglobin as well.[24, 97, 99] Additionally, cooximeters tend to interpret low levels (<2.5%) of carboxyhemoglobin inconsistently.[57] Fortunately, this rarely has clinical implications.

Chest Radiography

Radiographic detection of a pneumothorax or pneumomediastinum, cardiogenic pulmonary edema, ALI and ARDS, aspiration pneumonitis, or the presence of a foreign body is crucial, but can usually be delayed until the initial evaluation is completed. Confirmation of endotracheal tube placement is necessary but initially can be ascertained by auscultating bilateral breath sounds following compression of a bag valve mask, or using a variety of marketed devices such as end tidal CO_2 detectors designed to help confirm tube placement. For patients with occupational disorders, the chest radiograph is essential to confirm and stage exposures to asbestos, silica, coal, and other causes of pneumoconiosis.

Therapeutic Options

Supplemental Oxygen

Supplemental oxygen is indicated for all patients with suspected or confirmed respiratory insufficiency. Although it is generally advisable to begin with high flow (12 L/min) via a nonrebreather mask, lower concentrations of oxygen can be used in more stable

patients. It is important to remember that a normal saturation on pulse oximetry does not imply that there is no need for supplemental oxygen. This can be determined only after a more complete assessment. Initially, there should be limited concern over worsening hypercapnia in patients with chronic obstructive pulmonary disease (COPD) and respiratory failure. This concern should not deter one from providing needed oxygen as many of these patients will require intubation for their hypoventilation. If time and the patient's clinical condition permit, an arterial blood-gas analysis should be obtained prior to administering supplemental oxygen or mechanical ventilation so that the patient's intrinsic respiratory status can be adequately defined. In many situations, the patient's condition will not permit delay, and subsequent arterial blood-gas analyses will be needed to determine the ability to decrease the FiO_2 or the need for intubation. Hyperbaric oxygen is indicated for carbon monoxide poisoning and rarely other exposures (see Antidotes in Depth: Hyperbaric Oxygen).

Additional respiratory support can be offered from bilevel positive airway pressure (BiPAP). Some experimental evidence supports the use of BiPAP for patients with acute respiratory dysfunction in the emergency department.[70] Although this technique may be useful in overdosed patients, it should be considered only as a temporizing measure for patients who are expected to recover rapidly, or while preparing for intubation.

Intubation

After the decision for mechanical ventilation has been made, the route needs to be selected. The editors of this text prefer oral intubation because it permits the use of a larger endotracheal tubeâ€”usually 8 mm or larger in adultsâ€”than does nasal intubation. If the patient later needs bronchoscopy, it can be done through the endotracheal tube. Some data suggest that

bronchoscopy with bronchoalveolar lavage may be of both diagnostic[87] and therapeutic[51] benefit for selected poisoned patients. However, in an awake patient, nasotracheal intubation done blindly or with the aid of a flexible fiberoptic laryngoscope may be more easily performed. An advantage of nasotracheal intubation over oral intubation is that orogastric lavage can be performed more easily when the oral cavity is unimpeded. After the trachea is intubated, the tube should be checked to ensure that it is correctly positioned.

All patients who sustain overdoses and show signs or symptoms of respiratory insufficiency should have chest radiographs performed. Unfortunately, intubated patients usually have portable radiographs performed and the carina may be difficult to visualize because of the poor quality of the study. When seen, the carina is visualized between T-5 and T-7 in most patients. Thus, the tip of the endotracheal tube should be above T-5 for proper (safe) placement. When a portable chest radiograph is obtained, the patient's neck may

be extended or flexed, altering the location of the endotracheal tube tip. For this reason it is essential to note the position of the neck during the radiograph, because the tip of the endotracheal tube may move up (with flexion) or down (with extension) by almost 2 cm.[10]

Mechanical Ventilation

After a patient is intubated for ventilatory support, the respirator modeâ€”assist, control, or intermittent mandatory ventilation (IMV)â€”is selected. Patients with pure hypoventilation usually require a controlled fixed rate that can be easily adjusted based on serial arterial blood-gas analyses. Patients with pulmonary parenchymal processes, such as ALI, ARDS, or pneumonia, usually do well when placed on either assist or IMV mode. With the IMV

mode, a given number of mandatory breaths is administered at the set tidal volume. The patient may take additional breaths without assistance, permitting lower mean airway pressure, which theoretically may reduce the risk of barotrauma and hemodynamic compromise. Although the lower airway pressures associated with IMV are desirable, many authorities recommend the use of the assist mode because it eliminates the patient's work of breathing.[50]

The next step is to determine the appropriate FiO_2 to be delivered to the patient. A number of formulas have been devised. One simple approach is to intubate a patient, control breathing, administer 100% oxygen, and decrease to an FiO_2 of less than 50% as quickly as possible in an attempt to prevent oxygen toxicity.[3] Although the toxic effects of oxygen are well known for paraquat (Chap. 111), evidence suggests that oxygen may be an important mediator of other xenobiotic-induced pulmonary injuries such as with iron.[40] A PO_2 of 55 mm Hg or a measured oxygen saturation greater than 88% is generally acceptable; thus, there is little reason to expose patients to much higher concentrations of oxygen once these conditions are met.[1 , 90] Many clinicians feel more comfortable establishing a â€œbufferâ€• against deterioration by increasing the PO_2 somewhat above 55 mm Hg, but prolonged exposure to higher values is rarely indicated. In patients with pure alveolar hypoventilation, the tidal volume should be set at 10â€“15 mL/kg/breath. If oxygenation cannot be maintained with FiO_2 of 50% or less, PEEP may be used, with careful reassessment of serial arterial blood-gas analyses, changes in effective compliance, and hemodynamic data with each increment in PEEP. In patients with ALI or ARDS, however, lower tidal volumes (on the order of 6 mL/kg/breath) decrease both mortality and the total number of days on the ventilator.[1]

Pharmacologic Adjuncts

Only a few pharmacologic agents have a significant place in reversing xenobiotic-induced respiratory dysfunction. Naloxone may have the greatest role. Atropine and pralidoxime may be useful for respiratory dysfunction from cholinesterase inhibitors (see Antidotes in Depth: Pralidoxime and Chap. 109). Elapid antivenom and botulinum antitoxin are rarely used but may be lifesaving. Neostigmine can reverse muscle weakness from nondepolarizing neuromuscular blockers (Chap. 66). More commonly, clinicians are required to treat bronchospasm from exposure to pulmonary irritants. The use of $\hat{I}^2_2$ -selective adrenergic-agonist bronchodilators is effective in these cases.[30] The role of corticosteroids remains controversial.[3] An inhaled solution of 2% sodium bicarbonate may provide symptomatic relief for patients with exposure to hydrogen chloride or to chlorine (See Antidotes in Depth: Sodium Bicarbonate).

Exogenous nitric oxide has been considered for a variety of pulmonary conditions. Specifically, nitric oxide may be useful as a bronchodilator,[14] a means to reverse hypoxic pulmonary vasoconstriction,[3] and as a treatment for ARDS.[2] Unfortunately, controlled studies fail to demonstrate a benefit for nitric oxide in ALI/ARDS patients.[3 , 90] Similarly, the results are disappointing for glucocorticoids, surfactants, and a variety of antiinflammatory agents.[4 , 90]

Applications in Poisoned Patients

Two 30-year-old patients who overdosed were brought to the ED. Each had ingested substantial amounts of barbiturates and diazepam. An arterial blood gas drawn from patient 1 while he was breathing room air revealed a pH of 7.18, PCO_2 of 70 mm Hg, PO_2 of 50 mm Hg, and a calculated bicarbonate of 24 mEq/L. An arterial blood gas drawn from patient 2, also breathing room air, revealed a pH of 7.31, PCO_2 of 50 mm Hg, PO_2 of 50 mm Hg, and a calculated bicarbonate of 25 mEq/L. Quick analysis showed that

patient 1 was hypercapnic with a significant respiratory acidosis. Patient 2 did not appear as ill; his PCO_2 was not very elevated and his pH was not significantly reduced. The A-a gradients were calculated to be 12.5 mm Hg for patient 1 and 37.5 mm Hg for patient 2 (Fig. 22-4A and B).

A. Arterial PCO_2 approximates alveolar PCO_2 and is substituted as:

$$PAO_2 = PiO_2 - \frac{PCO_2}{R}$$

$$PiO_2 = (FiO_2)\,(PB - PH_2O)$$

where PAO_2 is alveolar PO_2, PiO_2 is partial pressure of inspired O_2, $PaCO_2$ is arterial PCO_2, and R is the respiratory exchange ratio. Therefore:

$$PAO_2 = [(FiO_2)(PB - PH_2O)] - \frac{PCO_2}{R}$$

where FiO_2 is the inspired O_2 fraction, PH_2O is water vapor pressure, and PB is barometric pressure. On room air at sea level, FiO_2 −21%. At steady state, R = 0.8. At sea level, PB = 760 mm Hg, and PH_2O = 47 mm Hg. Therefore:

$$PAO_2 = [(FiO_2)(PB - PH_2O)] - \frac{PCO_2}{R}$$

$$= [(0.21)(760 - 47)] - \frac{PCO_2}{R}$$

$$= 150 - [(1.25)(PCO_2)]$$

Because the A-a gradient is equal to $PAO_2 - PaO_2$ it can be expressed as:

$$150 - [(1.25)(PCO_2)] - PaO_2 \quad \text{or} \quad 150 - [(1.25)(PCO_2) + PaO_2]$$

A normal A-a gradient is 10–15 mm Hg, but this increases with age. A rough estimate of the normal A-a gradient is one-third the patient's age.

B. Referring to the two overdosed patients above, the A-a gradient for patient 1 is:

$$150 - [(1.25)(70) + 50] = 12.5 \text{ mm Hg}$$

This calculation reveals a normal gradient, indicating that the etiology for hypoxemia and hypoventilation is extrinsic to the lung itself.

In patient 2 the A-a gradient is:

$$150 - [(1.25)(50) + 50] = 37.5 \text{ mm Hg}$$

This abnormally high A-a gradient is consistent with the aspiration which was pneumonia seen on the patient's chest radiograph.

Figure 22-4. A. Derivation of the definition of alveolar-arterial (A-a) oxygen gradients. B. Using the A-a gradients.

The A-a gradient should be no more than one-third of a patient's age.[38] Patient 1 has a normal A-a gradient (12.5 mm Hg). Therefore, the mechanism for his hypoxemia must be purely alveolar hypoventilation, because that is the only mechanism that does not disrupt gas exchange. The treatment is to reverse the hypoventilation by assisting the patient's ventilation. Mechanical ventilation will reduce the PCO_2 , increase the PO_2 , and stabilize the patient until he is no longer under the influence of the xenobiotics he has ingested.

Alternatively, the A-a gradient of patient 2 (37.5 mm Hg) is significantly elevated. There are two possible mechanisms for this hypoxemia: V/Q mismatch or shunting. To discern which of these two mechanisms is responsible, the patient should be given 100% oxygen. In either case, however, the increased A-a gradient suggests that there is intrinsic pulmonary pathology causing the hypoxemia. On finding an increased A-a gradient, a chest radiograph should be examined for an intrinsic pulmonary cause of the gas exchange abnormality. Patient 2 had a significant right-lower-lobe infiltrate. He had aspirated and a pneumonitis developed, which contributed to his hypoxemia. His treatment, therefore, included antibiotic therapy and respiratory support.

Summary

Xenobiotics adversely affect tissue oxygenation at every step required for oxygen delivery. This process begins with lowering the partial pressure of inspired oxygen (simple asphyxiants) and ends with inhibition or blockade of cytochrome oxidase (carbon monoxide, cyanide, hydrogen sulfide). Although the clinical manifestations of hypoxia are constant regardless of the etiology, the history, physical examination, and some simple laboratory testing will often allow the clinician to determine the specific mechanism of hypoxia. Once the specific mechanism for hypoxia is identified, potential etiologies can be appreciated, and specific

treatments begun. While the diagnosis is being established, the first responses to tissue hypoxia always involve administration of supplemental oxygen, assisted ventilation if necessary, and assuring the adequacy of circulation.

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Chapter 23
Cardiovascular Principles

Robert A Hessler

The maintenance of adequate tissue perfusion depends on the volume status and vascular resistance, cardiac contractility, and cardiac rhythm. These components of the hemodynamic system are all vulnerable to the effects of xenobiotics. Cardiovascular toxicity may therefore be manifeste by the development of (a) hemodynamic instability, (b) heart failure, (c) cardiac conduction abnormalities, or (d) dysrhythmias. The presence of these specific cardiovascular abnormalities might be helpful in determinir the type of toxic exposure. Even when multiple cardiovascular abnormalities occur, the specific pattern of the anomalies (toxicologic syndrome or â€œtoxidromeâ€•) may suggest a particular class or type o xenobiotic.

Mechanisms of Cardiovascular Toxicity

An alteration in hemodynamic functioning may be a result of either indire metabolic effects or direct effects on the nervous system, heart, or blood vessels. Poisoning may lead indirectly to hemodynamic changes secondar to the development of acidemia, alkalemia, hypoxia, or electrolyte

abnormalities. In these patients, supportive care with ventilation, oxygenation, and fluid and electrolyte repletion will usually improve the cardiovascular status. These cardiovascular abnormalities are caused by metabolic changes and are generally not useful in the identification of a specific ingested xenobiotic.

Xenobiotics can also cause specific hemodynamic abnormalities as a resu of direct effects on the myocardial cells, the cardiac conduction system, o on the arteriolar smooth muscle cells. These effects are frequently mediated by interactions with cellular ion channels or cell membrane receptors. A rational approach to treatment of xenobiotic-induced hemodynamic effects is based on the underlying pharmacology and pathophysiology of the neurohormonal receptors, membrane ion channels intracellular calcium regulation, and the autonomic nervous system.

Ion Channels of the Myocardial Cell Membrane

Electrophysiologic studies have identified the functional types of membrane receptors and ion channels. Molecular genetic studies have identified the gene coding for the key cardiac ion channels and have elucidated the structural and physiologic relationships that lead to toxicologic effects of many xenobiotics. These channels are critical for maintenance of the intracellular ion concentrations necessary for action potential development, impulse conduction throughout the heart, and myocyte contraction.

Potassium Channel

Ion channels that change their conductance of current with changes in th transmembrane voltage potential are called *rectifying channels.* The voltage sensitive potassium channels are categorized based upon their speed of activation and their voltage response. These include the â€œdelayed rectifierâ€• potassium currents, particularly the I_{Kr} (rapidly activating) and the I_{Ks} (slowly activating) channels.[80]

The various voltage gated potassium channels share an underlying structural similarity. The Î± subunit is a protein molecule with 6 membrane-spanning Î±-helical domains, termed S1â€“S6 (Fig. 23-1A). The pore domain is located between the S5 and S6 regions of the Î± subunit, and the S4 region is the voltage sensor region.[53 , 93] Four of these Î± subunits assemble with Î² subunits to form the functional potassium channel complex. Four of the Î± subunits encoded by the KvLQT1 gene assemble with Î² units encoded by the minK gene (originally thought to be the minimal potassium channel subunit) to form the I_{Ks} potassium channel.[53] HERG (human ether a-go-go related gene) encodes the Î± subunit that assembles with Î² subunit proteins encoded by the MiRP1 (minK related protein 1) gene to form the I_{Kr} potassium channel. The C-terminus region of the Î± subunit encoded by HERG has a cyclic nucleotide binding domain and an N-terminus region similar to domains involved in signal transduction in cells.[53]

Many xenobiotics interact with the HERG-encoded subunit of the potassiu channel to reduce the current through the I_{Kr} channel and prolong the action potential duration. The HERG Î± subunit of the channel is particularly susceptible to xenobiotic-induced interactions due to two important differences from the other channels. First, the S6 domain of th HERG channel has aromatic domains on the inner cavity pore that can bir to aromatic xenobiotics. Additionally, the inner cavity and entrance of the HERG channel is larger than the other voltage-gated potassium channels.[53] This larger pore can accommodate larger xenobiotics that are then trapped within the pore when the channel closes.[53 , 92 , 93 , 114]

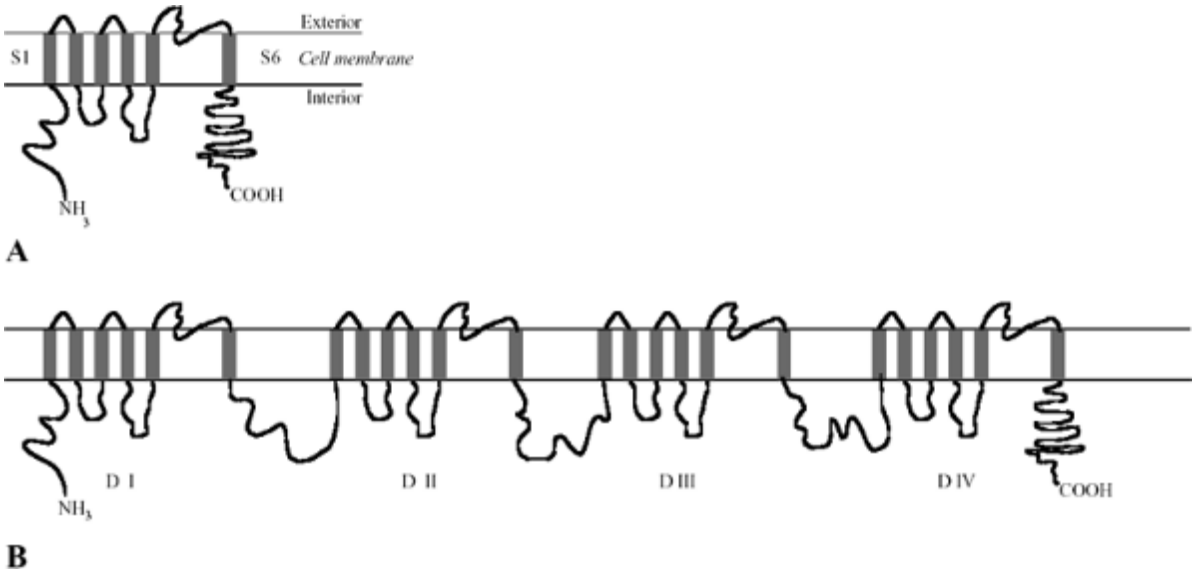

Figure 23-1. Structure of the potassium and sodium ion channels. A . Th structure of the Î± subunit of the voltage-gated potassium channel. The protein molecule has 6 membrane-spanning regions (S1â€“S6); the voltage-sensitive region is S4 and the actual ion channel is located between S5 and S6. Four of these Î± subunits assemble with 4 Î² subunit to form the potassium channel complex. B . The structure of the Î± subunit of the sodium channel. The protein molecule has 4 domains (D Iâ€”D IV), each analogous to one of the potassium channel Î± subunits. One of these molecules assembles with Î² subunits to form the membrane sodium channel.

Sodium Channel

The voltage-responsive sodium channels are responsible for the initiation of depolarization of the myocardial membrane. All currently identified voltage-responsive channels, including the sodium and calcium channel, have structures similar to the functional potassium channel assembly. The sodium channel gene encodes a single protein that contains 4 functional domains (D Iâ€”D IV). Each of these domains has the 6 membrane-spanning regions characteristic of the voltage-gated potassium channel

and is structurally similar to an Î± subunit of the potassium channel (Fig. 23-1). The single, large Î± subunit of the sodium channel assembles wit regulatory Î² subunits to form the functional unit of the sodium channel. The best characterized of the sodium channels, the SCN5A gene-encoded Î± channel, is inactivated by xenobiotic interactions between the D III ar the D IV domains to physically block the inner mouth of the sodium channel pore.[53]

Calcium Channel

Calcium channel conductivity across the myocardial cell membrane is critical for appropriate duration of cell membrane depolarization and for initiation of cellular contraction. The best characterized of the calcium channels are the slow L-type, the fast T-type, and the ryanodine receptor calcium channel (encoded by the RyR2 gene). This RyR2 channel is structurally similar to the sodium channel with 4 pore domain units in a single protein chain.[53] The RyR2 calcium channel is located on the membrane of the sarcoplasmic reticulum (SR) and mediates calcium release from the SR in myocardial cells. Calcium that enters the cell through the plasma membrane L-type calcium channels during depolarization activates the RyR2 channels on the SR. This triggers the release of large amounts of calcium from the SR into the cell cytosol to initiate myofibril contraction.

Ion Channels and the Myocardial Cell Actio Potential

An understanding of the basic electrophysiology of the myocardial cell is essential to understand the toxicity of xenobiotics and to plan appropriate therapy. Figure 23-2 shows the typical action potential of myocardial cell depolarization, the electrolyte fluxes responsible for the action potential, and the resulting ECG complex. The action potentials of the contractile ar the conductive cells are depicted.

The action potential is divided into 5 phases: phase 0, depolarization;

phase 1, overshoot; phase 2, plateau; phase 3, repolarization; and phase 4, resting. Phase 0 begins when the cell is excited either by a stimulus from an adjoining cell or by spontaneous depolarization of a pacemaker cell. Selective voltage-gated fast sodium channels (I_{Na^+}) open, resulting in rapid depolarization of the membrane. At the end of phase 0, the voltage-sensitive sodium channels close and a transient outward potassium current (I_{T0}) occurs, resulting in a partial repolarization of the membrane.

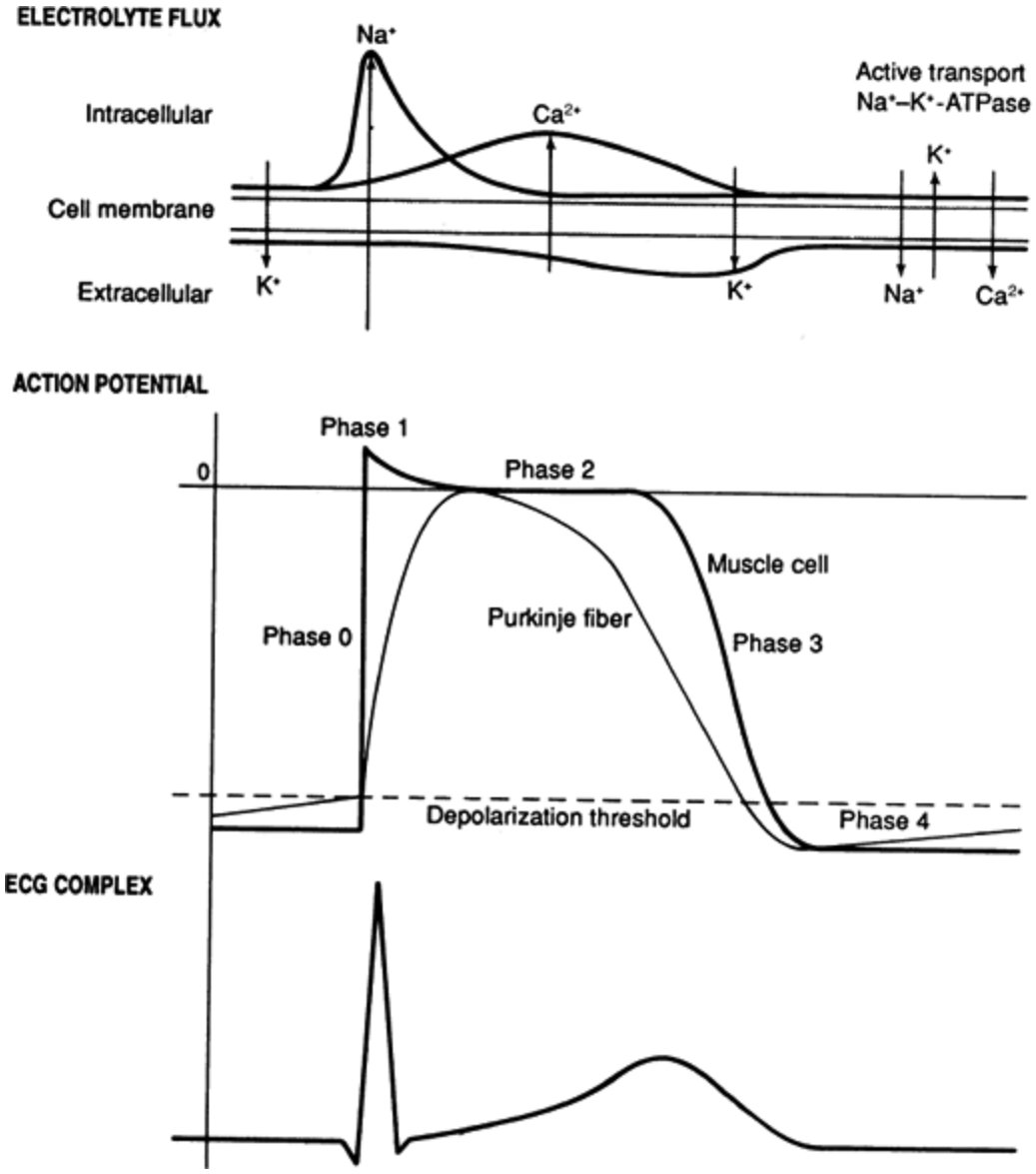

Figure 23-2. Relationship of electrolyte movement across the cell

membrane to the action potential and the ECG.

During phase 2 (plateau phase), the inward depolarizing calcium currents are largely balanced by the outward repolarizing potassium currents. Voltage-sensitive calcium channels open that allow Ca^{2+} movement down the concentration gradient into the cell. The intracellular Ca^{2+} concentration is 5â€“10,000 times lower than the extracellular concentration. The voltage-gated calcium channels that allow movement Ca^{2+} down its concentration gradient into the cell are categorized based on their conductance (fast or slow) and their sensitivity to voltage changes.[100, 116] The calcium currents (mostly the â€œlong-lastingâ€• current) gradually decrease as the channels inactivate. Simultaneously, the outward potassium â€œdelayed rectifierâ€• currents, particularly the I_{Kr} (rapidly activating) and the I_{Ks} (slowly activating) currents, increase terminating the plateau phase of the action potential and initiating cellular repolarization (phase 3). Other, smaller, outward potassium currents (not shown in Fig. 23-2) play a lesser role in the duration of the action potential and development of phase 3, including I_{Kur} (ultrarapid), I_{Kp} (plateau), $I_{K\text{-}Ach}$ (acetylcholine-dependent), and $I_{K\text{-}ATP}$ (adenosine triphosphate-dependent) currents.

Phase 4 is the resting state for much of the myocardium, except the pacemaker cells, and corresponds to diastole in the cardiac cycle. During phases 3 and 4, active transport of Na^+ , K^+ , and Ca^{2+} against their electrochemical gradients return the myocyte to the baseline resting state. The immense transmembrane electrochemical gradient is maintained during the resting state by a Ca^{2+} -Na^+ exchange mechanism and by ATP-dependent pumps in the membrane that together move Ca^{2+} out of the cells.[83, 84, 85 and 86] In the pacemaker cells, during phase 4 of the action potential, gradual electrical depolarization of the membrane occurs due to potassium currents (called the I_f for â€œfunnyâ€• or the I_h for â€œhyperpolarization-activatedâ€• current). The membrane potential gradually increases in these pacemaker cells until the threshold potential is reached, the fast inward sodium channels open, and the I_{Na} current

initiates the next phase 0. This electrical impulse is then propagated via the His-Purkinje conducting system of the heart. Electrophysiologic and molecular genetic studies have identified multiple subtypes of the sodium potassium, and calcium channels.

During phases 0â€“2, the cell cannot be depolarized again with another stimulus; the cell is *absolutely refractory.* During the latter half of phase 3, as the calcium channels convert from their inactivated to their resting state, an electrical stimulus of sufficient magnitude may cause another depolarization; the cell is *relatively refractory.* During phase 4, the cell is no longer refractory and any appropriate stimulus that reaches the threshold level may cause depolarization.

Calcium, Calcium Channels, and Cell Contraction

The contraction and relaxation cycle of the myocyte is controlled by the flux of calcium into and out of the SR into the cytoplasm.[6 , 59] Only a small proportion of the Ca^{2+} involved in myofibril contraction actually enters the cell through the exterior cell membrane during the action potential and membrane depolarization. The contraction and relaxation cycle of the myocyte are controlled by the flux of Ca^{2+} into and out of the SR into the cell cytoplasm.[6 , 59] When Ca^{2+} enters the cell cytoplasm, RyR2 channels open on the SR membrane and release Ca^{2+} from the intracellular SR stores into the cytoplasm. This phenomenon of calcium-induced calcium release results in a rapid increase in the intracellular Ca^{2} concentration, and initiates a rapid myosin and actin interaction. At the conclusion of cellular contraction, an SR-associated calcium ATPase adenosine triphosphatase pump returns the cytosolic Ca^{2+} into the SR. This SR associated calcium ATPase pump is regulated by phospholamban, cellular protein. Phosphorylation of phospholamban decreases its affinity for binding to the calcium pump; dissociation of the phosphorylated phospholamban increases the activity of the calcium ATPase pump. Î²-Adrenergic stimulation leads to phosphorylation of phospholamban. Phosphorylated phospholamban dissociates from the pump, the activity o

the pump increases, and the total SR calcium stores increase.[31, 32] Increased activity of the SR associated calcium pump increases the rate o relaxation (ie, lusitropy) and enhances contractility (ie, inotropy).

Cellular contraction occurs when myosin filaments interact with the actin-tropomyosin helix. A complex of troponin T, troponin I, and troponin C binds to the actin helix near the myosin binding site and act as regulators of the interaction. Troponin T actually binds the regulatory complex to th actin helix, troponin I prevents myosin from accessing its binding site on the actin helix, and troponin C acts as a calcium trigger to initiate contraction. When the intracellular Ca^{2+} concentration increases, 4 molecules of Ca^{2+} bind to troponin C and a conformational shift occurs in the troponin complex. Troponin I shifts and the myosin-binding site is exposed; myosin binds to the exposed site and myofibril contraction occurs (Fig. 23-3).[50, 51, 94, 95]

Calcium transport through the cellular membrane ion channels is critical for normal muscle function and contractility, for cell membrane conductance and electrical impulse generation, for cardiac muscle contraction and rhythm generation, and for maintenance of vascular smooth muscle tone. The physiologic response to calcium channel-blockin agents and to xenobiotics that interact with the Î±- or Î²-adrenergic receptors is mediated through changes in the intracellular calcium. Calcium channel blockers in current clinical use primarily block the L-type calcium channel, although their specificity differs for calcium channels on the vascular smooth muscle cells versus myocardial cells. This results in variable effects of different calcium channel blockers on the vascular tone and

peripheral vascular resistance, and on the contractility and electrical activity of the myocardial cells.

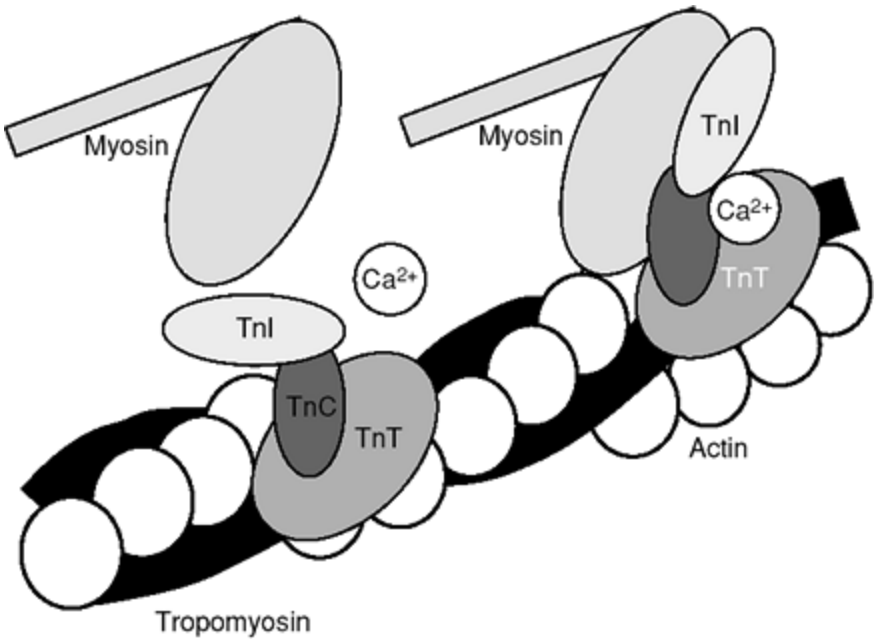

Figure 23-3. Troponin regulation of actin and myosin interaction. On the left, troponin I (TnI) blocks the binding site for myosin on the tropomyosin-actin helix. On the right, calcium binding to troponin C (TnC causes a conformational shift in the troponin molecules, and myosin is able to bind to the actin helix and initiate myofibril contraction. TnT is Troponin T.

Patients poisoned by calcium channel blockers have less Ca^{2+} entry into the cell during cardiac membrane depolarization. Administration of exogenous Ca^{2+} increases the concentration gradient across the cell membrane, enhances flow through available Ca^{2+} channels and restores the triggered response of the RyR2 channels to release Ca^{2+} from the sarcoplasmic reticulum (see Antidotes in Depth: Calcium). Because Î²-adrenergic antagonists have negative effects on Ca^{2+} handling by the SR similar effects are expected in the myocyte affected by these agents.

Cardiac Dysrhythmias and Conduction Abnormalities

Xenobiotics may produce adverse effects on the electrical activity of the

heart, often by acting directly on the myocardial cells. Because metabolic abnormalities (especially acidemia, hypotension, hypoxia, and electrolyte abnormalities) can further exacerbate the toxicity, or can actually be the sole cause of the cardiovascular abnormalities, correction of metabolic abnormalities must be a high priority in the treatment of patients with cardiovascular manifestations of poisoning. The terminal phase of any serious poisoning may include nonspecific hemodynamic abnormalities an cardiac dysrhythmias. However, many xenobiotics directly or primarily affect cardiac rhythm or conduction, often through effects on the cardiac ion channels.

Mechanisms of Cardiac Conduction Abnormalities and Dysrhythmias

Xenobiotics that directly cause dysrhythmias or cardiac conduction abnormalities usually affect the myocardial cell membrane. The myocyte ion channel composition and conduction characteristics vary regionally throughout the heart (eg, subendocardial cells have a longer action potential duration than do epicardial cells; this is called dispersion of repolarization and is normal). This is important to allow the heart to contract as a unit even though the impulse takes time to travel through the full thickness of the myocardial wall, from endocardium to epicardium Furthermore, xenobiotics that modify ion channels may alter the transmembrane potentials within myocytes and may result in the spontaneous generation of an abnormal rhythm.

Mechanisms of Dysrhythmia Initiation and Propagation

Abnormal cardiac rhythms, or dysrhythmias, can be commonly related to mechanisms: abnormal spontaneous depolarization (enhanced automaticity), afterdepolarization (triggered automaticity), and reentry. I normal myocardium, spontaneous phase 4 depolarization occurs most rapidly in the sinus node, the normal pacemaker for the heart. Speeding

slowing the rate of phase 4 depolarization of the pacemaker cell results i sinus tachycardia or sinus bradycardia, respectively. However, xenobiotic can also speed the depolarization of other myocardial cells that have pacemaker potential allowing them to overtake the sinus node as the heart's primary pacemaker. This mechanism, called increased automaticity, accounts for many of the dysrhythmias that occur with cardioactive steroid and Î²-adrenergic agonist poisoning.

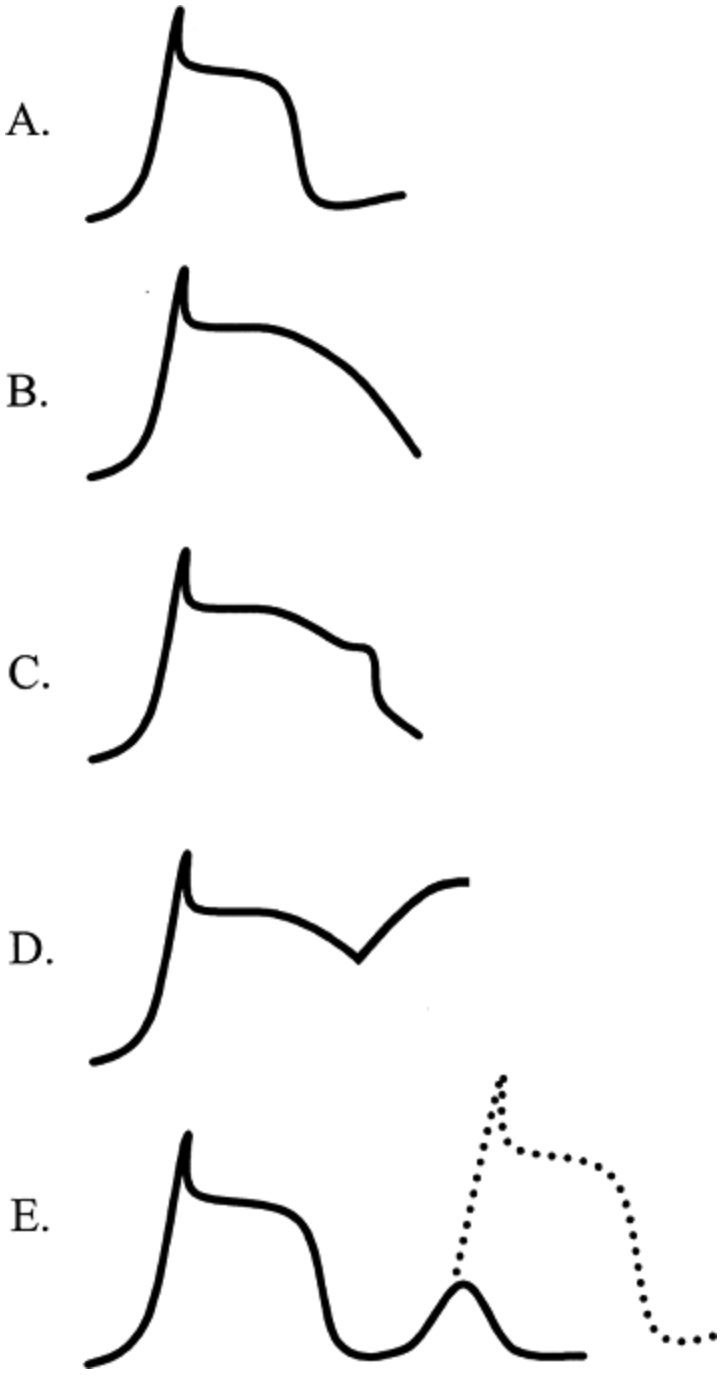

Figure 23-4. Afterdepolarization. A. The normal action potential. B. Prolonged duration action potential. C. Prolonged duration action potentia with an early afterdepolarization (EAD) occurring during the downslope o phase 3 of the action potential. D. Early afterdepolarization that reaches the depolarization threshold and initiates another depolarization, or a

triggered beat. E. Delayed afterdepolarization, which occurs after repolarization is complete.

Dysrhythmias can also result from spontaneous oscillations in the membrane potential, called afterdepolarizations, that occur during phase or 4 of the action potential. If the oscillations are of sufficient magnitude to reach the threshold potential, the fast sodium channels open and an action potential occurs (Fig. 23-4). These spontaneous oscillating depolarizations are mediated by depolarizing inward calcium currents, primarily through the L-type calcium channels. Early afterdepolarizations (EADs) occur during the plateau phase (phase 2) or during the downslope (phase 3) of the action potential. Oscillations in the membrane potential that occur after repolarization is complete, during phase 4, are called delayed afterdepolarizations (DADs). EADs most commonly occur in situations in which the action potential is prolonged, typically as a consequence of the blockade of I_{Kr} (such as by antidysrhythmic agents). EADs account for the â€œtrigger beatsâ€• that initiate episodes of torsades de pointes (TdP) discussed below. DADs occur primarily under conditions of increased intracellular Ca^{2+} , and account for many of the dysrhythmias that are associated with cardioactive steroid toxicity.[80]

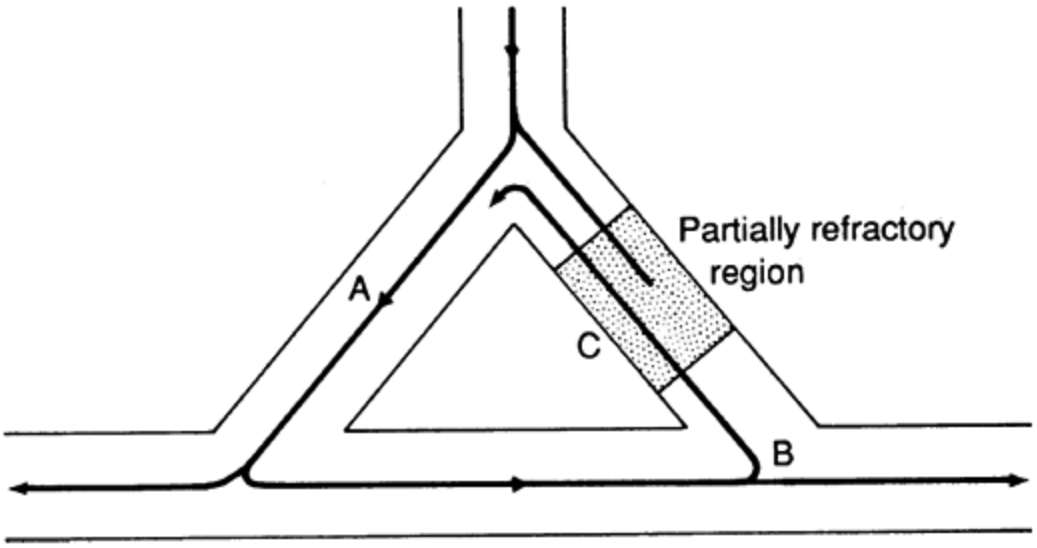

Figure 23-5. Mechanism of reentry dysrhythmias. An impulse traveling

down a conduction pathway reaches a branch point with one branch refractory (*C*). The impulse is conducted down branch *A* and spreads through the myocardium eventually to reach *B* , the distal end of the originally refractory branch. However, branch *C* is no longer refractory, and the impulse is conducted retrograde up through branch *C* , again to b conducted down branch *A* . The myocardium is depolarized during each loop around the circuit as the impulse spreads from the distal end of branch *A* to the rest of the heart.

Most afterdepolarizations propagate rapidly throughout the myocardium and generate ectopic beats. However, because the normal dispersion of repolarization is increased by certain xenobiotics, ectopic beats (eg, an atrial premature contraction or ventricular premature contraction) may propagate abnormally within the myocardium. Occasionally, because of th altered regional repolarization, an impulse may reach a branch point with a partial block (ie, relatively refractory) to conduction in one of the branches (Fig. 23-5). The impulse is carried through only one of the branches and then spreads through the myocardial cells. After a short delay, the impulse reaches the distal end of the previously blocked pathway. By this time, the region is no longer refractory and conducts th impulse in a retrograde fashion. The impulse may continue in a continuou loop circuit, depolarizing the heart with each passage; this process is called reentry. Reentry mechanisms appear to be responsible for the majority of the tachydysrhythmias attributable to poisoning.

Bradycardic Dysrhythmias

Bradycardia, heart block, and asystole are frequently the terminal events in patients with massive overdose. These dysrhythmias may occur as a result of direct effects on the myocardial system or of indirect metabolic effects. For instance, severe hyperkalemia (which may accompany any acidosis) results in a wide complex, sinusoidal bradycardic rhythm.

Many xenobiotics (Table 23-1) produce bradycardia through several

different mechanisms. The xenobiotic may affect the central or periphera nervous system, or may affect rhythm generation or conduction in the heart. Central nervous system-mediated bradycardia is probably the mos common xenobiotic-induced cause for mild sinus bradycardia. Xenobiotics that cause CNS sedation, such as the sedative-hypnotic agents, opioids, and Î±$_2$ -adrenergic receptor agonist (â€œcentrally actingâ€•) antihypertensive drugs, will usually decrease sympathetic outflow to the heart and produce a heart rate in the range of 40â€“60 beats/min.

The most profound bradycardia results from overdoses of xenobiotics tha have direct depressant effects on the cardiac

pacemaker. The ultimate manifestation of pacemaker and conduction failure is asystole. Examples of medications that in overdose can produce these effects include calcium channel blockers and Î²-adrenergic antagonists.

Î±$_1$ -Adrenergic agonists (reflex bradycardia)
- Phenylephrine
- Phenylpropanolamine

Î±$_2$ -Adrenergic agonists (centrally acting)
- Clonidine
- Guanfacine
- Guanabenz
- Methyldopa

Antidysrhythmics
- Amiodarone
- Sotalol

Î²-Adrenergic antagonists

Calcium channel blockers

Cardioactive steroids

Cholinergics

Carbamates or organic phosphorus compounds
- Edrophonium
- Neostigmine

Physostigmine
Opioids
Sedative hypnotics
Sodium channel openers
Aconitine
Andromedotoxin
Ciguatoxin
Veratridine

TABLE 23-1. Xenobiotics that Cause Bradycardia

Î ±$_1$ -Adrenergic agonists
Î ±$_2$ -Adrenergic agonists
Amantadine
Anesthetics (local)
Antidysrhythmics (class I and III)
Antihistamines
Antimicrobials
Chloroquine and quinine
Macrolides
Quinolones
Antipsychotics
Atypical antipsychotics
Droperidol
Haloperidol
Phenothiazines
Î²-Adrenergic antagonists
Calcium channel blockers
Carbamazepine
Cardioactive steroids
Cholinergics
Cocaine
Cyclic antidepressants
Cyclobenzaprine

Electrolytes
  Potassium
  Magnesium
Metal salts
  Arsenic
Methadone
Pentamidine
Propoxyphene

TABLE 23-2. Xenobiotics that Cause Conduction Abnormalities and/or Heart Block

Conduction Abnormalities and Atrioventricular Nodal Block

The cardiac toxicity of some xenobiotics results from their effects on the propagation of the electrical impulse through the conduction system of th heart. The ECG abnormalities produced by these agents may be a result c effects on the atrioventricular (AV) node, producing first-, second-, or third-degree (complete) heart block, or on the His-Purkinje system, producing intraventricular conduction delays such as bundle-branch block The effects of xenobiotics on myocardial conduction are often mediated through interactions with the sodium or potassium membrane channels. For example, xenobiotics that affect the fast inward I_{Na} currents (such as the type I antidysrhythmics and tricyclic antidepressants) prolong the action potential duration, slow ventricular myocyte depolarization, and slow intraventricular conduction. This produces widening of the QRS complex and prolongation of the QTc interval on the ECG (Chaps. 61 , 62 and 71). Table 23-2 lists some of the xenobiotics that cause conduction abnormalities. Many of the antidysrhythmic agents derive their clinical benefit from their ability to alter sodium and potassium channel function and slow conduction through the myocardium. Xenobiotics that depress phase 0 (the inward I_{Na} currents) produce slowing of conduction and

widening of the QRS complex. Xenobiotics that prolong depolarization and repolarization (phase 2 or phase 3 of the action potential) produce prolongation of the QTc interval on the ECG. The classes of the antidysrhythmic agents, their effects on the ion channels and on the action potential, and the resulting ECG abnormalities, are shown in Table 23-3 and discussed in detail in Chap. 61 .

Tachycardic Dysrhythmias

Both supraventricular and ventricular tachydysrhythmias can occur in poisoned patients (Table 23-4). Sinus tachycardia is the most common rhythm disturbance that occurs in poisoned patients. Parasympatholytic drugs, such as atropine, raise the heart rate to its innate rate by eliminating the inhibitory tonic vagal influence. However, more rapid rates require direct myocardial stimulatory effects, generally mediated by Î²-adrenergic agonism. For

example, catecholamine excess (eg, cocaine, psychomotor agitation, fever) may cause sinus tachycardia with rates faster than 150 beats/min. Ventricular dysrhythmias frequently accompany hypotension, hypoxia, acidemia, electrolyte abnormalities, and other metabolic derangements that may be present in poisoned patients or may be a direct effect of the xenobiotic (Table 23-4).

Sodium channel blockers
IA
+ + / + + +
+ +
0
Â ±
â †‘
â †‘
Disopyramide
Procainamide
Quinidine

IB
+/++
Â±
0
Â±
Â±
Â±
Lidocaine
Phenyloin
Mexiletine
Tocainide
IC
+++
++/+++
0
â†‘
â†‘
â†‘â†‘
Encainide
Flecainide
Propafenone
Moricizine
Î²-Adrenergic antagonists
II
0
0
+ (indirect)
â†‘
Â±
Â±
Propranolol
Atenolol
Esmolol
Metoprolol

Timolol
Potassium channel blockers
III
+
++
0
â†‘
Â±
â†‘
Amiodarone
Bretylium
Sotalol
Dofetilide
Ibutilide[a]
Calcium channel blockers
IV
0
0
+++
â†‘
Â±
Â±
Verapamil
Diltiazem

+ = Mild blockade; ++ = moderate blockade; +++ = marked blockade; â†‘ = increases; Â± = no significant effect

[a] Ibutilide actually activates a slow inward sodium channel rather than blocking outward potassium currents, but is classified as class III because of its increased action potential duration and atrial and ventricular refractoriness, which are typical of class III agents.

	Pharmacologic Blockade			Prolongation of ECG Intervals			
Class	Sodium Channels	Potassium Channels	Calcium Channels	PR	QRS	QT	Examples

TABLE 23-3. Classes of Antidysrhythmics

Amantadine
Antidysrhythmics
Anticholinergics
Antihistamines
Botanicals and plants (Chap. 114)
Carbamazepine
Cardioactive steroids
Chloroquine and quinine
Cyclic antidepressants
Cyclobenzaprine
Flumazenil
Hydrocarbons and solvents
  Halogenated hydrocarbons
  Inhalational anesthetics
Jellyfish venom
Metal salts
  Arsenic
  Iron
  Lithium
  Magnesium
  Potassium
Pentamidine
Phenothiazines
Phosphodiesterase inhibitors
  Amrinone

Methylxanthines
Propoxyphene
Sedative-hypnotics
Chloral Hydrate
Ethanol
Sympathomimetics
Catecholamines
Cocaine
Thyroid hormone preparations

TABLE 23-4. Xenobiotics that Cause Ventricular and Supraventricular Tachydysrhythmias

Dysrhythmias Associated with a Prolonged QTc Interval: Torsades De Pointes

Prolongation of the QT interval corresponds to an increase in the duration of phase 2 or phase 3 of the action potential. Although there is agreement that the QT interval includes the entire period of cardiac activation and recovery, there is no universal standard accepted by experts for the measurement of the QT interval. The QT interval normally varies because of biologic diurnal effects and autonomic tone; technical issues with the environment or with processing and acquiring the ECG; and intra- and interobserver variability.[2,73,75] The QT interval corresponds to the duration of the ventricular action potential, and should be measured from the beginning of the QRS to the end of the T wave. However, variations in the speed of the paper,[28] T-wave morphology, irregular baseline, and the presence of U waves may make this determination difficult.[5] U waves are particularly important because they are thought to correspond to late repolarization of myocardial cells in the mid-myocardium, and are implicated in the initiation of cardiac dysrhythmias.[5] QT interval measurements from the computerized ECG algorithms are less accurate than careful manual determinations of the interval.[52] In August 2000, a

panel of experts convened to address these issues and suggested that the QT interval should be measured manually in one of the limb leads that best shows the end T wave; the QT interval should be measured and averaged over 3 to 5 beats; and large U waves should be included in the QT interval measurement if they merge into the T wave and obscure the end of the T wave.[5] However, a subsequent study of 334 healthcare practitioners found that only 60% of the physicians were able to correctly measure a sample QT interval on the survey, even though nearly all correctly indicated the measurement should be from the beginning of the QRS to the end of the T wave.[57]

The QT interval is normally prolonged at slower heart rates and shortens as the heart rate increases. This is especially important since many of the xenobiotics that affect the QT interval also affect the heart rate. A variety of correction formulas have been utilized in order to correct for the effects of heart rate on the QT interval. With a rate of 50–90 beats/min, the commonly used Bazett formula (QTc [msec] = QT [msec]/$\sqrt{\text{R-R interval}}$ (sec) is adequate for determining a rate corrected QT interval (QTc). In this heart rate range, 99% of men have a QTc <450 msec and 99% of women have a QTc <460 msec,[77] and a QTc interval >500 msec weakly correlates with an increased risk of developing ventricular dysrhythmias. However, at higher heart rates, a normal patient will have an inaccurately calculated "prolonged" QTc interval using this Bazett formula.[5,72] Studies suggest that medications such as bupropion[48] and quetiapine[10] prolong the QT interval when the "increase" in the QTc may be only a result of the increased heart rate. A variety of formulas and corrections are proposed to attempt to identify normal QT intervals on ECGs at higher heart rates,[8,24,45,66,67] including the Friderician formula (QTc = $\sqrt{\text{QT/R-R interval}}$) and the Framingham linear regression analysis (based on large population observation). None of these formulas, however, are validated clinically (Chap. 5).

Ventricular tachycardia, including TdP, is usually a reentrant-type rhythm that requires an initiating impulse that spreads through the myocardial tissue and a branch point with unequal refractory periods (Fig. 23-5). The presence of a prolonged QTc interval on the ECG may indicate the possible existence of conditions within the myocardium that favor occurrence of

reentry dysrhythmias, as discussed above. The long action potential duration resulting from prolongation in the duration of phase 2 or phase 3 increases the occurrence of EADs. These, in combination with an increase dispersion of repolarization, increase the risk for reentrant dysrhythmias, particularly TdP (Chap. 5).

Many xenobiotics may also interact with cardiac membrane ion channels and increase the risk of TdP. Most of these agents interact with the HERG encoded Î± subunit of the potassium channel to reduce the current through the I_{Kr} channel and prolong the action potential duration. The HERG Î± subunit of the channel is particularly susceptible to xenobiotic interactions because of the larger inner cavity with aromatic binding domains.[53 , 92 , 93 , 114] Acquired QTc interval prolongation and TdP from xenobiotics occur most often with class Ia and Ic antidysrhythmics, the cyclic antidepressants,

and the phenothiazines. Although the newer class Ic antidysrhythmics (such as encainide and flecainide) cause greater QTc interval prolongatio the class Ia agents (such as quinidine and procainamide) are responsible for more reported cases. This is probably a result of the relatively infrequent use of the class Ic antidysrhythmics (due, paradoxically, to concerns about the higher risk of prodysrhythmic effects). Class Ib agent such as lidocaine, have no significant effect on K^+ channels and the QTc interval, and do not cause TdP. Acquired QTc interval prolongation and Tc also commonly result from metabolic and electrolyte abnormalities, particularly hypocalcemia, hypomagnesemia, and hypokalemia (Chap. 61).

Decreased Cardiac Contractility and Congestive Heart Failure

Xenobiotics can reduce cardiac contractility with a resulting decrease in cardiac ejection fraction and cardiac output, a decrease in blood pressure and development of congestive heart failure (CHF). Cardiogenic pulmonar edema generally occurs as a result of the direct effects of the xenobiotic

on the contractility, or inotropy, of the heart, or through increases in the preload or afterload. Acute cardiogenic pulmonary edema, resulting from decreased cardiac output, occurs primarily in patients poisoned by a calcium channel blocker or Î²-adrenergic receptor antagonist. Other xenobiotics that can exert direct depressant effects on cardiac contractili include antihistamines, phenothiazines, antidysrhythmics, and local anesthetics. Many of these agents reduce contractility through sodium channel blockade, which, by slowing intraventricular conduction, reduces the ability of the heart to contract efficiently. Pulmonary edema may also result from the fluid overload accompanying ingestion of large quantities of sodium-containing xenobiotics (eg, sodium penicillin), the renal effects of medications such as nonsteroidal antiinflammatory drugs, or as a late consequence of xenobiotics that cause renal failure.

Other xenobiotics can exert chronic toxic effects on the myocardium, either directly, or indirectly through effects on blood pressure or cardiac vasculature, and result in the development of cardiomyopathy. Xenobiotic causing cardiomyopathy include anthracycline antineoplastic agents (dactinomycin, daunorubicin, idarubicin, and doxorubicin),[4 , 30 , 47 , 63] amphetamines,[46 , 121] antimony,[3] cobalt,[69 , 70 , 76] cocaine,[21 , 43] ethanol,[99 , 129] and syrup of ipecac.[98] In most cases, the exact mechanism of the toxicity is not known. However, free radical generation nitrous oxide formation, myocardial ischemia, mechanical overload, and persistent tachycardia are each implicated in the cellular toxicity of the various xenobiotics and development of cardiomyopathy.

Patients with acute xenobiotic-induced congestive heart failure or xenobiotic-induced cardiogenic shock should receive aggressive hemodynamic support. Acutely poisoned patients often have a completely reversible process. Every effort must be made to support the patient's vital functions until the poison can be eliminated or removed. If the patient is bradycardic, an electrical pacemaker may be indicated, althoug its usefulness may be limited by the reduced electrical sensitivity of the heart affected by certain xenobiotics, such as calcium channel blockers.[1 68 , 105 , 118] Patients may recover completely even after prolonged cardiopulmonary resuscitation (CPR),[1 , 56] extracorporeal membrane

oxygenation,[7 , 23 , 26 , 39 , 101] intraaortic balloon pump use,[33 , 42 , 56 , 96] or cardiopulmonary bypass.[42 , 118]

The Autonomic Nervous System and Hemodynamics

In addition to the voltage dependent ion channels, the cell membrane contains channels that open in response to receptor binding of neurotransmitters or neurohormones.[83 , 84 and 85] A large number of xenobiotics exert their effects via interactions with membrane receptors. These receptor-binding agents include such diverse xenobiotics as pertussis and cholera toxins,[17] Î³-aminobutyric acid (GABA),[60] nicotine,[18 , 19 , 25] calcium channel antagonists, and adrenergic agonists and antagonists.

The hemodynamic effects of many xenobiotics are mediated by changes i the autonomic nervous system. The autonomic nervous system is functionally divided into the sympathetic (ie, adrenergic) and parasympathetic (ie, cholinergic) systems. These two systems, which share certain common features, function semi-independently of each other. Through complex feedback, the two systems provide the balance needed for existence under changing external conditions.

The sympathetic nervous system is primarily responsible for the maintenance of arteriolar tone and cardiac function. Although the ganglionic neurotransmitter of the sympathetic nervous system is acetylcholine, norepinephrine is its primary postganglionic neurotransmitter (Fig. 23-6). On release into the synapse, norepinephrir

binds to the postsynaptic adrenergic receptors to elicit an effect by the postsynaptic cell.

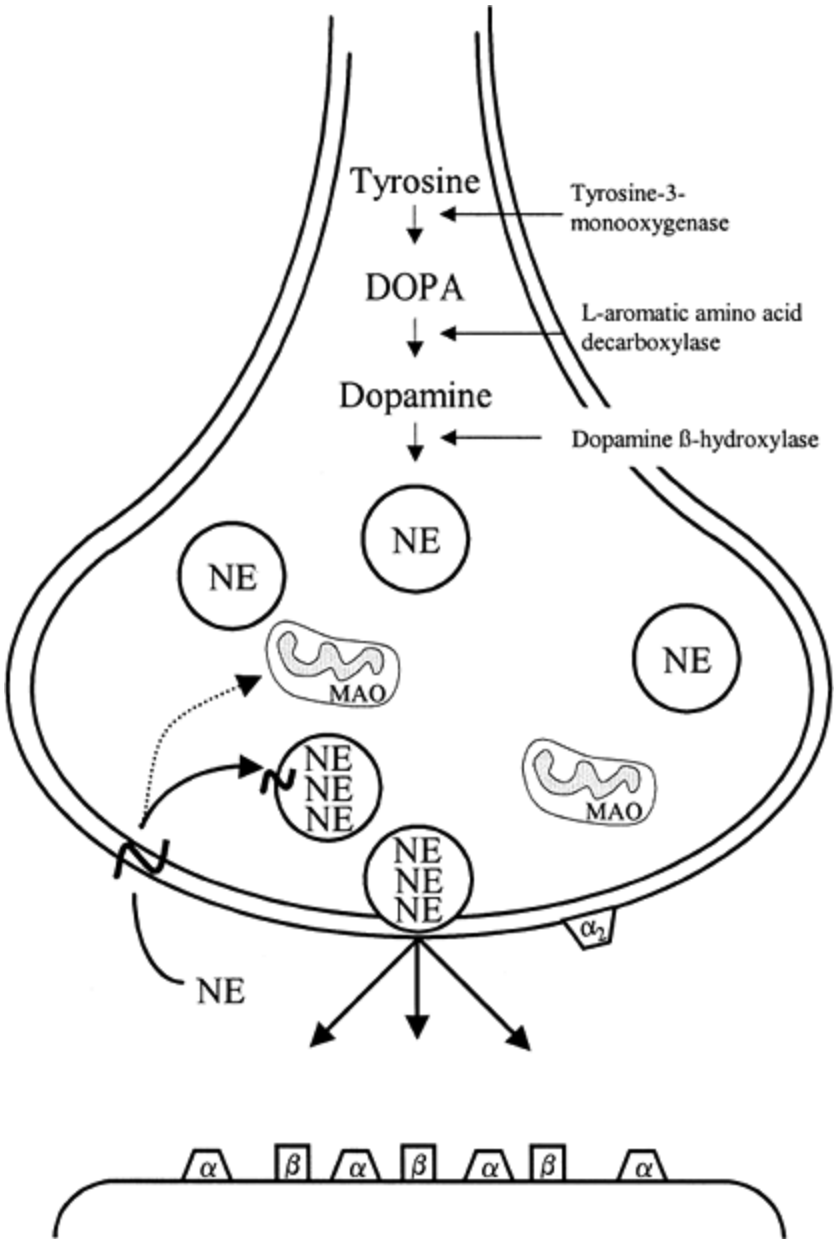

Figure 23-6. Shown is the synthesis in storage granules, release, reuptake, and degradation of norepinephrine (NE). NE is synthesized in storage vesicles in the nerve ending. These vesicles fuse with the neuron membrane in response to stimulation and release the NE into the synapti space. The NE binds postsynaptic adrenergic receptors, following which it either undergoes active reuptake into the proximal neuron or is metabolized. MAO = monoamine oxidase; N = reuptake mechanism.

Adrenergic Receptors

The existence of two types of adrenergic receptors, Î± and Î², was first proposed in 1948 to explain both the excitatory and the inhibitory effects of catecholamines on different smooth muscle tissue.[1] The Î± receptor was subsequently further subdivided into $Î±_1$ and $Î±_2$ when norepinephri and other Î±-adrenergic agonists were found to inhibit the release of additional norepinephrine from neurons into the synapse. These â€œautoregulatoryâ€• $Î±_2$ receptors are primarily located on the presynaptic neuronal membrane; however some $Î±_2$ -adrenergic receptor are found on the postsynaptic membrane. Activation of these postsynapti $Î±_2$ receptors in the cardiovascular control centers in the medulla and elsewhere in the central nervous system decreases sympathetic outflow from the brain. Therefore, $Î±_2$ -adrenergic agonists generally cause decreased peripheral vascular resistance, decreased heart rate, and decreased blood pressure (even though some blood vessels have $Î±_2$ -adrenergic receptors that mediate vasoconstriction). The $Î±_1$ -adrenergic receptors are located on postsynaptic cells outside the central nervous system, primarily on blood vessels, and mediate arteriole constriction. Th adrenergic receptors also interact with circulating catecholamines and other sympathomimetic agents. The effects that catecholamines produce vary based on the organ system. These diverse effects are caused by variations in the adrenergic receptors and to differences in the cellular responses to the receptor interactions.

The Î²-adrenergic receptors have been subclassified into 3 subtypes: $Î²_1$ $Î²_2$, and $Î²_3$ (Table 23-5). The most prevalent Î²-adrenergic subtype in the heart is $Î²_1$, although $Î²_2$ and $Î²_3$ receptors are also present.[15 , 27 , 35 , 104] Stimulation of the $Î²_1$ -adrenergic receptors increases heart rate, contractility, conduction velocity, and automaticity. The $Î²_2$ -adrenergic receptors are primarily responsible for relaxation of smooth muscle with resulting bronchodilation and arteriolar dilation. The $Î²_3$ receptors are located primarily on adipocytes where they play a role in lipolysis and thermogenesis.[27] $Î²_3$ -Adrenergic receptors in the heart may increase contractility,[119] but the bulk of evidence suggests that the $Î²_3$ receptors

are mediators of negative inotropy.[34 , 35 and 36 , 74] The Î²-adrenergic antagonists in current clinical use are ineffective at blocking $Î²_3$ -adrenoreceptors and may even act as agonists at these receptor sites.[106 107]

$Î²_1$
Heart
Increase rate
Increase inotropy
Increase SA and AV node conduction
Kidney
Increase renin
Eye
Increase aqueous humor
Adipose tissue
increase lipolysis
$Î²_2$
Heart
Increase rate (?)
Increase inotropy
Liver
Increase glycogenolysis
Increase gluconeogenesis
Skeletal muscle
Increase glycogenolysis
Smooth muscle (bronchi, arterioles, GI tract, uterus)
Relaxation
$Î²_3$
Adipose tissue
Increase lipolysis
Increase thermogenesis
Heart
Decrease inotropy (?)

Type Location Function

TABLE 23-5. Types and Functions of the Î²-Adrenergic Receptor

Cellular Physiology of the Adrenergic Receptors

The effects of adrenergic agents on the cell are primarily mediated through a secondary messenger system of cyclic adenosine monophosphate (cAMP). The intracellular cAMP concentration is regulated by the membrane interaction of three components: the actual adrenergic receptor, a â€œG-proteinâ€• complex, and adenyl cyclase, the enzyme that synthesizes cAMP in the cell.[17 , 37 , 112 , 113] These receptors are described in detail in Chap. 14 .

The G protein serves as a â€œsignal transducerâ€• between the receptor molecule and the effector enzyme, adenyl cyclase. The G proteins consist of 3 subunits: Î±, Î², and Î³.[22 , 78 , 79] The Î± subunit of the G protein complex binds to the COOH-terminal tail and to the intracytoplasmic loop of the adrenergic receptor, as well as to the adenyl cyclase enzyme. The Î± subunit of the G protein complex exists in several isomeric forms, depending on their interactions with the adenyl cyclase enzyme. G_s proteins contain $Î±_s$ subunits that stimulate adenyl cyclase when â€œactivatedâ€• by adrenergic receptor interaction. The $Î±_i$ subunits of G_i proteins inhibit the activity of adenyl cyclase. $Î²_1$ - and $Î²_2$ -adrenergic receptors interact primarily with $Î²_s$ subunits in stimulatory G_s protein complexes. $Î²_2$ -Adrenergic receptors also interact with G_i proteins. The $Î±_2$ -adrenergic receptors interact with inhibitory G_i proteins. A third form G_q , interacts with the $Î±_1$ -adrenergic receptors, but does not interact directly with the adenyl cyclase. The G_q interacts with phospholipase C to mediate cell response to $Î±_1$ -adrenergic stimulation.

When not stimulated by the presence of a catecholamine, the receptor protein is bound to the Î² and Î²Î³ dimers of the G protein, and guanosine diphosphate (GDP) is bound to the Î± subunit. Catecholamine binding to the receptor causes a conformational change in the Î± subunit; GDP

dissociates and guanosine triphosphate (GTP) binds to the Î± subunit. Th Î± subunit (with GTP bound) then dissociates from the receptor and from the Î²Î³ dimer. This â€œactivatedâ€• Î± subunit can now interact with adenyl cyclase or other effector enzymes. Interaction of the $Î±_S$ subunit with adenyl cyclase increases the activity of the enzyme resulting in a rapid increase in the intracellular cAMP (Fig. 23-7).[17 , 22 , 62 , 78 , 97]

The cAMP acts as a secondary messenger in the cell. cAMP interacts with protein kinase A (PKA) and other cAMP-dependent protein kinases to increase their protein phosphorylating activity.[61] In the absence of cAMP, PKA is a tetramer of two regulatory and two catalytic subunits. cAMP binc to the regulatory subunits to release the active enzymatic units from the tetramer (Fig. 23-7). Protein kinases then transfer phosphate groups fro ATP to serine (as well as to threonine and tyrosine amino acid groups) on enzymes that are involved in intracellular regulation and activities. Phosphorylation may increase or decrease the activity of specific enzyme and specific protein kinases are highly selective in the proteins that they phosphorylate.[109 , 110]

PKA phosphorylates a variety of cellular proteins involved in calcium regulation, including the voltage-sensitive calcium channel, phospholamban, and troponin.[41 , 44 , 108] Phosphorylation of the

L-type calcium channel increases the entry of calcium ions during membrane depolarization.[87 , 88 , 127] Phosphorylation of phospholamban decreases its activity to inhibit the calcium ATPase pump on the SR. This decreased inhibition of the calcium ATPase pump increases the efficiency of Ca^{2+} storage in the SR, which enhances both cellular contractility,[6 , 3 , 32 , 127] as the Ca^{2+} is released into the cell cytosol, and the relaxation muscle fibers, as the Ca^{2+} is pumped back into the SR.[59]

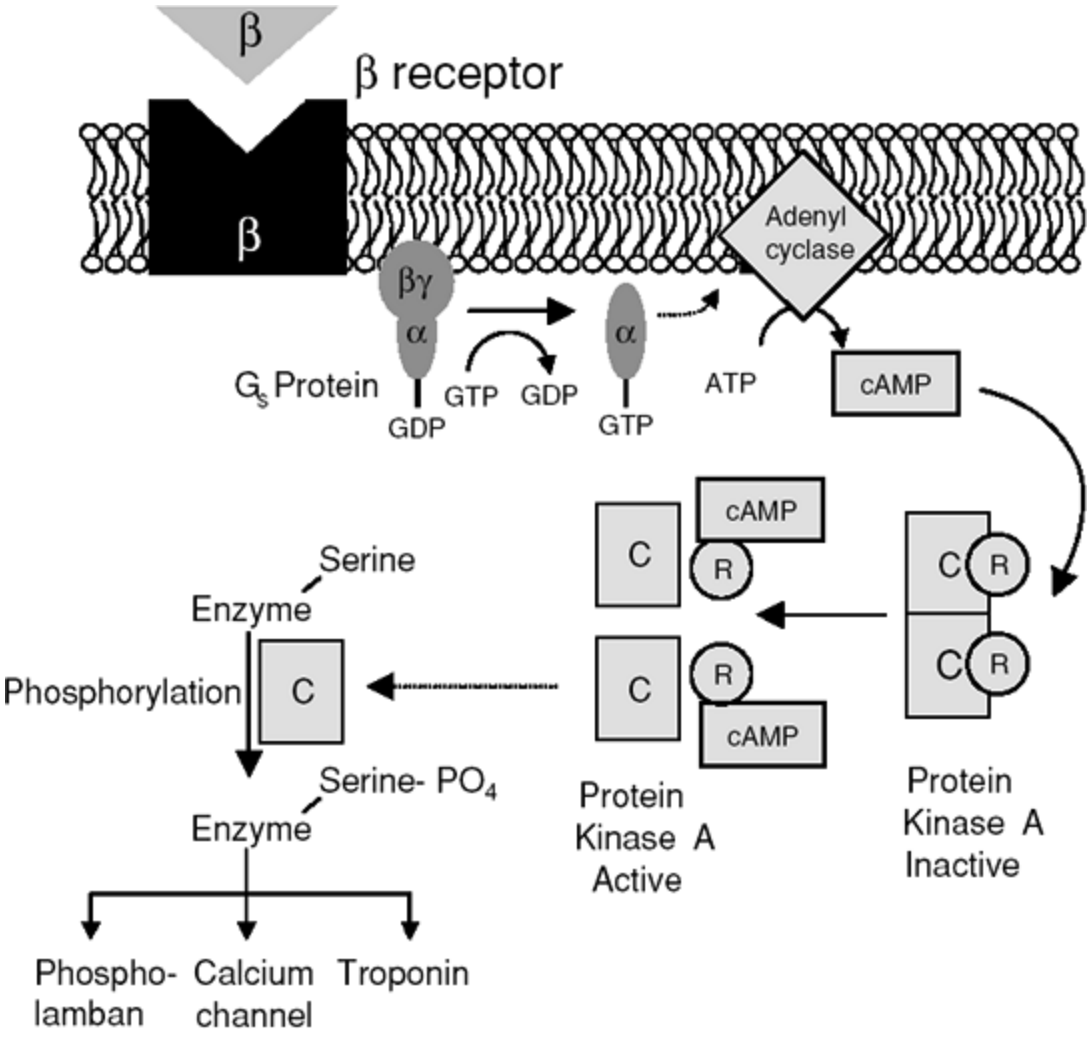

Figure 23-7. Binding of the Î² agonist to the Î² receptor causes the G_s protein to release bound GDP and bind GTP to activate the Î± subunit. Th activates adenyl cyclase to produce cAMP. The cAMP interacts with protei kinase A to activate the enzyme. Phosphorylation by protein kinase A changes the activity of various cellular proteins (see text).

Physiologic Effects of Adrenergic Receptors

The $Î²_1$, $Î²_2$, and $Î±_2$ adrenergic receptors all interact with G_s proteins and stimulate the adenyl cyclase enzyme. Differences in the resultant clinical effects are primarily related to the location and number of the different receptors in different tissues and to differences in the specificity

of the protein kinases activated by cAMP Table 23-5 shows the function and tissue distribution of the types of Î² receptors. Stimulation of the $Î²_1$ receptor results in increased heart rate and increased contractility. However, $Î²_2$ stimulation causes relaxation, as opposed to contraction, of smooth muscle. Because both Î²-adrenergic receptor subtypes interact with stimulatory G_s proteins, their clinical effects would appear to be paradoxical. However, there are two primary reasons for the different effect. First, PKA is not a single enzyme, but a group of related isoenzymes variably expressed in different tissues.[12, 49, 81] The actions and the substrates of the varied protein kinase isoenzymes may differ between $Î²_1$ - and $Î²_2$ -responsive tissues. Secondly, whereas $Î²_1$ stimulation results in cAMP-mediated effects throughout the cytoplasm, Î stimulation is compartmentalized within the cell. The effect of $Î²_2$ stimulation of G_s type receptors is localized phosphorylation of the L-type calcium channels, increasing their activity.[20, 54, 124, 125] $Î²_2$ receptors are also coupled to G_i -type receptors that inhibit adenyl cyclase and prevent the diffuse cytoplasmic increases in cAMP.[103, 104, 124] Additionally, $Î²_2$ -receptor stimulation does not result in phosphorylation phospholamban[54] or troponins.[20]

The $Î±_2$ -adrenergic receptor interacts with a G_i protein that has an inhibitory interaction with adenyl cyclase. Binding of $Î±_2$ -adrenergic agents to the receptor results in inhibition (not stimulation) of adenyl cyclase and to a decrease in the intracellular cAMP.

The $Î±_1$ -adrenergic receptors also are associated with G proteins. However, rather than being associated with G_s proteins and adenyl cyclase, the $Î±_1$ -adrenergic receptors are associated with G_q proteins th are linked to phospholipase C. Binding to the receptor activates the hydrolysis of phosphatidyl inositol 4,5-bisphosphate (PIP_2) to 1,2-diacylglycerol (DAG) and inositol triphosphate (IP_3).[40] The IP_3 , acting a an intracellular messenger, binds to receptors on the SR and initiates the release of calcium ion.[11] DAG activates protein kinase C, which phosphorylates slow calcium channels and other intracellular proteins, an increases the influx of calcium ion into the cell (Fig. 23-8).[41, 44, 87, 88, 102, 108, 111, 127]

Many xenobiotics and antidotal agents interact with G-protein membrane receptors and alter the intracellular cAMP or Ca^{2+} concentration. Î²-Adrenergic antagonist overdose results in decreased stimulation of adeny cyclase by G_S proteins, decreased production of cAMP, decreased activation of the cAMP-dependent kinases, and decreased calcium release (Chap. 59). Similarly, by different mechanisms, calcium channel-blocker overdose results in decreased cytoplasmic calcium concentration (Chap. 5).

Glucagon receptors, which are similar to the Î²-adrenergic receptors, are coupled to G_S proteins and stimulate adenyl cyclase activity.[9 , 29 , 38 , 58 , 117 , 126] Glucagon's activity to increase cAMP is further enhanced by its inhibitory activity on phosphodiesterase

(preventing cAMP breakdown).[71] Phosphodiesterase inhibitors, such as amrinone, milrinone, and enoximone, exert at least some of their inotrop activity by preventing the degradation of cAMP and enhancing calcium cycling.[59 , 64 , 115 , 120] In a canine model of propranolol poisoning, amrinone significantly increased inotropy, stroke volume, and cardiac output.[64]

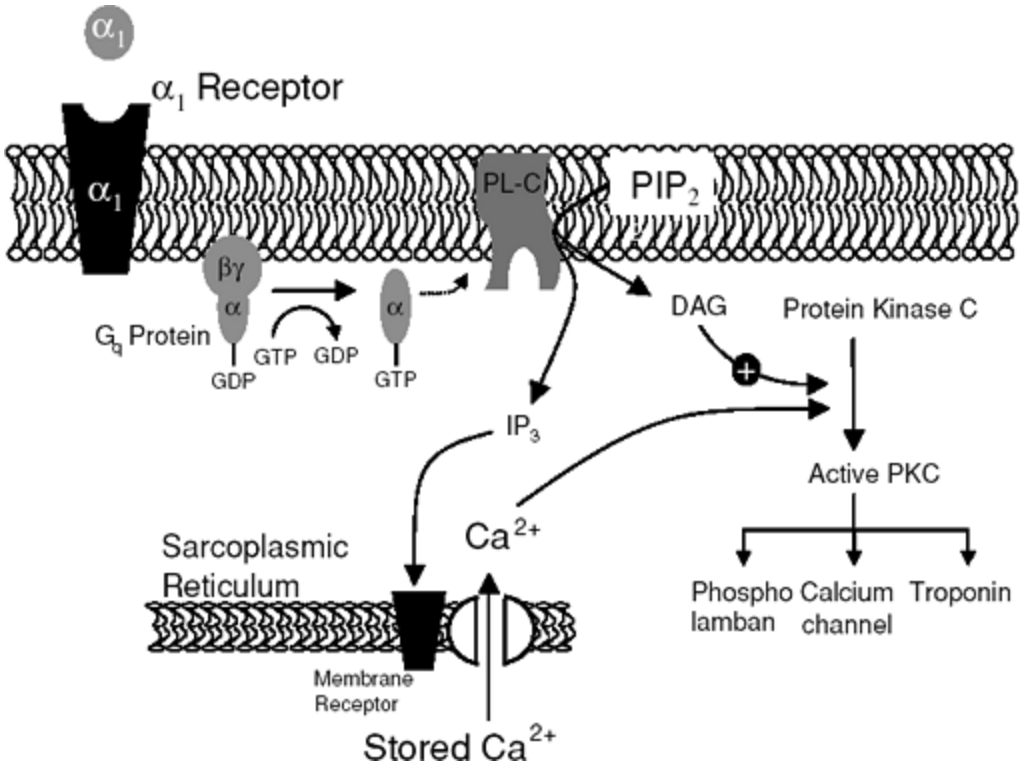

Figure 23-8. Binding of the Î± agonist to the Î±$_1$ receptor causes the G_q protein to release bound GDP and to bind GTP to activate the Î± subunit. This activates phospholipase C (PL-C) to catalyze the hydrolysis of phosphatidylinositol to 4,5-bisphosphate (PIP_2) to produce 1,2-diacylglycerol (DAG) and inositol triphosphate (IP_3). IP_3 interacts with a membrane receptor on the sarcoplasmic reticulum to enhance release of calcium from the cellular stores. The calcium and DAG interact with prote kinase C (PKC) to activate the enzyme. PKC phosphorylates and changes the activity of various cellular proteins (see text).

Hemodynamic effects of Xenobiotics

Xenobiotics that act directly on the cardiovascular or nervous system ma cause a characteristic alteration of blood pressure, heart rate (ie, chronotropy), and cardiac rhythm. Recognizing these patterns (toxic syndromes or â€œtoxidromesâ€•) and understanding their etiology allow for specific, rather than empiric, therapy.

Blood Pressure Abnormalities

Blood pressure is dependent upon normal cardiac and vascular function. The blood pressure (BP) is directly related to the heart rate (HR), the stroke volume (SV), and the systemic vascular resistance (SVR): BP = HR Ã— SV Ã— SVR. The systolic component of the blood pressure measurement is a reflection of the inotropic state of the myocardium, whereas the diastolic component reflects the vascular tone. It is important, as described below, to consider both components of the blood pressure, because the many compensatory mechanisms within the cardiovascular system produce recognizable patterns of blood pressure alteration.

Many xenobiotics affect blood pressure by modulation of the normal chemical interactions at the postganglionic sympathetic neurons. The interaction between these nerve endings and the receptors on vascular and cardiac smooth muscle largely determines the patient's blood pressure. Xenobiotics may initiate complex interactions at this postganglionic neuron (Table 23-6) that results in hypotension or hypertension.

Hypertension Caused by Xenobiotics

Hypertension may be the result of an increase in either inotropy or vascular resistance or both. For example, stimulation of the $\hat{I}\pm_1$ -adrenergic receptor causes hypertension through vasoconstriction, and stimulation of the $\hat{I}^2_1$ -receptor causes hypertension through enhanced myocardial contractility (Table 23-6).

Because of the functional overlap of most sympathomimetics, physical examination alone seldom identifies the specific causative agent in any toxic exposure. However, often a clinical constellation of signs and symptoms can be identified that is associated with this general class. For example, patients who ingest sympathomimetic amines such as cocaine or amphetamines typically have central nervous system stimulation. The presence of lethargy or coma in a patient suspected of a cocaine or

amphetamine overdose should suggest other possible diagnoses, includin mixed overdose, metabolic disorders, a postictal state, or central nervous system infection or hemorrhage.

The hemodynamic results of an overdose depend on the specific agent ingested and the relative action on the various types of Î²-adrenergic receptors (see Table 23-5). The pattern of blood pressure elevation is sometimes helpful in determining the specific class of sympathomimetic ingested. For example, nonselective Î²-adrenergic agonists (those that agonize at both $Î²_1$ and $Î²_2$) produce $Î²_1$ -mediated systolic hypertension (through inotropic effects) with $Î²_2$ -mediated vascular vasodilatation and diastolic hypotension. This results in a widened pulse pressure, which is the numerical difference between the systolic and diastolic pressures.

Hypertensive effects mediated by Î±-adrenergic receptor interaction

- Direct Î±-receptor agonists
  - Clonidine[a]
  - Epinephrine
  - Ergotamines
  - Methoxamine
  - Norepinephrine
  - Phenylephrine
  - Tetrahydrozoline
- Indirect-acting agonists
  - Amphetamines
  - Cocaine
  - Dexfenfluramine
  - Monoamine oxidase inhibitors
  - Phencyclidine
  - Yohimbine
- Direct- and indirect-acting agonists
  - Dopamine
  - Ephedrine
  - Metaraminol

Naphazoline
Oxymetazoline
Phenylpropanolamine
Pseudoephedrine

Hypertensive effects not mediated by Î±-adrenergic receptor interaction

Î²-Adrenergic receptor agonists[b]
Nonselective
Isoproterenol
Cholinergics[a]
Corticosteroids
Nicotine[a]
Vasopressin

[a] These may cause transient hypertension followed by hypotension.
[b] These can also cause hypotension.

TABLE 23-6. Xenobiotics that Commonly Cause Hypertension

$Î²_1$ -Adrenergic receptors cause increased inotropy and chronotropy, whereas $Î²_2$ -adrenergic receptors mediate vasodilation.[55] This suggests that, among Î²-adrenergic agonists, only those with a predominant $Î²_1$ -adrenergic effect cause hypertension. However, 10â€“50% of the heart's Î²-adrenergic receptors may be of the $Î²_2$ -adrenergic subtype.[13, 14, 16, 82, 128] In overdose, the relative specificity of the agents no longer is apparent, so even relatively selective $Î²_2$ -adrenergic agonists may cause increased inotropy and chronotropy. The resulting blood pressure depend on the relative physiologic balance between inotropy and vasodilation. Norepinephrine is primarily an $Î±_1$ - and Î²-adrenergic agonist and profound hypertension is the primary hemodynamic toxic effect. This relates to the effects of norepinephrine as both a positive inotrope ($Î²_1$), and a vasoconstrictor ($Î±_1$).

Hypotension Caused by Xenobiotics

An extremely large number of xenobiotics are reported to cause

hypotension. However, the hypotension often is not a direct action of the xenobiotic. Rather, the cause of hypotension is coexisting hypoxia, acidosis, anaphylaxis, volume depletion, or dysrhythmias. The terminal event in any patient with massive poisoning may be cardiovascular collapse and hypotension.

Typically, hypotension in adults is arbitrarily defined as a systolic blood pressure of less than 90 mm Hg. However, this is not an adequate clinical parameter. Young children and adults with a small body habitus may have a normal systolic pressure less than 90 mm Hg (Chap. 3). Patients with hypothermia have decreased metabolic demands, and a lower blood pressure may be considered â€œnormalâ€•

for these patients. Most importantly, patients with long-standing hypertension may have inadequate tissue perfusion even with systolic pressures greater than 90 mm Hg. The cerebral arterioles constrict or dilate to maintain a relatively constant cerebrovascular blood flow despite changes in the peripheral blood pressure. Chronically hypertensive patients lose this autoregulatory response as a consequence of atherosclerotic disease, arteriolar hypertrophy, or arteriolar smooth muscle constriction. These narrowed arterioles may require a higher peripheral blood pressure to properly perfuse the brain. Because the tolerable blood pressure shifts upward in chronically hypertensive patient they may manifest the clinical findings of hypotension at blood pressures in the â€œnormalâ€• range.

Hypotension is best clinically defined as a blood pressure that is inadequate to perfuse tissues. The clinical assessment of tissue perfusion is based on the vital signs, skin color, capillary refill, mental status, urine output and concentration, and acidâ€“base balance. However, if a xenobiotic directly affects one or more of these clinical parameters, the clinical assessment of volume and hemodynamic status may be difficult. Measurement of central venous pressure is beneficial in the early treatment of the sepsis syndrome,[89 , 90 and 91] and most likely would be beneficial in the treatment of other potentially hypotensive states, including that occurring in poisoned patients. Cardiac filling pressure,

cardiac output, systemic vascular resistance, and precise arterial pressures may be necessary in critically ill patients with severe poisoning

Poor tissue perfusion may result from hypovolemia, decreased peripheral vascular resistance, myocardial depression, or a dysrhythmia that reduce the cardiac output. A single xenobiotic may exert several effects on the hemodynamic system. Appropriate treatment of the hypotension requires an understanding of the pathophysiologic consequences of the xenobiotic and the resultant hemodynamic derangement.

A common etiology of hypotension in a poisoned patient is intravascular volume depletion. Intravascular volume may decrease due to gastrointestinal, urinary, or insensible losses, and fluid may redistribute from the intravascular space into the intracellular, interstitial, pleural, or peritoneal spaces. Xenobiotics can cause significant intravascular volume depletion through all of these mechanisms.

Hypotension may also be caused by xenobiotics that affect the venous tone. These xenobiotics increase venous capacitance, decrease the centra venous pressure, and result in a relative hypovolemia. The effects may b mediated via central effects on the sympathetic nervous system or direct effects on the peripheral vasculature. Sedative-hypnotics and central Î±$_2$ adrenergic agonists (eg, clonidine) decrease the central sympathetic outflow and may result in hypotension. Other xenobiotics directly block peripheral Î±$_1$ -adrenergic receptors or stimulate Î²$_2$ -adrenergic recepto on the blood vessels to produce vascular smooth muscle relaxation, venodilation, and hypotension. Tricyclic antidepressant agents, phenothiazines, theophylline, and cocaine may deplete catecholamines in the presynaptic nerve endings with resultant hypotension.

Assessment of Volume Status in the Poisoned Patient

Assessment of volume status may be particularly difficult in the poisoned patient because of functional alterations in the patient's autonomic nervous system and the pharmacologic effects of the xenobiotic. For

example, the usual signs of dehydration, such as dry mucous membranes dry skin, low blood pressure, tachycardia, narrowed pulse pressure, clouded sensorium, and decreased urine output, can be mimicked by a number of xenobiotics, including tricyclic antidepressants. Moreover, hypovolemic patients may present with diaphoresis, flushed skin, hypertension, bradycardia, or increased urine output after the exposure t a cholinergic agent such as an organic phosphorus compound. In most cases, clinical assessment of central venous pressures and neck vein distension[123] or the hemodynamic response to a fluid bolus can assist in the determination of

the patient's volume status. A central venous or pulmonary artery pressure catheter may be required in some critically ill patients.

Bradycardia
Î±2 -Adrenergic agonists
Î²-Adrenergic antagonists
Digoxin
Opioids
Calcium channel blockers
Plant toxins
Sedative-hypnotics
Cholinergics
  Aconitine
Vancomycin
Digoxin
Magnesium (severe)
Propafenone
Sotalol
  Andromedotoxin
  Veratrine
Propafenone
Propoxyphene
Sotalol
Tachycardia

Angiotensin-converting enzyme inhibitors
Anticholinergics
Anticholinergics
Antidysrhythmics
Antidysrhythmics
Arterial dilators
Antihistamines
Antihistamines
Belladonna alkaloids
Cocaine
Arsenic
Bupropion
Cyclic antidepressants
Chloral hydrate
Cocaine
Phenothiazines
Cocaine
Disulfiram
Quinine/chloroquine
Cyclic antidepressants
Diuretics
Methylxanthines
Iron
Noncyclic antidepressants
Noncyclic antidepressants
Phenothiazines
Yohimbine
Sympathomimetics

	Characteristic ECG Abnormalities		
Heart Rate	No Change	Heart Block or Prolonged Intervals	Dysrhythmia

TABLE 23-7. Heart Rate and ECG Abnormalities of Xenobiotics that Cause Hypotension

Additional information about the adequacy of the patient's volume status may be obtained by orthostatic vital sign testing. Even with a 30% or greater volume loss, the supine blood pressure may remain normal in young, previously healthy patients. Normally, the cardiovascular system responds to sitting or standing with vasoconstriction and a slight increase in heart rate. Patients with hypovolemia are unable to maintain adequate intravascular pressure when upright and have either an exaggerated refle increase in heart rate or a drop in blood pressure (ie, orthostasis).

A variety of xenobiotics can produce orthostatic blood pressure changes (see Table 23-7).[65 , 122] Volume depletion is the most common cause of xenobiotic-induced orthostatic vital sign changes. However, xenobiotics may mimic orthostatic vital sign changes. For instance, Î±$_1$ -adrenergic antagonists may prevent an adequate vasoconstrictor response or may block the normal slight heart rate increase, and result in positive orthostatic vital sign testing. In these cases, cardiac output and blood pressure decrease when the patient is upright.

Identification of the specific xenobiotic causing hypotension requires the integration of a detailed history, complete physical examination, and laboratory studies. Often the identification of the specific xenobiotic responsible for hypotension is based on other physical findings associated with the xenobiotic or recognition of a specific toxic syndrome. Some toxins that produce hypotension also exert specific cardiac effects that ca help to identify them as the causative xenobiotic (Table 23-8). Various medications and xenobiotics can be separated into groups depending on their effects on the heart rate and possible effects on the ECG. The presence of cardiac conduction abnormalities or dysrhythmias could suggest a particular class or group of medications. Similarly, the absence of specific pulse or ECG changes may reduce the likelihood

of a particular xenobiotic as the cause for hypotension (although not completely eliminating the possibility). Although Table 23-7 lists common ECG manifestations associated with particular xenobiotics, individual xenobiotics in specific cases may demonstrate different heart rate or ECG findings.

Antianginals
- Î²-Adrenergic antagonists
- Calcium channel blockers
- Nitrates

Antidepressants
- Cyclic
- MAO inhibitors

Antihypertensives
- Angiotensin-converting enzyme inhibitors
- Angiotensin receptor antagonists
- Central $\hat{I}\pm_1$ -adrenergic agonists
  - Clonidine
  - Guanabenz
  - Guanfacine
  - Methyldopa

Antiparkinsons
- Bromocriptine
- L-Dopa
- Pergolide mesylate

Antipsychotics
- Butyrophenones
- Phenothiazines

CNS depressants
- Ethanol
- Opioids
- Sedative-hypnotics

Diuretics
- Loop diuretics
- Thiazides

Ganglionic blockers
Miscellaneous
Reserpine
Peripheral Î±-adrenergic antagonists
Phenoxybenzamine
Prazosin
Trimethaphan
Vasodilators
Hydralazine

TABLE 23-8. Xenobiotics that Cause Orthostatic Hypotension

History
New-onset, concomitant seizure
Gastrointestinal disturbances (colicky pain, nausea, vomiting, diarrhea)
Prior ingestion of medications (consider possibility that the container is mislabeled or misidentified)
Depression (even if patient denies ingestion)
Suspected myocardial ischemia in patient younger than 35 years old
Past medical history
Treatment with *any* cardiac medications (especially antidysrhythmics or digoxin)
History of psychiatric illness, asthma, or hypertension
History of drug use or abuse
Physical examination and vital signs
Heart rate
Sinus tachycardia with rate >130 beat/min
Sinus tachycardia without apparent identified cause
Sinus bradycardia
Respiratory rate
Any unexplained depression or elevation in rate
Temperature
Elevation especially if >106Â°F (>41.1Â°C)

- Hypothermia
- Dissociation between typically paired changes, for example:
  - Hypotension and bradycardia (tachycardia expected)
  - Fever and dry skin (diaphoresis expected)
  - Hypertension and tachycardia (reflex bradycardia anticipated)
  - Depressed mental status and tachypnea (decreased respirations common)
- Relatively rapid changes in vital signs
  - Initial hypertension becomes hypotension
  - Increasing sinus tachycardia or hypertension

General

- Alteration in consciousness, such as depressed mental status, confusion or agitation
- Findings usually not associated with cardiovascular diseases
  - Ataxia, bullae, dry mucous membranes, lacrimation, miosis or mydriasis nystagmus, unusual odor, flushed skin, salivation, tinnitus, tremor, visual disturbances
- Findings consistent with a toxic syndrome
  - Especially findings consistent with anticholinergics, sympathomimetics or sedative hypnotics

Laboratory tests

- Any unexpected or unexplained laboratory result, especially:
  - Metabolic acidosis
  - Respiratory alkalosis
  - Hypokalemia or hyperkalemia

TABLE 23-9. Clues that an Unanticipated Xenobiotic Might be the Cause of Hemodynamic Compromise or Dysrhythmia

Summary

Xenobiotics can interact with the heart or blood vessels to produce hypotension or hypertension, congestive heart failure, dysrhythmias (including bradycardias and tachycardias), or cardiac conduction delays.

These toxic effects often occur through interactions with specific receptor or with the ion channels in the cell membrane. Disruption of the normal cellular regulation of metabolic processes or of the cellular ionic status leads to the cardiovascular and hemodynamic compromise.

The occurrence of these abnormalities, individually or in combination, might suggest a particular xenobiotic or class of xenobiotics as the etiologic agent (toxic syndrome or â€œtoxidromeâ€•) and might dictate initial treatment. Often, however, significant abnormalities in vital signs must be corrected before the xenobiotic is identified. By understanding both the pharmacology of the xenobiotic and the physiology of the heart and vasculature, appropriate treatment can be delivered.

Definitive care of the poisoned patient with hemodynamic compromise or dysrhythmia begins with recognition that a xenobiotic may be present. Infectious, cardiovascular disease, and other metabolic disorders must always be considered; however, the toxic effects of xenobiotics must be included in the differential diagnosis. A variety of clinical clues, when present, should heighten the physician's suspicion that a xenobiotic effec may be responsible for the hemodynamic or dysrhythmic problem. Table 23-9 identifies some of these clues.

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Chapter 24
Hematologic Principles

Marco L.A. Sivilotti

Blood is rightfully considered the vital fluid, as every organ system depends on the normal function of blood. Blood delivers oxygen and other essential substances throughout the body, removes waste products of metabolism, transports hormones from their origin to site of action, signals and defends against threatened infection, promotes healing via the inflammatory response and maintains the vascular integrity of the circulatory system. It also contains the central compartment of classical pharmacokinetics, and thereby comes into direct contact with virtually every toxin that acts on the organism.[155] The ease and frequency with which blood is assayed, its central role in functions vital to the organism, and the ability to analyze its characteristics, at first by light microscopy and more recently with molecular techniques, have enabled a detailed understanding of blood that has advanced the frontier of molecular medicine.

In addition to transporting xenobiotics throughout the body, blood and the blood-forming organs can at times be directly affected by these same xenobiotics. For example, decreased blood cell

production, increased blood cell destruction, alteration of hemoglobin, and impairment of coagulation can all result from exposure to a large variety of xenobiotics. The response in many cases depends on the nature and quantity of the xenobiotic, and the capacity of the system to respond to the insult. In other cases, no clear and predictable doseâ€“response relationship can be determined, especially when an interaction with the heterogeneous immune system is involved. These latter reactions are often termed idiosyncratic, reflecting an incomplete understanding of their causative mechanism. In general, such reactions can often be reclassified when advancing knowledge identifies the characteristics which render the individual vulnerable. For example, the observation of hemoglobinuria following primaquine administration to healthy, African American military recruits led to the recognition of the importance of glucose-6-phosphate dehydrogenase activity in protecting the erythrocyte from oxidative injury.

Hematopoiesis

Hematopoiesis is the development of the cellular elements of blood. The majority of the cells of the blood system may be classified as either lymphoid (B, T, and natural-killer lymphocytes) or myeloid (erythrocytes, megakaryocytes, granulocytes, and macrophages).[123] All of these cells are descended from a small common pool of totipotent cells called hematopoietic stem cells.[176] Indeed, the study of this process and its regulation has provided fundamental insight into embryogenesis, stem cell pluripotency, and complex cell-to-cell signaling and interaction.

Bone Marrow

Marrow spaces within bone begin to form in humans at about the 5th fetal month and become the sole site of granulocyte and megakaryocyte proliferation. Erythropoiesis moves from the liver to the marrow by the end of the last trimester. At birth, the red marrow

can be found in the fingers, toes, ribs, vertebrae, pelvis, long bones, and cranium. By adulthood, the same volume of hematopoietic marrow is located in the sternum, ribs, pelvis, and scapulae, and represents the normal site for blood cell formation. So-called extramedullary hematopoiesis in the liver and spleen may reemerge as a compensatory mechanism under severe stimulation.

The arterial blood supply of the bone marrow comes from nutrient arteries, which penetrate the outer cortex and form periosteal capillaries. Blood from these two systems mixes and enters the marrow sinus system, from which blood drains into the systemic circulation via emissary veins.[98]

In mammals, blood formation takes place in marrow spaces between the venous sinuses. The developing blood cells are closely and systematically related to the sinuses and must traverse the wall of the sinus before entering the general circulation.[123] The sinus wall is composed of a layer of endothelial cells, a thin basement membrane, and a layer of adventitial reticular cells that form the outer layer and the cell layer in closest approximation to the hematopoietic spaces.[97] A central arteriole runs along the hematopoietic spaces. Developing cell lines cluster into territories specific to their lineage. Granulopoietic cells are distributed along the walls of the central arteriole. Erythropoietic cells are distributed in a continuous network of cords around the sinus wall.[123] Megakaryocytes exist in close proximity to the surface of the sinus wall.[97] Erythrocytes are found closely associated with macrophages whose function may be to phagocytose the nuclear material extruded from red cells and megakaryocytes in the final stages of development.[98] Mature cells apparently enter the systemic circulation by passing through the cytoplasm of the endothelial cells.[185]

Progenitor cells must interact with a supportive microenvironment to sustain hematopoiesis. The hematopoietic stroma consists of macrophages, fibroblasts, adipocytes, and endothelial cells.[98] The extracellular matrix is composed of various fibrous proteins,

glycoproteins, and proteoglycans, which are produced by the stromal

cells and include collagen, fibronectin, laminin, hemonectin, thrombospondin, and proteoglycans.[97] Hematopoietic progenitor cells have receptors that bind to particular matrix molecules. The extracellular matrix provides a structural network to which the progenitors are anchored. As the cells approach maturity, they lose their surface receptors, presumptively allowing them to leave the hematopoietic space and enter the venous sinuses. Blood cell release depends upon the development of a pressure gradient that drives mature cells through channels in endothelial cell cytoplasm.[185] Pressure within the marrow is increased by erythropoietin and by granulocyte colony-stimulating factor (G-CSF).[74,75]

Stem Cells

A stem cell is capable of self-renewal as well as differentiating into a specific cell type. The pluripotent hematopoietic stem cell can therefore continuously replicate, while awaiting the appropriate signal to differentiate into either a myeloid stem cell (for myelo-, erythro-, mono-, or megakaryopoiesis) or a lymphoid stem cell (for lymphopoiesis of T, B, null, and natural-killer cells) (Fig. 24-1). The stem cell pool represents approximately 1 in 100,000 of the nucleated cells of the bone marrow, and the majority of these stem cells are usually quiescent. Nevertheless, these relatively few cells are directly responsible for the estimated 3 billion red cells, 2.5 billion platelets, and 1.5 billion granulocytes per kilogram of body weight produced each day. In response to hemolysis or infection, substantially larger numbers of blood cells can be produced.[123,125]

Hematopoietic stem cells are found in umbilical cord blood, bone marrow, and peripheral blood.[58] With subsequent division and maturation, these cells progressively display the antigenic, biochemical, and morphologic features characteristic of mature cells of the appropriate lineages, and lose their capacity for self-renewal.

Multiple steps are involved in the commitment of less-differentiated cells to more mature cell lines. The final steps in the maturation of erythrocytes alone, for example, involve extensive remodeling, the restructuring of cellular membranes, the accumulation of hemoglobin, and the loss of nuclei and organelles. In the case of granulocytes, granules containing proteolytic enzymes are formed in cell cytoplasm, and the nucleus condenses to form the multilobulated nucleus of the mature cell. Megakaryocyte cytoplasm demarcates into units that are eventually split off as platelets. This traditional hierarchical model has been challenged recently by the observation that hematopoietic stem cells can also differentiate into nonblood tissues, including tissues originating from the endo- and ectoderm, with profound implications for organ homeostasis and repair throughout the organism.[88,96]

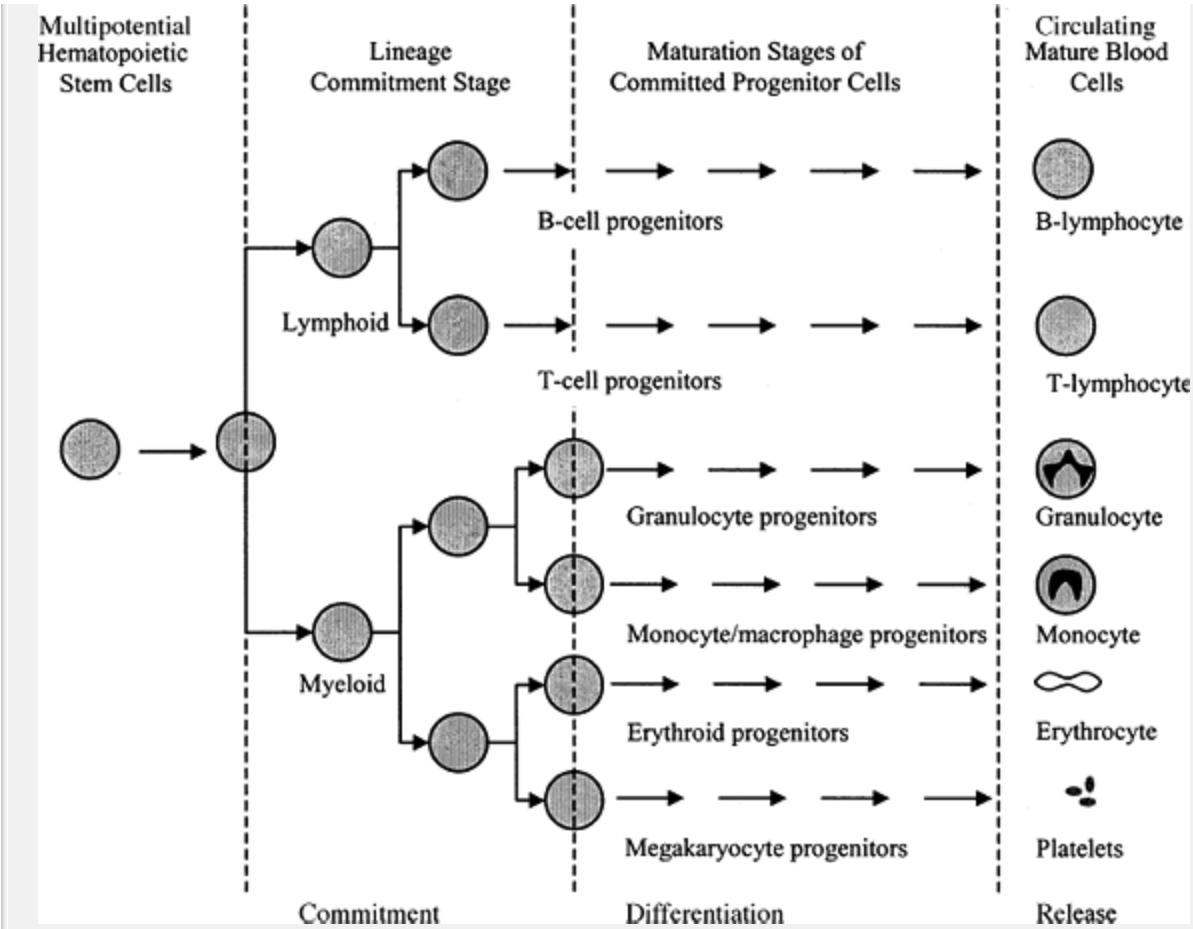

Figure 24-1. Principles of hematopoiesis. Commitment refers to the apparent inability of progenitor cells to generate hematopoietic stem cells. Following differentiation, the various mature blood cells are released into the circulation.

Cytokines

Cytokines are soluble mediators secreted by cells for cell-to-cell communication. Initially termed growth factors, it is now recognized that not all cytokines are growth factors. Cytokines promote or inhibit the differentiation, proliferation, and trafficking of blood cells and their precursors. Importantly, they can also inhibit apoptosis,

and their absence therefore results in the self-destruction of unwanted cells. They include growth factors or colony-stimulating factors (CSFs), interleukins, monokines, interferons, and chemokines. At baseline, these act in concert to maintain normal blood counts. In response to antigens or other stimuli, cytokines are released to combat perceived infection. Recombinant cytokines are being developed for therapeutic use in immunocompromised patients, transplant recipients, sepsis, and cancer. They have also been used in clinical toxicology for the treatment of colchicine and podophyllum toxicity.[37,64]

Growth factors are glycoproteins necessary for the differentiation and maturation of individual or multiple cell lines.[74,83,84,116] They fall into two families based on their target receptors. The ligands of the cytokine receptor family include growth hormone, interleukin-2 (IL-2), macrophage colony-stimulating factor-1 (CSF-1), granulocyte-macrophage colony-stimulating factor (GM-CSF), Î³-interferon, and granulocyte colony-stimulating factor (G-CSF), to name a few. The second group, the tyrosine kinase family, includes Kit ligand and insulinlike growth factor-I receptor (IGF-1R), a member of the insulin family. The complete development of all of the mature blood cells from stem cells or multilineage progenitors requires the action of growth factors, either alone or in combination, for successful differentiation and final maturation.

Cell Surface Antigens

With the use of monoclonal antibody technology, cell surface antigens can be identified and are used increasingly to characterize cell types. The cluster designation (CD) nomenclature is used, and more than 160 types have been classified.[192] For example, the CD34 antigen is a 115-kilodalton (kDa) highly glycosylated transmembrane protein that is selectively expressed by primitive multipotent hematopoietic stem cells shortly after activation, but is absent from mature T and B lymphocytes.[161] Cells expressing the CD34 antigen

can repopulate all hematopoietic cell lines, although more primitive pluripotent cells lacking this antigen have also been identified.[45] Combined with flow cytometry, the ability to subtype blood cells phenotypically has transformed the approach to the leukemias, autoimmune disease, transplantation medicine and thromboembolic disease.

Aplastic Anemia

Aplastic anemia is characterized by pancytopenia on peripheral smear, a hypocellular marrow, and delayed plasma iron clearance.

Severe aplastic anemia denotes a granulocyte count of less than 500 cells/mm^3, a platelet count of less than 20,000/mm^3, and a reticulocyte count of less than 1% after correction for anemia. Following acute insult and depletion of extracirculatory reserves, cell line counts fall at a rate inversely proportional to their life span: granulocytes (half-life 6â€“12 hours in the circulation) disappear within days, platelets (life span of 7â€“10 days) decline by half in about 5 days, erythrocytes (normal life span 120 days) take up to 2 months before being reduced to 50% of their baseline counts. Approximately 1000 new cases of aplastic anemia are diagnosed yearly in the United States. The incidence is much higher in Asia, especially in individuals between the ages of 10 and 40 years, presumably because of the greater prevalence of hepatitis. Aplastic anemia may be inborn (as in Fanconi anemia) or acquired. Specific etiologies of acquired aplastic anemia include certain xenobiotics (Table 24-1).[25,189] Although the vast majority of acquired cases are ascribed to medications, the pathogenesis in most of these cases is idiosyncratic, precluding a reliable predictive test.

Generally speaking, the mechanism is believed to involve the acquisition of intrinsic defects of the hematopoietic stem cells, and abnormal humoral and cellular immune control of hematopoiesis. Because approximately 10% of the pluripotent stem cells are active

at baseline, it can be assumed that well over 90% of these stem cells must be affected before pancytopenia develops.[190] Allogenic stem cell transplantation is used for patients with a suitably matched donor, usually identified in large registries. Otherwise, immunosuppressive therapy is needed to allow recovery of hematopoiesis.

Xenobiotic-Induced Immune-Mediated Causes of Aplastic Anemia

It is now believed that the majority of cases of aplastic anemia previously determined to be idiosyncratic are caused by immunologically mediated tissue specific destruction of CD34+ hematopoietic progenitor cells.[190,191] Following an exposure to an inciting antigen, T cells and cytokines act destructively on stem cells, reducing their numbers so that normal levels of circulating mature leukocytes, erythrocytes and platelets fall to dangerously low levels.[192] Toxicity may be mediated through intermediate metabolites that bind covalently to protein and DNA. These reactive metabolites are formed and degraded by complex metabolic pathways; genetic variation in the enzyme systems involved may contribute to the rarity of idiosyncratic drug reactions.[189] Human leukocyte antigen (HLA) DR2 is overrepresented among European and American patients with aplastic anemia. Clozapine-induced agranulocytosis is associated with the HLA B38, DR4, and DQ3 haplotypes, underlining a genetic predisposition to acquired aplastic anemia.[127]

TABLE 24-1. Xenobiotics Associated with Aplastic Anemia

Analgesics
Acetaminophen
Acetylsalicylic acid

- Diclofenac
- Dipyrone
- Indomethacin
- Phenylbutazone

Antibiotics

- Adriamycin[a]
- Azidothymidine
- Chloramphenicol
- Daunorubicin[a]
- Mefloquine
- Penicillin

Anticonvulsants

- Carbamazepine
- Felbamate

Antidysrhythmics

- Tocainide

Antihistamines

- Cimetidine

Antiplatelets

- Ticlopidine
- Chlorpromazine
- Clozapine

Antirheumatics

- Gold salts
- Methotrexate
- D-Penicillamine

Antithyroids

- Propylthiouracil

Diuretics

- Acetazolamide
- Metolazone

Occupational

- Arsenic[a]
- Benzene[a]

Cadmium
Copper
Pesticides
Antineoplastics[a]
Antimetabolites
Colchicine
Mustards
Vinblastine
Vincristine
Radiation[a]
[a] Denotes agents that predictably result in bone marrow aplasia following a sufficiently large exposure.

The peripheral blood and bone marrow of patients with aplastic anemia produces a soluble factor identified as Î³-interferon (INF-Î³) that inhibits hematopoiesis; normal lymphocytes can be stimulated to produce the same factor.[193] Both the blood and bone marrow of patients with aplastic anemia contain increased numbers of activated cytotoxic lymphocytes. The numbers and activity of activated cells decrease with immunosuppressive therapy.[92,137] The T cells of patients with aplastic anemia overproduce INF-Î³ and tumor necrosis factor (TNF).[179] Both cytokines are capable of suppressing proliferating early and late hematopoietic progenitor and stem cells.[157] In addition to the inhibition of the mitotic cycle, it is likely that the pathology includes the induction of programmed cell death through the induced expression (by TNF and INF-Î³) of the Fas receptor on CD34+ progenitor cells. Fas (CD95) is a receptor molecule that mediates signal transduction for apoptosis, or programmed cell death. Apoptosis is a morphologic pattern of genetically programmed cell death marked by cell shrinkage, condensation of chromatin, the formation of cytoplasmic blebs, and the fragmentation of the cell into membrane bound bodies that are

eliminated by phagocytosis. It is a physiologic mechanism for cell deletion in the regulation of cell populations. Fas is a member of the TNF receptor family. Engagement of the Fas receptor by another cell surface molecule triggers apoptosis in the Fas-expressing cell. The initial focus of immune attack may be limited. As more tissue is damaged, the exposure of previously hidden cellular antigens increases the range of immune targets in a process known as antigenic spread.[41] In normal individuals, Fas is rarely expressed on CD34+ cells. In patients with aplastic anemia, CD34+ bone marrow cells express Fas receptors to a much greater extent, resulting in anti-Fas antibody-mediated inhibition of hematopoiesis.[101,124] The genes for INF-Î³ and TNF are overexpressed in the marrow and blood cells of patients with aplastic anemia. The expression of Fas is also associated with infection by viruses implicated in marrow suppression such as the human immunodeficiency virus (HIV) and hepatitis C.[128] INF-Î³ expression is eliminated in patients successfully treated with immunosuppressive therapy, usually with antithymocyte globulin, cyclosporine, or cyclophosphamide. INF-Î³ again becomes detectable in those patients who have relapsed following therapy. It is not detectable in patients with Fanconi anemia.[128]

The Erythron

The erythron can be considered to be a single tissue, defined as the entire mass of erythroid cells beginning with the first committed progenitor cell and ending with the mature circulating

erythrocyte. This functional definition emphasizes the distributed nature yet integrated regulation of the erythron, both in health and disease. Homeostasis of the erythron is primarily maintained by the equilibrium between stimulation via the hormone erythropoietin, and apoptosis controlled by two receptors, Fas and FasL, expressed on the membranes of erythroid precursors. At the other extreme, erythrocytes are culled from the circulation at the end of their life span, primarily by the action of the spleen. Erythrocytes less able to

negotiate the narrow red pulp passages are phagocytosed by macrophages, thereby minimizing both entrapment in the capillary beds of the microvasculature, and spillage of intracellular contents into the intravascular circulation.

The primary function of the erythron is to transport molecular oxygen throughout the organism. To accomplish this, adequate numbers of circulating erythrocytes must be maintained. These erythrocytes must be able to preserve their structure and flexibility to circuit repeatedly through the microcirculation and to resist oxidant stress accumulated during their life span.[145] It is recognized that interactions between oxyhemoglobin and nitric oxide are also key to the modulation of vascular tone, potentially matching vasomotor tone to local tissue oxygen demands.[38,58,63,112,153]

Erythropoietin

Erythropoietin (EPO) is a glycoprotein hormone of molecular weight 34,000 daltons that is produced in the epithelial cells lining the peritubular capillaries in the normal kidney. Anemia and hypoxemia stimulate its synthesis.[1,2] EPO receptors are found in human erythroid cells, megakaryocytes, and fetal liver. EPO promotes erythroid differentiation, the mobilization of marrow progenitor cells, and the premature release of marrow reticulocytes.[1] The cell most sensitive to EPO is a cell between the erythroid colony-forming unit (CFU-E) and the proerythroblast.[2] In the absence of EPO, rapid DNA cleavage, in a pattern characteristic of apoptosis, results in erythroid cell death.

The Mature Erythrocyte

The mature erythrocyte (red blood cell) is a highly specialized cell, designed primarily for oxygen transport. Accordingly, it is densely packed with hemoglobin, which constitutes approximately 90% of the dry weight of the erythrocyte, or 30â€“35 g/dL. During maturation,

the erythrocyte loses its nucleus, mitochondria and other organelles, rendering it incapable of synthesizing new protein, replicating, or using the oxygen being transported for oxidative phosphorylation. Its metabolic repertoire is also severely limited, and largely restricted to a few pathways described below under Metabolism. In general, the enzymatic pathways are those required for optimizing oxygen and carbon dioxide exchange, transiting the microcirculation while maintaining cellular integrity and flexibility, and resisting oxidant stress especially on the iron and protein of the cell. The characteristic biconcave discocyte shape is dynamically maintained, allowing an excess of membrane surface to cell volume.[111] This shape both decreases intracellular diffusion distances to the extracellular membrane[95] and allows plastic deformation when squeezing through the microcirculation.[28,154] The shape is the net sum of elastic and electrostatic forces within the membrane, surface tension, and osmotic and hydrostatic pressures. The cell membrane contains globular proteins floating within the phospholipid bilayer. The major blood group antigens are carried on membrane ceramide glycolipids and proteins, particularly glycophorin A and the Rh proteins.[32] Membrane proteins generally serve to maintain the structure of the cell, to transport ions and other substances across the membrane, or to catalyze a limited number of specific chemical reactions for the cell.

Structural Proteins

The cell membrane is coupled to, and interacts dynamically with, the cytoskeleton, allowing changes in cell shape as well as tank treading or rotation of the membrane relative to the cytoplasm. This cytoskeleton consists of a hexagonal lattice of proteins, especially spectrin, actin, and protein 4.1, which interact with ankyrin and band 3 in the membrane to provide a strong but flexible structure to the membrane.[13,90,152] Other essential structural proteins include tropomyosin, tropomodulin, and adducin. Absence or abnormalities of these proteins can result in abnormal erythrocyte shapes such as

spherocytes and elliptocytes.

Transport Proteins

Many specialized transport proteins are embedded in the erythrocyte membrane. These include anion and cation transporters, glucose and urea transporters, and water channels.[172] The erythrocyte membrane is relatively impermeable to ion flux. Band 3 anion-exchange protein plays an important role in the chloride-bicarbonate exchanges that occur as the erythrocyte moves between the lung and tissues. Glucose, the sole source of energy of the erythrocyte, crosses the membrane by facilitated diffusion mediated by a transmembrane glucose transporter. Sodium-potassium adenosine triphosphatase (Na^+-K^+-ATPase) maintains the primary cation gradient by pumping sodium out of the erythrocyte in exchange for potassium.

Membrane-Associated Enzymes

At least 50 membrane-bound or -associated enzymes are known to exist in the human erythrocyte. Acetylcholinesterase is an externally oriented enzyme whose role in the function of the erythrocyte remains obscure.[173] Its function is inhibited by certain xenobiotics, most notably the organic phosphorus insecticides, and can be conveniently assayed as a marker for such exposures.

Metabolism

Without mitochondria and the ability to efficiently generate adenosine triphosphate (ATP) using molecular oxygen, the mature erythrocyte has a severely limited repertoire of intermediary metabolism compared to most mammalian cells. Without the ability to synthesize new enzymes, its metabolic capacity is also limited once its nucleus, ribosomes, and translational apparatus are lost. This capacity, in fact, declines over the lifetime of the cell because of declining enzyme function with time. Fortunately, the metabolic

demands of the erythrocyte are usually modest, but under conditions of stress this capacity can be overwhelmed, especially among senescent cells. The greatest expenditure of energy under physiologic conditions is for the maintenance of transmembrane gradients and for the contraction of cytoskeletal elements. However, oxidant stress can put severe strain on the metabolic reserves of the erythrocyte, and lead ultimately to the destruction of the cell, a process termed hemolysis.

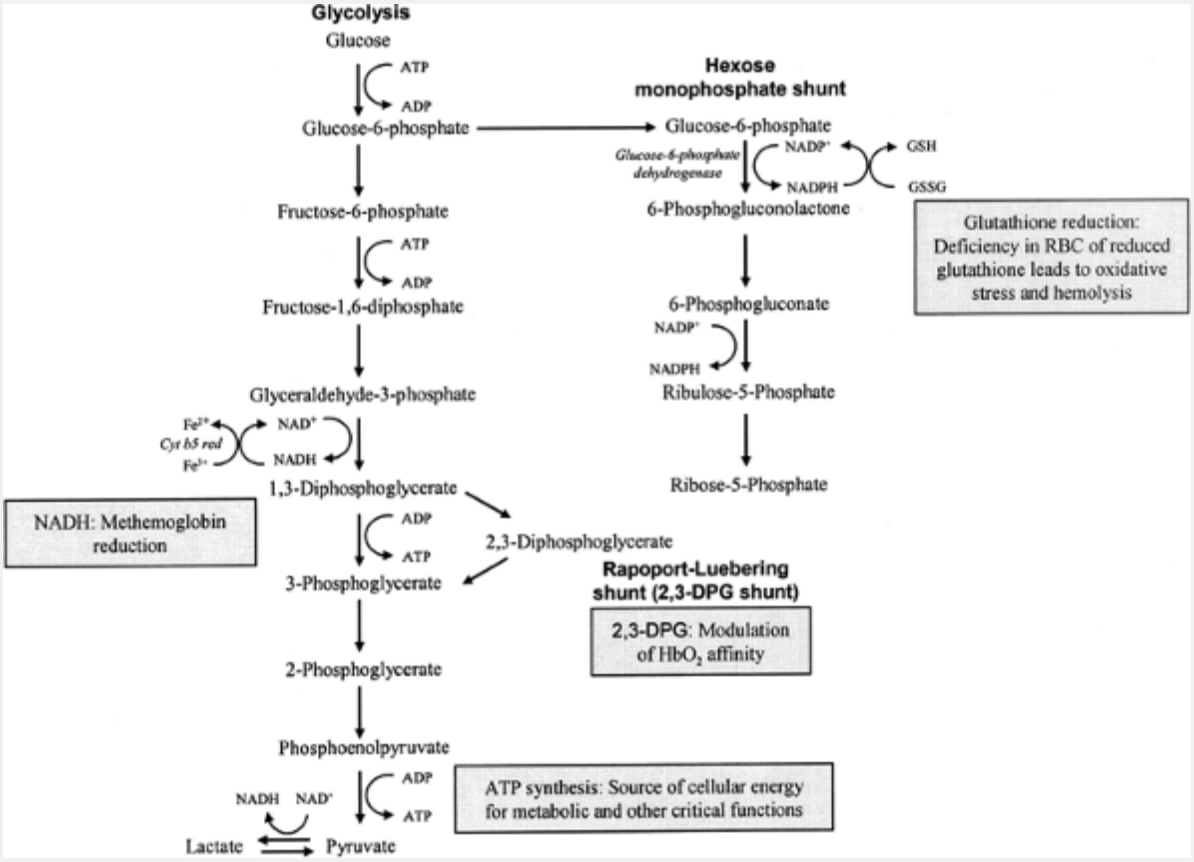

Figure 24-2. Metabolic pathways of the erythrocyte. The main metabolic pathways available to the mature erythrocyte are shown (rectangles). Glucose is imported into the cell, while pyruvate, lactate, and oxidized glutathione (GSSG) are exported. 2,3-DPG = 2,3-Diphosphoglycerate; ADP = adenosine

diphosphate; ATP = adenosine triphosphate; cyt b5 red = cytochrome b5 reductase; G6PD = glucose-6-phosphate dehydrogenase; GSH = reduced glutathione; Hb = hemoglobin; NADH = reduced form of nicotinamide adenine dinucleotide (NAD^+); NADPH = reduced form of nicotinamide adenine dinucleotide phosphate ($NADP^+$); RBC = red blood cell (erythrocyte).

Figure 24-2 illustrates the main metabolic pathways and their purpose. The Embden-Meyerhof glycolysis is the only source of ATP for the erythrocyte, and accounts for approximately 90% of the glucose imported by the cell. The reduced nicotinamide adenine dinucleotide (NADH) generated during glycolysis, which would ordinarily be used for oxidative phosphorylation in cells containing mitochondria, is directed toward the reduction of either methemoglobin to hemoglobin by cytochrome b5 reductase, or of pyruvate to lactate. Both pyruvate and lactate are exported from the cell. During glycolysis, metabolism can be diverted into the Rapoport-Luebering shunt, generating 2,3-bisphosphoglycerate (2,3-BPG, formerly known as 2,3-diphosphoglycerate or 2,3-DPG) in lieu of ATP. 2,3-BPG binds to deoxyhemoglobin to modulate oxygen affinity and allow unloading of oxygen at the capillaries. In response to anemia, altitude, or changes in cellular pH, the activity of the shunt increases, thereby favoring synthesis of 2,3-BPG and increasing oxygen delivery considerably.[33,107] Reduced levels of 2,3-BPG in stored blood are believed to result in impaired oxygen delivery for approximately 12 hours following massive transfusion.[177]

As an alternative to glycolysis, glucose can be directed toward the hexose monophosphate shunt during times of oxidant stress. This pathway results in the generation of reduced nicotinamide adenine dinucleotide phosphate (NADPH), which the erythrocyte uses to maintain reduced glutathione which, in turn, inactivates oxidants and

protects the sulfhydryl groups of hemoglobin and other proteins. The initial, rate-limiting step of this pathway is controlled by glucose-6-phosphate dehydrogenase (G6PD). Accordingly, cells deficient in this enzyme are less able to maintain glutathione in a reduced state, and are vulnerable to irreversible damage under oxidant stress. The consequences of this deficiency are discussed in greater detail below under Glucose-6-Phosphate Dehydrogenase Deficiencies.

The erythrocyte also contains enzymes to synthesize glutathione (Î³-glutamyl-cysteine synthetase and glutathione synthetase), to convert CO_2 to bicarbonate ion (carbonic anhydrase I), to remove

pyrimidines resulting from the degradation of RNA (pyrimidine 5â€²-nucleotidase), to protect against free radicals (catalase, superoxide dismutase, glutathione peroxidase), and to conjugate glutathione to electrophiles (Ï•-*S*-transferase).

Hemoglobin

Hemoglobin, the major constituent of the cytoplasm of the erythrocyte, is a conjugated protein with a molecular weight of 64,500 daltons. One molecule is composed of 4 protein or globin chains, each attached to a prosthetic group called heme. Heme contains an iron molecule complexed at the center of a porphyrin ring. The globin chains are held together by noncovalent electrostatic attraction into a tetrahedral array. Hemoglobin is so efficient at binding and carrying oxygen that it enables blood to transport 100 times as much oxygen as could be carried by plasma alone (Chap. 22). In addition, the capacity of hemoglobin to modulate oxygen binding under different conditions allows adaptation to a wide variety of environments and demands. Three complex and integrated pathways are required for the formation of hemoglobin: globin synthesis, protoporphyrin synthesis, and iron metabolism.

Globin Synthesis

The protein chains of hemoglobin are produced with information from two different genetic loci. The Î±-globin gene cluster spans 30 kb on the short arm of chromosome 16, and codes for 2 identical adult Î±-chain genes, as well as the Î¶-chain, an embryonic globulin. The Î² cluster is 50 kb on chromosome 11, and codes for the two adult globins Î² and Î´, as well as two nearly identical Î³ chains expressed in the fetus and an embryonic globulin Îµ. The expression of genes in each family changes during embryonic, fetal, neonatal, and adult development. Until 8 weeks of intrauterine life, Îµ, Î¶, Î³, and Î± chains are produced and assembled in various combinations in yolk sac-derived erythrocytes. With the shift in erythropoiesis from yolk sac to fetal liver and spleen, embryonic hemoglobin is no longer detectable, and the Î± and Î³ globin chains are paired into fetal hemoglobin (HbF = $Î±_2Î³_2$). Erythrocytes containing HbF have a higher O_2 affinity than does adult hemoglobin, which is important for oxygen transfer across the placenta into the relatively hypoxic uterine environment. Beginning shortly before birth, expression shifts to the Î± and Î² globins, which constitute the predominant adult hemoglobin termed hemoglobin A ($Î±_2Î²_2$). Approximately 2.5% of normal adult hemoglobin is in the form of hemoglobin A_2 ($Î±_2Î´_2$).

The rate of globin synthesis is increased in the presence of heme, and inhibited in its absence.[110] As the globin chains are released from the ribosomes, they spontaneously assemble into Î±Î² dimers, and then into $Î±_2Î²_2$ tetramers. The thalassemias, a group of inherited disorders, result from defective synthesis of one or more of the globin chains. Clinically this results in a hypochromic, microcytic anemia.[60,110]

Heme Synthesis

Heme is the iron complex of protoporphyrin IX. Protoporphyrin IX is a tetramer composed of four porphyrin rings joined in a closed, flat-ring structure. The IX designation refers to the order in which it was synthesized in the laboratory by Hans Fischer. Of the 15 possible

isomers, only protoporphyrin IX occurs in living organisms. Technically, only iron complexes with the iron in the Fe^{2+} state can be called heme, but the term is commonly used to refer to the prosthetic group of metalloproteins such as peroxidase and cytochrome c, whether the iron is in the Fe^{2+} or Fe^{3+} state. The terms â€œhemiglobinâ€• and â€œferrihemoglobinâ€• are synonymous with methemoglobin but rarely used. All animal cells can synthesize heme, with the notable exception of mature erythrocytes.[138] Hemoproteins are involved in a multitude of biologic functions, including oxygen binding (hemoglobin, myoglobin), oxygen metabolism (oxidases, peroxidases, catalases, and hydroxylases), and electron transport (cytochromes).[22,139] Erythroid cells synthesize 85% of total body heme, with the liver synthesizing most of the balance. Hemoglobin is the most abundant hemoprotein, containing 70% of total body iron.[138]

The first step in the synthesis of heme takes place in the mitochondrion and is the condensation of glycine- and succinyl-coenzyme A (CoA) to form Î´-aminolevulinic acid (Î´-ALA) (see Fig. 24-3).[22,110] The formation of Î´-ALA is catalyzed by aminolevulinic acid synthase (ALAS). It is possible that mammals may also synthesize ALA as do plants, namely via the transamination of Î±-ketoglutaric acid, using the mitochondrial enzyme alanine-dioxovalerate aminotransferase. Of the two isoforms of ALAS known to exist, erythroid cells contain the ALAS 2 isoform which resides on the X chromosome. Comparatively more is known about ALAS 1 (chromosome 3), which is derived from hepatic tissue. ALAS 1 activity is induced by many factors, and strongly inhibited by heme in a classical negative feedback fashion.[138] Pyridoxal phosphate (active vitamin B_6) serves as a cofactor to both isoforms of ALAS. The clinical consequences of pyridoxine deficiency may include a hypochromic, microcytic anemia, iron overload, and neurologic impairment. Xenobiotics that increase the rate of synthesis of Î´-ALA may precipitate an inducible porphyric crisis.[40,139] This may occur in hepatocytes through drug-mediated induction in the rate of

transcription of the ALAS 1 gene.[110] The

result is an accumulation of porphyrins, clinically expressed as abdominal pain and neuropsychiatric symptoms.

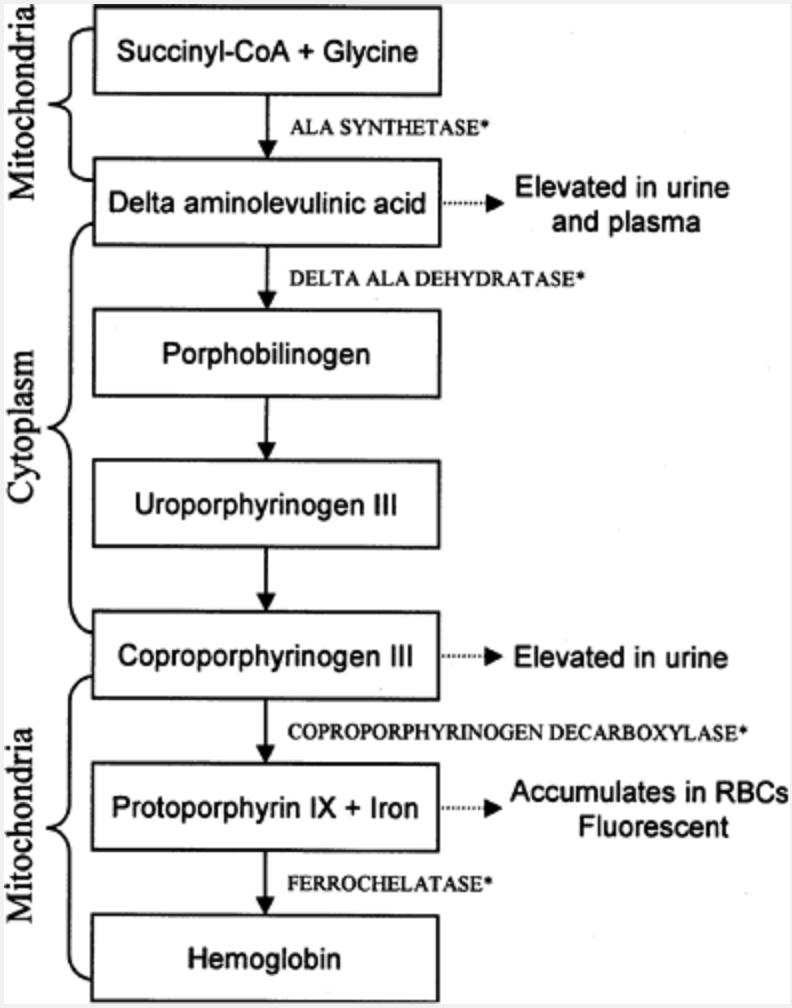

Figure 24-3. The heme synthesis pathway. The enzymatic steps inhibited by lead are marked with an asterisk (*) RBCs = red blood cells.

The next step in the synthesis of hemoglobin is the formation of the

monopyrrole porphobilinogen via the condensation of 2 molecules of ALA. This reaction is catalyzed by ALA dehydratase, and is inhibited by lead (Fig. 24-3). Porphobilinogen is excreted in large quantities by patients with acute intermittent porphyria, coloring the urine a deep red wine color.[22]

The subsequent steps in heme synthesis involve the condensation of 4 molecules of porphobilinogen into a ring, which is transported back into the mitochondrion by an unknown mechanism. The final step is the insertion of iron into protoporphyrin IX, a reaction that is catalyzed by ferrochelatase to form heme. Given that ALAS 2 is constitutively expressed at such high levels in erythroid precursors, this last reaction is the likely site of feedback inhibition of heme and of heme synthesis control in immature erythrocytes.[22,138] Most steps in the heme biosynthetic pathway are inhibited by lead (Fig. 24-3; Chap. 91). ALA dehydratase is the most sensitive, followed by ferrochelatase, coproporphyrinogen oxidase, and porphobilinogen (PBG) deaminase. As a consequence, urinary ALA is greatly increased.

Iron Metabolism

Unless appropriately chelated, free iron not bound by transport or storage proteins can generate harmful oxygen free radicals that damage cellular structures and metabolism (Chaps. 12 and 40).[140] For this reason, it is imperative to bind iron in the circulation to the transfer protein, transferrin, and to store iron in the tissues using ferritin. Although each molecule of transferrin can bind two iron atoms, ferritin has a large internal cavity, approximately 80 Ã… in diameter, that can hold up to 4500 iron atoms per molecule. The amount of iron transported through plasma depends on total-body iron stores and the rate of erythropoiesis. Only about one-third of the iron-binding sites of circulating transferrin are normally saturated, as demonstrated by the usual serum iron content of 60â€“170 Âµg/dL (10â€“30 Âµmol/L) as compared to the total iron-

binding capacity of 280â€“390 Âµg/dL (50â€“70 Âµmol/L). It is likely that transferrin bound iron is a regulator of heme synthesis.[2,138] The expression of ALAS 2 in human erythroid cells is limited by the availability of iron.[138,140]

Only transferrin can directly supply iron for hemoglobin synthesis.[138] The ironâ€“transferrin complex binds to transferrin receptors on the surface of developing erythroid cells in bone marrow. Iron in the erythroid cell is used for hemoglobin synthesis or is stored in the form of ferritin. Lead limits the delivery of iron to ferrochelatase, contributing to the anemia of lead poisoning. In its place, zinc is inserted into protoporphyrin, resulting in the accumulation of zinc protoporphyrin.

The senescent erythrocyte is usually culled from the circulation by splenic macrophages. Heme is degraded by heme oxygenase to carbon monoxide and biliverdin, and the iron is extracted from hemoglobin.[140] Some iron may remain in macrophages in the form of ferritin or hemosiderin. Most is delivered back to the plasma where it is again bound to transferrin.

Oxygen-Carbon Dioxide Exchange

The evolutionary transition of organisms from anaerobic to aerobic life allowed the liberation of 18 times more energy from glucose. Vertebrates have developed two important systems to overcome the relatively small quantities of oxygen dissolved in aqueous solutions under atmospheric conditions: the circulatory system and hemoglobin. The circulatory system allows delivery of oxygen and removal of carbon dioxide throughout the organism. Hemoglobin also plays an essential role in the transport and exchange of both gases.[68] Moreover, the interactions between these gases and hemoglobin are directly linked in a remarkable story of molecular evolution. Understanding these interactions has allowed fundamental insight into protein conformation and the importance of allosteric interactions between molecules.

The binding of oxygen to each of the 4 iron molecules in heme results in conformational changes that affect binding of oxygen at the remaining sites. This phenomenon is known as cooperativity, and is a fundamental property to allow both the transport of relatively large quantities of oxygen and the unloading of most of this oxygen at tissue sites. Cooperativity results from the intramolecular interactions of the tetrameric hemoglobin, and is expressed in the sigmoidal shape of the oxyhemoglobin dissociation curve (Chap. 22). Conversely, the monomeric myoglobin has a hyperbolic oxygen binding curve. The partial pressure of oxygen at which 50% of the oxygen bindings sites of hemoglobin are occupied is about 26 mm Hg, in contrast with about 1 mm Hg for myoglobin. Moreover, hemoglobin is nearly 100% saturated at partial oxygen pressures of about 100 mm Hg in the pulmonary capillaries, transporting 1.34 mL of oxygen per gram of hemoglobin A. About one-third of this oxygen can be unloaded under normal conditions at tissue capillaries with partial oxygen pressures around 35 mm Hg. This proportion rises during exercise and sepsis, and with poisons that uncouple oxidative phosphorylation. Elite athletes can extract up to 80% of the available oxygen under conditions of maximal aerobic effort.

This oxygen reserve, however, is only one of the reasons for the large quantity of hemoglobin in circulation. The ability of hemoglobin to buffer the acid equivalent of CO_2 in solution is equally vital to respiratory physiology, as it allows the removal of large quantities of CO_2 from metabolically active tissues with minimal changes in blood pH. To put things in perspective, the typical adult male has approximately 75 mL/kg of blood containing 15 g/100 mL of hemoglobin, or nearly 1 kg of hemoglobin. His 0.3-kg heart must also pump this entire mass of hemoglobin every minute at rest, a substantial work expenditure. This inefficiency is partly explained by the observation that hemoglobin is by far the largest buffer in circulation, accounting for nearly 7 times the buffer capacity of the serum proteins combined (28 vs. 4 mEq H^+/L of whole blood). For every 1 mol of oxygen unloaded in the tissue, about 0.5 mol of H^+ is

loaded onto hemoglobin.

The linked interaction between oxygen and carbon dioxide transport can be first considered from the perspective of oxygen binding to hemoglobin. The affinity of oxygen for hemoglobin is directly affected by pH, which is a function of the CO_2 content of the blood. The oxyhemoglobin dissociation curve shifts to the left in lungs, where the level of carbon dioxide, and thus carbonic acid, are kept relatively low as a result of ventilation, an effect that promotes oxygen binding. The curve shifts to the right in tissues where cellular respiration increases CO_2 concentrations. This phenomenon, known as the *Bohr effect*, promotes the uptake of oxygen in the lungs and the release of oxygen at tissue sites.

From the perspective of carbon dioxide, while it does not bind directly to hemoglobin, hemoglobin plays an essential role in its transport nevertheless. Carbon dioxide dissolves into serum, and is slowly hydrated to carbonic acid which dissociates to H+ and HCO_3^- (pK_a 6.35). The hydration reaction is accelerated from

about 40 seconds to 10 msec by the abundant enzyme carbonic anhydrase, which is located within the erythrocyte. Most carbon dioxide collected at the tissues diffuses into erythrocytes where it becomes H^+ and HCO_3^-. This HCO_3^- is then rapidly transported back to the serum in exchange for chloride ion via the band 3 anion exchange transporter located in the erythrocyte membrane, thereby shifting serum Cl^- into the erythrocyte (the *chloride shift*).[172] The hydrogen ion is accepted by hemoglobin, largely at the imidazole ring of histidine residues which have a pK_a of about 7.0. A small amount of CO_2 reacts directly with the amino terminal of the globin chains to form carbamino residues ($HbNHCOO^-$). Thus, most of the transported carbon dioxide is transformed by the erythrocyte into bicarbonate ion that is returned to the serum, and hydrogen ion that is buffered by hemoglobin. Each liter of venous blood typically carries 0.8 mEq dissolved CO_2 and 16 mEq HCO_3^- in the serum, and 0.4 mEq dissolved CO_2, 4.6 mEq HCO_3^-, and 1.2 mEq $HbNHCOO^-$ in the

erythrocyte (a total of 23 mEq CO_2, equivalent to 510 mL CO_2/L blood). Whereas two-thirds of the total CO_2 content appears to be carried in the serum, essentially all of the serum bicarbonate is originally generated within erythrocytes. In the capillaries of the lungs, the reverse reactions occur to eliminate CO_2. Because deoxyhemoglobin is better able to buffer hydrogen ions, the release of oxygen from hemoglobin at the tissues facilitates the uptake of carbon dioxide into venous blood. This effect is known as the Haldane effect. In fact, 1 L of venous blood at 70% oxygen saturation can transport an additional 20 mL of CO_2 compared to arterial blood. Both the Bohr and Haldane effects can have important consequences, either at the extremes of acidâ€“base perturbations or because of interference with oxygen metabolism, as can occur in a number of poisonings.

Abnormal Hemoglobins

Several alterations of the hemoglobin molecule are encountered in clinical toxicology. A detailed understanding of their molecular basis, clinical manifestations, and effects on gas exchange are essential. Unfortunately, the nomenclature can be ambiguous and overlap with distinct clinical entities such as oxidant injury and hemolysis. Therefore, although a detailed discussion of these abnormal hemoglobins appears elsewhere (Chaps. 120 and 122), an overview of the subject is presented here. It is helpful to recall that the iron atom has 6 binding positions. Four of these positions are attached in a single plane to the protoporphyrin ring to form heme. The remaining 2 binding positions lie on opposite sides of this plane. Iron is ordinarily bonded on one side to the F8 proximal histidine residue of the globin chain. The remaining site is available for binding molecular oxygen, but can also bind carbon monoxide, nitric oxide, cyanide, hydroxide ion, or water. The E7 distal histidine residue facilitates the binding of oxygen, while stearically hindering carbon monoxide binding.

Methemoglobin

Methemoglobin (ferrihemoglobin or hemiglobin) is the oxidized form of deoxyhemoglobin in which at least 1 heme iron is in the oxidized (Fe^{3+}) valence state. A number of valency hybrids can occur depending on the number of ferric versus ferrous heme units within the tetramer. Methemoglobin therefore represents oxidation (loss of electrons) of hemoglobin molecule at the iron atom. It occurs spontaneously as a consequence of interactions between the iron and oxygen. Normally, in deoxygenated hemoglobin, the heme iron is in the ferrous (Fe^{2+}) valence state. In this state, there are 6 electrons in the outer shell, 4 of which are unpaired. When oxygen is bound, one of these electrons is partially transferred to it and the iron is reversibly oxidized. When O_2 is released, the electron is usually transferred back to heme iron, yielding the normal reduced state. Sometimes, the electron remains with the O_2 yielding a superoxide anion radical O_2^- rather than molecular oxygen. In this case, heme iron is left in the Fe^{3+}, or oxidized, state and is unable to release another electron to bind oxygen. This oxidation is primarily reversed via the action of cytochrome b5 reductase, also known as NADH methemoglobin reductase, which uses the electron carrier NADH regenerated by glycolysis (Chap. 13).[70,106] Minor pathways are also involved in methemoglobin reduction, including NADPH methemoglobin reductase, which normally reduces only approximately 5% of the methemoglobin, and vitamin C, a nonenzymatic reducing agent. The activity of NADPH methemoglobin reductase may be significantly accelerated by the presence of the electron donor methylene blue (see Antidotes in Depth: Methylene Blue and Chap. 122) or riboflavin.[81] Equilibrium is maintained with methemoglobin concentrations of 1% of total hemoglobin. Many xenobiotics are capable of increasing the rate of methemoglobin formation as much as 1000-fold. Nitrites, nitrates, chlorates, and quinones are capable of directly oxidizing hemoglobin.[23] Certain individuals may be especially vulnerable because of deficient methemoglobin reduction.[35] The fetus and neonate are more

susceptible to methemoglobinemia than the adult, as HbF is more susceptible to oxidation of the heme iron than adult hemoglobin. The newborn also has a limited capacity to reduce methemoglobin, because levels of cytochrome b5 reductase only reach adult levels around 6 months of age.

Carboxyhemoglobin

Carbon monoxide (CO) can reversibly bind to heme iron in lieu of molecular oxygen. The affinity of CO for hemoglobin is 200â€“300 times that of oxygen, despite the stearic hindrance of the E7 distal histidine. The presence of CO thereby precludes the binding of oxygen. In addition, CO binding within any one heme subunit degrades the cooperative binding of oxygen at the remaining heme groups of the same hemoglobin molecule. The oxyhemoglobin dissociation curve is therefore shifted to the left, reflecting the fact that oxygen is more tightly bound by hemoglobin and less able to be unloaded to the tissues. In addition, CO binds to the heme group of myoglobin and the cytochromes, interfering with cellular respiration, exacerbating the clinical symptoms of hypoxia (Chap. 120).[61]

Sulfhemoglobin

Sulfhemoglobin is a bright green molecule in which the hydrosulfide anion HS^- irreversibly binds to ferrous hemoglobin. The sulfur atom is probably attached to a Î² carbon in the porphyrin ring, and not at the normal oxygen-binding site.[118] It has a spectrophotometric absorption band at approximately 618 nm,[15] is ineffective in oxygen transport, and clinically produces cyanosis. The oxygen affinity of sulfhemoglobin is approximately 100 times less than that of oxyhemoglobin, shifting the oxyhemoglobin dissociation curve to the right, in favor of O_2 unbinding. Thus, the symptoms of hypoxia are not as severe with sulfhemoglobinemia as with carboxy- or methemoglobinemia.[132]

Oxidation of the Globin Chain

Oxidation can also occur at the amino acid side chains of the globin protein. In particular, sulfhydryl groups can oxidize to form disulfide links between cysteine residues, which leads to the unfolding of the protein chain, exposure of other side chains and further oxidation. When these

disulfide links join adjacent hemoglobin molecules, they cause the precipitation of the concentrated hemoglobin molecules out of solution. Covalent links can also form between hemoglobin and other cytoskeletal and membrane proteins.[31] Eventually, aggregates of denatured and insoluble protein are visible on light microscopy as Heinz bodies. The distortion of the cellular architecture, and the loss of fluidity in particular, is a signal to reticuloendothelial macrophages to excise sections of erythrocyte membrane (â€œbite cellsâ€•) or to remove the entire erythrocyte from the circulation (â€œhemolysisâ€•; see Hemolysis below). To guard against these oxidation reactions, the erythrocyte maintains a pool of reduced glutathione via the actions of the NADPH generated in the hexose monophosphate shunt (assuming adequate G6PD activity to initiate this pathway). This glutathione transfers electrons to break open disulfide links and to preserve sulfhydryl groups in their reduced state.

Hemolysis

Hemolysis is merely the acceleration of the normal process by which senescent or compromised erythrocytes are removed from the circulation.[162] The normal life span of a circulating erythrocyte is approximately 120 days, and any reduction in this life span represents some degree of hemolysis. If sufficiently rapid, hemolysis can overwhelm the regenerative capacity of the erythron, resulting in anemia. Intravascular hemolysis occurs when the rate of hemolysis exceeds the capacity of the reticuloendothelial macrophages to

remove damaged erythrocytes, and free hemoglobin and other intracellular contents of the erythrocyte appear in the circulation. Reticulocytosis, polychromasia, unconjugated hyperbilirubinemia, increased serum lactate dehydrogenase, and decreased serum haptoglobin are characteristic of hemolysis. Hemoglobinemia, hemoglobinuria, and hemosiderinuria can occur with intravascular hemolysis. Specialized tests to measure hemolysis include shortened erythrocyte survival, increased endogenous carbon monoxide generation from heme oxygenase,[170] and increased fecal urobilinogen.

Table 24-2 presents a brief classification of acquired causes of hemolysis relevant to toxicology. Oxidant injury following xenobiotic exposure is one of the triggers of hemolysis, as it may cause irreversible changes in the erythrocyte. Xenobiotics can also interact with the immune system to cause hemolysis. Finally, erythrocytes deficient in G6PD by virtue of cell age or enzyme mutations are particularly vulnerable to hemolysis following oxidant stress due to limited capacity to generate NADPH and reduced glutathione.

TABLE 24-2. Xenobiotics Causing Acquired Hemolysis

Immune-mediated
  Type I: Drug-red cell complex; IgG triggers complement
  Type II: Immune complex mediated; IgM triggers complement
  Type III: True autoimmune response to red cell membrane
Nonimmune-mediated
  Oxidants (see Table 24-3)
  Nonoxidants
    Arsine (AsH_3)
    Copper
    Lead

Pyrogallic acid
Stibine (SbH_3)
Microangiopathic (eg, ticlopidine, clopidogrel, cyclosporine, tacrolimus)[8,11,12,42,67,100,159,181]
Venoms (snake, spider)[55,71,120,183]
Osmotic agents (eg, water)[69,87]
Hypophosphatemia[3,80,113]

TABLE 24-3. Selected Xenobiotics Causing Oxidative Hemolysis in Normal Host

p-Aminosalicylic acid
Aniline[99]
Benzocaine[47,94]
Chlorates[39,76]
Cresol[36]
Dapsone[78]
Hydrogen peroxide
Hydroxylamine[169]
Isobutyl nitrite
Methylene blue[160]
Naphthalene[178]
Nitrites[12,20,24,149]
Nitrofurantoin
Oxygen[91,114]
Phenacetin[115]
Phenazopyridine[48,126]
Phenol
Platin salts[103]
Sulfonamides[184]

Nonimmune-Mediated Causes of Xenobiotic-Induced Hemolysis

A number of xenobiotics or their reactive metabolites can cause hemolysis via oxidant injury; Table 24-3 provides a partial list. A Heinz-body hemolytic anemia can result, which typically resolves within a few weeks of drug discontinuation. Some xenobiotics cause hemolysis in the absence of overt oxidant injury (Table 24-2). Copper sulfate hemolysis is described in Chap. 90, and the delayed hemolysis following exposure to arsine or stibine are described below.

Arsine

Arsine is a colorless, odorless, nonirritating gas that is 2.5 times denser than air (Chap. 85). It is produced by the action of water on a metallic arsenide, as can occur during the processing of crude metal ores. It is also widely used as a dopant in the semiconductor industry, and less frequently for galvanizing, soldering, etching, and lead plating. Clinical signs and symptoms appear after a latent period of up to 24 hours after exposure to concentrations above 30 ppm, and may include headache, malaise, dyspnea, abdominal pain with nausea and vomiting, hepatomegaly, hemolysis with hemoglobinuric renal failure, and death.[30,49,77,86,136] Delayed effects include bone marrow suppression, desquamation, and peripheral neuropathy. The mechanism of hemolysis is believed to involve the fixation of arsine by sulfhydryl groups of hemoglobin and other essential proteins.[59,187] Interestingly, hemolysis is prevented in vitro by conversion to carboxy- or methemoglobin.[65] Impairment of membrane proteins including Na^+-K^+-ATPase is another potential mechanism for arsine-induced hemolysis.[143] Chronic exposure to low levels of arsine can produce clinically significant disease.[30] The treatment of choice is cessation of exposure and supportive care. In extreme cases, exchange transfusion can be used, in part to reduce

the body burden of arsenic. Stibine likely causes hemolysis via similar mechanisms.

Immune-Mediated Hemolytic Anemia

The immune-mediated hemolytic anemias occur when ingested xenobiotics trigger an antigen antibody reaction (see Table 24-2).[134] In general, drug molecules are too small to be sensitizing agents. Antigenicity is acquired following the binding of molecules to carrier proteins in blood. The particulars of the xenobiotic-carrier immune activation sequence form the basis for the classification of this group of hemolytic anemias.[158,159]

The first class of reaction (hapten model) occurs when the xenobiotic acts as a hapten and binds to cell membrane glycoproteins on the surface of the erythrocyte. This results in the formation of a neoantigen, against which IgG develop, and subsequent removal of the erythrocyte by splenic macrophages. The prototype of this reaction is the hemolytic anemia observed following high-dose penicillin therapy.[50] Historically, approximately 3% of patients treated with megadose penicillin over weeks for infectious endocarditis developed a positive direct Coombs test, demonstrating the erythrocytes were coated with IgG or complement. The positive direct Coombs test is a necessary, but insufficient, condition for the hemolytic reaction. Discontinuation of the xenobiotic results in cessation of hemolysis, because its presence is needed for antibody binding.

The second class of reaction (immune complex) occurs with drugs that have a low affinity for cellular membrane glycoproteins. Examples are quinine, quinidine, and newer-generation cephalosporins, such as cefotetan, cefotaxime, and ceftriaxone. Small doses of xenobiotics result in hemolysis, and erythrocyte injury is primarily mediated by complement. Complexes of drug and IgM are implicated as the complement trigger in this second process.

The third class of reaction (true autoimmune) occurs when the xenobiotic alters the natural suppressor system, allowing the formation of antibody to cellular components. This is a true autoantibody reaction directed against erythrocyte surface antigen.[9] The classic example is Î±-methyldopa, but chlorpromazine, cladribine, cyclosporine, fludarabine, levodopa, and procainamide can also trigger autoimmune hemolysis.[93,121,148] An indirect Coombs test that is positive in the absence of drug demonstrates the presence of IgG autoantibodies in the patient's serum when incubated with normal erythrocytes. The severity of hemolysis is variable, but can continue for weeks to months despite removal of the inciting agent.

Glucose-6-Phosphate Dehydrogenase Deficiencies

G6PD is the enzyme that catalyzes the first step of the hexose monophosphate shunt: the conversion of glucose-6-phosphate to phosphogluconolactone. In the process, $NADP^+$ is reduced to NADPH, which the erythrocyte uses to maintain a supply of reduced glutathione and to defend against oxidation. It follows that erythrocytes deficient in G6PD activity are less able to resist oxidant attack and, in particular, to maintain sulfhydryl groups of hemoglobin in their reduced state, resulting in hemolysis. It is important to recognize that the term G6PD deficiency encompasses a wide range of differences in enzyme activities among individuals. These differences may result from decreased enzyme synthesis, altered catalytic activity, or reduced stability of the enzyme. Approximately 7.5% of the world population is affected to some degree, with more than 400 variants having been identified. Most cases involve relatively mild deficiency and minimal morbidity.[17,29,108] Ethnic populations from tropical and subtropical countries (the so-called malaria belt) have a much higher prevalence of G6PD deficiency, possibly because that phenotype protects against malaria.[122]

The gene that encodes for G6PD resides near the end of the long arm

of the X-chromosome. Most mutations consist of a single amino acid substitution, as complete absence of this enzyme is lethal. Although males hemizygous for a deficient gene are more severely affected, females randomly inactivate one X-chromosome during cellular differentiation according to the Lyon hypothesis. Thus, female carriers heterozygous for a deficient G6PD gene have a mosaic of erythrocytes, some proportion of which express the deficient gene during maturation. Accordingly, approximately 10% of carrier females may be nearly as severely affected as a male hemizygous for the same deficient gene. Because of the high gene frequency in certain ethnic groups, another approximately 10% of females may be homozygous for the deficient gene.

Normal G6PD has a half-life of about 60 days. Because the erythrocyte cannot synthesize new protein, the activity of G6PD normally declines by approximately 75% over its 120-day life span. Consequently, even in unaffected individuals, susceptibility to oxidant stress varies based on the age mix of circulating erythrocytes. In all cases, older erythrocytes are less likely to recover following exposure to an oxidant and will hemolyze first. Moreover, after an episode of hemolysis following acute exposure to an oxidant stress, the higher G6PD activity of surviving erythrocytes will confer some resistance against further hemolysis in most individuals with relatively mild deficiency, even if the offending xenobiotic is continued. In fact, phenotypic testing for G6PD deficiency is best done 2 to 3 months after a hemolytic crisis, after the reticulocyte count has normalized.

The World Health Organization classification of G6PD is based on the degree of enzyme deficiency and severity of hemolysis.[19] Both classes I and II patients are severely deficient, with less than 10% of normal G6PD activity. Class I individuals are prone to chronic hemolytic anemia, whereas class II patients experience intermittent hemolytic crises. Class III patients have only moderate (10â€“60%) enzyme deficiency, and experience self-limiting hemolysis in response to certain drugs and infections. Approximately 11% of

African Americans have a class III deficiency, traditionally termed type A^-, and experience a decline of no more than 30% of the red blood cell mass during any single hemolytic episode. Another 20% of African Americans have type A^+ G6PD enzyme, which is functionally normal, and therefore of no consequence despite a 1-base substitution compared to wild-type B of G6PD. The Mediterranean type found in Sardinia, Corsica, Greece, the Middle East, and India is a class II deficiency, and hemolysis can occur spontaneously or in response to ingestion of Î²-glycosides found in *Vicia fava* beans.

The most common clinical presentation of previously unrecognized G6PD deficiency is the acute hemolytic crisis. Typically, hemolysis begins 1 to 4 days following the exposure to an offending xenobiotic (Table 24-4). Infections such as pneumonia, viral

hepatitis, and *Salmonella* also frequently cause hemolysis. Jaundice, pallor, and dark urine may occur with abdominal and back pain. A decrease in the concentration of hemoglobin occurs. The peripheral smear demonstrates cell fragments and cells that have had Heinz bodies excised. Bone marrow stimulation results in a reticulocytosis by day 5 and an increased erythrocyte mass. In general, a normal bone marrow can compensate for ongoing hemolysis, and can return the hemoglobin concentration to normal. Most crises are self-limiting because of the higher G6PD activity of younger erythrocytes. Historically, the anemia observed when primaquine was administered to type A^- military recruits for malaria prophylaxis resolved within 3 to 6 weeks in most cases.[18] Some xenobiotics, including acetaminophen, vitamin C, and sulfisoxazole, are safe at therapeutic doses but can cause hemolysis in G6PD-deficient patients following overdose.[161,164,188]

TABLE 24-4. Xenobiotics That Can Cause Hemolysis in Patients with Class I, II, or III G6PD Deficiency

Doxorubicin	Phenylhydrazine
Furazolidone	Primaquine
Isobutyl nitrite	Sulfacetamide
Methylene blue	Sulfamethoxazole
Nalidixic acid	Sulfanilamide
Naphthalene	Sulfapyridine
Nitrofurantoin	Toluidine blue
Phenazopyridine	Trinitrotoluene

Adapted from Beutler E: Glucose-6-phosphate dehydrogenase deficiency. N Engl J Med 1991;324:169â€“174, and Beutler E: G6PD deficiency. Blood 1994;84:3613â€“3636.

Other presentations of more severe variants of G6PD include neonatal jaundice and kernicterus, chronic hemolysis with splenomegaly and black pigment gallstones, megaloblastic crisis caused by folate deficiency, and aplastic crisis after parvovirus B19 infection.

Megaloblastic Anemia

Vitamin B_{12} and folate are essential for DNA synthesis. They serve as cofactors in the methylation of deoxyuridine monophosphate to deoxythymidine monophosphate. A deficiency of B_{12} or folate may result from nutritional factors, or the use of the folate antagonists methotrexate, pyrimethamine, proguanil, and trimethoprim-sulfamethoxazole. Vitamin B_{12} metabolism can be affected by chronic exposure to nitrous oxide, biguanides, colchicine, and neomycin. Purine analogs (eg, azathioprine, 6-mercaptopurine, 6-thioguanine, acyclovir) and pyrimidine analogs (eg, 5-fluorouracil, 5-azacitidine, and zidovudine) can also disrupt nucleic acid synthesis. Typically, the result is a megaloblastic anemia, with characteristic nuclear-cytoplasmic asynchrony in erythrocyte precursors in the marrow and ineffective erythropoiesis.[141] Chronic ethanol abuse can result in a macrocytic anemia, with increased size of circulating erythrocytes.

Pure Red Cell Aplasia

Pure red cell aplasia is an uncommon condition in which erythrocyte precursors are absent from an otherwise normal bone marrow. It results in a normocytic anemia with inappropriately low reticulocyte count. The other blood cell lines are unaffected, unlike aplastic anemia. Drugs cause less than 5% of cases of this uncommon condition, having been implicated in fewer than 100 human reports.[175] Applying the Naranjo scale of causality to these reports, only phenytoin, azathioprine, and isoniazid meet the threshold of definite causality; chlorpropamide and valproic acid can only be considered as possible causes.[175] Most other xenobiotics are cited only in single case reports, and drug rechallenge was not used, making the association uncertain.

Erythrocytosis

Erythrocytosis denotes an increase in the red cell mass, either in

absolute terms or relative to a reduced plasma volume. An increasingly recognized cause of drug-induced absolute erythrocytosis is the abuse of recombinant human erythropoietin by athletes to enhance aerobic capacity.[27,52,57,168] Autologous blood transfusions (doping) are also used in this population, and both can cause dangerous increases in blood viscosity. Cobalt can cause a secondary erythrocytosis by inhibiting oxidative phosphorylation (histotoxic anoxia), and once was considered for the treatment of chronic anemia.[43]

The Leukon

The leukon represents all leukocytes (white blood cells), including precursor cells, cells in the circulation, and the large number of extravascular cells, which include the granulocytes (neutrophils, eosinophils, and basophils), lymphocytes, and monocytes. Neutrophils (polymorphonuclear leukocytes) are highly specialized mediators of the inflammatory response, and are a primary focus of concern regarding hematologic toxicity of xenobiotics. B and T lymphocytes are involved in antibody production and cell-mediated immunity. Monocytes migrate out of the vascular compartment to become tissue macrophages and to regulate immune system function.

Neutrophils provide the primary defense against the invasion of bacterial and fungal pathogens. They emerge from the bone marrow with the biochemical and metabolic machinery needed for the efficient killing of microorganisms. Neutrophils are activated when circulating cells detect low levels of chemokines released from sites of inflammation.[102] On activation by invading organisms, they undergo conformational and biochemical changes that transform them from resting cells into powerful host defenders.[109] These changes allow rolling along the endothelial lining of postcapillary venules, migration toward the site of inflammation, adherence to the endothelium, migration through the endothelium to tissue sites,

ingestion, killing, and digestion of the inciting agent.[109]

Neutrophils migrate to sites of infection along gradients of chemoattractant mediators. An acute inflammatory stimulus leads to the accumulation of neutrophils along the endothelium of postcapillary venules.[26] The major molecules involved in this process fall into a few basic superfamilies: the selectins and their mucin ligands, the integrins and their extracellular matrix, or immunoglobulin superfamily ligands. Loose adhesions between neutrophils and endothelium are made and broken, resulting in the slow movement of leukocytes along endothelium and a more intense exposure of neutrophils to activating factors. Chemotaxis requires responses involving actin polymerizationâ€“depolymerization adhesion events mediated by integrins and involving microfilamentâ€“membrane interactions.[21] Colchicine depolymerizes microfilaments, causing the dissolution of the fibrillar microtubules in granulocytes and other motile cells, impairing cellular function.

Opsonized particles, immune complexes, and chemotactic factors activate neutrophils in tissues by binding to cell surface receptors.[166] The neutrophil makes tight contact with its target, and the plasma membrane surrounds the organism completely enclosing it. Phagocytosing neutrophils undergo a burst of oxygen consumption caused by an NADPH oxidase complex that assembles at the phagosomal membrane. Electrons are transferred from cytoplasmic NADPH to oxygen on the phagosomal side of the membrane, generating superoxide, hydrogen peroxide, hydroxyl radical, singlet oxygen, hypochlorous acid, chloramines, nitric oxide, and peroxynitrite.[62] Cytoplasmic granules within the neutrophil fuse with the phagosome and empty their contents into it. There are at least 4 different classes of granules.[62] The components of these granules include myeloperoxidase (MPO), elastase, lipases, metalloproteinases, and a pool of CD11b/CD18 proteins,

which must be rapidly mobilized upon neutrophil activation for adhesion and migration.[144] Finally, the phagocytized organism is

digested and eliminated by the neutrophil. Overstimulation of this complex and highly regulated system can at times become deleterious, as is postulated to occur with reperfusion injury or carbon monoxide poisoning, to cite two examples.[174,182]

Neutropenia and Agranulocytosis

Neutropenia is a reduction in circulating neutrophils at least 2 standard deviations below the age norm. Severe neutropenia is termed *agranulocytosis*, and is generally defined to be an absolute neutrophil count of less than 0.5 Ã— 10^9/L. Neutropenia can result from decreased production, increased destruction or retention of neutrophils in the various storage pools. Their high rate of turnover renders neutrophils vulnerable to any xenobiotic that inhibits cellular reproduction. As such, the various antineoplastic xenobiotics including antimetabolites, alkylating agents and antimitotics will predictably cause neutropenia. This predictable, dose-dependent reaction serves as an important dose-limiting adverse effect of therapy. On the other hand, a number of xenobiotics are implicated in idiosyncratic neutropenia. Table 24-5 provides an abbreviated list.[171]

Eosinophilia

Eosinophilia is arbitrarily classified as mild (absolute eosinophil counts of 0.35â€“1.5 Ã— 10^9/L), moderate (1.5â€“5 Ã— 10^9/L) or severe (>5 Ã— 10^9/L). Allergic or inflammatory reactions, infections with parasites, and certain malignancies, such as lymphoma, are the most common causes of eosinophilia.[150] Two unusual toxicologic outbreaks were characterized by eosinophilia. The first outbreak, named the toxic oil syndrome, took place in central Spain in 1981, when industrial-use rapeseed oil denatured with 2% aniline was fraudulently sold as olive oil by door-to-door salesmen.[53] The ingestion of this oil resulted in the acute onset of cough, fever, and pulmonary infiltrates, followed by severe myalgia, neuropathy, and

eosinophilia. The precise causative agent remains uncertain, but may include fatty acid esters of 3-(*N*-phenylamino)-1,2-propanediol.[53] The second outbreak, called the eosinophilia-myalgia syndrome, occurred during 1988 and 1989 in users of L-tryptophan supplements traced back to a single wholesaler in Japan.[5] The causative contaminant has not been identified, but is believed to have been present in only trace quantities in the L-tryptophan purified from microbial culture. Both syndromes appear to be mediated by immunologic mechanisms.

Leukemia

The leukemias represent the malignant, unregulated proliferation of hematopoietic cells. Although monoclonal in origin, they affect all cell lines derived from the progenitor cell. Acute myeloid leukemia (AML) and the myelodysplastic syndromes are the most common leukemias associated with xenobiotics. The long-recognized association between AML and occupational benzene exposure, radiation, or treatment with alkylating antineoplastic agents has helped to advance understanding of the molecular mechanisms underlying leukemogenesis.[14] The necessary events are believed to involve several sequential genetic and epigenetic alterations, as evidenced by a distinct pattern of chromosomal deletions preceding the development of AML.[72,73] Other recognized xenobiotics that can cause leukemia include topoisomerase II inhibitors, 1,3-butanediol, styrol, ethylene oxide, and vinyl chloride.[82] In many cases, the latency period between exposure and illness is prolonged. For example, leukemia linked to benzene is preceded by several months of anemia, neutropenia, and thrombocytopenia. Benzene or other petroleum products are not believed to cause multiple myeloma.[14]

TABLE 24-5. Selected Causes of Idiosyncratic Drug-Induced Agranulocytosis

- Anticonvulsants
  - Carbamazepine
  - Phenytoin
- Antiinflammatory agents
  - Aminopyrine
  - Ibuprofen
  - Indomethacin
  - Phenylbutazone
- Antimicrobials
  - Î²-Lactams
  - Cephalosporins
  - Chloramphenicol
  - Dapsone
  - Ganciclovir
  - Isoniazid
  - Rifampicin
  - Sulfonamides
  - Vancomycin
- Antirheumatics
  - Gold
  - Levamisole
  - Penicillamine
- Antipsychotics
  - Clozapine
  - Phenothiazines
- Antithyroid agents
  - Methimazole
  - Propylthiouracil
- Cardiovascular agents
  - Hydralazine
  - Lidocaine
  - Procainamide
  - Quinidine
  - Ticlopidine

- Vesnarinone

Diuretics
- Acetazolamide
- Hydrochlorothiazide

Hypoglycemics
- Chlorpropamide
- Tolbutamide

Sedative-hypnotics
- Barbiturates
- Flurazepam

Hemostasis

In the absence of pathology, blood remains in a liquid, flowing form with cells in suspension. In response to injury, the processes of coagulation and thrombosis are triggered. The result, including clot formation, retraction, and dissolution involves an interaction between the vessel endothelium, soluble constituents of the coagulation system, and receptors and intracellular proteins contained on the surface of and within platelets. Platelet function is influenced by the physical properties of flowing blood, as well as by the chemical constituents within it. Platelets respond to signals within their immediate environment and from injured components of the distant microcirculation. A dynamic balance must be maintained between coagulation and fibrinolysis to maintain the integrity of the circulatory system (Fig. 24-4).

Coagulation

Two basic pathways are involved in the initiation of coagulation. Activation of the intrinsic system occurs when blood is exposed to tissue factor in damaged blood vessels or on the surface of activated leukocytes. Tissue factor binds factor VIIa, forming the intrinsic

tenase complex, which activates factors IX and X. Factor IXa binds to the surface of activated platelets together with VIIIa and calcium, forming the extrinsic tenase complex. Factor X, which is activated by extrinsic and intrinsic tenase, binds to factor Va on the surface of activated platelets, forming the prothrombinase complex. The prothrombinase complex activates prothrombin, which results in the generation of thrombin activity. Thrombin

activates platelets, promotes its own generation by activation factors V, VIII, and XI, and converts fibrinogen to fibrin (Chap. 57).[66]

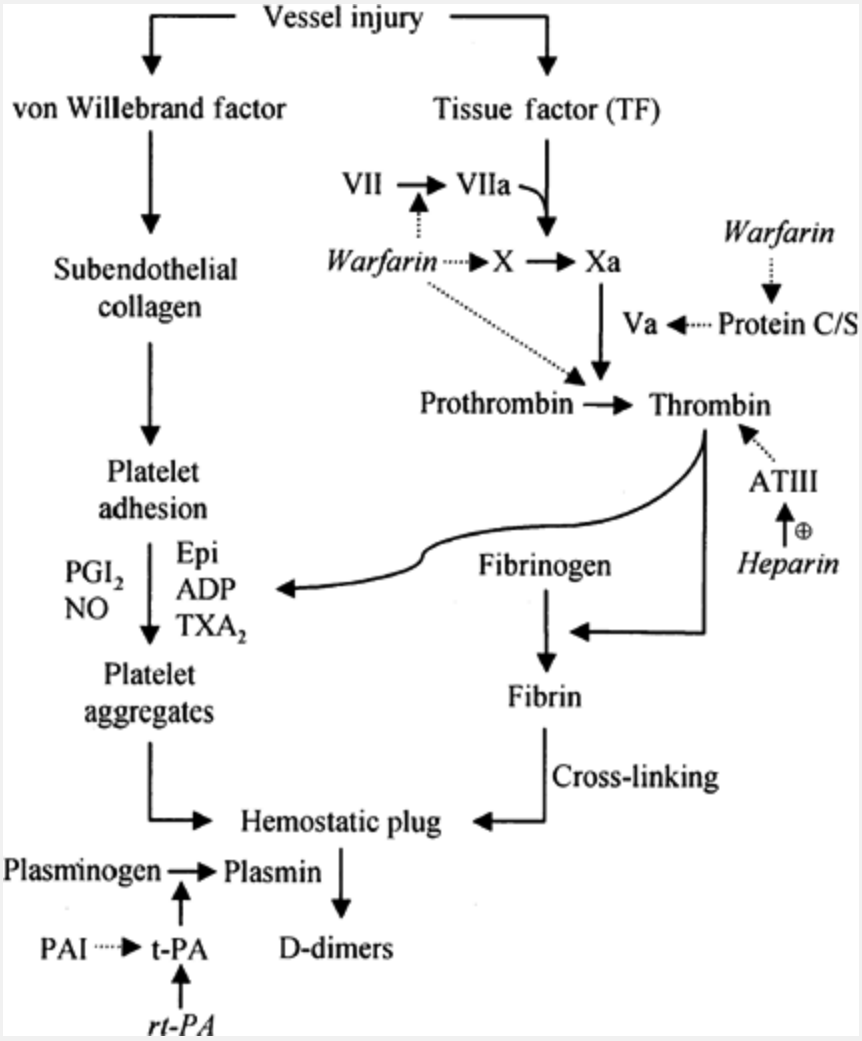

Figure 24-4. The relationships between thrombosis, coagulation, and fibrinolysis. Although these pathways are shown independently, they are intricately linked as outlined in the text. Dotted lines indicate inhibition; drugs are shown in italics. ATIII = antithrombin III; PAI = plasminogen activator inhibitor; t-PA = tissue plasminogen activator; rt-PA = recombinant t-PA; [circled plus] = activation of catalytic activity.

Fibrinolysis

The coagulation system is opposed by three major inhibitory systems. As with the coagulation cascade, components of the fibrinolytic system circulate as zymogens, activators, inhibitors, and cofactors.[46] Plasminogen can be activated to plasmin by an intrinsic pathway involving factor XII, prekallikrein, and high-molecular-weight kininogen. This produces the degradation products and fibrin monomers that are found in disseminated intravascular coagulation. The extrinsic pathway involves the release of tissue plasminogen activator (t-PA) from tissues and urokinase plasminogen activator (u-PA) from secretions.[46] Once activated, plasmin can degrade fibrinogen, fibrin, and coagulation factors V and VIII. The degradation of cross-linked fibrin strands results in the formation of D-dimers.

Several inhibitors oppose the fibrinolytic system, including Î±$_2$-antiplasmin, Î±$_2$-macroglobulin, both of which oppose plasmin activity, and plasminogen activator inhibitor (PAI) types 1 and 2, which oppose t-PA. PAI-1 and -2 are opposed by activated protein C and protein S. Activated protein C is activated by thrombin. Congenital deficiencies of proteins C and S may result in pathologic venous thrombosis. Decreased fibrinolytic activity may result from decreased synthesis, release of t-PA, or from an elevation of the PAI-1 level. Both conditions have been observed postoperatively, with the use of oral contraceptives, in the third trimester of pregnancy,

and in obesity. The activity of Î±$_2$-antiplasmin and Î±$_2$-macroglobulin are increased in pulmonary fibrosis, malignancy, infection, and myocardial infarction, and in thromboembolic disease.[46]

Platelets

In the resting state, platelets maintain a discoid shape. The platelet membrane is a typical trilaminal membrane with glycoproteins, glycolipids, and cholesterol embedded in a phospholipid bilayer. The plasma membrane is in direct continuity with a series of channels, the surface-connected canalicular system (SCCS), which is sometimes referred to as the open canalicular system. The SCCS provides a route of entry and exit for various molecules, a storage pool for platelet glycoproteins, and an internal reservoir of membrane that may be recruited to increase platelet surface area.[129] This facilitates platelet spreading and pseudopod formation during the process of cell adhesion.

The glycocalyx, or outer coat, is heavily invested with glycoproteins that serve as receptors for a wide variety of stimuli. The Î²$_1$-integrin family includes receptors that mediate interactions between cells and mediators in the extracellular matrix, including collagen, laminin, and fibronectin.[163] The Î²$_2$-integrin receptors are present in inflammatory cells and platelets and are important in immune activation. The Î²$_3$-integrin receptors (also known as cytoadhesins) include the glycoprotein (GP) IIb-IIIa fibrinogen receptor, as well as vitronectin.[66] Vitronectin has binding sites for other integrins, collagen, heparin, and components of complement. All of the integrins are active in the process of platelet adhesion to surfaces. Platelet aggregation is mediated by the GP IIb-IIIa receptors.[66]

The submembrane region contains actin filaments that stabilize the platelets' discoid shape and are involved in the formation and stabilization of pseudopods. They also generate the force needed for the movement of receptor-ligand complexes from the outer plasma membrane to the SCCS. These mobile receptors are important in the

spreading of platelets on surfaces, and for binding fibrin strands and other platelets. Platelet cytoplasm contains three types of membrane bound secretory granules.[66] The Î± granules contain Î²-thromboglobulin, which mediates inflammation, binds and inactivates heparin, and blocks the endothelial release of prostacyclin. In addition, platelet factor-4, which inactivates heparin, and fibrinogen are contained within the Î± granules. Dense granules store adenine nucleotides, serotonin, and calcium, which are secreted during the release reaction. Platelet lysosomes contain hydrolytic enzymes. Stimulation by platelet agonists causes the granules to fuse with the channels of the SCCS, driving the contents out of the platelets and into the surrounding media.

Platelet Adhesion

In the vessel wall, collagen, von Willebrand factor (vWF), and fibronectin are the adhesive proteins that play the most prominent role in the adhesion of platelets to vascular subendothelium.[163] On the exposure of collagen (eg, following a laceration or the rupture of an atherosclerotic plaque), platelet adhesion is triggered. Under conditions of high shear (flowing blood), platelet adhesion is mediated by the binding of GP Ib-IX receptors on platelet membranes to vWF in the vascular subendothelium.[66,163] Following adherence of platelets to subendothelial vWF, a conformational change in GP IIb-IIIa on platelet membrane occurs, activating this receptor complex to ligate vWF and fibrinogen. The result is the amplification of platelet adhesion and aggregation. An important interaction occurs between thrombosis and inflammation. Platelet-activating factor is synthesized and coexpressed with P-selectin on

the surface of the endothelium in response to mediators such as histamine or thrombin. Platelet-activating factor interacts with a receptor on the surface of neutrophils that activates the CD11/CD18 adhesion complex, and results in adhesion of neutrophils to endothelium and to platelets. This results in the synthesis of

leukotrienes and other mediators of inflammation.

Platelet Activation

Thrombin, collagen, and epinephrine can activate platelets. In response to thrombin, Î± granules fuse with each other and with elements of the SCCS to form secretory vesicles.[129] These vesicles are believed to fuse with the surface membrane, releasing their contents into the surrounding medium. The membranes of the secretory granules become incorporated into the platelet surface membrane.

Platelet Aggregation

Following activation, GP IIb-IIIa is expressed in active form on platelet surface. This receptor binds exogenous calcium and fibrinogen. GP IIb-IIIa ligates fibrinogen along with fibronectin, vitronectin, and vWF, resulting in the binding of platelets to other platelets, and ultimately the formation of the platelet plug. Collagen-induced platelet aggregation is mediated by adenosine diphosphate (ADP) and thromboxane A_2. ADP binds to the metabotropic purine receptors P2Y1 and P2Y12, leading to transient and sustained aggregation, respectively.[51] Thromboxane A_2 is formed from arachidonic acid by the action of cyclooxygenase (COX) 1. It is a potent vasoconstrictor and inducer of platelet aggregation and release reactions.[66] Platelets participate in triggering the coagulation cascade by binding coagulation factors II, VII, IX, and X to membrane phospholipid, a calcium-dependent process.

Xenobiotic-Induced Defects in Coagulation

Warfarin

The recognition of a hemorrhagic disease in cattle in the 1920s and

the isolation of the causative agent dicoumarol from spoiled sweet clover in the 1940s resulted in the development of the warfarin-type anticoagulants (Chap. 57). This group of anticoagulants indirectly inhibits hepatic synthesis of coagulation factors II, VII, IX, X, and proteins C and S.[135] Hepatic Î³-carboxylation of glutamic acid residues by vitamin K-dependent carboxylase results in the formation of the vitamin K-dependent clotting factors. Vitamin K must be available in its reduced form, vitamin K quinol, to effectively catalyze this reaction. The carboxylation reaction oxidizes vitamin K quinol to vitamin $K_{2,3}$ epoxide, which must be reduced to vitamin K by reductase enzymes. The warfarin anticoagulants inhibit the reductase that is responsible for the regeneration of vitamin K quinone from vitamin K epoxide, impairing the synthesis of the vitamin K-dependent proteins.[85,165]

Heparin

Heparin is a highly sulfated glycosaminoglycan that is normally present in tissues. Commercial unfractionated heparin is either bovine or porcine in origin, and consists of a mixture of polysaccharides with molecular weights ranging from 4000â€“30,000 daltons. It is used extensively for the prophylaxis and treatment of venous thrombosis and thromboembolism. It is ineffective orally because it cannot cross membranes. This same property makes it safe for use during pregnancy because heparin cannot cross the placenta.[151] The anticoagulant activity of heparin is through its catalytic activation of antithrombin III. Antithrombin III is a serine protease that inactivates thrombin and factor X.[119]

TABLE 24-6. Xenobiotics Associated with Disorders of Fibrinolysis Resulting in Thrombosis

Antineoplastics
Anthracyclines
L-Asparaginase
Mithramycin
Aprotinin and other antifibrinolytics
Coagulation factors
Cytokines
Erythropoietin
Thrombopoietin
Hormones

Adapted from Fareed J, Hoppensteadt DZ, Jeske WP, et al: Acquired defects of fibrinolysis associated with thrombosis. Semin Thromb Hemost 1999;25:367â€“374.

The low-molecular-weight heparins (LMWHs) have a mean molecular weight of 4000â€“6000 Da.[66] The pharmacokinetics and bioavailability of the LMWHs are more predictable, eliminating the need for close monitoring. They exhibit lower protein binding and a longer half-life, making them more convenient to use.[119]

Xenobiotic-Induced Defects in Fibrinolysis

Table 24-6 lists xenobiotics associated with an acquired defect of fibrinolysis. The antitumor agents may result in a reduction in serine protease inhibitors such as antithrombin. L-Asparaginase is associated with a reduction in circulating t-PA levels. Methotrexate can damage vascular endothelium, which may trigger thrombosis (Chap. 52).[46] Hemostatic drugs used therapeutically include the

synthetic lysine derivatives aminocaproic acid and tranexamic acid, which bind reversibly to plasminogen; the bovine protease inhibitor aprotinin, which inhibits kallikrein; the vasopressin analog desmopressin, which increases plasma concentrations of factor VIII and vWF; and conjugated estrogens, which normalize bleeding times in uremia.[105]

Antiplatelet Agents

Aspirin

Aspirin inhibits COX by the irreversible acetylation of a serine residue at the active site of the enzyme. Aspirin inhibition of the COX-1 isoform of this enzyme is 100â€“150 times more potent than its inhibition of the COX-2 isoform. The inhibition of COX-1 results in the irreversible inhibition of thromboxane A_2 formation. Because platelet activation by other mechanisms, such as thrombin, remain intact, thrombosis can develop despite aspirin therapy (Chap. 35).[156]

Selective COX-2 Inhibitors

Platelets express primarily COX-1 and use it to produce mostly thromboxane A_2, which leads to platelet aggregation and vasoconstriction. Endothelial cells express COX-2 and use it to produce prostaglandin I_2, an inhibitor of platelet aggregation and a vasodilator. Whereas aspirin and traditional (nonselective) nonsteroidal antiinflammatory medications inhibit the production of thromboxane A_2 and prostaglandin I_2 at both sites, the selective COX-2 inhibitors do not affect platelet-derived thromboxane A_2, perhaps accounting for the increase in cardiovascular events associated with long-term use of some of these xenobiotics.[34,79,89,104,167,180]

GP IIb-IIIa Antagonists

The GP IIb-IIIa antagonist abciximab is a chimeric human-murine monoclonal antibody that binds the GP IIb-IIIa receptor of platelets and megakaryocytes. Two synthetic GP IIb-IIIa receptor antagonists have been developed: eptifibatide and tirofiban. These agents are used primarily in patients undergoing

percutaneous coronary interventions.[66] Reversible thrombocytopenia can occur within hours of initiation of these xenobiotics.

Thienopyridines

The prodrugs clopidogrel and ticlopidine antagonize ADP-mediated platelet aggregation by noncompetitive inhibition of ADP binding to the P2Y12 receptor.[133,142] Both prodrugs are associated with thrombotic thrombocytopenic purpura, as well as neutropenia and aplastic anemia.[11,12,130,131,142] Thrombotic thrombocytopenic purpura is characterized by microangiopathic hemolytic anemia, severe thrombocytopenia, and fluctuating neurologic abnormalities.[117] The hallmark is the presence of platelet aggregates throughout the microvasculature, without fibrin clot, and therefore involves a derangement of platelet aggregation. It is believed that drug-induced autoantibodies inactivate a metalloprotein ADAMTS13, thereby blocking its ability to depolymerize large multimers of vWF and leading to platelet clumping.[6,7,11,181]

Dipyridamole

The pyrimidopyrimidine derivative dipyridamole inhibits cyclic nucleotide phosphodiesterase in platelets, resulting in the accumulation of cyclic adenosine monophosphate and perhaps cyclic guanine monophosphate.

Xenobiotic-Induced Thrombocytopenia

Multiple drugs are reported to cause thrombocytopenia, generally

mediated via the formation of drug-dependent antiplatelet antibodies. Drug-induced platelet antibodies are estimated to occur in 1 in 100,000 drug exposures. Reversible drug binding to platelet epitopes such as GP Ib-IX, GP IIb-IIIa, and plateletâ€“endothelial cell adhesion molecule-1, lead to a structural change that can form or expose a neoepitope target for antibody formation.[6,147] The presence of the drug is required for antibody binding and increased platelet destruction, but there is no covalent bond (as occurs in the hapten model of penicillin binding to the erythrocyte membrane).

Thrombocytopenia can also occur as a result of heparin-induced thrombocytopenia (discussed in Chap. 57), bone marrow toxicity, and thrombotic thrombocytopenic purpura. After excluding these conditions and nontherapeutic exposures, a systematic literature search updated annually lists more than 1000 cases reported in English involving more than 150 xenobiotics.[186] Table 24-7 lists the xenobiotics appearing in multiple cases satisfying criteria for probable to definite causality including drug rechallenge. Nevertheless, a common clinical problem is to distinguish drug-induced thrombocytopenia from idiopathic thrombocytopenic purpura in a patient on multiple medications who develops thrombocytopenia. In the absence of validated laboratory assays for drug-dependent platelet antibodies other than heparin, diagnosis still depends on the clinical course following drug discontinuation and perhaps rechallenge. Large databases exist to provide some guidance regarding past reported experience.[54,146,186]

In patients administered the sensitizing agent de novo, at least 7 days are typically required for the development of the immune response. During rechallenge, thrombocytopenia can develop within 12 hours. Interestingly, the unique ability of GP IIa/IIIb inhibitors such as abciximab to cause thrombocytopenia within hours of first use suggests the presence of preformed antibodies directed against platelet epitopes, perhaps accounting for ex vivo clumping of platelets observed in approximately 0.2% of normal patients having routine automated blood counts.[147] Clinically, fever, chills, pruritus,

and lethargy may occur. The onset of bleeding may be abrupt. Hemorrhagic vesicles may be seen in the oral mucosa.[44] Life-threatening hemorrhage may develop. Laboratory investigations will demonstrate an absence of platelets on peripheral smear, prolongation of the bleeding time, deficient clot retraction, and an abnormal prothrombin consumption test. Bone marrow aspiration will demonstrate normal or increased numbers of megakaryocytes and immature forms. Treatment includes the transfusion of blood products, glucocorticoids, and the withdrawal of the offending agent.

TABLE 24-7. Xenobiotics Reported to Cause Thrombocytopenia as a Result of Antiplatelet Antibodies[a]

Abciximab
Acetaminophen
Aminoglutethimide
Aminosalicylic acid
Amiodarone
Amphotericin B
Carbamazepine
Cimetidine
Danazol
Diclofenac
Digoxin
Eptifibatide
Gold
Heparin
Indinavir
Levamisole
Meclofenamic acid
Methyldopa
Nalidixic acid
Oxprenolol

Procainamide
Quinidine
Quinine
Rifampin
Tirofiban
Trimethoprim-sulfamethoxazole
Vancomycin

[a] Xenobiotics reported in at least 2 cases to have definitely caused immune thrombocytopenia, or in at least 5 cases to have probably caused immune thrombocytopenia following therapeutic use.
Adapted from George JN, Raskob GE, Shah SR, et al: Drug-induced thrombocytopenia: A systematic review of published case reports. Ann Intern Med 1998;129:886â€“890; Rizvi MA, Kojouri K, George JN: Drug-induced thrombocytopenia: An updated systematic review. Ann Intern Med 2001; 134:346; and WHO Working Group. Glucose-6-phosphate dehydrogenase deficiency. Bull WHO 1989;67:601â€“611.

Heparin-Induced Thrombocytopenia

An immune response to heparin, manifested clinically by the development of thrombocytopenia and, at times, venous thrombosis, is now recognized to result from antibodies to a complex of heparin and platelet factor 4. The heparinâ€“platelet factor 4 antibody complex can directly activate platelets, and is believed to be the mechanism for the paradoxical thrombosis associated with this condition. Indeed, although bleeding is uncommon, the thrombotic complications that develop in approximately 20% of patients with heparin-induced thrombocytopenia are associated with a mortality rate of up to 30% (Chap. 57).[4]

Summary

The mechanisms of toxic injury to the blood are extremely varied and complex. The response to injury may be idiosyncratic, as in many xenobiotic-related causes of agranulocytosis and aplastic anemia, or predictable, as in the case of significant exposures to ionizing radiation or to benzene. Injury may depend on the presence of certain host factors, such as G6PD deficiency. Xenobiotics may directly injure mature cells or the stem cell pool, thus prohibiting the development of mature cells. Toxicity may result from the amplification of a potentially therapeutic intervention, such as occurs with many chemotherapeutic agents and anticoagulants. Finally, a common theme in hematologic toxicity is the perturbation of homeostatic equilibria that exist between cell proliferation and apoptosis, between immune activation and suppression, or between thrombophilia and thrombolysis. It is therefore important to be aware of these complex pathways in order to better understand, diagnose, and treat toxic injury to the blood.

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Chapter 25
Gastrointestinal Principles

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The gastrointestinal (GI) mucosa, like other mucous membranes, occupies a discrete anatomic niche: the interface between a sterile internal environment and a contaminated external, or luminal environment. Humans are continuously in contact with potential xenobiotics, and the GI mucosa forms part of the initial line of defense. Despite this important responsibility, the GI mucosa lacks a strong physical barrier, with the interface between the internal and external environments being the apical cell membranes of epithelial cells. The reason for this seemingly paradoxical situation is that epithelial cells require intimate contact with the luminal environment in order to carry out their primary functionâ€”the absorption of nutrients, ions, and water. The need for such intimate contact with the external environment makes the GI tract inherently vulnerable. The task of mucosal defense is confounded by a large surface area, which is an adaptation that maximizes absorptive capacity.

The GI tract may be exposed to a wide variety of potentially toxic xenobiotics, including those with diffuse, nonspecific pathogenic effects, such as caustic agents and ionizing radiation, as well as highly specific xenobiotics and microbial pathogens. The GI tract also is vulnerable to the physical effects of foreign bodies, unlike the situation in most other organ systems. The GI tract, including the liver and pancreas, may be targeted specifically by xenobiotics. Alternatively, the gut may play a permissive role by absorbing xenobiotics with systemic toxicity.

Antimicrobial defense in the GI tract is complicated and involves both nonspecific and specific processes. The nonspecific processes include antiinfective and other factors in saliva and other endogenous secretions, gastric acid, the mucus layer overlying the epithelial surface, intestinal motility, and the endogenous flora. In addition, specific molecular pumps, as well as biotransforming enzymes within the epithelial cell, may modify potentially toxic xenobiotics. The mucosal immune system of the GI tract is the largest lymphoid compartment in the body.[15] Antimicrobial defenses include both innate and adaptive immunity. Innate immunity is an antimicrobial defense system that is based on the recognition of nonspecific, nonâ€“self antigens and is mediated through such nonspecific processes as complement activation. In contrast, adaptive immunity is based on the recognition of specific epitopes, and the responses are directed specifically at the invading microbe.

This chapter discusses the role of the GI tract as it relates to toxicology. Anatomic, physiologic, and microbiologic principles are discussed, including the role of the GI tract in the metabolism of xenobiotics. Although the liver is the body's major metabolic organ, the intestines also contribute significantly. Examples of specific GI toxicities and their clinical GI manifestations are discussed.

Anatomic Principles

The luminal GI tract can be divided into 5 distinct structures and luminal environments: oral cavity and hypopharynx; esophagus; stomach; small intestine; and colon. These environments differ in luminal pH, specific epithelial cell receptors, and endogenous flora. The transitional areas between these distinct organs have specialized epithelia and muscular sphincters, with specific functions and vulnerabilities. Knowledge of the anatomy of the transitional areas is particularly important to the localization and management of foreign bodies. The functions of the pancreas and liver are closely integrated with those of the luminal organs, although they are not within the nutrient stream. The liver and its metabolic functions are discussed extensively in Chaps. 13 and 26; the pancreas is discussed below.

The organs of the GI tract are composed of 5 layers: the epithelium, lamina propria, submucosa, muscle layers (circular and longitudinal), and serosa, the latter only in intraperitoneal organs. Some authors combine the epithelial layer, the lamina propria, and the muscularis mucosa into a single compartment, the mucosa. Neural tissue is found diffusely in the intestine, and organized into a neural plexus in the submucosa and between the muscle layers. Immunocompetent cells also are located in all of the layers, with the subpopulations in the epithelium and lamina propria being the best studied.

The major structural adaptations of the intestine are designed to increase the surface area available for absorption. These adaptations include mucosal folds; the so-called valves of Kerckring, which triple surface area; villus formation, which also increases the surface area by a factor of 10; and microvilli on the apical surface of epithelial cells, which increase surface area by a factor of 20. Because of all these anatomic adaptations, the surface area of the intestine is 600-fold greater than that of a simple tube.[103] To provide the cells to cover the surface, cell

proliferation is continuous in the intestinal crypts. Intestinal epithelium is one of the most rapidly proliferating cell compartments in the body, which makes it vulnerable to xenobiotics that affect the cell cycle.

The most specialized cell type in the intestine is the epithelial cell. There is a polarity, distinct to epithelia, in which one side of

the cell (basal) faces â€œselfâ€• while the other side (apical) faces â€œnonâ€“self.â€• To adapt to these different environments and to facilitate the different functions, the apical and basal membranes of the epithelial cell contain different receptors and other surface molecules. The basal layer of the epithelial cell faces the lamina propria and the lamina propria mononuclear cells. In addition to its role as an absorptive organ, the epithelial cell also functions as part of mucosal immune defense, as it communicates with lamina propria cells, both in heralding the presence of microbial pathogens and in downregulating the immune system in the presence of nonpathogenic or probiotic microbes.

An elaborate system has evolved to protect the GI tract from pathogens, which is part of a common mucosal immune system.[94] Mucosal immunity can be divided into an afferent limb, which recognizes a pathogen and induces the proliferation and differentiation of immunocompetent cells, and an efferent limb, which coordinates and effects the immune response. The afferent and efferent limbs of the mucosal immune system are anatomically separate, but intermingled. The afferent system includes discrete lymphoid follicles, which are overlaid by a follicle-associated epithelium, including microfold, or M cells, that promote transit of particulate and soluble antigens to antigen-presenting cells.[69] Once sensitized, immune cells undergo a complicated process of clonal expansion and differentiation, which occurs in mucosal and mesenteric lymphoid follicles, as well as in extraintestinal sites. Immunocompetent cells then return to the intestine and other

mucous membranes, and are scattered diffusely within the epithelial and lamina propria compartments.

The function of the muscle layers is integrated with the enteric nervous system to provide for a coordinated movement of luminal contents through the GI tract so as to maximize absorption and minimize bacterial growth. One level of integration provides for an aborad flow of chyme, which requires a coordinated sequence of muscular contractions and relaxations and leads to segmenting and to peristaltic movements. For unidirectional flow to occur, the intestine distal to the contraction of circular muscle must decrease its muscular tone and increase compliance, while the intestine proximal to the contraction must increase muscle tone and decrease compliance. Furthermore, this gradient of muscular tone and compliance must, itself, move down the intestine. This level of neural control is maintained within the intestine, using a variety of neurotransmitters. The various neural circuits also can be affected by external stimuli originating in the central nervous system, or via xenobiotics. Destruction of the neural circuits at the level of the intestine abolishes neuromuscular coordination and leads to stasis, which presents clinically as pseudoobstruction, that is, absence of propulsion of a meal in the absence of an organic, obstructing lesion.

A second level of neural integration relates to the overall speed of intestinal transit. Digestion and absorption are time-dependent processes and optimal absorption requires adjustment of the luminal environment through secretion of ions and water, to accommodate meals that vary considerably in nutrient composition and density. Osmoreceptors and chemoreceptors in the GI tract fine-tune the digestive and absorptive process by regulating transit and secretion, using a variety of neurocrine, paracrine, and endocrine mechanisms, allowing optimum absorption under a variety of circumstances. For example, hyperosmolar solutions empty more slowly from the stomach than isosmolar solutions.[65] Interference with this integrated response may lead to stasis and

bacterial overgrowth, or rapid transit with decreased absorption and the development of diarrhea. A large number of mediators affect motility, including common neurotransmitters, such as acetylcholine and norepinephrine as well as peptidergic nerves, hormones, cytokines, inflammatory compounds, and others; typically, multiple agents affect motility. In general, parasympathetic impulses promote motility, whereas sympathetic impulses inhibit motility. Other transmitters, such as serotonin, promote transit while others, such as dopamine and enkephalins, slow transit.

The luminal contents also can be considered an anatomic structure, especially the endogenous flora. There are two subcompartments of endogenous flora. Microbes within the bulk luminal contents play a relative small role in the body's economy, except for possible biotransforming functions. Organisms, predominantly anaerobes, also bind to specific receptors in the mucus layer overlying the epithelial cells and may play a more important, but perhaps a poorly understood role, including effects on epithelial cell gene expression. The importance of the endogenous flora is best illustrated by the result of their unintentional eradication during antibiotic therapy, when the pathogenic or toxigenic bacteria that replace them cause functional alterations and clinical symptoms.[7] Differences in the luminal environment in young infants, compared to adults, underlie the endogenous production of botulinum toxin, with the clinical consequence being infant botulism.[18]

Physiologic Principles

Intestinal Absorption

The microenvironment between the bulk luminal contents and the epithelial cells has special properties. An â€œunstirred layerâ€• is characteristic of all tubular structures through which fluids flow.[92]

Whereas the bulk luminal contents move through the GI tract with a velocity that is dependent primarily upon muscle activity, water molecules immediately adjacent to the epithelial cell membrane do not move at all, and water molecules slightly more distant from the epithelial cell may move with a velocity below that of the bulk luminal contents. The unstirred layer has an estimated thickness of about 35 microns, as compared to the (approximately) 5-cm diameter of the small intestine.[57] Although this layer presents little impediment to the diffusion of water-soluble materials, it poses a more substantial problem to the diffusion of lipid-soluble materials. In the stomach, secretion of bicarbonate into the unstirred layer below a mucus layer protects the epithelial cells from gastric acid (pH [congruent] 1).[28] The chemical composition of the unstirred layer also may differ from that of the bulk luminal contents, resulting in a pH immediately adjacent to the epithelial cell that is lower than the pH of the bulk luminal contents. Based on the absorption rates of weak acids, an acidic microenvironment is hypothesized to face the small intestinal epithelium.[85]

The major barrier to the penetration of xenobiotics and microbes is the GI epithelium, a single-cell-thick membrane.[24] The cell membrane is a lipid bilayer that contains proteins, which act as aqueous pores through which certain materials can pass, based on size or molecular structure, providing the basis for semipermeability. The membrane is not continuous as it consists of epithelial cells. However, the epithelial cells are attached to one another by structures known as tight junctions, which are located on the lateral surfaces of the cells, near their apical membranes. The tight junctions have a gap of about 8 Ã…, which allows passage only of water, ions, and low-molecular-weight materials.

Of all the functions of the intestine, the absorption of nutrients, ions, and water is the most important for survival. Nutrient

absorption is a function of the small intestine, while the colon contributes to the absorption of ions and water, and salvages

some malabsorbed carbohydrates. The role of the other GI organs is to prepare food for absorption and to deliver it to the absorptive surface at a rate promoting optimal absorption. For example, the major digestive functions of the oral cavity are to initiate the mechanical and enzymatic breakdown of foods into a form that is optimal for absorption. This process is continued in the stomach, where the gastric antrum further grind foods to particle sizes less than 0.2 mm, in addition to continuing protein digestion.[66] Gastric emptying rates vary in accordance with the chemical and physical characteristics of the meal, and in a manner that optimizes nutrient absorption. Bicarbonate in bile and pancreatic juice neutralize gastric acid. In addition, pancreatic secretions continue the digestive process and yield small molecules that are capable of being hydrolyzed and transported by the intestinal mucosa, while bile salts and lecithin form micelles that maintain products of lipid digestion in solution (emulsion) so that absorption can occur. Ingested food also is diluted with endogenous secretions in order to optimize nutrient absorption. In addition to absorbing ions and water, the colon converts indigestible and unabsorbed materials plus bacteria to solid feces, which are stored and then eliminated.

Multiple factors affect absorption from the intestine, transport from the lumen into the body may occur via transcellular or intercellular routes; absorption may occur by passive or active (energy-using) processes. Passive diffusion through the luminal membrane is directly related to the surface area of the membrane, to the concentration or concentration difference on the two sides of the membrane, to the degree of lipid solubility, and to a diffusion constant that varies with each chemical; passive diffusion is *inversely* related to diffusion distance. Written as an equation, these factors would appear as:

Flux = (Diffusion Constant)(Surface Area)(Concentration Difference)/Diffusion Difference

The diffusion constant, and thus the flux rate, is related to

molecular size. This relationship establishes the principles for clinical permeability tests performed clinically, such as the lactulose-mannitol permeability test, which compares the relative absorption rates of nonmetabolizable monosaccharides and disaccharides.[48] Transcellular transport of many nutrients, ions, and xenobioticsâ€”both uptake at the lumen and excretion at the basolateral membranesâ€”occur via carrier-mediated mechanisms.[1] These transport processes are subject to multiple controls allowing positive and negative adaptations to optimize absorption and limit toxicity, as described for such diverse nutrients as glucose and iron.[67 , 78] Net absorption is a combination of active and passive processes, plus secretion in some situations. The same transport processes may be used both by essential and toxic materials. For example, the absorption of both lead and calcium are increased by vitamin D.[31] The chemotherapeutic agent 5-fluorouracil, and the nucleoside reverse transcriptase inhibitor zidovudine, are absorbed by the same transport process used for the absorption of naturally occurring pyrimidines.

The pH of the luminal contents is important in modulating the absorption of acids and bases. Many xenobiotics are either weak acids or weak bases and the effect of ambient pH is to affect water versus lipid solubility. For example, acids are ionized at basic pH, but nonionized at acid pH.

In contrast, bases are nonionized at basic pH and ionized at acid pH. In general, ionized molecules are more water soluble, whereas nonionized molecules are more lipid soluble. Because the total area of membrane lipid is much greater than that of the membrane's aqueous pores, nonionized xenobiotics typically are absorbed more rapidly than ionized xenobiotics. Thus, one would expect weak acids to be better absorbed in the stomach and weak bases to be better absorbed in the small intestine. This may not always be the case, because surface area is much greater in the intestine than in the stomach.

Salicylate toxicity to the gastric mucosa is a classic example of pH-dependent absorption.[81] Acetyl salicylate (aspirin) is a water-soluble salt of the weak acid salicylic acid, which is poorly soluble in water. At gastric pH, aspirin is converted to the nonionized salicylic acid, which facilitates its uptake through the luminal membrane of the gastric epithelial cell. Once intracellular, the acid dissociates, leading to elevated intracellular concentrations of water-soluble salicylate, which is toxic to the cell.

The pH in the small intestine and colon are higher than in the stomach, which would be expected to favor the uptake of weak bases. However, there is evidence that the pH at the epithelial microenvironment in the intestine is lower than the pH of the bulk luminal contents as a result of the active secretion of an acidic compound; the lower pH at the cell surface facilitates the absorption of weak acids in the small intestine.[85] The actual relationship between nonionized and ionized compounds and pH is specific for each xenobiotic and is related to its ionization constant (pK_a), which is the pH at which 50% of the compound is ionized.

Variation in the diffusion of chemicals across the intestinal membrane also may be important in elimination. For example, acidification of colonic contents may occur as a result of lactulose therapy for hepatic encephalopathy, via production of lactic acid and other short-chain fatty acids in the colon which trap ammonia as NH_4^+ and promote its fecal excretion.[19] Such a process also might affect the ability of multiple doses of activated charcoal to promote elimination of already absorbed xenobiotics.[10]

Other luminal factors affecting absorption include particle size, which is relevant for the ingestion of mercury and other heavy metals. Intestinal transit time can also theoretically modify the absorption of potential xenobiotics, although evidence of efficacy in overdoses is lacking. With respect to the absorption of medications, different types of drug formulations, such as timed release via enteric coating, slowly dissolving matrices, dissolution

control via osmotic pumps, ion exchange resins, pH-sensitive mechanisms, or other mechanisms, can limit bioavailability. In the case of analgesics and other medications with potent CNS effects, the potential for unintentional overdose may be diminished by these formulations, although external manipulation of the product, such as crushing time-release beads prior to ingestion, may circumvent the pharmaceutical design.[71] Stimulation of intestinal transit using magnesium salts or other cathartics is an outdated approach to manipulating transit time in attempting to decrease the absorption of xenobiotics. However, apart from the paucity of any reliable data demonstrating beneficial effects, adverse effects on fluid and electrolyte balance were often problematic. The use of whole-bowel irrigation (WBI) with polyethylene glycol electrolyte lavage solution (PEG-ELS) in toxicologic management may be thought of as the modern therapeutic approach to decrease transit time of harmful xenobiotics without interfering with fluid and electrolyte balance. Unfortunately, with the possible exception of its use to ameliorate the effects of intentional or unintentional overdoses with iron tablets, the scientific evidence to substantiate the beneficial effects of WBI is limited. Anticholinergic and other antidiarrheal agents may exacerbate microbial or other luminal xenobiotics by

increasing contact time and absorption, and by preventing the innate response of flushing away noxious material. In fact, the Infectious Disease Society of America guidelines on the management of acute diarrhea strongly recommend avoiding the use of antimotility agents in the management of acute diarrhea.

Xenobiotic Metabolism

Although the liver is usually identified as the site of xenobiotic metabolism, similar functions also are found in the luminal GI tract. The stomach has long been known to contain alcohol dehydrogenase activity. Biotransformation is a property both of

luminal bacteria and enterocytes. The consequences of metabolism differ for diverse xenobiotics. Metabolism by the intestine affects the amount of orally administered xenobiotic that enters the body and contributes to the first-pass effect, or presystemic disposition. Variations in intestinal metabolism also may influence the pharmacokinetics of a xenobiotic. Metabolism can result in detoxification or the production of xenobiotics, and the rate of metabolism affects the exposure to xenobiotics by the body as a whole and the epithelial cell.

Intestinal epithelial cells metabolize xenobiotics by multiple types of reactions such as hydroxylation, sulfation, acetylation, and glucuronidation. Intestinal epithelial cells contain many of the same metabolic enzymes as the liver. In addition, epithelial cells contain export pumps, as do hepatocytes and other cells.[101] The responsible agent, P-glycoprotein, is related to the cystic fibrosis transmembrane regulator.[98] P-glycoprotein is involved in chloride secretion and the regulation of cell volume, and is encoded by the multidrug-resistance gene. Its function in the enterocyte likely is the secretion of unmetabolized and metabolized xenobiotic agents directly into the intestinal lumen.

Intestinal epithelial cells contain many metabolic enzymes, with variable specificities. Clinical studies have been performed using pharmacologic â€œcocktailsâ€• of probe substrates, whose metabolic disposal is well understood. For example, the clearance of caffeine, administered orally, is mediated by cytochrome CYP1A2, whereas the clearance of midazolam is mediated by CYP3A. Providing both xenobiotics would allow understanding of the relative metabolic rates of these two enzymes in a given subject. To further determine the relative contributions of intestine and liver in drug metabolism, the relative clearance rates after oral and intravenous administration can be compared. A greater or lesser clearance after oral administration is evidence of metabolic induction and inhibition, respectively.

There is wide variation in the rates of metabolism of xenobiotics between individuals. Demographic variables, such as age and sex,[43] and inherited variables, such as specific polymorphisms, are demonstrated. Metabolism of individual xenobiotics may be affected by foods, herbal products, and other xenobiotics. For example, clinical observations associated the intake of grapefruit juice and Brussels sprouts with xenobiotic toxicity or ineffectiveness. Formal studies then demonstrated the effects of these foods on the pharmacokinetics of certain xenobiotics.[6, 73] Grapefruit juice inhibits intestinal CYP3A and other enzymes, including the P-glycoprotein transporter, which, following ingestion, may lead to exaggerated pharmacologic effects from medications such as calcium channel blockers and statins.[25, 80] One compound in grapefruit juice, 6,7-dihydroxybergamottin, not only directly inhibits CYP3A but also promotes its degradation.[60] The same pharmacokinetic effects were not observed when the some medications were administered intravenously, implying that the effect may be limited to drug metabolism during its transport across the intestinal epithelium, rather than in the liver. This interaction is especially problematic when the grapefruit juice is taken intermittently rather than consistently, as the pattern may be erratic and may consequently go unnoticed.

Many interactions between allopathic medications and herbal products also have been described. For example, observational studies demonstrated that plasma levels of indinavir, digoxin, and other drugs are lowered by concomitant long-term use of St. John's wort.[47, 75] The FDA has further reported interactions between St. John's wort and a wide variety of medications, including oral contraceptives, selective serotonin reuptake inhibitors, HIV protease inhibitors, cyclosporine, and sildenafil.[17] St. John's wort is associated with breakthrough menstrual bleeding and pregnancies occurring in women using oral contraceptives.[83]

The interactions of St. John's wort and the intestine are complex, as the xenobiotic has been found to inhibit intestinal CYP3A4 over

the short-term and to induce intestinal CYP3A and P-glycoprotein over the long-term. Thus, the actual effect of St. John's wort on a drug metabolized by CYP3A4 and/or P-glycoprotein will differ when the drug is initiated, when it is continued, and when it is stopped. Echinacea also affects drug-metabolizing enzymes, specifically inhibiting CYP3A4, CYP2C9, and CYP1A2, and inducing CYP3A activities, leading to reported interactions with theophylline, phenytoin, and cyclosporine.[37]

Drugâ€“drug interactions also may affect the intestine. The interactions may include inhibition or induction. A prominent example is rifampin, which induces CYP3A4 enzymes and P-glycoprotein in both the intestine and liver.[82] Both activities would lead to enhanced drug disposition and decreased effectiveness. Rifampin exerts these effects binding to and activating the pregnane X receptor nuclear transcription factor, and promoting transcription of relevant mRNA in the intestinal epithelium and liver.[35] On the other hand, ketoconazole inhibits P-glycoprotein transporter, which could lead to higher concentrations than expected of administered drug.

Biotransformation and Carcinogenesis

The processes of biotransformation in the intestine are relevant to colonic carcinogenesis. For example, environmental factors, such as diet and tobacco use increase the risk of developing adenomatous polyps or colorectal cancer.[68 , 90] Uridine diphosphate glucuronosyltransferase (UDPGT) catalyzes the conjugation of numerous xenobiotics with uridine diphosphate glucuronic acid. Colonic epithelial cells express several UDPGT isoforms, which may be involved in the detoxification of colorectal carcinogens.[91] Glucuronidation is a critical detoxification pathway for the two major classes of tobacco smoke carcinogens, as well as heterocyclic amines, which are mutagenic compounds that are abundant in tobacco smoke and in fried and broiled meats. It is

possible that other environmental xenobiotics could have similar effects over a period of years. The activities of these detoxifying enzymes vary greatly in different individuals.[89] These differences lead to variable rates of disappearance of the potential carcinogen and, in combination with dose of carcinogen and other factors, could influence the development of carcinoma in an individual.

Microbiologic Considerations

The endogenous flora in the GI tract includes more than 400 different species of bacteria. The number of bacterial â€œcellsâ€• in the intestinal lumen is greater than the total number of host cells, the mass of bacteria is more metabolically active than the liver, and the bacteria have a greater diversity in genetic material than the host. The

concentration of luminal bacteria varies by site, from lowest in the proximal small bowel to highest in the colon. Endogenous bacteria occupy unique niches related to host physiology, environmental pressures, and microbial interactions, which result in long-term stability.[41] There is considerable variation in the composition of the endogenous flora between individuals. The flora may be altered by various insults but returns to baseline once the insults are removed. The endogenous flora affects enterocyte and lamina propria mononuclear cell functions. This is best shown in studies of germ-free animals that are colonized with a single species of bacteria. The intestinal microflora also modifies the intestinal and systemic responses to intestinal injury, as demonstrated by the mild nature of graft-versus-host disease in germ-free animals.[8]

The endogenous flora has multiple metabolic functions. A primary function in the colon is the salvage of malabsorbed carbohydrates by fermentation and production of short-chain fatty acids, which is a preferred substrate for colonic epithelial cells. Hydrolysis of urea occurs following its passive diffusion into the intestinal lumen,

producing NH_3 and a carbon skeleton. Elevated levels of nitrogenous compounds, including ammonia, may result from increased dietary load, or from gastrointestinal hemorrhage, by decreased excretion caused by renal failure, or by decreased clearance, such as occurs in end-stage liver disease with hepatic encephalopathy. Bacterial fermentation of the nonabsorbable disaccharide lactulose in the colonic lumen leads to the production of lactic acid and other short-chain fatty acids, which decrease intraluminal pH and trap nitrogen in the lumen as NH_4^+, conditions that are useful in treating patients with hepatic encephalopathy.[19]

Bacterial metabolism also may affect the disposition of intraluminal compounds. Bacterial metabolism of digoxin contributes to its steady-state concentrations in the body, and antibiotic treatment may reduce or eradicate the intestinal flora, affecting the steady state and predisposing to digoxin toxicity.[20] Bacterial contribution to vitamin K metabolism also is demonstrated by changes in the prothrombin time, necessitating adjustments in the therapeutic doses of warfarin after antibiotic therapy. Bacterial metabolism also affects the composition and concentration of various bile acids and steroid hormones. Bacterial enzymes have been incorporated into treatment strategies, for example, as in the treatment of ulcerative colitis. The first effective drug treatment for this disease was developed by linking 5-aminosalicylic acid, an antiinflammatory agent, to sulfapyridine, thus making it nonabsorbable in the small intestine. This medication only becomes active when bacterial azoreductases in the terminal ileum and colon break the azo bonds, making the products absorbable in the colon at the site of inflammation.[86]

There is considerable evidence that the endogenous flora also might affect carcinogenesis in the intestinal lumen. Because many lipophilic xenobiotics are excreted from the liver after conjugation with glucuronic acid, bacterial Î²-glucuronidases might lead to reabsorption and recirculation of these compounds. In addition,

bacterial Î²-glucosidases may activate carcinogens. For example, germ-free animals do not develop tumors when fed cycasin, but in nonâ€“germ-free animals bacterial metabolism produces methazoxymethanol, a known carcinogen found in the colon.[55] Consumption of a high-beef diet leads to increased fecal bile acid excretion and changes in colonic bacterial metabolism,[39] which may convert a bile salt, chenodeoxycholic acid, into a carcinogen. Bacterial sulfatases also are capable of converting dietary cyclamate to cycloheximine, which is a bladder carcinogen.[13]

The term *probiotics* connotes live, nonpathogenic bacteria and fungi that are part of the normal flora, and which can be used as prophylactic or therapeutic agents. These bacteria compete for and displace pathogenic bacteria from ecologic niches, they directly modulate intestinal immune function, and they exert a trophic effect on the gut. They are being studied to decrease traveler's diarrhea, suppress recurrent *Clostridium difficile* toxin-associated diarrhea, and to reduce the inflammation in ileal pouches after colectomy in patients with ulcerative colitis, among other uses.[14]

An Anatomic Approach to Xenobiotics and the Gastrointestinal Tract

An anatomic approach to the effects of xenobiotics on the lips, mouth, and oropharynx (Table 25-1), the esophagus (Table 25-2),

the stomach (Table 25-3), and the small and large intestines (Table 25-4) is offered in brief in these tables.

Gingivitis, stomatitis (loose teeth)
Inflammation and irritation
Antineoplastics
Caustics
Ciguatera (tooth pain)

Ionizing radiation
Metals (arsenic trioxide, mercuric chloride, lead, thallium, zinc chloride)
Oxalates
Phenol
Phenytoin
Phosphorous
Edema
Allergic
Penicillin
Angioedema
Angiotensin-converting enzyme inhibitors
Mechanical irritation and injury
Caustics
Oxalate-containing plants
Pain and ulceration
Early
Caustics
Paraquat
Delayed
Clozapine
Antineoplastics
Drooling
Increased saliva
Aminopyridine
Cholinergics
Nicotine
Phencyclidine
Dysphagia
Foreign bodies (drug packets, batteries)
Dry mouth
Decreased saliva

Direct

Anticholinergics
Botulism
From hypovolemia

Diuresis
Diuretics
Lithium
Insensible loss
Salicylates
CNS stimulants
Decreased fluid intake
CNS depressants
Increased GI fluid losses
Cathartics
Colchicine
Tongue discoloration
Direct toxic effects
Blueâ€”methylene blue
Brownâ€”bromide, bismuth
Greenâ€”vanadium

Type of Effect	Mechanism	Example

TABLE 25-1. Toxic Effects on the Lips, Mouth, and Oropharynx

Painâ€”retrosternal
Pain fiber stimulation
Alcohol
Caustics
Increased muscle tension caused by

Obstruction
Foreign body/drug packets

	Spasm	
Caustics		
Mediastinitis/esophageal	perforation	
Caustics		
Emetics		
Foreign body		
Dysphagia/odynophagia		
Neuromuscular		
Botulism		
Diphtheria		
Paralytic shellfish		
Strychnine		
Tetrodotoxin		
Thallium		
Mechanicalâ€”obstruction		
Diphtheria		
Foreign body (drug packets)		
Large pill size or large number of pills		
Mechanicalâ€”irritation and injury		
Caustics		
Iodine		
Mercuric chloride		
Paraquat, diqua		

Type of Effect	Mechanism	Examples

TABLE 25-2. Xenobiotics that Affect the Esophagus

The Pancreas and Pancreatic Disease

The pancreas lies in the retroperitoneum, in a transverse fashion, between the second portion of the duodenum and the spleen. The gland serves both exocrine and endocrine functions, with the secretion of pancreatic juice and enzymes as exocrine functions,

and the secretion of insulin, glucagon, and other hormones as endocrine functions. The pancreatic acini contain cells producing digestive enzymes, which flow to the duodenum through the pancreatic ducts. Endocrine cells are found in the islets of Langerhans, which are found diffusely throughout the pancreas.

Pancreatic exocrine function responds to neural, hormonal, and luminal stimuli. The strongest stimulus is the presence of partially digested food in the duodenum, which leads to the release of cholecystokinin and subsequent stimulation of pancreatic secretion and fluid flow, among other effects. Pancreatic exocrine function is inhibited by hormones derived from the distal intestine. Pancreatic enzyme activities are further regulated by the secretion of inactive precursors, which require activation in the intestinal lumen. This is accomplished by the action of trypsin, after the activation of trypsinogen by enterokinase in the duodenum. In fact, amylase and lipase are the only pancreatic enzymes to be secreted in an active form.

Pain
Epigastric pain fiber stimulation
Alcohols
Antineoplastics
Arsenic
Caustics
Colchicine
Iron
Mercuric chloride
NSAIDs
Podophyllin
Salicylates
Perforation (peritonitis)
Caustics
Salicylates
Pill concretions

Obstruction
Bezoars
Foreign body
NSAIDs
Salicylates
Vomiting
Local stimulation
Caustics
Colchicine
Detergents/soap (strong)
Fluoride
Metals (iron, mercury, thallium, arsenic)
Mushrooms
Salicylates
Solvents
Staphylococcal exotoxin
Zinc chloride
Central chemoreceptor trigger zone
Cardioactive steroids
CO (?)
Opioids
Nicotine
Local and central
Methylxanthines
Syrup of ipecac
Increased intracranial pressure

Toxin-induced hemorrhage
Amphetamine
Cocaine
Ephedrine
Edema
Vitamin A
Postanoxic brain injury

Hemorrhage or infarct
Hypertension
Hypotension
Coagulopathy
Anticoagulants
Crotaline envenomation
Hematemesis
Direct mucosal injury
Alcohols (ethanol, isopropyl)
Caustics
Metals
Plants
Radiation
Salicylates and NSAIDs
Zinc chloride
Coagulopathy
Anticoagulants
Hepatic failure

Type of Effect Mechanism Examples

TABLE 25-3. Xenobiotics that Affect the Stomach

Pain
Increased contraction
Local irritation
Caustics
Colchicine
Metals
Mushrooms
Solanine-containing plants
Stimulant cathartics
Cholinergic stimulation
Cholinergics

Opioid withdrawal
Obstruction
Foreign body/drug-containing packets
Diarrhea
Mechanical irritation and injury
Bacterial endo- and exotoxins (food poisoning)
Cathartic stimulants
Caustics
Colchicine
Metals
Mushrooms
Solanine-containing plants
Failure of mucosal regeneration
Colchicine
Daunorubicin
Etoposide
Fluorouracil
Ionizing radiation
Podophyllin
Cholinergic stimulation
Cholinergics
Nicotine
Opioid withdrawal
Other mechanisms
Methylxanthines
Constipation
Local effects
Fluid and electrolyte depletion Opioids
Central effects
Anticholinergics
Infant botulism
CNS depressants

Type of Effect	Mechanism	Examples

TABLE 25-4. Xenobiotics that Affect the Small and Large Intestines

Pancreatitis connotes tissue damage and inflammation. Pancreatitis can be categorized clinically as acute or chronic, based upon course and mild or severe, based upon organ function, systemic effect, complications, and recovery time. Pancreatitis also can be categorized pathologically as interstitial or hemorrhagic. Interstitial pancreatitis features edema and inflammation histologically, plus acinar cell necrosis. In contrast, hemorrhagic pancreatitis features more widespread necrosis and widespread tissue hemorrhage and vascular thrombosis.

Pathogenically, acute pancreatitis usually involves premature activation of pancreatic enzymes in the acinus. Pathogenic mechanisms include both pancreatic hypersecretion and inhibition of secretion. The activity of the pancreatic proteases and other digestive enzymes is opposed by circulating protease inhibitors, $\hat{I}\pm_2$ -macroglobulin, $\hat{I}\pm_1$ -antitrypsin, and others. These latter proteins are acute-phase reactants and are released in response to tissue damage. They act to localize the damage, limit its severity, and prepare for tissue repair, but they respond to the development of pancreatitis and do not play a preventive role.

Although there are multiple etiologies underlying acute pancreatitis, alcohol, and gallstones are the most important. The specific effects of alcohol are uncertain, but may include hypersecretion, sphincter of Oddi spasm, and hypertriglyceridemia.[36] The delivery of ethanol to the pancreatic interstitium and ductal space results in premature release of free fatty acids, hypertriglyceridemia, and subsequent epithelial damage.

Evidence of chronic pancreatitis occurs in the majority, but not all

alcoholic patients with pancreatitis. In contrast, the effect of gallstones in promoting pancreatitis is likely to be physical in nature, that is, an impacted gallstone directly blocks the pancreatic duct. Recent evidence suggests that excess free radicals may exacerbate pancreatitis from many causes.

Xenobiotic-induced pancreatitis is a broad topic with multiple agents, whose association with disease can be listed as definite, likely, or possible (Table 25-5). The pathogenic mechanism varies with the specific xenobiotic, although some xenobiotics, such as the nucleoside reverse transcriptase 2â€²,3â€²-dideoxyinosine, may promote pancreatitis as a result of mitochondrial toxicity.[84] Multiple mechanisms account for xenobiotic-induced pancreatitis. Overstimulation is recognized with exposure to cholinesterase inhibitors, such as parathion[56] or scorpion venom;[76] vasospasm, secondary to ergot alkaloids, is also reported.[23] Acute exposure to excessive amounts of dioxin led to acute pancreatitis in an assassination attempt during the 2004 presidential campaign in the Ukraine.[49] Of more widespread concern, environmental exposures to dioxins are known to produce pancreatic disease with ultrastructural studies demonstrating evidence of mitochondrial damage.[70 , 79]

Direct Toxicity to the GI Tract

There are several important categories of xenobiotics that are directly toxic to the GI tract. Among them are â€œtraditional agentsâ€• such as caustics, ethanol, and other alcohols. In recent years, the potential damage of biologic, chemical, or radiologic weapons to the body in general, and to the GI tract in particular, has become a great concern. Among the biologic agents considered to be potential weapons, botulism, ricin, and staphylococcal enterotoxin B are of particular concern to the GI tract. Exposure to ionizing radiation affects the GI tract to a greater extent than most other areas of the body because of the

rapid cell turnover in the GI tract.

Caustics

Caustics are a commonly available, serious source of direct toxicity to the upper GI tract. Alkaline caustics such as sodium hydroxide (NaOH), the main ingredient in lye, drain cleaners, and oven cleaners, produce liquefactive destruction of the mucosa that may involve all layers of the esophagus and stomach. In contrast, hydrogen ions desiccate epithelial cells and denature proteins, producing an eschar and resulting in what is histologically referred to as coagulation necrosis. In some series, both the gastric and esophageal mucosae are equally affected by acids,[105] while in others, the esophagus is spared and the stomach is severely injured.[38] Although the esophageal lining is well equipped to withstand the effects of brief exposure to pH 1, which is the same concentration of hydrochloric acid as is present in gastric acid, much higher concentrations can be obtained commercially, and the risk of acid damage to the esophagus is most likely related to concentration.

Perhaps as a result of the coagulation necrosis produced by acids in that location, the acid damage to the esophagus may not be as great

as the damage caused there by strong alkalis. However, in marked contrast, the damage to the stomach and the resultant systemic effects of acid ingestion may be devastating. Because of its tendency to perforate the stomach, acid ingestion may result in widespread damage to other abdominal organs including the spleen, pancreas, and biliary tract.[104] Late effects of acid ingestions include esophageal pseudodiverticula, gastric atony, decreased acid secretion, and gastric outlet obstruction.[53] Both acid and alkali ingestions are linked to the subsequent development of squamous cell carcinoma of the esophagus and

stomach, particularly at the gastroesophageal junction.[45]

- Alcohols
  - Ethanol
  - Methanol
- Analgesics and NSAIDs
  - Acetaminophen
  - Opioids
  - Salicylates[a]
  - Sulindac
- Antibiotics
  - Pentamidine
  - Rifampin
  - Sulfonamides
  - Tetracycline
- Anticonvulsants
  - Valproic acid
- Antihypertensives
  - ACE inhibitors
  - Diazoxide[a]
  - Methyldopa[a]
- Antimitotics
  - Azathioprine
  - L-Asparaginase
  - Mercaptopurine
- Antivirals for HIV Disease
  - Nucleoside analog
    - Reverse transcriptase inhibitors
      - Didanosine
      - Zalcitabine
      - Zidovudine
- Diuretics
  - Chlorthalidone[a]
  - Ethacrynic acid[a]
  - Furosemide

Thiazides

Hormones

Corticosteroids

Estrogens

Others

Organic phosphorous compounds

Phenformin

Alpha Cells

Cobalt salts

Decamethylene diguanidine

Phenylethylbiguanide

Beta Cells

Alloxan

Androgens

Cyclizine

Cyproheptadine

Diazoxide

Dihydromorphanthridine

Epinephrine

Glucagon

Glucocorticoids

Growth hormone

Pentamidine

Streptozocin

Sulfonamides

Vacor

Zinc chelators

Delta Cells

None known

[a] Based on single or rare case reports.

Modified after Riddell RH, Strauss FH: The pancreas. In: Riddell RH, ed: Pathology ot Drug-Induced and Toxic Diseases. New York. Churchill Livingstone, 1982, pp. 611â€“629.

Exocrine Pancreas	Endocrine (Islets of Langerhans) Pancreas

TABLE 25-5. Xenobiotics Associated with Pancreatitis

Endoscopy cannot provide information about the depth of injury and is best at determining whether there is little or no injury. The most serious toxicity is full-thickness ulceration, with esophageal perforation and the development of mediastinitis. When perforation does not occur, healing is characterized by dense scarring, despite steroid or other therapies,[42, 77] with strictures that can be so irregular and severe as to require surgical intervention to allow food intake (see Fig. 6-22).

For the clinical presentation and treatment of caustic acid and alkali injuries, see Chap. 100 .

Biologics

Botulism is an old disease whose presentation has evolved.[18] Classically a food-borne disease, it also became recognized as a complication of wounds, and is recognized to occur in infants. In addition, the potential use of botulinum toxin as a weapon has been emphasized. In fact, the toxin has been applied both therapeutically and cosmetically.

The toxin is a product of the anaerobic Gram-positive bacterium *Clostridium botulinum* . In food-borne botulism, the toxin is ingested, whereas in young infants, poorly formed normal flora and other products fail to inhibit the organism's growth. For this reason, in situ production of toxin may occur and lead to neurologic impairment. Rarely, a similar complication may occur in an adult.

Ricin is extracted from the seeds of the castor bean, whose

ingestion can be lethal. The toxin is protein in nature and is largely degraded in the GI tract, so that toxicity is 1/100 that of a dose administered parenterally. Ricin and the related compound abrin are dimers. One chain inhibits protein synthesis via an enzymatic effect on the 60 S ribosome subunit. The other chain is a lectin and acts as an agglutinin after being taken up by cells. Clinically, ricin produces a severe inflammatory response resembling, in an experimental mouse model, the hemolytic uremic syndrome.[54] Because of its protein composition, protective vaccination is possible and is being investigated.

Staphylococcal enterotoxins are exoproteins produced by *Staphylococcus aureus* . Exposure to these toxins produces a wide range of GI effects, ranging from mild upset to lethal toxic shock. There are multiple types of staphylococcal enterotoxins. Staphylococcal enterotoxin B may produce typical food poisoning, with 12â€“24 hours of fever, vomiting, diarrhea, and more prolonged anorexia. In addition, the enterotoxin may act as a superantigen and bind directly to major histocompatibility complex class II and T-cell receptors in large numbers of T lymphocytes, leading to massive stimulation and release of huge amounts of proinflammatory cytokines, presenting clinically as toxic shock. The toxin has the ability to bind to a receptor on the apical surface of the intestinal epithelial cell, to be transcytosed intact, and to gain access to the systemic circulation. In experimental animals, lymphoid hyperplasia developed after lethal exposure to the toxin, which is consistent with widespread immune activation.[99] In addition to lymphoid effects, direct toxicity on pulmonary and renal endothelium can be demonstrated. Clinically, a biphasic response occurred, with an early GI syndrome and a later systemic shock syndrome and renal failure.

Radiation

The GI tract is a major site of acute and chronic radiation injury

related either to environmental contamination or to radiation applied for medical use. Radiation damage to normal tissues occurs

by the same mechanisms as the damage intended for a targeted neoplasm.[26] Electrons ejected by high-energy photons as they pass through the body (Compton effect) damage DNA directly or through the generation of free radicals.[59] The result is abnormal cross-linking of the DNA strands (guanineâ€“guanine bonds), which must be excised and repaired, as they interfere with DNA replication and subsequent cell mitosis. The degree of damage is related to the dose of radiation as well as factors intrinsic to individual cells and tissues, such as degree of oxygenation, the cell cycle of the individual cells, and others.[27] As damage from radiation and other agents is a normal phenomenon, the cell has the machinery to repair damaged DNA. Excess radiation injury overwhelms the reparative processes and leads to programmed cell death (apoptosis). Individual variation in the efficiency of the DNA repair processes also may influence the fate of radiation injury, especially the buildup of mutations leading to enhanced carcinogenesis.[46] Such a process underlies the pathogenic mechanism in several familial cancer syndromes (Chap. 128).[62]

The pathology of radiation injury is related to its effect on DNA and subsequent inhibition of cell replication. The vulnerability to radiation-induced damage is related to cell proliferation rate. As stated above, the intestine is one of the most rapidly proliferating organs of the body. Damage is greatest with alpha particles intermediate with beta particles and least with gamma irradiation. However, gamma radiation may penetrate and produce deep injury. Radiation injury can occur to the whole body or may be localized, and can be divided into acute and chronic forms, with the chronic form subdivided into chronic damage and secondary carcinogenesis of either epithelial or stromal origin.

Clinically, acute response to radiation exposure is comprised of

nausea, vomiting, cramps, diarrhea, and dehydration, and may have a neurogenic origin.[50] If there has been significant environmental exposure, or the patient has received total-body irradiation sufficient to ablate the bone marrow, this phase is followed within a few days by diffuse destruction of many cell types in the intestine, including lymphocytes, epithelial cells, and vascular endothelial cells. Damage to the intestinal epithelium is enhanced because of its rapid turnover rate under normal situations. The injury persists at higher doses of radiation, leading to diffuse enteropathy, fluid and protein losses through the GI tract, and Gram-negative bacterial and candidal sepsis of presumed enteric source. Healing is associated with neovascularization and dense fibrogenesis, which promotes stricture formation.

The clinical manifestations of radiation injury in the GI tract are dependent on the specific part of the tract involved.[52] Acute and chronic injury to the esophagus leads to dysphagia from ulcers and edema acutely, and from stricture chronically. Rarely, the injury leads to fistulization. The stomach is relatively radioresistant, although affected in cases of high radiation exposure. In contrast, the small intestine is relatively radiosensitive.[95] Radiation injury is very common clinically, and is usually reversible. Although the colon is thought to be relatively radioresistant, it is frequently involved in cases of pelvic irradiation. The situation is worse in segments fixed in the retroperitoneal space, like the rectum, or in segments immobilized by previous surgery.

Acute injury is related to epithelial cell injury and is usually reversed within 2 weeks. In contrast, chronic radiation injury is a progressive process with an initiation within a few years of radiation but progressive damage for decades.[32] Progressive disease may occur even after resection of severely damaged segments and preservation of â€œhealthyâ€• intestine.[63]

Ethanol

Many studies have documented a wide range of GI toxicity in experimental models of alcohol excess and in people who consume large quantities of ethanol (Table 25-6). The toxicities of alcohols other than ethanol, such as methanol and isopropanol, are generally systemic rather than intestinal, but hemorrhagic gastritis or other effects may occur. The major gastrointestinal toxicity of ethanol occurs in the stomach. Alcohol-induced lesions tend to occur after acute ingestions of 8% or higher concentrations in total volume of intake, and alcohol-associated erosive gastritis (sometimes with the concomitant use of aspirin and/or NSAIDs) may be responsible for a majority of cases of upper GI hemorrhage.[22] As commonly used, the term *alcoholic gastritis* describes the gastric erosions and subepithelial hemorrhages, with or without inflammatory cell infiltrates, seen endoscopically in alcoholics.

Alcohol stimulates the secretion of gastric acid and reduces the transmucosal potential difference, allowing back diffusion of hydrogen ions and increased mucosal permeability.[34] Microscopically, alcohol-induced lesions initially alter cell cytoplasm and nuclei, which is followed by widening of intercellular spaces, focal separation of tight junctions, and disruption of apical membranes.

Most studies of small intestinal mucosa show only minimal light microscopic changes induced by alcohol. However, many people who drink large amounts of ethanol, acutely or chronically, note alterations in bowel habits. On investigation, a number of abnormalities in the GI tract are found, including rapid intestinal transit, decreased intestinal disaccharidase activity, decreased bile secretion as a consequence of alcoholic liver disease, and decreased

pancreatic exocrine secretion as a consequence of chronic

pancreatitis. Markedly decreased absorption of fluid and electrolytes together with ileal and colonic fluid malabsorption has been documented in clinically ill subjects, although the role played specifically by alcohol is uncertain.

Mouth
- Nutritional stomatitis
- Cheilosis

Esophagus
- Esophagitis
- Diffuse esophageal spasm
- Mallory-Weiss tear
- Rupture with mediastinitis (Boerhaave syndrome)

Stomach
- Acute gastritis
- Chronic hypertrophic gastritis
- Peptic ulcer
- Hematemesis

Small and Large Intestines
- Malabsorption
- Diarrhea

Liver
- Steatosis
- Alcoholic hepatitis
- Cirrhosis

Pancreas
- Acute pancreatitis
- Chronic pancreatitis
- Pancreatic pseudocyst

Adapted from West LF, Maxwell DS, Noble EP, Solomon DH: Alcoholism. Ann Intern Med 1984;100:412â€“420.

TABLE 25-6. Gastrointestinal Effects of Ethanol

Other gastrointestinal lesions that occur with consumption of large quantities of alcohol include reflux esophagitis associated with reduced lower esophageal sphincter pressure, GI hemorrhage associated with mucosal tears at the gastroesophageal junction (Mallory-Weiss syndrome), and esophageal perforation associated with vomiting (Boerhaave syndrome), as well as acute and chronic pancreatitis, hepatitis, and cirrhosis. In a Scandinavian study of 591 first episodes of acute alcoholic pancreatitis, 260 (46%) of the 562 patients who survived the episode developed recurrent disease. The overwhelming majority of patients were men (503) and 80% of the first relapses occurred within 4 years.[74]

Iatrogenic Diseases

Foreign Bodies

For obvious reasons, the esophagus is the site of most foreign bodies, which may be found in the cervical esophagus, at the level of the aortic notch, just above the gastroesophageal junction, or just proximal to an esophageal narrowing.[16] Food impaction is a foreign body composed of ingested food and is often found in the presence of some esophageal narrowing. The likelihood that a foreign object will lodge in the esophagus is related to its size and shape. The major symptoms related to foreign objects in the upper GI tract are pain, bleeding, perforation, or obstruction. The general rule is that nonoperative means can be employed for up to 12 hours, after which time surgery should be considered, as the chances of tissue necrosis and perforation increase after this time.[12]

Foreign bodies also are commonly found in the stomach. Many small foreign bodies will pass through the stomach and the rest of the GI tract without problems, although objects greater than 5 cm in the largest diameter or 2 cm in the smallest diameter may not be able to traverse the duodenum and must be removed

endoscopically[33] or surgically.

Once in the small intestine, the narrowest area and a site for obstruction is the ileocecal valve, whose maximal opening is about 2.5 cm. Probably the most common type of â€œforeignâ€• body to become impacted at the ileocecal valve is a large gallstone, which gives rise to â€œgallstone ileus.â€•

Foreign objects in the rectum usually are introduced retrograde and may be low-lying in the rectum, or high-lying, above the rectosigmoid junction.[51] Low-lying foreign objects usually can be removed transanally. For more proximally placed objects, the same 12-hour rule can be followed, after which time surgical intervention may be considered.

Gastrointestinal Therapies

A variety of techniques have been applied to the GI tract over the years to minimize local or systemic damage related to xenobiotics, including the induction of vomiting with ipecac,[40,88,97,100] the use of activated charcoal,[2,10,58] prokinetic agents, WBI[4] and luminal acidification.[19] The literature is large but varied, with a relative lack of randomized, controlled studies and great variability in the clinical material available for treatment and for study.[102] It may be difficult to distinguish complications from the poisoning from those related to therapy, for example, aspiration pneumonitis (Table 25-7).[44]

There is little evidence that cathartic use alters the outcomes of activated charcoal therapy,[64] and repeated use of cathartics may have its own toxicities. WBI with a balanced polyethylene glycol and electrolyte solution, decreases the effectiveness of activated charcoal in both in vitro and in vivo studies.

The application of multiple doses of activated charcoal has two rationales: (a) to prevent absorption of xenobiotics, and (b) to speed the elimination of xenobiotics that have already been

absorbed.[3, 29]

Many agents promote intestinal evacuation, and are referred to as laxatives, cathartics, purgatives, promotility agents, and evacuants. These descriptions connote varying degrees of activity. Laxatives and cathartics act within the intestinal lumen, while promotility agents are systemic drugs that have effects on neuromuscular activity. Evacuants typically are used to prepare the colon for diagnostic or therapeutic procedures, but also are used in the case of toxic ingestion. In the past, saline cathartics, such as magnesium salts, and hyperosmolar agents, such as nonabsorbable sugars,

often were used, but there were problems with fluid and electrolyte balances. Currently, bowel evacuation is typically performed using a solution of polyethylene glycol (PEG) with added electrolytes. The PEG is minimally absorbed, and increases the amount of intraluminal water by osmotic means, while the added electrolytes minimize solute fluxes into or out of the intestine. This treatment is ideal for ingestion of sustained-release or enteric-coated drugs, drug packets used for illicit smuggling,[87] and for xenobiotics that are slowly absorbed, like iron and lead.[4]

Orogastric lavage
Emesis
Esophageal tears or perforation (Mallory-Weiss or Boerhaave syndromes)
Gastric perforation
Hemorrhage
Activated charcoal
Constipation
Diarrhea
Intestinal obstruction or pseudo-obstruction (especially after repetitive doses in the setting of dehydration or prior bowel adhesions)

Procedure	Adverse Effect
	Vomiting and aspiration
Cathartics	
	Abdominal cramping (sorbitol)
	Diarrhea and frequent watery stools (sorbitol)
	Electrolyte imbalance: increased Mg^{2+}, decreased K^{+} and Na^{+} (also increased PO_4^{3-} and decreased Ca^{2+} and K^{+} from phosphate enemas)
	Nausea and vomiting
	Rectal prolapse
	Volume depletion and consequent metabolic alkalosis
Emesis with syrup of ipecac	
	Delayed emesis after loss of gag reflex
	Diarrhea
	Electrolyte imbalance with chronic use
	Esophageal (Mallory-Weiss) tears
	Gastric rupture or herniation
	Intractable vomiting and aspiration
Whole-bowel irrigation	
	Bloating
	Colonic perforation (in the presence of severe diverticulitis)
	Rectal itching (from excessive wiping)
	Vomiting, especially with rapid administration

TABLE 25-7. Gastrointestinal Complications of Gastric Decontamination Measures

Saline cathartics, such as magnesium salts, are poorly absorbed, and increase intraluminal osmolality, leading to a flux of water into the intestine, dependent upon the permeability characteristics of the small intestine. Intraluminal magnesium also stimulates the release of cholecystokinin. Among other effects, cholecystokinin stimulates gallbladder emptying and biliary pancreatic flow, as well

as intestinal motor activity.[11]

Hyperosmotic laxatives include sorbitol (D-Glucitol) and lactulose (Cephulac). Milk is an effective hyperosmotic laxative in people who are lactase deficient, as is any nonabsorbable sugar. By remaining in the lumen, the sugar prevents isosmolar water absorption in the duodenum and jejunum, where carbohydrate and water absorption is maximal. Thus, a larger-than-normal amount of fluid, electrolytes, and solute (sugar) enters the colon. Once in the colon, bacteria ferment the sugars, producing 2-, 3-, and 4-carbon compounds that further increase luminal osmolality, as well as hydrogen gas, leading to the production of flatus. Motility also is affected, leading to the symptom of cramping. PEG is a nonabsorbable, nonmetabolizable sugar in polymeric form, that exerts similar osmotic effects as the laxatives mentioned above. However, the PEG is inert, so that it is not metabolized. In addition, the electrolyte composition is balanced so that significant ion or water fluxes do not occur, and symptoms typically are minor. Many studies document its safety and efficacy.[93, 96]

Cathartics have long been recommended for basic poison management but there is little evidence of clinical effectiveness. Bowel evacuation with PEG solutions is currently recommended to speed the elimination of poorly absorbed xenobiotics or sustained-release medications, although evidence, once again, is limited. It is unlikely that evidence will ever be developed to support the efficacy of PEG-ELS based on large, randomized clinical trials; in its absence, reliance on case series and volunteer studies will continue. In one study using orally administered radiopaque markers, administration of PEG solution 30 minutes later did not lead to clearance. Abdominal radiographs taken after the administration of the PEG showed that, in 8 of 10 subjects, some radiopaque markers remained in the right colon, whereas the markers were present throughout the intestine in the other 2 subjects.[61] Thus, some care in the clinical application of this technique in a variety of circumstances is warranted, especially in

the follow up of treatment in cases where the offending agent can be detected, such as iron tablets and drug packets (see Figs. 6-8 , 40-1 , and 40-2).

Alterations in fluid and electrolyte balance are the major potential adverse effects of cathartics and other agents, especially when used repetitively. Nausea, vomiting, and cramping are most common, while other problems, such as rectal prolapse, have been reported. Morbidity may be higher in the elderly[9] and in young infants. Antiemetics may be used, if needed.

While antiemetic therapies are not usually considered in discussions of toxicology, they may play a role in the management of symptoms related to toxic agents. A number of antiemetic agents with differing mechanisms of activity have been developed. Phenothiazines and butyrophenones prevent nausea and vomiting via central nervous system dopamine antagonism. Metoclopramide is a substituted benzamide and procainamide derivative with a variety of central and peripheral effects, predominantly dopamine antagonism, but also 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonism and cholinomimetic effects. Domperidone is a benzimidazole derivative that blocks peripheral dopamine receptors and is thought not to cross the bloodâ€“brain barrier, although it does affect the circumventricular areas where the barrier is incomplete, such as the area postrema. It is not approved for any specific indication by the FDA, but is available in many other countries. Anticholinergics, such as transdermally administered scopolamine, are not antiemetics, but decrease the sensation of nausea, especially related to motion sickness. Based on studies that show that nausea and vomiting may be mediated via 5-HT_3 receptors,[30] particularly in the area postrema, a number of inhibitors have been developed and are in wide clinical use.

Summary

The GI tract is vulnerable to a wide variety of pathogenic agents

with diverse physical, chemical, and biologic forms. Understanding the effects of such xenobiotics on the intestine and the body requires an understanding of the normal anatomy and physiology of the intestine. Except when injured or perforated by agents such as caustics, ionizing radiation, and alcohol, or obstructed by drug-containing packets or batteries, the GI tract is typically not regarded as a significant site of drug toxicity. Nevertheless, because of both its potential as a site of severe local or systemic effects and the role that GI signs and symptoms play in various diagnostic toxic syndromes, the GI tract is an important consideration in almost any toxicologic emergency.

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Chapter 26
Hepatic Principles

Kathleen A. Delaney

The liver plays an essential role in the maintenance of physiologic homeo include the synthesis, storage, and breakdown of glycogen; the metabolis synthesis of albumin, clotting factors, and other important proteins; synth acids necessary for the absorption of lipids and fat-soluble vitamins; the cholesterol; the excretion of metals, most importantly iron, copper, zinc, mercury, and aluminum; and the detoxification of products of metabolism and ammonia.[28, 62, 129] Generalized disruption of these important functi familiar manifestations of liver failure: hyperbilirubinemia, coagulopathy, hyperammonemia, and hypoglycemia.[40, 74] Disturbances of more specific accumulation of fat, toxic metals, hypercholesterolemia, and fat-soluble deficiencies.[20]

The liver is also the primary site of biotransformation and detoxification contains the highest concentration of enzymes involved in phase I oxida reactions.[46] Its interposition between the gut and systemic circulation ma recipient of xenobiotics absorbed from the gastrointestinal tract into the also receives blood from the systemic circulation and participates in the elimination of xenobiotics that reach the bloodstream through other route

or cutaneous absorption. Many detoxified xenobiotics are excreted in the the biliary tract provides a second essential route for the elimination of and products of metabolism.[20 , 28]

Many xenobiotics are lipophilic, inert substances requiring chemical activa sufficiently soluble to be eliminated. This is accomplished by conjugation products of phase I biotransformation with molecules such as glucuronide or biliary excretion. Although phase I activation followed by phase II cor results in detoxification of these xenobiotics, it occasionally leads to the xenobiotics with increased toxicity, which is often manifest at the site of [83] Because of its location at the end of the portal system and its substan biotransformation enzymes, the liver is especially vulnerable to toxic inju for a more in-depth discussion of the biotransformation reactions.)

Morphology and Function of the Liver

Approximately 75% of the blood supply to the liver is derived from the p drains the alimentary tract, spleen, and pancreas. This blood is enriched other absorbed xenobiotics and is poor in oxygen. The remainder of the l comes from the hepatic artery, which delivers well-oxygenated blood from circulation.[20 , 129] Blood from the hepatic artery and portal vein mixes in coming in close contact with cords of hepatocytes before it exits through wall of the vein. Oxygen content diminishes several fold as blood flows fr to the central vein, affecting the localization of oxygen-dependent mecha [, 16] The sinusoidal lining formed by endothelial cells is thin and fenestrat of fluid, chylomicrons, and proteins across the space of Disse, an extrasi with microvilli.[20] Macrophages (Kupffer cells) within the sinusoids scaven materials and cell debris. When immunologically activated by xenobiotics, contribute to the generation of oxygen free radicals and may also particip production of autoimmune injury to hepatocytes.[33] Ito cells found betwee cells and hepatocytes are a primary site for the storage of fat and vitamin

Bile acids, organic anions, bilirubin, phospholipids, xenobiotics, and other in bile are actively transported across the hepatocyte plasma membrane i canaliculi at sites that have specificity for acids, bases, and neutral comp junctions separate the contents of the bile canaliculi from the sinusoids a

maintaining a rigid and functionally necessary compartmentalization. Bile
transport systems: a sodium-dependent bile salt transporter in the sinuso
adenosine triphosphate (ATP)-dependent bile salt carrier in the canalicular
canalicular membrane transport site driven by the membrane voltage po
Glucuronidated xenobiotics are substrates for the bile acid transport syste
secreted into bile. Xenobiotics with molecular weights greater than 350 d
preferentially secreted into bile. Like the transport and concentration of
sinusoids and hepatocytes, the flow of bile through the canaliculi is an ac
facilitated by ATP-dependent contractions of actin filaments that encircle
[139] Xenobiotics induce cholestasis by targeting specific mechanisms of bil
flow.[67]

The enterohepatic circulation of bile acids and some vitamins plays a cruc
conservation. Unfortunately, this physiologically important process impede
elimination of some xenobiotics by reabsorbing and returning them back
circulation, prolonging their half lives and toxicity. Xenobiotics that are n
intestinal pH and that have low

molecular weights, such as methyl mercury, phencyclidine, and nortriptyli
to be reabsorbed.[28 , 114]

Two basic pathologic concepts are used to describe the appearance and f
a structural one represented by the hepatic lobule, and a functional one
acinus. The basic morphologic unit of the liver characterized by light micr
hepatic lobule, a hexagon with the central vein at the center and the port
angles. Cords of hepatocytes are oriented radially around the hepatic veir
â€œmetabolic lobuleâ€• is a functional unit of the liver. Located betweer
it is bisected by terminal branches of the hepatic artery and portal vein t
bases of the acini toward hepatic venules at the apices. The acinus is sul
metabolically distinct zones. Zone 1 lies near the portal triad, zone 3 nea
and zone 2 is intermediate. Figure 26-1 illustrates the relationship of the
functional concepts of the liver. The different metabolic functions of these
cellular location of biotransformation reactions affect the anatomic distribu
produced by xenobiotics. There is useful correlation between these anato
conceptualizations of the liver. Hepatocellular injury that occurs near the
periportal necrosis. This term describes injury in zone 1.[20] The terms *cen*

necrosis refer to injury that surrounds the central vein. Figure 26-2 show necrosis caused by exposure to bromobenzene.

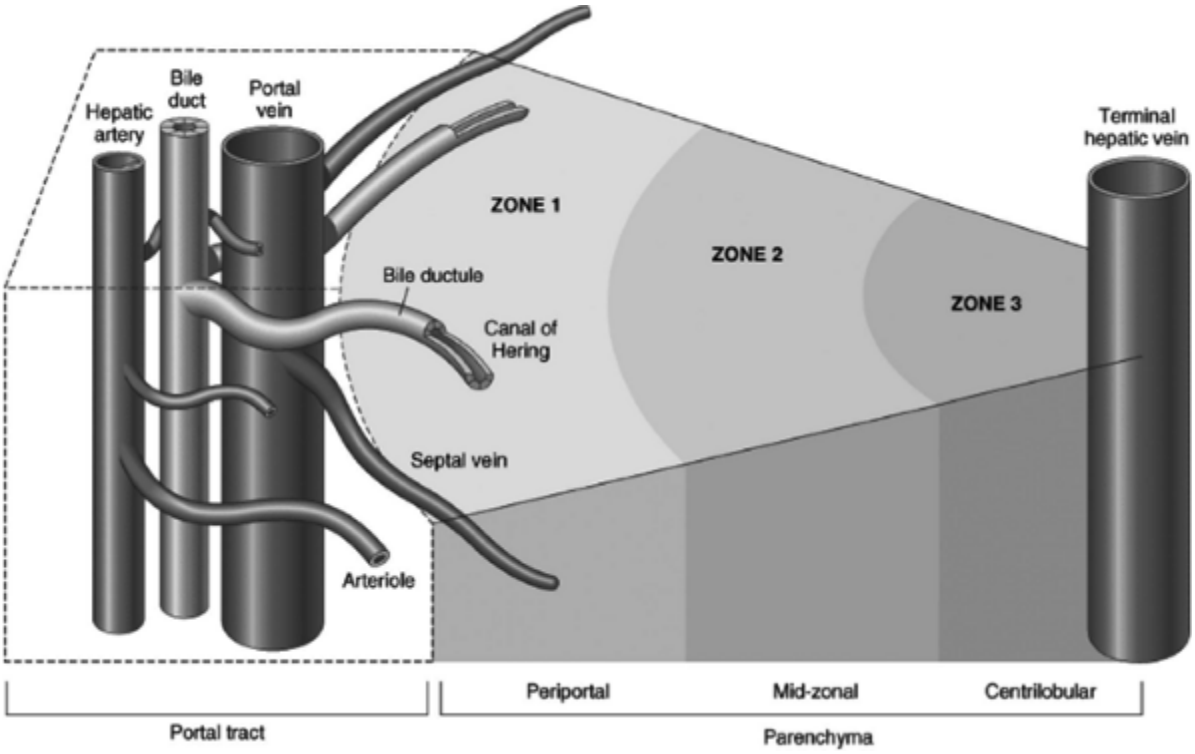

Figure 26-1. The acinus is defined by three functional zones. Specific co zone to the biotransformation of xenobiotics reflect the declining oxygen c it flows along sinusoids from the oxygen-rich portal area to the central h Hepatocytes that form the parenchyma of these three zones also have er metabolic functions that are specific to each of the three zones. The hepa shown) is a structural concept, a hexagon with the central vein at the cer portal areas that contain branches of the hepatic artery, bile duct, and po hepatocytes that is confined to zone 3 is called â€œcentrilobularâ€• beca of the lobule, zone 3 encircles the central vein, which is the center of the *(Adapted with permission from Crawford JM: The liver and the biliary trac Fausto N, Abbas A, eds: Robbins and Cotran's Pathologic Basis of Disease, Philadelphia, Elsevier, 2004,* Fig. 18.1 *, p. 879.)*

Factors Affecting the Localization of Hepat

Metabolic characteristics of the three zones of the acinus have important anatomic distribution of toxic liver injury. Zone 1, which begins in the pe closest to the vascular supply and has a 2-fold higher oxygen content tha Predictably, hepatic injury that results from the metabolic production of predominates in zone 1.[7] The tendency for centrilobular or zone 3 accumu patients with alcoholic steatosis is attributed to the effect of relative hypo vein area on the oxidation potential of the hepatocyte.[80] The availability detoxification and the localization of enzymes involved in biotransformatio site of injury. Zone 1 has a higher concentration of glutathione, whereas capacity for glucuronidation and sulfation.[134] Zone 3 has higher levels of dehydrogenase, which may lead to increased production of toxic acetaldeh centrilobular sites.[80 , 84] Zone 3 also has high levels of cytochrome oxid (CYP) 2E1, which converts acetaminophen, nitrosamines, benzene, and CCl_4) to reactive intermediates that may cause centrilobular injury. In proliferation of the smooth endoplasmic reticulum in the centrilobular are increased activity of CYP2E1.

This increases the risk of liver injury in alcoholic patients exposed to xen metabolized by CYP2E1 (Table 26-1).[48 , 81 , 99]

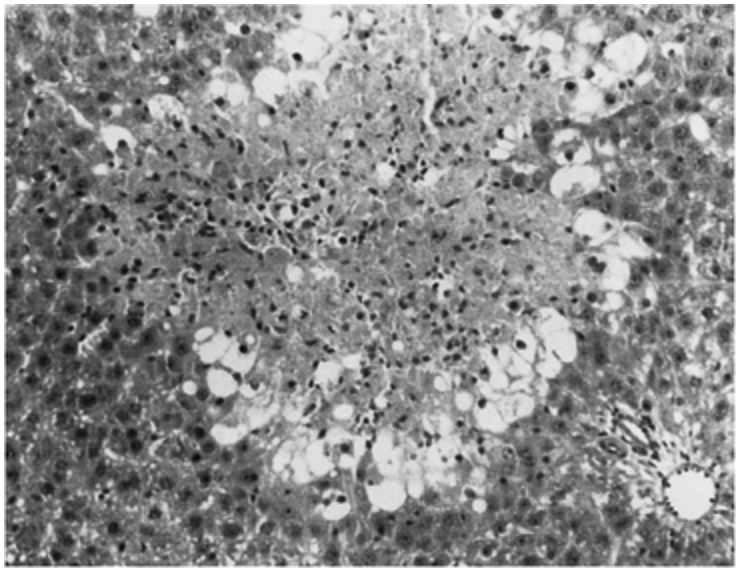

Figure 26-2. Centrilobular necrosis in a rat liver caused by bromobenze Note the polymorphonuclear leukocyte infiltration surrounded by vacuolat

the necrotic area. *(Reprinted with permission from Hetu C, Dumont A, Joly chronic ethanol administration on bromobenzene liver toxicity in the rat. 1983;676:166.)*

The behavior of free radicals produced by the metabolism of CCl_4 has be studied in the laboratory. The following steps are proposed to explain the hepatic injury by CCl_4 . The trichloromethyl free radical ($Â·CCl_3$) is gene CYP2E1 in a reduced form of nicotinamide adenine dinucleotide (NADPH) reaction.[2 , 81] This occurs primarily in zone 3, which has the higher conc activity. It can form covalent bonds with cellular proteins, cause lipid pe spontaneously react with oxygen to form the more highly reactive trichlo radical (CCl_3 OOÂ·).[2 , 33] Low oxygen tension in zone 3 limits synthesis o whereas high oxygen tension in zone 1 fosters its formation. The highly that predominates in zone 1 is rapidly detoxified by glutathione; however $Â·CCl_3$ that predominates in zone 3 is not. Therefore, zone 3 incurs the g injury. Hyperbaric oxygen increases the oxygen tension throughout the li liver injury caused by exposure to CCl_4 , possibly by increasing the forma zone 3, which is then efficiently detoxified by glutathione.[16]

1		
Periportal		
High oxygen content		
High glutathione content		
Oxygen free radical-mediated necrosis		
2		
Mid-zonal		
Shared functions, zones 1 and 3		
Shared functions, zones 1 and 3		
3		
Centrilobular		
Low oxygen content		
High capacity of glucuronidation and sulfation		
Necrosis caused by toxic metabolites of CYP2E1		
High CYP2E1, alcohol dehydrogenase		

Increased CCl_4 and ethanol injury caused by reducing environment

Zone	Location	Biochemistry	Types of Injury

TABLE 26-1. Metabolic Zones of the Liver

The observed effects of isoniazid (an inhibitor of the enzyme CYP2E1) an intake (an inducer of the CYP2E1 gene) on injury in cell cultures from the centrilobular areas exposed to CCl_4 support the association of CCl_4 injury of CYP2E1 activity. Acute exposure to isoniazid significantly decreases th with exposure of cultured zone 3 cells to CCl_4 , whereas chronic treatmer significantly enhances it (see Table 26-1).[81]

Factors that affect the Development of He

Xenobiotics that produce liver damage in all humans in a predictable and manner, such as acetaminophen, CCl_4 , and yellow phosphorous, are call hepatotoxins. Those that cause liver damage in a small number of individ effect is not apparently dose dependent or predictable are called *idiosync* Some cause hepatotoxicity very rarely, whereas others produce it commo hepatotoxins fall into the category of idiosyncratic xenobiotics.[75 , 83] The agent halothane is both an intrinsic and an idiosyncratic hepatotoxin. A m hepatitis occurs in as many as 20% of patients exposed to halothane.[32] T halothane hepatitis, which can be reliably induced in animals, is likely cau toxicity.[117] A more severe idiosyncratic form appears to be caused by an response induced by halothane that targets liver proteins.[13 , 127 , 135]

Sporadic unpredicted hepatotoxicity is not really idiosyncratic, but more lik the combined effects of genetic and other factors that result in the overp decreased clearance of toxic metabolites. Idiosyncratic toxicity is related variability in the capacity to metabolize a specific xenobiotic and would b than â€œidiosyncratic,â€• if the exposed individual's metabolic capabilitie prospectively defined (Chap. 13). An individual's susceptibility to a hepa numerous factors, including the activity of biotransformation enzymes, th substrates, and the immune competence of the individual. In turn, these

sex, diet, underlying diseases, concurrent exposure to other xenobiotics, The susceptibility to toxic effects of a drug may be determined by inherit enzymes. Many enzymes involved in biotransformation show genetic poly example, approximately 8% of whites are deficient in CYP2D6 (formally hydroxylase), which is responsible for the metabolism of a number of dru debrisoquine (an antihypertensive first identified as the substrate of this antidepressants and antidysrhythmics, some opioids, and phenformin.[75] F antianginal agent marketed in Europe in the 1980s, caused severe liver d peripheral neuropathy in persons with a demonstrated inability to metab The congenital disorder that results in Gilbert syndrome is characterized glucuronyltransferase. These patients demonstrate decreased glucuronidat bioactivation of acetaminophen during chronic therapeutic dosing, sugges risk of hepatic injury following ingestions of acetaminophen.[25]

Effects of Other Xenobiotics on Enzyme Fu

Changes in the activities of biotransformation enzymes that result in incr hepatotoxic metabolites increase susceptibility to hepatic injury. Induction gene by the chronic ingestion of ethanol results in a 5- to 10-fold increas activity.[23, 80] Chronic administration of isoniazid (INH) to slow acetylato CYP2E1 activity.[145] Anecdotal observations in humans suggest the possib toxicity caused by solvents such as CCl_4, dimethylformamide, and bromo exacerbated by the chronic ingestion of ethanol.[6, 107] Currently, no data contention that using ethanol increases the clinical risk of acetaminophe [103, 121, 148]

The major studies that describe these xenobiotic interactions were done animals.[48] Bromobenzene is a xenobiotic whose metabolism and hepatoto that of acetaminophen. When administered to rats chronically exposed to of hepatotoxicity occurs more rapidly in study animals, with only a small extent of hepatic necrosis. The dose of bromobenzene required for hepatic not altered by pretreatment with ethanol.[48] Conversely, chronic administr phenobarbital to rats results in a very significant increase in the hepatotc bromobenzene.[109] In other rat studies, prior administration of CYP inhibit

cimetidine may protect against acetaminophen-induced hepatic necrosis.[1] hepatocytes of ethanol-treated rats show increased in vitro susceptibility effects of CCl_4 .[81]

Some xenobiotic combinations increase the possibility of hepatotoxic reac xenobiotic alters the metabolism of the other, leading to the production This is the case with combinations of rifampin and isoniazid; amoxicillin a and trimethoprim and sulfamethoxazole.[3 , 55 , 72 , 102 , 106]

Hypersensitivity

Immune-mediated liver injury is an idiosyncratic and host-dependent hy response to exposure to xenobiotic.[83] It is differentiated from liver injury autoimmune disorders by the absence of self-perpetuation, that is, the n exposure to the xenobiotic to perpetuate the injury.[83] Hypersensitivity rea forms of liver injury that include hepatitis, cholestasis, and mixed disorde hypersensitivity reactions that typically present with hepatitis include ha trimethoprim-sulfamethoxazole, anticonvulsants, and allopurinol.[3 , 4 , 86] present with cholestatic signs and symptoms (pruritus, jaundice, insignifi aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) i chlorpromazine, erythromycin, penicillins, rifampin, and sulfonamides.[27] injury typically begin 1â€“8 weeks following the initiation of the drug, alt begin as late as 20 weeks for drugs such as INH or dantrolene.[37] The ons associated with the oxypenicillins may occur up to 2 weeks after the drug all cases, the onset is earlier when the patient is rechallenged with the d eosinophilia, atypical lymphocytosis, fever, and rash are common clinical hypersensitivity, their absence does not exclude the diagnosis of drug as injury.[63 , 64 , 83 , 86]

How the immune response ultimately leads to cell injury is not well defin the hepatocyte may be mediated by complement- or antibody-directed lys mediated cytotoxicity; or by an inflammatory response induced by immun complement.[10 , 14 , 59 , 61 , 92 , 118] The covalent binding of a reactive e metabolite with a hepatocellular protein resulting in the formation of a ne defined first step in the development of xenobiotic-related autoimmune li covalent binding creates an â€œadductâ€• that is perceived as foreign b

system and induces an immune response. In cases where the metabolite the electrophilic attack is directed against the CYP enzyme at the site of metabolite.[13 , 77 , 83] Adducts and associated autoantibodies have been acetaminophen,[18] minocycline,[10] halothane,[13 , 127] dihydralazine,[14] phen germander.[71] The most severe form of idiosyncratic halothane liver injury fulminant hepatic failure associated with formation of adducts of its trifl (TFA) metabolite with numerous hepatoproteins.[9 , 135] TFA binds and for hepatic enzymes that include pyruvate dehydrogenase.[31 , 59 , 127] It also CYP2E1, the enzyme that metabolizes halothane to TFA. Studies demons against the CYP2E1 enzyme (Chap. 65).[13 , 59 , 118 , 135] Autoantibodies against CYP enzymes have also been demonstrated for dihydralazine,[14] a trifluoroacetyl protein adduct similar to that associated with halothane he in workers who developed hepatic necrosis following exposure to hydro Whether autoantibodies stimulated by the xenobiotic-protein adducts are of cell injury is not clear.

Early reports of lymphocyte sensitization in cases of xenobiotic-mediated suggested that cell-mediated immunity may play a role.[137] Cell-mediated cytotoxicity is implicated in the idiosyncratic type of halothane hepatitis.[3] autoimmune mechanisms are suspected in an increasing number of mode xenobiotic-mediated liver injury. Polymorphonucleocyte activation appears factor in one experimental rat model, where exposure to Î±-naphthyl-isc causes acute cholangitis associated with polymorphonucleocyte (PMN) infi exposure to ANIT stimulates the release of cytotoxic lysosomal enzymes a radicals by activated PMNs.[92] In addition, antibodies directed against cir decrease the extent of liver damage caused by ANIT.[22] Natural killer T ce ubiquitous in the liver, and their possible role in facilitation of cell-media injury is currently being investigated in other models.[21 , 45]

Availability of Substrates

The availability of substrates for detoxification may significantly affect th hepatic injury. The metabolism of acetaminophen illustrates the effect of concentration on the delicate balance between detoxification and the pro metabolites. In healthy adults taking therapeutic amounts of acetaminop

90% of hepatic metabolism results in formation of glucuronidated or sul
Most of the remainder undergoes oxidative metabolism to the toxic elect
benzoquinoneimine (NAPQI) and is rapidly detoxified by conjugation with
Glutathione may be depleted during the course of metabolism of acetami
normal livers, or it may be decreased by inadequate nutrition or liver dis
Excessive amounts of acetaminophen result in increased synthesis of NAP
absence of glutathione, reacts avidly with hepatocellular macromolecules.
concentration of glutathione correlates inversely with the demonstrable c
NAPQI to liver cells.[18]

Morphologic and Biochemical Manifestations Injury

The liver responds to injury in a limited number of ways. Cells may swell
degeneration) and accumulate fat (steatosis) or biliary material. They ma
or undergo the slower process of apoptosis, forming shrunken, nonfunct
bodies. Necrosis may be focal or bridging, linking the periportal or centri
or pan acinar; or it may be massive. An inflammatory cell response may
necrosis.[20 , 75] Injury to the bile ducts results in cholestasis. Vascular in
obstruction to venous or arterial flow. The variety and spectrum of injury
azathioprine illustrates the difficulty in categorizing and characterizing all
causes of xenobiotic hepatic injury. This single agent is associated with m
including asymptomatic aminotransferase elevations, simple cholestasis, h
injury, and vascular injury.[37] All of these manifestations of toxic injury a
Table 26-2 lists characteristic morphologies of hepatic injury and associa

Acute Hepatocellular Necrosis

Acute necrosis of a hepatocyte disrupts all aspects of its function. Because
deal of functional reserve in the liver, hepatic function may be preserved
development of focal necrosis. Extensive necrosis results in functional live
processes that lead to cell necrosis are not well known. Cell lysis is prece
of blebs in the lipid membrane and leakage of cytosolic enzymes, prima

and lactate dehydrogenase. Coalescence of blebs leads to rupture of the and acute irreversible cell death, with disintegration of the nucleus and t cellular function. Prior to membrane rupture, this injury is reversible by processes.[20] The release of intracellular constituents, caused by disruptior membrane, attracts circulating leukocytes and results in an inflammatory hepatic parenchyma.[37] A proposed mechanism of rapid injury to the cell i cascading lipid peroxidation reaction following attack by a free radical. Th has a significant potential to produce oxygen free radicals, as do activate cells.[23, 33, 92] Mechanisms such as covalent binding to cellular enzymes membrane lipids are not the only causes of cell necrosis. The oxidation o phospholipid fatty acyl side chains, and nucleosides also appear to be wi Mitochondrial injury and its associated ATP depletion is also associated w NAPQI, the reactive metabolite of acetaminophen, may target mitochond xenobiotics known to cause mitochondrial injury include antiviral drugs,[79] valproic acid,[11] hypoglycin, margosa oil, and cerulide.[85, 119] Although th calcium ion that precedes the onset of cellular injury accompanies cell dea this simple concept of

calcium as a final mediator of cell death does not account for all observe

Acute Hepatocellular Necrosis

- Acetaminophen[a]
- Allopurinol
- Arsenic
- Atomoxetine
- Carbamazepine
- Carbon tetrachloride[a]
- Cyclopeptide-containing mushrooms[a]
- Dantrolene
- Halothane
- Hydralazine
- Infliximab
- Iron
- Isoniazid
- Methotrexate[a]

Methyldopa
Nitrofurantoin
Phenytoin
Phosphorus (yellow)[a]
Procainamide
Propythiouracil
Quinine
Sulfonamides
Tetracycline
Troglitazone

Steatohepatitis

Amiodarone
Ethanol
Perhexiline
Vitamin A

Microvesicular Steatosis

Aflatoxin
Cerulide
Fialuridine
Hypoglycin
Margosa oil
Nucleoside analogs (antiretrovirals)
Tetracycline
Valproic acid

Granulomatous Hepatitis

Allopurinol
Aspirin
Carbamazepine
Diltiazem
Halothane
Hydralazine

Isoniazid
Metolazone
Methyldopa
Nitrofurantoin
Penicillins
Phenytoin
Procainamide
Quinidine
Quinine
Sulfonamides
Sulfonylureas

Fibrosis
Ethanol
Methotrexate
Vitamin A

Neoplasms
Androgens
Contraceptive steroids
Vinyl chloride

Venoocclusive Disease
Cyclophosphamide
Pyrrozolidine alkaloids

Cholestasis
Allopurinol
Amoxacillin/clavulanic acid
Androgens
Chlorpromazine
Chlorpropamide
Erythromycin estolate
Hydralazine
Nitrofurantoin

Oral contraceptives
Rifampin
Tetracycline
Trimethqprim-sulfamethoxazole

[a] Intrinsic hepatotoxin.

TABLE 26-2. Morphology of Liver Injury by Common Xenobiotics

Acetaminophen is a common cause of acute hepatic injury, as are herbal risks are increasingly recognized.[1,34,51,52,71,97] Many halogenated include carbon tetrachloride, bromobenzene, monochlorobenzene, hydr and halothane also produce hepatocellular necrosis.[6,48,49] A recent stu 11,000 patients exposed to isoniazid during preventive treatment showed injury occurred in 0.10% of those starting treatment, and in 0.15% of th treatment.[93,94,101] Risk factors for the development of hepatotoxicity are female sex, increasing age, coadministration with rifampin, and alcol discussed extensively in Chap. 55 . The thiazolidinedione agents troglitaz rosiglitazone, marketed for the treatment of type 2 diabetes, are associat hepatocellular necrosis.[5,44] The much higher incidence of liver injury at troglitazone led to its withdrawal from the market in March 2000.[78] Table the pharmacologic and toxic xenobiotics that have been reported to caus

Steatosis

Steatosis is the abnormal accumulation of fat in hepatocytes. It occurs in metabolic conditions that include responses to xenobiotics. Two forms of described: macrovesicular steatosis, in which the nucleus is displaced by intracellular fat, and microvesicular steatosis, which is characterized by fa not displace the nucleus. The intracellular fat accumulation reflects abnc metabolism and may occur as a result of any one or more of the followin impaired synthesis of lipoproteins; increased mobilization of peripheral a increased uptake of circulating lipids; increased triglyceride production; d triglycerides to lipoprotein; decreased release of very-low-density lipoprot hepatocytes; and decreased Î²-oxidation of fatty acids.[80] Steatosis is a c usually well tolerated by hepatocytes and is reversible following withdraw

When associated with hepatocellular injury by xenobiotics, it signals the underlying metabolic dysfunction that may lead to cell injury and death. associated with macrovesicular steatosis include ethanol and amiodarone. the uptake of fatty acids into hepatocytes and decreases lipoprotein secr the increased ratio of the reduced form of nicotinamide adenine dinucleoti oxidized form of nicotinamide adenine dinucleotide (NAD^+), associated w metabolism of ethanol, decreases oxidation of fatty acids and promotes f The initial pathologic lesion that occurs in alcoholic liver disease is reve steatosis. Mallory bodies, eosinophilic cytoplasmic deposits of keratin fila degenerating hepatocytes, are also common microscopic findings in alcoh Amiodarone is concentrated in the liver and may account for up to 1% of during chronic therapy.[37] Amiodarone hepatic toxicity resembles that of with steatosis, Mallory bodies, and potential for progression to cirrhosis. intralysosomal phospholipid inclusion bodies were found in all cases in one be specific for amiodarone toxicity.[112] Figure 26-3 shows macrovesicular Mallory bodies caused by administration of amiodarone.

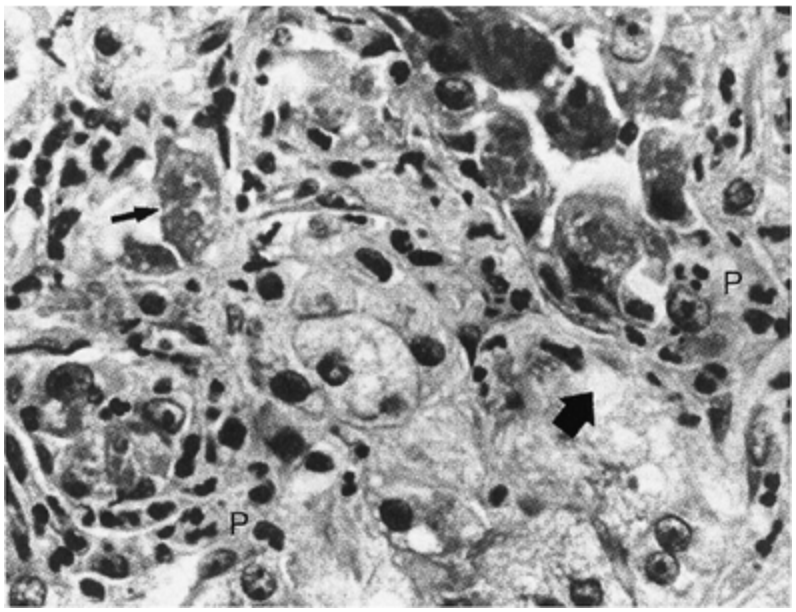

Figure 26-3. Macrovesicular steatosis associated with administration of *small arrow* indicates the presence of Mallory bodies. The *large arrow* poi intracellular fat. (Note that the nuclei are displaced.) Polymorphonuclear also present. *(Reprinted with permission from Lee WM: Drug-induced hep*

Med 1995;333:1118.)

Microvesicular steatosis is attributed to impairment of ATP-dependent Î²-
acids within hepatocyte mitochondria and is a sign of failure of hepatic r
oxidative phosphorylation.[42 , 90 , 119 , 122] It is associated with a much n
hepatocellular dysfunction. High doses of tetracycline produce microvesic
associated with moderate elevations of aminotransferases, markedly pro
time, and progression to fulminant hepatic failure.[122] Recently, microvesic
been reported in patients taking nucleoside analogs (zidovudine, zalcitabi
for the treatment of HIV infection.[119 , 131] This is attributed to disruption
DNA synthesis.[19] The nucleoside analog fialuridine caused severe hepatot
deaths during a study of its use in the treatment of chronic hepatitis B i
examinations of liver specimens showed marked accumulation of fat with
structural injury. In these cases, severe acidosis with minimal elevation
enzymes and bilirubin, and failure of hepatic synthetic function suggested
the mitochondria. Mitochondria examined under the electron microscope
abnormal.[90] Microvesicular steatosis attributed to mitochondrial failure was
case of *Bacillus cereus* food poisoning, where high levels of the bacterial
cereulide were found in the bile and liver. In this case, microvesicular ste
associated with extensive hepatocellular necrosis.[85] In all cases, lactic ac
biochemical manifestation of impaired energy production.[42 , 119] In additi
other xenobiotics associated with mitochondrial failure are hypoglycin, the
vomiting sickness, aflatoxin, and margosa oil.[119] Figure 26-4 demonstrat
steatosis in a patient with fialuridine hepatotoxicity.

Sodium valproate causes mild elevations of aminotransferases in approxin
patients, usually during the first few months of therapy. The earliest patl
signals progression of liver injury is microvesicular steatosis, which occurs
necrosis. A small percentage of patients progress to

fulminant hepatic failure characterized by centrilobular necrosis.[146] The i
hepatocellular injury is highest in children, approaching 1 in 800 children
years.[104] Carnitine is an amino acid that has an essential role in the tran
into the mitochondria and their subsequent Î²-oxidation. An association b
carnitine and the development of hyperammonemia is observed in childre

valproic acid.[104 , 136] It is not yet known whether valproic acid causes c that results in hepatic injury, or whether patients with preexisting metab in carnitine deficiency are at greater risk of hepatic injury. A retrospective patients showed a significant decrease in the mortality rate in patients w acidâ€“induced hyperammonemia treated with carnitine.[11]

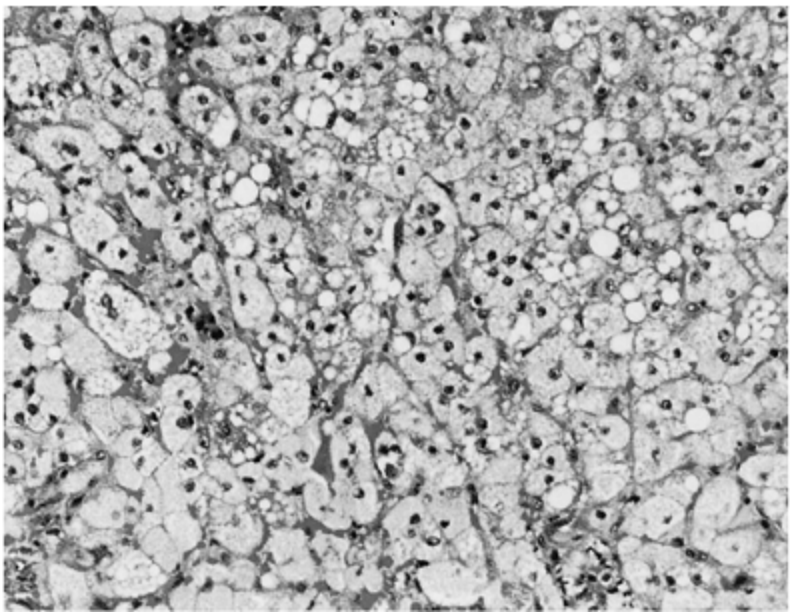

Figure 26-4. This figure shows severe microvesicular steatosis in a patie fialuridine. Note the central location of the nuclei. *(Reprinted with permis R, Fried MW, Sallie R, et al: Hepatic failure and lactic acidosis due to fial investigational nucleoside analogue for chronic hepatitis B. N Engl J Med*

Steatosis is also observed following exposure to the industrial solvent d The mechanism of hepatotoxicity in humans is unknown. Liver biopsies in illness show focal hepatocellular necrosis and microvesicular steatosis. M symptomatic exposures result in significant macrovesicular steatosis with aminotransferase elevations.[107 , 108]

Cholestasis

Cholestasis results from a number of toxic mechanisms. It may occur with associated hepatitis. The development of jaundice following hepatic necros

manifestation of general failure of liver function. More specific mechanism postulated to result in cholestasis include (a) impairment of the integrity junctions that functionally isolate the canaliculus from the hepatocyte and failure of transport of bile components across the hepatocytes; (c) blocka membrane active transport sites; (d) decreased membrane fluidity resulti transport; and (e) decreased canalicular contractility resulting in decrease 5).[67]

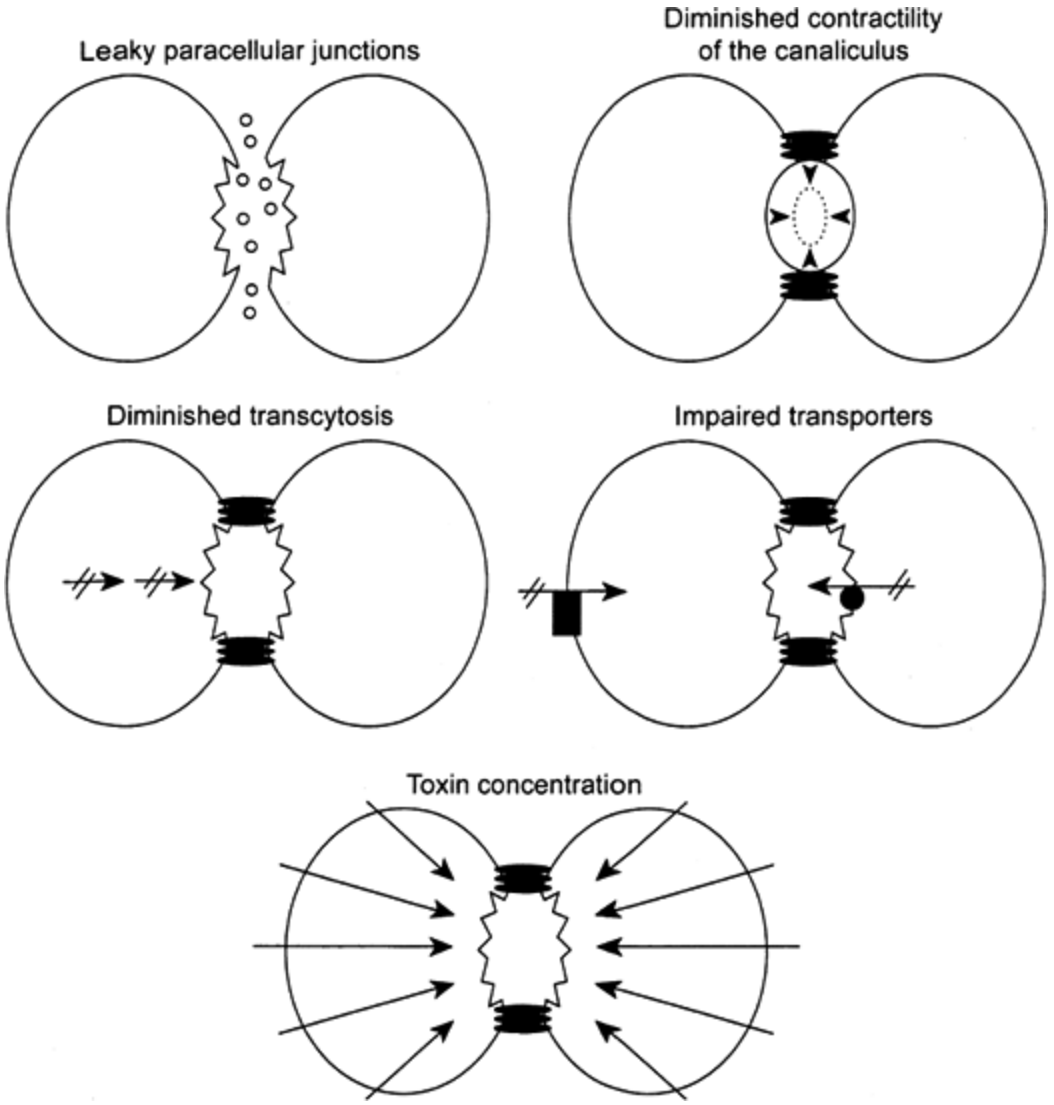

Figure 26-5. Potential mechanisms of xenobiotic-induced cholestasis. *(Re permission from Moslen MT: Toxic responses of the liver. In: Klaassen CD Doull's Toxicology, The Basic Science of Poisons. New York, McGraw-Hill,*

Estrogens cause intrahepatic cholestasis by altering the composition of th and inhibiting the rate of secretion of bile into the canaliculi.[67 , 78] Rifamp uptake of bilirubin into hepatocytes. Methyltestosterone and C-17 alkylat impair the secretion of bilirubin into canaliculi.[78] Exposure to chlorpromaz with cholestasis and periductal inflammation. This may be caused by inhib adenosine triphosphatase (ATPase), which results in decreased canalicula [116] Cyclosporine inhibits sodium-dependent uptake of bile salts across th membrane, and blocks ATP-dependent bile salt transport across the cana Floxacillin causes cholestasis with minimal inflammation or evidence of l injury.[137] Exposure of rats to ANIT causes a specific injury localized to tl that separate the hepatocyte from the canaliculi. This results in reflux of the sinusoidal space and increased access of sinusoidal molecules to the

Venoocclusive Disease

Hepatic venoocclusive disease is caused by toxic injury to the endotheliur venules that results in intimal thickening, edema, and nonthrombotic obs sublobular hepatic veins may also become edematous and fibrosed. There sinusoidal dilation in the centrilobular areas associated with liver cell atro The injury is caused by an activated pyrrole derivative produced by the c system.[87 , 142] The gross pathologic appearance is that of a â€œnutmegâ Massive hepatic congestion and ascites ensue.[69 , 111] Hepatic venoocclusiv fatal in

15â€“20% of cases. It is also associated with exposure to pyrrolizidine al many plant species, and with the use of cytotoxic drugs, especially in pa bone marrow transplantation. A rapidly progressive form may follow high cyclophosphamide.[89] Hepatic venoocclusive disease is also associated wit comfrey tea (*Symphytum* species),[140 , 144] and other pyrrolizidine alkalo preparations that include *Heliotrope,* *Senecio* , and *Crotalaria* species.[69] I epidemic proportions, in South Africa after the ingestion of flour contami (*Senecio*); in Jamaica after the ingestion of â€œbush teasâ€• (*Crotalari* India and Afghanistan when food was contaminated with *Heliotropium* *la* *Crotalaria* .[15 , 95 , 124 , 132]

Peliosis Hepatis

Peliosis hepatis is characterized by large blood-filled cavities associated dilation (Chap. 44). It is most frequently associated with the use of and Although most patients are asymptomatic, occasionally the dilated sinuso cause hemoperitoneum.[8]

Chronic Hepatitis

A form of hepatitis that clinically resembles autoimmune hepatitis occurs administration of some drugs such as methyldopa, nitrofurantoin, propy dantrolene, and diclofenac.[4 , 60 , 88 , 110 , 115 , 123 , 130] Many of these c with positive antinuclear antibody (ANA), smooth muscle antibody (SMA), hyperglobulinemia. Jaundice is prominent and hepatocellular enzymes are fold. Liver biopsy commonly reveals intrahepatic cholestasis, as well as inflammation.[37 , 83]

Granulomatous hepatitis is associated with infiltration of the hepatic pare granulomata. As many as 60 drugs are associated with this disorder. Fev symptoms are common, 25% have splenomegaly. Liver enzymes are mix variable degrees of cholestasis and hepatocellular injury. Eosinophilia occu extrahepatic manifestation of drug hypersensitivity. Continued exposure m severe form of liver disease. Small vessel vasculitis, which may involve th kidney, is a disturbing sign associated with increased mortality.[37 , 75 , 9 lists some of the xenobiotics that have been implicated in this disorder.

Cirrhosis

Cirrhosis, which results in irreversible hepatic dysfunction and portal hyp by progressive fibrosis and scarring of the liver. Fibrosis is related to inc collagen. In alcoholic cirrhosis, â€œactivatedâ€• lipocytes in the centrilob play a major role in the production of septal and perivenular collagen tha collagen deposition in the space of Disse. Acetaldehyde also stimulates c lipocytes, as do other aldehydes that are products of lipid peroxidation.[80 generally precedes cirrhosis, although cirrhosis may develop in its absen

ingestion of excessive amounts of vitamin A (25,000 U/d for 6 years or 1 years) results in cirrhosis. An increase in the fat content of the sinusoidal increasing degrees of collagen formation are characteristic lesions that oc A toxicity (Chap. 41). Portal hypertension may be early and striking.[43] Li methyldopa and methotrexate also cause a slow progressive development minimal clinical symptoms.[76 , 141] Methotrexate-induced hepatic fibrosis is Risk factors include associated alcohol intake and preexisting liver diseas has largely eliminated the risk of the development of cirrhosis in patients methotrexate.[58 , 141]

Hepatic Tumors

There is persuasive evidence that the use of oral contraceptive steroids ir hepatic adenomas.[29 , 63] There is also evidence that oral contraceptives risk of hepatocellular carcinoma; however, the number of cases associate therapy is low.[53 , 70] Anabolic steroids are rarely associated with the dev benign and malignant hepatic tumors.[17 , 38 , 56] Angiosarcoma is strongly exposure to vinyl chloride, in addition to arsenic, thorium dioxide, and s [37]

Hepatic Injury Associated with Plants and

In addition to the venoocclusive disease associated with pyrrolizidine alk above, herbal remedies are increasingly recognized as a cause of acute Numerous plants or plant products are known or suspected to cause hepa and 114).[1 , 30 , 34 , 51 , 52 , 71 , 97 , 120]

Clinical Presentations

Two general types of clinical patterns occur with hepatic toxins: a chroni progression of injury that may elude diagnosis, and a more acute, somet progression of injury that is temporally related to exposure to the xenob

Chronic injury is associated with an initially asymptomatic or minimally s state, with mildly abnormal liver chemistries and slow progression to clin dysfunction or cirrhosis.[37 , 75 , 137] Over a period of time ranging from m

jaundice, coagulopathy, encephalopathy, hepatomegaly, or signs of cirrhos angiomata, ascites, caput medusa, and gynecomastia may be evident. Ar to cirrhosis with minimal symptoms occurs in some patients with chronic A, methotrexate, ethanol, amiodarone, and methyldopa.[43 , 75 , 80 , 84] Ch manifested primarily by jaundice and pruritus.

Symptoms of acute liver injury include fever, anorexia, nausea, vomiting, include coagulopathy, jaundice, percussion tenderness in the right upper encephalopathy. Rapid development of portal hypertension, ascites, and c onset of some cases of venoocclusive disease.[69] Patients with acute, large carbon tetrachloride, yellow phosphorus, acetaminophen, and cyclopept mushrooms present first with gastrointestinal symptoms. This is followed b being (1â€“3 days), and then signs of acute hepatic and renal failure, wi and nausea, followed by profound jaundice, hemorrhage, ascites, hepatic and death.[74 , 113] Patients with significant acute occupational exposure

present with abdominal pain, anorexia, and disulfiram-type reactions.[108]

Subclinical
Normal physical examination
Subtle impairment of neuromotor function â†’ driving or work injury haza
I
Euphoric, irritable, depressed, fluctuating mild confusion, poor attention, Poor coordination; may have asterixis alone
I I
Impaired memory, cognition, simple mathematical tasks
Slurred speech, tremor, ataxia
I I I
Difficult to arouse, persistent confusion, incoherent
Hyperactive reflexes, clonus, nystagmus
I V
Coma; may respond to noxious stimuli
May have decerebrate posturing; Cheyne-Stokes respirations; pupils are the oculocephalic reflex is intact; may have signs of intracranial pressure

Clinical Stage	Mental Status	Neuromotor Function

TABLE 26-3. Stages of Hepatic Encephalopathy

Fulminant hepatic failure (FHF) is defined as liver injury that progresses within 8 weeks of the onset of illness in a patient without preexisting live Complications from FHF include encephalopathy, cerebral edema, coagulo dysfunction, hypoglycemia, hypotension, acute lung injury, sepsis, and de a patient may progress from health to death in as little as 2â€“10 days.[74] 3 shows the clinical progression of liver failure as hepatic encephalopathy prognosis of FHF is related to the time that passes between the onset of onset of encephalopathy. Perhaps surprisingly, a better prognosis is asso (2â€“4 weeks) jaundice-to-encephalopathy intervals.[113] Most cases of fu failure are caused by xenobiotics or viral hepatitis. Fulminant hepatic failu associated with extensive necrosis, although it may occur in the absence necrosis, as occurs in exposures to xenobiotics that injure mitochondria, analogues and *Bacillus cereus* toxin.[85, 90, 131] Some xenobiotics that ar fulminant necrosis are clove oil, bromfenac, amanitin cyclopeptides, ace tetracycline, phosphorus, halogenated hydrocarbons, INH, methyldopa, an [41, 74, 96]

The Evaluation of the Patient with Liver Di

The history is critical in establishing the diagnosis of the patient with live medication history should include careful investigation of nonprescription acetaminophen and the possible use of herbal therapies. Nearly all chron medications should be suspect. An occupational history may indicate expo chloride (plastics industry), dimethylformamide (leather industry), or oth solvents. Table 26-4 lists some of the occupational exposures that result Alcohol abuse is a common cause of acute hepatitis and the most commo in this country.[80, 84] A history of male homosexual contacts, healthcare intravenous drug use indicates the possibility of hepatitis B, whereas rece underdeveloped country suggests the possibility of hepatitis A. In patient

pain, the possibility of cholelithiasis should be considered.

Clinical Laboratory

Aminotransferases

Laboratory tests are helpful and certain patterns may be suggestive of s (Table 26-5). Elevation of hepatocellular enzymes, especially the AST an hepatocellular injury, and within a given clinical context, has useful diag Aminotransferases may be increased up to 500 times normal when hepati extensive, such as in severe acute viral or toxic hepatitis.[74] The degree c always reflect the severity of injury as concentrations may decline as ful progresses. Only moderately elevated, or occasionally normal aminotran concentrations occur in some patients with hepatic failure caused by mit cirrhosis, or venoocclusive disease.[43 , 69 , 146] Processes associated with cholestasis in the absence of hepatitis also may not lead to significant a elevation.[98 , 106 , 147] Patients with acute liver injury caused by dimethy demonstrated

aminotransferase concentrations 2â€“30 times normal, and ALT greater th and alkaline phosphatase concentrations were often normal.[108] In alcohol contrast to other forms of hepatitis, the AST concentration is typically two greater than the ALT. This is attributed to impairment of ALT synthesis b 5â€²-phosphate deficiency in alcoholics. Elevation of either of these enzyn is inconsistent with injury caused by ethanol.[129] During acute extrahepatic biliary tract, the AST or ALT may be as high as 1000 IU/L, indicating infla reflux of bile acids into the biliary tree.[129] The measurement of Î³-glutar (GGTP) is not very useful as it is present throughout the liver and its elev nonspecific.[129]

Arsenic
Cirrhosis, angiosarcoma
Beryllium
Granulomatous hepatitis
Carbon tetrachloride

Acute necrosis
Chlordecone
Minor hepatocellular injury
Copper salts
Granulomatous hepatitis, angiosarcoma
Dimethylformamide
Steatohepatitis
Methylenedianiline
Acute cholestasis
Phosphorus
Acute necrosis
Tetrachloroethane
Acute, subacute necrosis
Tetrachloroethylene
Acute necrosis
Toluene
Steatosis, minor hepatocellular injury
Trichloroethane
Steatosis, minor hepatocellular injury
Trinitrotoluene
Acute necrosis
Vinyl chloride
Acute necrosis, fibrosis, angiosarcoma
Xylene
Steatosis, minor hepatocellular injury

Xenobiotic Type of Injury

TABLE 26-4. Occupational Exposures Associated with Liver Injury

Hepatocellular necrosis, acute focal (hepatitis)
N or â†‘
â†‘â†‘â†‘
N

N or â†‘
â†‘â†‘
N
N
Hepatocellular necrosis, acute massive
N or â†‘
â†‘â†‘â†‘
N
â†‘â†‘
â†‘â†‘â†‘
â†‘â†‘
â†‘
Chronic infiltrative disease (tumor, fatty liver)
â†‘â†‘
â†‘
N
N
N
N
N
Microvesicular steatosis, acute
N or â†‘
â†‘â†‘
â†“
â†‘â†‘
â†‘
â†‘â†‘
â†‘â†‘â†‘
Cholelithiasis
â†‘
â†‘
N
N
N or â†‘

N
N
Cholestatic hepatitis
â†‘â†‘
â†‘
N
N
â†‘
N
N
Chronic hepatitis
N or â†‘
â†‘
N or â†“
N
N or â†‘
N
N
Cirrhosis
N or â†‘
â†‘
â†“
N or â†‘
N or â†‘
N or â†‘
N
â†‘ = increase; â†“ = decrease; N = normal.

Disorder	Alkaline Phosphatase	AST, ALT	Albumin	Prothrombin Time	Bilirubin

TABLE 26-5. Laboratory Tests that Evaluate the Liver

Alkaline Phosphatase

In patients with cholestasis, bile acids stimulate the synthesis of alkaline hepatocytes and biliary epithelium in response to a number of pathologic liver. Elevations of the alkaline phosphatase as high as 10-fold may occu liver diseases, but are most commonly associated with extrahepatic obst Although the alkaline phosphatase may be normal or elevated only minin injury, it is unusual for obstruction to occur without some elevation of th phosphatase. Elevations of alkaline phosphatase and GGTP parallel each o the biliary tract.[129]

Bilirubin

Elevation of conjugated, or direct, bilirubin implies impairment of secretio elevation of unconjugated, or indirect, bilirubin implies impairment of co Unconjugated hyperbilirubinemia also occurs during hemolysis and in rare conjugation such as Gilbert or Crigler-Najjar syndromes. Except in cases unconjugated hyperbilirubinemia, the fractionation of bilirubin in the case disorders does not have any important diagnostic utility, and will not dis parenchymal disorders of the liver from intrinsic or extrinsic cholestatsis. bilirubin in the urine implies elevation of conjugated (direct) bilirubin and for laboratory fractionation.

Urobilinogen is produced by the bacterial metabolism of bilirubin in the bo absorbed and excreted in the urine. Its presence in the urine indicates th of bilirubin in bile, while its absence is associated with complete biliary o result of more modern methods of detection of complete obstruction of th test is mainly of historical interest.

Serum Albumin

Quantitatively, albumin is the most important protein that is made in the of up to 20 days, the albumin is usually normal in the previously healthy liver injury. In the absence of other disorders that affect albumin, such a syndrome, protein-losing enteropathy, or starvation, a low serum albumin for the severity of chronic liver disease.[129]

Coagulation Factors

Impairment of coagulation is a marker of the severity of hepatic dysfuncti and chronic liver disease. Unlike the case with serum albumin, with its ha the onset of coagulopathy as a consequence of impaired synthesis of the K-dependent clotting factors II, VII, IX, and X is rapid. Very acute chang reflect the concentration of factor VII, which has the shortest half life.[57] coagulation pathway, as measured by the prothrombin time (PT) or the normalized ratio (INR), is affected by reductions in factors II, VII, and X. or PT in acute hepatitis is associated with a higher risk of fulminant hepa In addition to failure of hepatic synthesis, inadequate levels of factors II, also result from ingestion of warfarin anticoagulants or malabsorption of v).[24]

International Normalized Ratio or Prothrombin

Because different thromboplastin reagents give different PT values on the INR was developed to normalize PT measurements in patients treated wi comparisons of therapeutic outcomes across different care settings and a The INR uses the ISI (International Sensitivity Index) that is derived from patients on stable anticoagulant therapy. It normalizes the responsiveness thromboplastin reagent in comparison to a WHO reference standard that i of 1.0.[66] There is little controversy regarding the value of the INR when c ratio for measuring the extent of warfarin-induced anticoagulation. Becau deficiencies in patients with liver disease are different from those in patie there is considerable

controversy regarding which measurement is best for patients with liver Although comparison of factor levels in warfarin-treated patients with tho showed no difference in factor VII, there are significant differences in fact fibrinogen. Comparison of the PT with INR in the evaluation of test result thromboplastin reagents showed consistency among the control groups c patients, but no consistency among PT or INR measurements using the s reagents in patients with liver disease.[66] Because of a failure to demonst liver specialists who have expressed an opinion support the continued use

describe the degree of liver injury, bemoaning the availability of a single that would help predict operative risk.[24, 26, 66] In patients with liver dis implies a normalized correlation that does not exist and is therefore pot The implication for toxicologists is that caution should be exercised in rely published INR values that purportedly predict the severity of illness in pa liver failure.

Ammonia

Severe generalized impairment of hepatic function leads to a rise in the concentration as a result of impairment of detoxification of ammonia pro catabolism of proteins. The absolute level of elevation is not clearly asso status alteration.[129] Elevations of serum ammonia concentrations occur in patients with hepatic encephalopathy, suggesting that ammonia may be a a primary cause of CNS dysfunction.[40]

Some patients treated with valproic acid have developed alterations in m associated with elevated ammonia levels, sometimes in the absence of o indicators of hepatic injury, and without demonstrable toxic levels of valp attributed to selective impairment of urea cycle enzymes ornithine transc carbamyl phosphate synthetase by pentanoic acid metabolites (Chap. 47

Other

Serologic studies for the presence of markers of hepatitis A, B, and C sho routinely in patients with hepatitis.

In the patient with severe liver injury, hypoglycemia is a major concern b impairment of glycogen storage and gluconeogenesis. Hyperglycemia also of the liver's inability to handle a large glucose load. The arterial blood-g commonly shows a respiratory alkalosis. Severe lactic acidosis occurs in failure caused by mitochondrial injury. Measurements of serum lactate co useful in identifying the cause of acidosis in a patient with suspected toxi [119]

The CT and MRI scans are useful tests for evaluation of parenchymal dise ultrasound examination reliably demonstrates dilation of the extrahepatic

biopsy may be helpful but is not specifically diagnostic of xenobiotic-indu

Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a severe, but potentially fully reversible, liver failure, even in cases of deep coma.[39, 40] Table 26-3 describes, in stages of acute HE. Ammonia levels are elevated in patients with nitrogen elevated in nonnitrogenous HE. Conditions associated with nonnitrogenous hypoglycemia, hypoxia, anemia, and exposure to sedative hypnotic agent is precipitated by processes that elevate CNS ammonia concentrations, su alkalosis, increased muscle wasting, volume depletion, azotemia, or gas bleeding.[40] Alkalosis and hypokalemia facilitate conversion of NH_4^+ to NI more easily across the bloodâ€“brain barrier. The clinical improvement in lowering of serum ammonia levels, continues to be accepted as evidence of ammonia in the pathogenesis of HE.[39] The demonstration that ammonia many cases suggests that it may be an epiphenomenon, or marker, for o endogenous toxins. There is evidence that liver failure is associated with substances that stimulate central benzodiazepine receptors, leading to in transmission. Although it is clear that sedatives that depress Î³-aminobut transmission can make encephalopathy worse, studies of the use of fluma of encephalopathy show conflicting results. There does seem to be a sig improvement in some patients who already have a highly favorable progr is no clear evidence that all patients will benefit from flumazenil, some i benefit for a short time. Certainly, the administration of benzodiazepines The pathophysiologic processes discussed above are not mutually exclusive HE is likely multifactorial.

Management

In many cases, toxic liver injury resolves with simple withdrawal of the In cases of severe injury, significant improvement in survival is associate supportive care in an intensive care environment.[74] Early referral to a tr patients with evidence of severe or rapidly progressive toxic injury is inc of indications for the use of *N* -acetylcysteine and discussion of indication transplantation, see Antidotes in Depth: *N* -Acetylcysteine and Chap. 34

Summary

The primary role of the liver in the biotransformation of xenobiotics resul risk of hepatotoxicity. The spectrum of liver injury includes combinations steatosis, and hepatocellular necrosis. Injury may be a result of cellular autoimmune mechanisms; free radical initiation of lipid peroxidation; mi formation of adducts with critical cellular enzymes; and other, less-well- Disturbances in intracellular calcium concentrations may play a role in th hepatocellular injury, although the common â€œfinal pathwayâ€• role of into question. Xenobiotic-induced liver injury can be dose-dependent and idiosyncratic and unpredictable. Idiosyncratic injury is affected by host c include genetic makeup, concomitant or previous exposure to drugs and t underlying condition of the liver.

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Chapter 27
Renal Principles

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Overview of Renal Function

Anatomic Considerations

The kidneys lie in the paravertebral grooves at the level of the T12-L3 ve while the lateral margins are convex, giving the organ a bean-shaped ap 10â€“12 cm in length, 5â€“7.5 cm in width, and 2.5â€“3.0 cm in thicknes 125â€“170 g; in the adult female, each kidney weighs 115â€“155 g.

At its concave surface is the hilum, through which the renal artery, vein, lymphatics pass. On the convex surface, the kidney is surrounded by a fil capsule with a fibroareolar capsule (called the *renal fascia*), which offers place.

The arterial supply begins with the renal artery, which is a direct branch artery subdivides into branches supplying the 5 major segments of each segment, the anteroinferior segment, the posterior segment, and the infe within each segment to become lobar arteries. In turn, these vessels give

sharply branching interlobular arteries, which directly supply the glomeru

The cut surface of the kidney reveals a pale outer rim and a dark inner r medulla, respectively. The cortex is 1 cm thick and surrounds the base o consists of between 8 and 18 cone-shaped areas called *medullary pyrami* containing the ends of the collecting ducts. Urine empties from these duct and, subsequently, into the urinary bladder.

The kidneys maintain the constancy of the extracellular fluid by creating free of cells and larger macromolecules, and then processing that filtrate, the rest escape as urine. Every 24 hours, an adult's kidneys filter about 1 25â€“60 L), and 25,000 mEq of sodium (total body Na^+ is 1200â€“2800 kidneys regulate these two substances independent of each other, depend 1% of the filtered water and 0.5â€“1% of the filtered Na^+ are excreted.

Renal function begins with filtration at the glomerulus, a highly permeabl arterioles in series. The relative constriction or dilation of these vessels (GFR). Under normal circumstances, approximately 20% of the plasma wa actually goes through the filter, carrying with it electrolytes, small metab and urea, and leaving behind the blood cells and nearly all the larger pr filtrate then enters a series of tubules that reabsorb most of it and secre and bases, into the urinary space. The proximal tubule performs bulk r of the filtrate. Distal to the proximal tubule are the loop of Henle, which urine, and the distal nephron, which does the fine-tuning in the balance Reabsorption of sodium is controlled proximally by hydrostatic and oncoti distally by hormones such as aldosterone. Control of water reclamation de of the loop of Henle, which absorbs solute without water. This produces a makes the medullary interstitium hypertonic. Final regulation of water rea antidiuretic hormone (ADH), which opens water-reabsorbing channels (aqu nephron segments (collecting ducts). The kidneys also regulate balance fo are influenced by the effect of aldosterone on the distal nephron), and ca influenced by the blood level of parathormone).

Injury to either the glomeruli or the tubules can lead to renal dysfunction filtration. As the kidneys fail, serum levels of the marker substances urea relationship between these levels and the level of GFR is hyperbolic, not l levels of these substances denotes a large decrease in renal function. By

creatinine exceeds the upper limit of normal, GFR is already reduced by r

Many xenobiotics cause or aggravate renal dysfunction. The kidneys are reasons;[141] (a) They receive 20â€“25% of cardiac output yet make up les metabolically active, and thus vulnerable to xenobiotics that disrupt meta

remove water from the filtrate and may build up a high concentration of interstitium are susceptible to attack by the immune system. Many factors individual's reaction to a particular nephrotoxin.[12] The clinician should be alter them to minimize the adverse effect after a toxic exposure.

Functional Toxic Renal Disorders

Although most toxic renal injury results in decreased renal function, there balance despite normal GFR in anatomically normal kidneys: renal tubula secretion of antidiuretic hormone, and nephrogenic diabetes insipidus.

Renal tubular acidosis (RTA) is a loss of ability to reclaim the filtered bic to generate new bicarbonate to replace that lost in buffering the daily acid nonanion-gap metabolic acidosis, usually accompanied by hypokalemia.

The primary defect in distal RTA involves the decreased secretion of hydr distal tubule. This most often denotes a defect in the H^+ -translocating a luminal surface of these cells. Less frequently occurring mechanisms inc exchanger, which is responsible for returning bicarbonate generated within given the voltage dependence of hydrogen secretion, if there is a decreas charge, there will be a decrease in this secretion. Most of this voltage is d on the peritubular capillary side of the adjacent cell. (*Note:* Cells adjacen cells and primarily control K^+ secretion.) As this pump malfunctions, less a decreased gradient from the lumen to the cell. Thus, the lumen becom transmembrane potential.

The primary defect in proximal RTA is incompletely understood. Normally, membrane, the Na^+ -K^+ -ATPase in the basolateral membrane, and the e systems necessary for proximal tubular bicarbonate reabsorption. It is pro become disordered and thereby diminish the resorptive capacity of the pr part of the *Fanconi syndrome* , a generalized failure of proximal tubular

renal glycosuria, and hyperphosphaturia).

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) occ fall in plasma osmolality, which normally inhibits ADH secretion. ADH prir increased water reabsorption by increasing the aquaporin channels in this altered physiology: there may be altered secretion of ADH, a resetting of secretion), or the inability to decrease ADH secretion in the face of a wat serves to augment normal free water retention, which subsequently leads concentrated urine (as reflected in a relative increase in urine osmolality) Although this most often occurs as a complication of intracranial lesions o in a diseased lung, many xenobiotics (eg, chlorpropamide, antidepressant methylenedioxymethamphetamine [MDMA or Ecstasy]) can also cause ina

Nephrogenic diabetes insipidus (NDI) is the reverse of SIADH. It denotes stimulation despite severe losses of body water. There are many causes c disease states. Several xenobiotics also cause NDI. Lithium, demeclocycl are noted drugs that can cause this syndrome (Chap. 17). Of these, our described, although the exact mechanism has not been elucidated. After through the sodium channel, it interferes with ADH-mediated water trans channels.

Major Toxic Syndromes of the Kidney

Most nephrotoxicity involves histologic renal injury. Although xenobiotics ca), there are three major syndromes of toxic renal injury: (a) chronic rena especially, (c) acute renal failure (Table 27-1). For purposes of continuit Because nephrotoxins usually affect the tubules, the most metabolically a nephrotoxicity involves either acute or chronic tubular injury, although gl xenobiotics. These processes are not mutually exclusive, and toxic nephrop the nephron (eg, nonsteroidal antiinflammatory drug [NSAID]-induced acu

Chronic renal failure refers to any disease process that causes progressive months to years. There is usually a gradual rise in BUN and serum crea falls; often there are no symptoms other than nocturia (indicating loss o

The most common lesion of nephrotoxic chronic renal failure is chronic in destruction of tubules over a prolonged period,[74] with tubular atrophy,

fibrosis, and a variable cellular infiltrate (Fig. 27-2), sometimes accomp
nephritis may progress to chronic interstitial nephritis, if exposure to xe
insidious and relatively asymptomatic, often presenting as secondary hyp
The major symptom is nonspecific nocturia. Papillary necrosis may lead t
ureteral space. There is mild to moderate proteinuria that remains well u
renal disorders, interstitial nephritis is characterized by failure of the dise
impairment, resulting in metabolic imbalances such as hyperchloremic me
hyperkalemia early in the disease course.[70] Injury to erythropoietin-secre
anemia.

Chronic Renal Failure (slowly increasing azotemia)
- Chronic interstitial nephritis
- Papillary necrosis
- Chronic glomerulosclerosis

Nephrotic Syndrome (proteinuria, hypoalbuminemia, edema)
- Minimal glomerular change
- Membranous nephropathy
- Focal segmental glomerulosclerosis

Acute Renal Failure (rapidly increasing azotemia)
- Acute prerenal failure
- Acute urinary obstruction
- Acute tubular necrosis
- Acute interstitial nephritis
- Acute vasculitis

TABLE 27-1. Major Nephrotoxic Syndromes

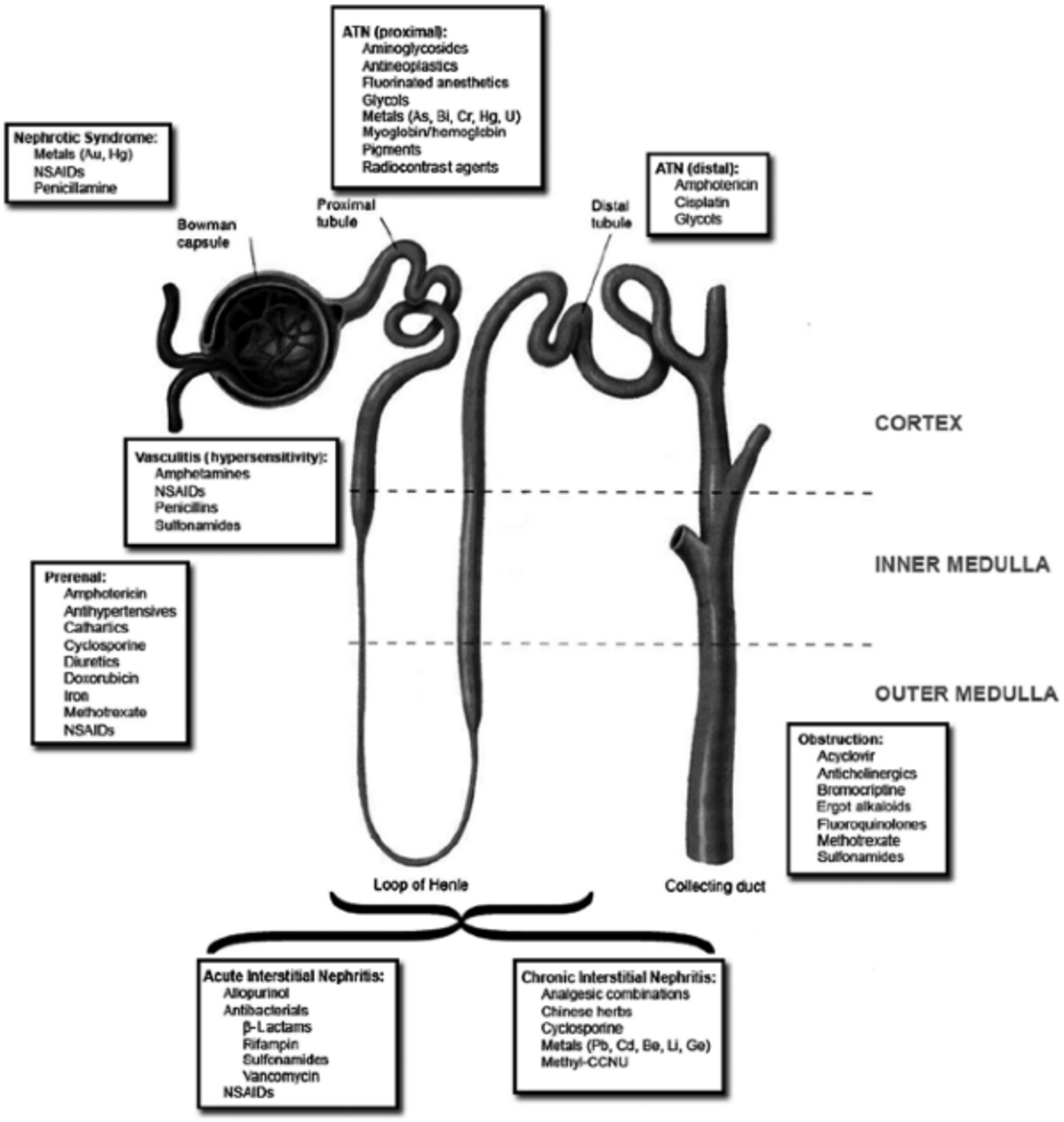


Figure 27-1. Schematic showing the major nephrotoxic processes and the affect. ATN = acute tubular necrosis. *(Courtesy of the National Institutes*

Nephrotic syndrome is characterized by massive proteinuria (>3 g/d in and the edema that usually prompts the patient to seek medical attentio findings are not completely understood, the underlying event is injury to macromolecules from passing from the capillary lumen into the urinary s

excretion as a result of renal tubular catabolism of filtered protein. The

of the extracellular space and edema. The glomerular lesion may progress continues. Xenobiotics induce nephrotic syndrome (Table 27-2) in 2 way the blood, which leads to antigenâ€“antibody complex formation after the complexes subsequently deposit in the glomerular basement membrane, t Fig. 27-3). Second, they can upset the immunoregulatory balance (eg, N hypersensitivity vasculitis.

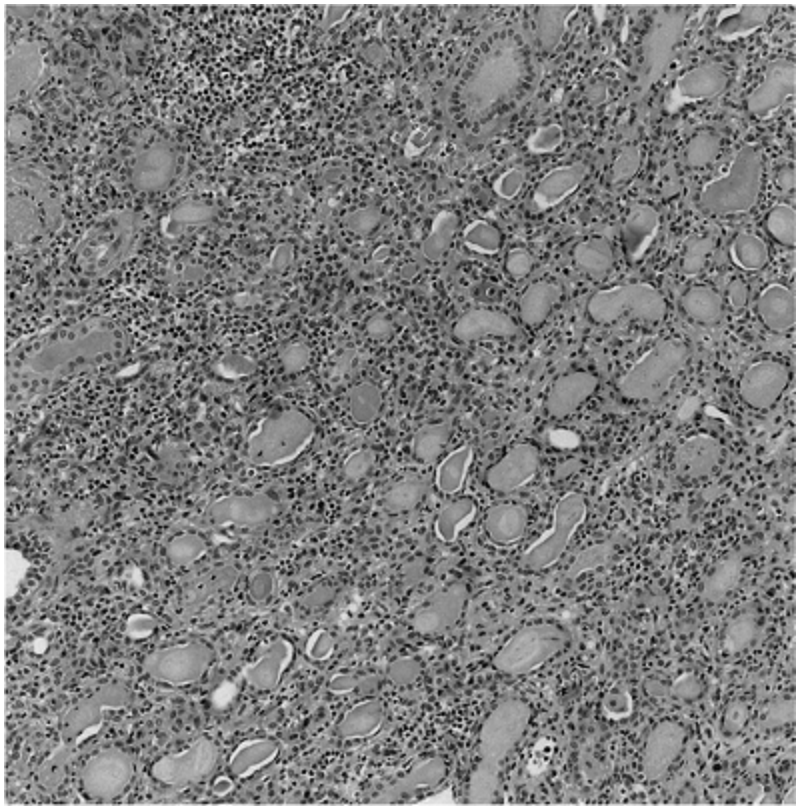


Figure 27-2. Chronic interstitial nephritis (secondary to NSAIDs). Inters tubular atrophy (H&E Ã— 225). *(Courtesy of Dr. Rabia Mir.)*

Acute renal failure is defined as any abrupt decline in renal function that metabolic balance. The 3 main categories of acute renal failure are prere

Prerenal failure involves impaired renal perfusion, which can occur with failure. Hence, toxic events that cause bleeding (overdose of anticoagula

or emetics), cardiac dysfunction (Î²-adrenergic antagonists), or hypotensio failure.[66]

One important cause of prerenal failure is the extreme renal hypoperfusic syndrome. This syndrome is characterized by impaired renal function and associated with severe chronic or acute hepatic failure. Many neurohumora systemic hemodynamic changes that occur in the syndrome. Specifically, greatly increased in hepatorenal syndrome. Angiotensin, norepinephrine, all contribute to the extreme cortical vasoconstriction. Furthermore, splar increases in endotoxin, nitrate, nitrite, and glucagon, all decrease mean renal blood flow. That this renal insufficiency is prerenal is best illustrated patient with hepatorenal syndrome is transplanted into a uremic patient, t normal.

Captopril
Drugs of abuse (heroin, cocaine)
Metals (gold, mercury)
NSAIDs
Penicillamine

TABLE 27-2. Xenobiotics Commonly Causing Nephrotic Syndrome

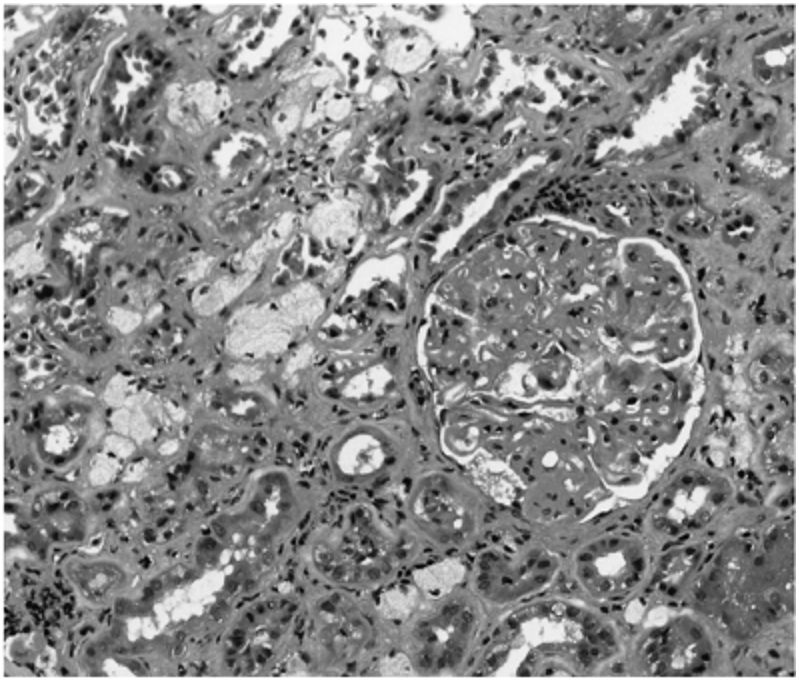


Figure 27-3. Membranous glomerulonephropathy (secondary to gold), a thickened glomerular capillaries and interstitial foam cells are seen (H&E

Postrenal failure , such as urinary tract obstruction, may result from crys poisoning) or blocked urinary flow (eg, bladder dysfunction from anticholi urinary tract obstruction, there are characteristic histologic and pathophy Microscopically, there is tubular dilation, predominantly in the distal neph distal tubules). There is initial preservation of the glomerular structure w finally, periglomerular fibrosis may develop.

Pathophysiologically, GFR falls as tubule pressure counteracts the capilla there is a fall in renal perfusion leading to ischemic damage to nephrons. concentrating ability, potassium secretory function, and urinary acidificatio common nephrotoxic lesions, however, are *intrinsic renal injuries* , partic interstitial nephritis (see Table 27-1).[5]

Acute tubular necrosis (Table 27-3), the most common nephrotoxic ever necrosis of tubules, usually the proximal segments (Fig. 27-4). This lesi processes: direct toxic injury, ischemic injury from renal hypoperfusion,

Direct toxicity accounts for approximately 35% of all cases of acute tubu

different

segments of the renal tubules; for example, uranium attacks the proxima (see Fig. 27-1). However, the clinical pattern of rapidly declining renal f identical in all forms of tubular necrosis. Poisoning may also lead to isch failure causes ischemia of nephron segments (proximal straight tubule an particularly vulnerable to hypoxia.

Acetaminophen
Antibacterials
  Aminoglycosides
  Amphotericin
  Pentamidine
  Polymyxins
Antineoplastics
  Cisplatin
  Ifosphamide
  Methotrexate
  Mithramycin
  Streptozotocin
Fluorinated anesthetics
Glycols
  Ethylene glycol
  Diethylene glycol
Halogenated hydrocarbons
Metals
  Arsenic
  Bismuth
  Chromium
  Mercury
Mushrooms
  Cortinarius spp
  Amanita smithiana
Pigments
  Myoglobin

Hemoglobin

Radiocontrast agents

Those that cause hypotension or hypovolemia

TABLE 27-3. Xenobiotics that Cause Acute Tubular Necrosis

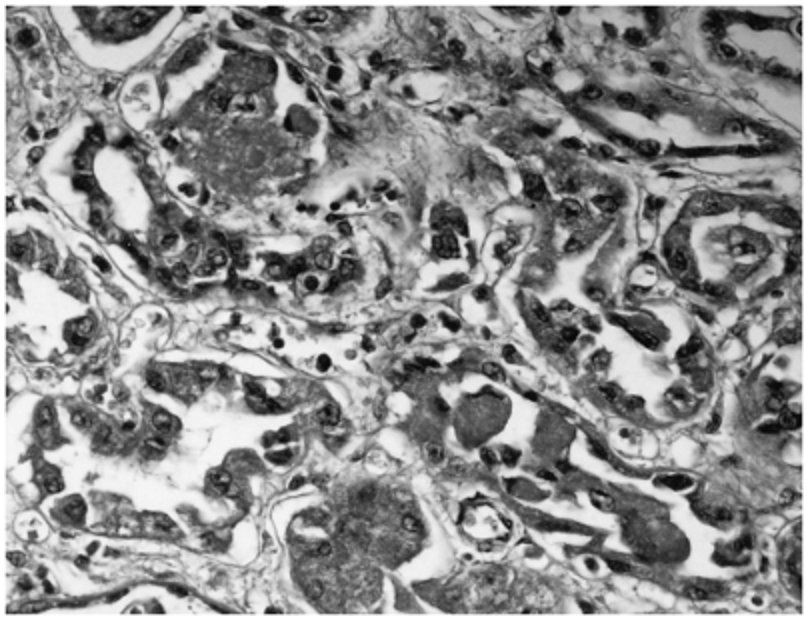


Figure 27-4. Acute tubular necrosis (secondary to mercury). Proximal tu associated with interstitial edema (H&E Ã— 450). *(Courtesy of Dr. Rabia*

Pigmenturia refers to either myoglobinuria from rhabdomyolysis (skeletal massive hemolysis.[59] Either pigment may cause tubular injury and necros [166] Myoglobinuria follows necrosis of striated muscle. Alcohol can be dire Î²-hydroxy-Î²-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors Xenobiotics that produce hypokalemia (eg, diuretics and laxatives) or pr cause muscle necrosis on this basis. Most often, poisoning leads to musc prolonged unconsciousness (opioids and sedative-hypnotics), excessive mu seizures (alcohol withdrawal, theophylline).[82] Pigmenturic acute renal fail carbon monoxide, copper sulfate, and zinc phosphate.[35 , 124 , 139]

Myoglobin is normally excreted without causing toxicity. A study of patien concentration of myoglobin in the urine may affect the development of re

tubular lumen because of renal hypoperfusion and high water absorption, environment as H^+ is secreted, releasing tubulotoxic hematin.[59] This toxi production of oxygen free radicals.

Myoglobinuric renal failure is diagnosed when acute renal failure occurs fo simultaneous elevation of concentration of serum muscle enzymes such as urine orthotolidine test, with no erythrocytes in the sediment, and urine because primary renal failure may itself cause detectable myoglobinuria th myoglobin in the urine does not prove the diagnosis.

Myoglobinuric renal failure can be prevented by early volume expansion if Alkalinizing the urine may prevent dissociation of myoglobin and minimiz rhabdomyolysis can lead to severe hypocalcemia from the release of large Alkalemia in this setting can cause tetany or seizures, worsening muscle must be weighed against the benefit.

Hemoglobinuria follows hemolysis, which can be caused by a number of venoms, cresol, phenol, aniline, arsine, naphthalene, and methylene chlo (hydralazine, quinine) can also cause hemolysis.[59] The pathophysiology o of myoglobinuria. The pigment deposits in the tubules and dissociates, ca and acidosis precipitate this disorder, so volume expansion and alkalinizat

Although there is controversy as to how a tubular lesion leads to glomeru obstruction, back-leak of filtrate across injured epithelium, renal hypoper surface combine to impair glomerular filtration.[215] Recent evidence sugge perhaps caused by an imbalance in the production of vasoconstrictors suc nitric oxide, is important in prolonging the renal dysfunction after the tu

Allopurinol
Anticonvulsants
Antibacterials
  Carbamazepine
Î²-Lactams, especially ampicillin, methicillin, penicillin
  Phenobarbital
  Phenytoin
  Rifampin
Captopril

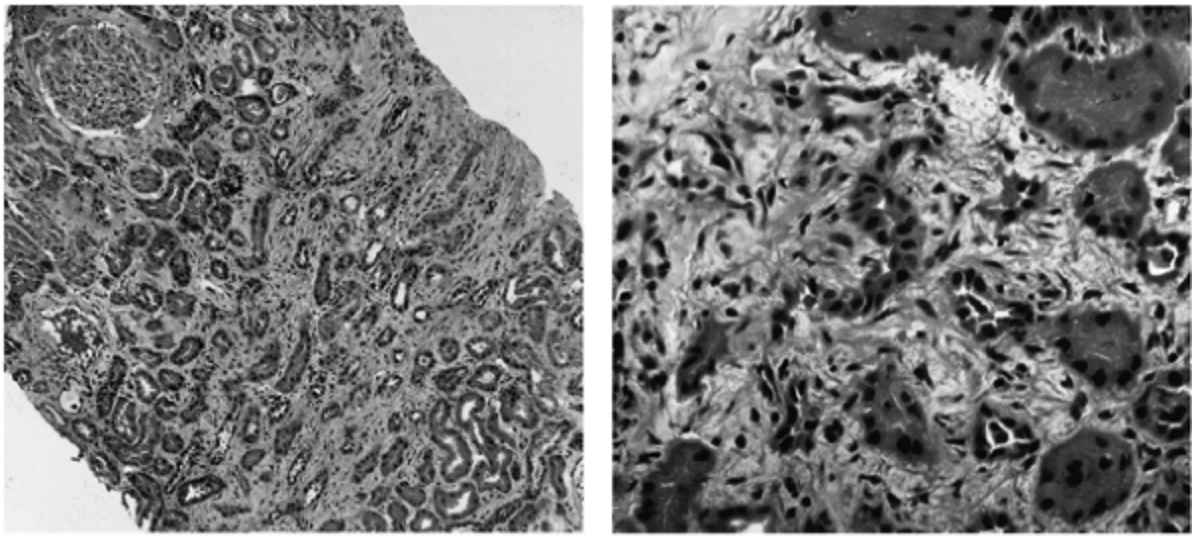
Sulfonamides
Diuretics
Vancomycin
Furosemide
Azathioprine
Thiazides
NSAIDs

More Common Less Common

TABLE 27-4. Xenobiotics that Cause Acute Interstitial Nephritis

Clinically, acute tubular necrosis presents as a rapid deterioration of rena Muddy brown casts or renal tubular cells may be seen in the urinary sed unusual. Disorders of metabolic balance, such as hyperkalemia and metal tubular sodium reabsorption is decreased, the fall in glomerular filtration balance, as renal output of these substances is fixed.[147]

Acute interstitial nephritis (Table 27-4) is clinically similar to acute tubu renal biopsy, which shows a cellular infiltrate separating tubular structure nephritis is caused by hypersensitivity.[219] In many cases, the renal failu systemic allergy such as fever, rash, or eosinophilia. Finding eosinophils i However, approximately 25% of patients with xenobiotic-induced interstiti Unlike those with tubular necrosis, most patients with acute interstitial r particularly eosinophiluria.[12] Secondary fever at the onset of azotemia is present. The lesion usually improves once the xenobiotic is removed. Co many physicians use this treatment only if the renal failure does not imp stopped.



A B

Figure 27-5. Acute interstitial nephritis (secondary to rifampin). Interstit cell, and eosinophil infiltration occurs without fibrosis. Tubular epithelium changes and mononuclear cell infiltration (tubulitis) (A , H&E Ã— 112; B

Differential Diagnosis of Acute Renal Failu

Patients who present with acutely deteriorating renal function often repre are there 3 major etiologic categories, but each category has several subc present. For example, a patient with an opioid overdose may have neuro muscle necrosis causing myoglobinuric renal failure (intrinsic renal) and Because renal, prerenal, and postrenal processes are not mutually exclus three should always be considered, even when one appears to be the mo

Prerenal failure (renal hypoperfusion) initiates a sequence of events leadir is released, causing production of angiotensin, which both enhances prox stimulates adrenal aldosterone release, thus increasing distal sodium rea accompanied by low urinary sodium excretion (Table 27-5). Release of retention. Unresolving renal hypoperfusion may cause tubular necrosis.

Xenobiotics may decrease renal blood flow without necessarily causing int cathartics can decrease blood volume and antihypertensive agents can e

reduce blood pressure. Some xenobiotics (eg, cyclosporine, amphotericin

vasoconstriction. NSAIDs lower filtration rate by inhibiting production of arteriole. Finally, cardiotoxins, such as doxorubicin, can cause severe hea hypersensitivity vasculitis (Fig. 27-1).

Acute

To differentiate prerenal failure from acute tubular necrosis:

1. BUN-to-creatinine ratio; usually >20:1 in prerenal failure
2. Urine Na^+ usually <20 mEq/L in prerenal failure; usually >40 mEq/L in acute tubular necrosis
3. Fractional Na^+ excretion (FE_{Na}) is most reliable test:[12,13]

$$FE_{Na} = \frac{\text{Urine [Na]/Plasma [Na}^+\text{]}}{\text{Urine [Creatinine]/Plasma [Creatinine]}} \times 100$$

FE_{Na} <1% (ie, normal) in prerenal failure, if the patient has not received diuretics or large infusions of sodium, which increase Na^+ excretion despite normal tubular function. In tubular necrosis or interstitial nephritis, renal Na^+ absorption is decreased, and FE_{Na} >1%. This is useful except in pigmenturic or iodinated radiocontrast-associated renal failure, when the test is of no benefit.

Chronic

Creatinine clearance (C_{cr}) = U × V/P (normal range 90–130 mL/min), where U is urine creatinine concentration, V is urine flow in mL/min, and P is plasma creatinine concentration. Urine collection must be complete (not necessarily 24 hours), and U and P must be in the same units.

In steady states, C_{cr} can be approximated by estimating a patient's 24-hour creatinine output (~12 mg/kg of body weight in females; ~15 mg/kg of body weight in males), dividing the estimated 24-hour creatinine by the plasma creatinine concentration, and multiplying the result by 0.07 to convert to mL/min; or from the Cockroft-Gault equation:[44a]

$$C_{cr} = \frac{(140 - \text{age}) \times \text{ideal body weight (kg)}}{72 \times \text{serum creatinine}} (\times 0.85 \text{ for women})$$

TABLE 27-5. Tests of Renal Fu

Urinary tract obstruction should always be considered when the kidneys leads to anuria, partial obstruction, which is more common, is usually as Continued production of urine in the presence of obstruction leads to dist

blockage. Calyceal dilatation is common. Obstruction of the bladder outlet

Bladder Dysfunction	Crystal Deposition
Anticholinergics	
Ethylene glycol	
Antihistamines	
Fluorinated anesthetics	
Antidepressants (cyclic)	
Fluoroquinolones	
Atropine	
Heme pigments	
Scopolamine	
Indinavir	
Antipsychotics	
Methotrexate	
Butyrophenones	
Phenylbutazone	
Phenothiazines	
Sulfonamides	
Bromocriptine	
CNS depressants	
Retroperitoneal Fibrosis	
Ergotamines (Methysergide)	
Chinese herbs (*Stephania*)	

TABLE 27-6. Xenobiotics that Cause Urinary Obstruction

Obstruction may be caused by xenobiotics (Table 27-6).[74] Most do so by anticholinergic action (atropine, tricyclic antidepressants). Rarely, certain cause retroperitoneal fibrosis and ureteral constriction. Finally, a few xen obstruction. Sometimes the xenobiotic itself forms precipitates (sulfonam excretion of a precipitating chemical such as oxalate (ethylene glycol an

Patient Evaluation

Evaluation of a patient with suspected toxic renal injury should include ex response to xenobiotics is affected by previous renal function, renal blood obstruction that can exert back-pressure on the nephrons, all of which m

History

A past history of renal disease or conditions that can affect the kidney disease) should be noted. Flank pain, hematuria, or any abnormal pattern patient's intravascular volume status affects renal perfusion. Thus, a histo plasma volume such as vomiting or diarrhea is important. Prior cancer ch methyl-CCNU (methyl-1-[2-chloroethyl]-3-cyclohexyl-1-nitrosourea) should b evaluated for potential renal effects, both those with direct and indirect alcohol and drugs of abuse should be explored. A careful occupational his are crucial, with emphasis on exposure to nephrotoxic xenobiotics.

Physical Examination

The patient's hemodynamic status should be carefully assessed. Postural c either engorgement or decreased filling of the neck veins, give important The skin should be examined for lesions. Pupillary abnormalities may sug reveal evidence of chronic hypertension or diabetes. All aspects of cardia or absence of edema. Injuries or scars in the suprapubic area or evidenc may suggest obstruction, as may a palpable or percussible bladder.

Laboratory Evaluation

Nephrotoxic injury is not always apparent clinically, so the laboratory is function may be suspected if urine output decreases, but oliguria is not renal function is glomerular filtration. Because urea and creatinine are lar these substances are used as markers of renal function. However, the blo production and excretion. Azotemiaâ€”elevation of BUN or creatinineâ€”is However, BUN or creatinine in the normal

range does not exclude a substantial degree of renal impairment because relationship between these parameters and GFR. In addition, decreased p or creatinine (amputation, muscle wasting) may result in a normal value f significant renal impairment. Conversely, decreased renal perfusion (prere disproportionate rise in BUN as compared to the rise in creatinine, becaus and water, whose reabsorption is increased when the kidneys are underp is suggestive of prerenal failure (Table 27-5). Because many nephrotoxi acute renal failure (urine volume >400 mL/d), progressive azotemia witho drug-related cause. Tubular injury, especially in lead poisoning and myo decreased tubular secretion of uric acid.

Antimony[36]
+

Arsenic[129 ,155 ,224 ,225]
+ + +
+ + +
+ +
+
+

Barium[190 ,234]
+

Beryllium[18]

+ +

Bismuth[22 ,23 ,217]
+ +

+

+
+

Cadmium[1 ,80 ,118 ,232]

+ + +
+ + +

Chromium[166 ,229]
+ + +

Copper[195]

+
+

Gadolinium[87 ,104 ,200]
+

Germanium[139a ,165]

+

Gold[8 ,56 ,161 ,222]

+

+ + +

Iron[42 ,143 ,221]

+ +

+

Lead[7 ,16 ,21 ,35 ,39 ,45 ,49 ,65 ,111 ,233]
+

+

+ + +
+ + +

Lithium[4 ,53 ,78 ,102 ,103 ,130 ,205]
+

+ +
+ +

Mercury[83 ,166 ,185]
+ + +
+

+
+

Platinum (cisplatin)[90 ,95 ,192 ,207 ,236]
+ +

+ +
+ +

Silicon[116]

+
Silver[140 ,143]
+

Thallium[199]						
+						
+						
Uranium[166,172]						
+						

+++ = common; + = uncommon.

Toxic Acute Tubular Necrosis	Shock Acute Tubular Necrosis	Hemolysis	Acute Interstitial Nephritis	Chronic Interstitial Nephritis	Tu Dys

TABLE 27-7. Nephrotoxic Effects of Metals

Certain xenobiotics alter measured levels of urea and creatinine in the ab most obvious is exogenous creatine taken to build muscle mass. Cefoxitir the same frequency as the creatinine reaction product, thus artifactually a component of rocket model fuel, produces extreme elevation of creatini

renal creatinine secretion, such as cimetidine and trimethoprim, may also raised independently of renal function by tetracycline or corticosteroids,

In patients with chronic renal insufficiency or failure, it is necessary to as the patient properly. Clearance measurements are generally used to dete common is endogenous creatinine clearance (see Table 27-5).

Determining creatinine clearance in acute renal failure is not helpful, as tl state. Changing GFR during a clearance time period distorts the resulting between changes in kidney function and changes in BUN or creatinine cor renal failure should be treated as if glomerular filtration were <10 mL/mi random sample of urine may be sent promptly to the laboratory for sodi

fractional sodium excretion, which may help differentiate prerenal azotem

Solvents

- Carbon tetrachloride[143,166,206,209]
  - Hepatic failure leading to hepatorenal syndrome
  - Occasional acute nephrotoxic renal failure
- Tetrachloroethylene[199]
  - Hepatic failure leading to hepatorenal syndrome
  - Occasional acute nephrotoxic renal failure
- Trichloroethylene[15]
  - Acute tubular necrosis
- Toluene[184]
  - Hippuric acidosis

Glycols

- Ethylene glycol[37,171]
  - Metabolized to glycolic acid (metabolic acidosis)
  - Further metabolized to oxalic acid (acute tubular necrosis)
- Diethylene glycol[96,166]
  - Direct tubular toxin (acute tubular necrosis)
  - Hyperoxaluria may add to renal injury
- Propylene glycol[121]
  - May cause hemolysis and hemoglobinuric renal failure

TABLE 27-8. Nephrotoxic Hydrocarbons and Their Mechanisms of

Acute tubular necrosis
- Aminoglycosides[28,54,169,191,204]
- Gentamicin,[109] tobramycin,[210] amikacin[131]
- Amphotericin[6,19,38,98]
- Fluoroquinolones (ciprofloxacin, levofloxacin)[88,211]
- Polymyxins B and E[125]
- Pentamidine[212]
- Acyclovir[24]
- Foscarnet[33]
- Ritonavir[55]
- Phenazopyridine[76]

Acute interstitial nephritis
- Î²-Lactams (penicillins,[11,157] cephalosporins[12,123])
- Sulfonamides[150] (including cotrimoxazole[136])
- Vancomycin[10,62]
- Rifampin[163,180,183]
- Nitrofurantoin[156]
- Aminoglycosides (rare)[152,193]
- Tetracyclines (rare)[230]
- Polymyxins[26]

Hypersensitivity vasculitis
- Penicillins[157]
- Sulfonamides[157]

Obstruction (crystalluria)
- Acyclovir[32]
- Indinavir[115]
- Sulfonamides[150]

Tubular dysfunction
Aminoglycosides (K^+ and Mg^{2+} wasting)[109]
Amphotericin
Renal tubular acidosis[144]
K+ and Mg^{2+} wasting[20]
Tetracyclines (Fanconi syndrome,[81] hypercatabolism[178])

TABLE 27-9. Nephrotoxic Antimicrobials

Acute tubular necrosis
Colchicine[214]
Acetaminophen[34,52]
Acute interstitial nephritis
Allopurinol[85]
Sulfinpyrazone[107,136]
Acute worsening of kidney function (prerenal)[84]
Indomethacin
Chronic interstitial nephritis[31]
5-Aminosalicylate[2]
Aspirin/phenacetin or aspirin/acetaminophen â€œanalgesic nephropath
Hyperkalemia[197]
Hyponatremia[44]
Nephrotic syndrome[31,75,231]
Penicillamine[188]
Probenecid[101]

TABLE 27-10. Nephrotoxic Effects of Antiarthritic drugs[41,44,6

Diuretics
Prerenal failure (volume depletion)
Acute interstitial nephritis[136,141,142]
Acute renal failure (mannitol)[29,93]
Hyperkalemia (K^+-sparing diuretics)[71]

Hyponatremia

Antihypertensives
- Prerenal failure (excessive dosage)
- Acute interstitial nephritis
  - Methyldopa[235]
  - Captopril[216]
- Nephrotic syndrome
  - Captopril[182]
- Obstruction (retroperitoneal fibrosis)
  - Methyldopa[132]

Anticonvulsants
- Acute interstitial nephritis
  - Carbamazepine[106]
  - Phenobarbital[167]
  - Phenytoin[11 ,110]
- Nephrotic syndrome
  - Trimethadione[17]
  - Paramethadione

Anesthetics
- Acute tubular necrosis
  - Methoxyflurane[168]
  - Halothane[86]
  - Enflurane[61]

Antineoplastics
- Acute tubular necrosis
  - Cisplatin[90 ,192]
  - Methotrexate[46 ,135 ,179]
  - Mithramycin[120]
  - Ifosfamide[203]
  - Streptozotocin[198]
- Chronic interstitial nephritis

Cisplatin[95]
Nitrosoureas[63 ,201]
Thrombotic microangiopathy
Mitomycin C[137 ,173]

Immunosuppressants
Acute tubular necrosis and/or chronic interstitial nephritis
Cyclosporine[73 ,108 ,146 ,160 ,175]
Tacrolimus[161 ,218]
Acute interstitial nephritis
Azathioprine[208]
Renal tubular acidosis
Tacrolimus[97]

Nephrotoxicity of radiocontrast agents
Acute renal failure, especially the high osmolal and ionic agents[13 ,29 ,6
Osmotic nephropathy and renal vasoconstriction

TABLE 27-11. Examples of Nephrotoxicity Medications

Acute tubular necrosis
Aluminum phosphide[122]
Deferoxamine[42]
Epinephrine (in neonate)[132]
Etidronate[168]
Mycotoxins[57]
Paraquat, diquat[227]
Acute interstitial nephritis
Cimetidine[136 ,145]
Clofibrate[50]
Phenylpropanolamine[27]
Ranitidine[79]
Ticlopidine[187]
Acute renal failure

Mushrooms
Amanita (especially *A. smithiana*)[148]
Cortinarius spp[128]
Pigments[66]
Hemoglobin
Myoglobin
Obstruction (retroperitoneal fibrosis)
Bromocriptine[30]
Renal stones and aminoaciduria
Worcestershire sauce[158]

TABLE 27-12. Nephrotoxicity of Miscellaneous Xenobiotics

Examination of the urine is essential in cases of poisoning. Even if urine is examined carefully by the physician. Standard dipsticks will detect albumin useful for confirming the presence of small amounts of blood or myoglobin microscopic examination of the sediment. Clinicians should look not only fo tubular elements, casts, and bacteria. If acute interstitial nephritis is a co stained for eosinophils.[164]

Nephrotic syndrome
Street heroin[51 ,127 ,138 ,149]
Street cocaine[51]
Amyloidosis
Street heroin (injection use)[48 ,113]
Obstruction (retroperitoneal fibrosis)
Lysergic acid diethylamide (LSD)[213]
Acute renal failure (myoglobinuria)
Amphetamines[100 ,119]
Cocaine[189]
Chronic renal failure (vasculitis)
Amphetamines[43]

TABLE 27-13. Nephrotoxicity of Drugs of Abuse

Acute interstitial nephritis

Stephania tetrandra, Magnolia officinalis[68,226] (â€œChinese herbs,â€• often irreversible)

Hypericum [68]

Ledum [68]

Acute tubular necrosis

Grass carp gallbladder[134]

Disodium edetate[45,168]

Obstruction (retroperitoneal fibrosis)

Stephania tetrandra, Magnolia officinalis [68,226]

TABLE 27-14. Nephrotoxicity of â€œAlternativeâ€• Medical Trea

Further evaluation of the patient with acute renal failure should include te number of substances (see Table 27-6). Renal ultrasonography should b Postvoiding residual urine volume may be measured as appropriate by cat 75â€“100 mL, one should suspect bladder dysfunction or obstruction.

Nephrotoxic complications of specific xenobiotics are found in Tables 27-7 13 and 27-14 .

Summary

The kidneys are exposed to exogenous or endogenous xenobiotics in thei xenobiotics entering the bloodstream. The environment, the workplace, a medications, all represent potential sources of nephrotoxicity. Consequentl and observation, to what xenobiotics a patient may have been exposed an kidneys. It is equally crucial to work the other way when a patient prese medications, both conventional and â€œalternative,â€• all xenobiotic exp adversely affect the kidneys.

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Chapter 28
Genitourinary Principles

Jason Chu

The genitourinary system encompasses two major organ systems: the reproductive and the urinary. Successful reproduction requires interaction between two sexually mature individuals. Xenobiotic exposures to either individual can have an adverse impact on fertility, which is the successful production of children, and fecundity, which is an individual's or a couple's capacity to produce children. However, the role of occupational and environmental exposures in the development of infertility is difficult to define.[11 , 49 , 120 , 125] Well-designed and conclusive epidemiologic studies are difficult to accomplish because of the following factors: laboratory tests used to evaluate fertility are relatively unreliable; clinical end points are unclear; xenobiotic exposure is difficult to monitor; and indicators of biologic effects are imprecise. The negative impact on fertility as an adverse effect of xenobiotics is often ignored, but the evaluation of infertility is incomplete without a thorough drug and occupational history. Differences in the toxicity of xenobiotics in individuals may be sex- and/or age-related. Xenobiotic-related, primary infertility may be

the result of effects on the hypothalamicâ€“pituitaryâ€“gonadal axis or of a direct toxic effect on the gonads.[105] Fertility is also affected by exposures that cause abnormal sexual performance. Table 28-1 lists xenobiotics associated with infertility.

Aphrodisiacs are used to heighten sexual desire and to counteract sexual dysfunction. Historically, humans have continued to search for the perfect aphrodisiac. Efficacy is variable, and toxic consequences occur commonly. Various treatments have been evaluated for male sexual dysfunction, but the perfect remedy remains a mystery.

Whereas many people search for a cure for impotence or infertility, many others explore drugs and plants that can be used as contraceptives and abortifacients. Routes of administration vary from oral to parenteral to intravaginal. Toxicity results not only in the termination of pregnancy but also from the systemic effects of the various xenobiotics.

This chapter examines all of these issues, as well as the impact of xenobiotics on the urinary system, specifically, urinary retention and incontinence and abnormalities detected in urine specimens. Renal (Chap. 27), teratogenic, and carcinogenic (Chap. 30) principles are discussed in further detail elsewhere in this text.

Male Fertility

The male reproductive system is comprised of the male gonads and the endocrine organs that provide the hormonal controls. Disruption of normal function at any part of the system affects fertility. There are a multitude of xenobiotics that adversely affect spermatogenesis and sexual function.

Spermatogenesis

Central to the male reproductive system is the process of spermatogenesis, which occurs in the testes. The bulk of the

testes consist of seminiferous tubules with germinal spermatogonia and Sertoli cells. The remainder of the gonadal tissue is comprised of the interstitium containing blood vessels, lymphatics, supporting cells, and Leydig cells. Spermatogenesis begins with the maturation and differentiation of the germinal spermatogonia. The process is controlled by the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which stimulates the pituitary to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH stimulates the development of Sertoli cells in the testes, which are responsible for the maturation of spermatids to spermatozoa. LH promotes production of testosterone by Leydig cells. Testosterone levels must be maintained to ensure the formation of spermatids.[27] Both FSH and testosterone are required for initiation of spermatogenesis, but testosterone alone is sufficient to maintain the process.

Testicular Xenobiotics

Xenobiotics can affect any part of the male reproductive tract, but, invariably, the end result is decreased sperm production, defined as oligospermia, or absent sperm production, azoospermia. Spermatogenesis is an ongoing process throughout life (as compared to oogenesis in women) and can be inhibited by decreases in FSH and/or LH or Sertoli cell toxicity. Spermatogenic capacity is evaluated by semen analysis, including sperm count, motility, sperm morphology, and penetrating ability. Normal sperm count is above 40 million sperm/mL of semen, and a count below 20 million sperm/mL of semen is indicative of infertility.[27] Decreased motility (asthenospermia) below 40% of normal or abnormal morphology (teratospermia) of more than 40% of the total number of sperm also indicates infertility.[27, 140]

Antineoplastics

Oligospermia and azoospermia are reported with cyclophosphamide, chlorambucil, and methotrexate when used as single agents.[27 , 138] Combination therapies with procarbazine, vinca alkaloids, or any of the above agents also decrease sperm production and fertility with variable recovery rates.[27]

Anabolic steroids
â†“ LH, oligospermia
Antineoplastics
Gonadal toxicity
Androgens
Suppress testosterone production
Cyclophosphamide
Ovarian failure
Antineoplastics
Gonadal toxicity
Busulphan
Amenorrhea
Cyclophosphamide
Oligospermia
Combination chemotherapy
Amenorrhea
Chlorambucil
Oligospermia
(MOPP, MVPP)

Methotrexate
Oligospermia
Diethylstilbestrol
Spontaneous abortions
Combination chemotherapy (COP, CVP, MOPP, MVPP)
Oligospermia
Ethylene oxide
Spontaneous abortions
Lead

Spontaneous abortions, still births
Carbon disulfide
â†“ FSH, â†“ LH, â†“ spermatogenesis
Oral contraceptives
Affect hypothalamicâ€“pituitary axis, end-organ resistance to hormones, amenorrhea
Cimetidine
Oligospermia

Chlordecone
Asthenospermia, oligospermia
Thyroid hormone
â†“ Ovulation
Dibromochloropropane (DBCP)
Azoospermia, oligospermia

Diethylstilbestrol
Testicular hypoplasia

Ethanol
â†“ Testosterone production, Leydig cell damage, asthenospermia, oligospermia, teratospermia

Ethylene oxide
Asthenospermia (in monkeys), oligospermia

Ionizing radiation
â†“ Spermatogenesis

Opioids
â†“ LH, â†“ testosterone

Lead
â†“ Spermatogenesis, asthenospermia, teratospermia

Nitrofurantoin
â†“ Spermatogenesis

Sulfasalazine
â†“ Spermatogenesis

Tobacco
â†“ Testoterone

Men	Women
Xenobiotic Effects	Xenobiotic Effects

TABLE 28-1. Xenobiotics Associated with Infertility

Hormonals

Diethylstilbestrol exposure in utero can lead to testicular hypoplasia in men, but may not lead to infertility or sexual dysfunction.[27, 160] Work-related exposure to estrogens and

progestins in the oral contraceptive industry may result in decreased libido, impotence, and gynecomastia caused by hyperestrogenism.[140] Anabolic steroid use can result in decreased libido, azoospermia, and decreased testicular size.

Radiation Therapy

Treatment of neoplasms with ionizing radiation leads to dose-dependent oligospermia and azoospermia. Time to recovery is dependent on dose and duration of exposure.[7]

Occupational Exposures

1,2-Dibromo-3-Chloropropane

A soil fumigant used in agriculture to control nematodes, 1,2-dibromo-3-chloropropane (DBCP) provides the clearest example of occupational exposure resulting in testicular toxicity and human reproductive dysfunction. In one small series, 7 of 10 patients who were exposed to DBCP had decreased or absent spermatogenic activity on testicular biopsy. This correlated with duration of exposure and was most consistently observed after inhalation exposure. A selective decrease or loss of spermatogenic activity was observed without any other consistent testicular defect, and all stages of differentiation were affected. In the most severe cases, the seminiferous tubules were devoid of germ cells.[17]

The mechanism of toxicity of DBCP is unknown but may be the result of transformation of the parent compound to an alkylating agent. Testosterone levels remain normal, although testicular size is decreased. After removal from exposure, improvement in sperm counts occurred in most oligospermic men, but those who had developed azoospermia showed no recovery of spermatogenic function.[159]

Lead

Painters and artisans are commonly exposed to inorganic lead, which is also a hazard in the smelting and battery industries.[89] Lead is a proven spermicide, and lead exposure is associated with decreased libido, asthenospermia, oligospermia, teratospermia, and testicular atrophy. An increase in the frequency of stillbirths and spontaneous abortions results when the male partner is a lead worker.[162] Lead levels of 35â€“50 Âµg/dL are associated with direct spermatogenic toxicity. Indirect effects result from the inhibition of general metabolic processes by lead (Chaps. 91).[162]

Glycol Ethers

Glycol ethers are used as fuel, deicers, and as components in paints, varnishes, thinners, and printing inks. Animal studies with methoxymethanol and ethoxyethanol show oligospermia, azoospermia, and testicular atrophy. One study documents decreased sperm counts in human workers exposed to ethylene glycol ether.[124]

Male Sexual Dysfunction

Sexual dysfunction can be a result of decreased libido (sexual desire), impotence, diminished ejaculation, and erectile dysfunction. Libido can be decreased by xenobiotics that block dopaminergic pathways or testosterone production, or by xenobiotics that produce dysphoria. Xenobiotics that affect spinal reflexes can cause diminished ejaculation and erectile dysfunction.[161]

Approximately 30 million men in the United States suffer from erectile dysfunction, with an increased prevalence in older men.[70] Erectile dysfunction, as defined by the National Institutes of Health (NIH), is the inability to achieve and/or maintain an erection for a period of time that is long enough to permit satisfactory sexual

intercourse[116] and can be divided into the following classifications: psychogenic, vasculogenic, neurologic, endocrinologic,

and xenobiotic-induced. Xenobiotic-induced erectile dysfunction is associated with the following categories of xenobiotics: antidepressants; antipsychotics; centrally and peripherally acting antihypertensives; CNS depressants; anticholinergics; exogenous hormones; antibiotics; and chemotherapeutic agents.[97, 139, 161] Treatment of this disorder is varied and includes vacuum-constriction devices, penile prostheses, vascular surgery, and medications (intracavernosal, transdermal, and oral agents).

The following section contains a discussion of the physiology of erection followed by a discussion of agents that cause sexual dysfunction in men, agents that are used to treat erectile dysfunction, and priapism.

Physiology of Erection

Normal penile erection is a result of both neural and vascular effects leading to smooth muscle relaxation and increased blood flow into the corpora cavernosa sinusoids of the penis. Psychogenic neural stimulation arising from the cerebral cortex is mediated through the thoracolumbar sympathetic and sacral parasympathetic tracts. In animals, dopamine and nitric oxide play a role in erection.[111] Reflex stimulation can also occur from the sacral spinal cord. The afferent limb of the reflex arc is supplied by the pudendal nerves and the efferent limb by the nervi erigentes (pelvic splanchnic nerves).

The internal pudendal arteries supply blood to the penis via 4 branches. Blood outflow is via multiple emissary veins draining into the dorsal vein of the penis and plexus of Santorini. Within the penis, the corpora cavernosa share vascular supply and drainage as a result of extensive arteriolar, arteriovenous, and sinusoidal anastomoses.[166] When penile blood flow is above

20â€“50 mL/min, erection occurs. Maintenance of tumescence occurs with flow rates of 12 mL/min. The tunica albuginea limits the absolute size of erection.

Penile erection depends on corpus cavernosal smooth muscle relaxation to allow increased blood flow and involves parasympathetic dominance, either by stimulation of parasympathetic receptors or inhibition of the sympathetic axis. Both cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) pathways mediate smooth muscle relaxation. Cholinergic nerves release acetylcholine, which stimulates endothelial cells via M_3 receptors to produce nitric oxide and prostaglandin E_2 (PGE_2). Prostaglandin E_2 and nerves containing vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP) increase cellular cAMP to potentiate smooth muscle relaxation. Nonadrenergic-noncholinergic nerves and endothelial cells produce nitric oxide, which activates guanylate cyclase conversion of guanosine triphosphate (GTP) to cGMP. Increasing levels of cGMP act as a second messenger, mediating arteriolar and trabecular smooth muscle relaxation to enable increased cavernosal blood flow and penile erection.[111]

In the flaccid state, sympathetic efferent nerves maintain helicine-resistant arteriole constriction primarily through norepinephrine-induced Î±-adrenergic agonism. Î±-Adrenergic receptor agonism in the erectile tissues decreases cAMP to produce flaccidity, whereas Î±-adrenergic antagonism can result in pathologic erection (priapism) as a consequence of parasympathetic dominance.[166] Other vasoconstrictors, such as endothelin, prostaglandin F_{2a} , and thromboxane A_2 play a role in maintaining corpus cavernosal smooth muscle tone in contraction, which results in a flaccid state.[111]

Antihypertensives

Erectile dysfunction is reported as an adverse effect with all

antihypertensives and may be caused, in part, by a decrease in hypogastric artery pressure, which impairs blood flow to the pelvis.[159] Methyldopa and clonidine both are centrally acting Î±$_2$-adrenergic agonists that inhibit sympathetic outflow from the brain. Sexual dysfunction is reported in 26% of patients taking methyldopa and in 24% of those patients receiving clonidine.[16, 114] Erectile dysfunction associated with thiazide diuretics may be related to decreased vascular resistance, diverting blood from the penis.[29] Spironolactone acts as an antiandrogen by inhibiting the binding of dihydrotestosterone to its receptors. Impotence related to use of Î²-adrenergic antagonists is well documented[1, 77, 156] and may be caused by unopposed Î±-mediated vasoconstriction resulting in reduced penile blood flow.

Ethanol

Ethanol is directly toxic to Leydig cells

Chronic alcohol abuse causes decreased libido, erectile dysfunction, and testicular atrophy. In alcoholics, liver disease contributes to sexual dysfunction because of decreased testosterone and increased estrogen production. Alcoholics also can have autonomic neuropathies affecting penile nerves and subsequent erection. Alcoholics suffer more erectile dysfunction than do episodic drinkers.[158]

Psychotropics

Individuals who take psychotropics therapeutically have varying levels of sexual dysfunction related to both their underlying disease and their medications. All psychotropic agents are associated with sexual dysfunction to some degree. Monoamine oxidase inhibitors (MAOIs), cyclic antidepressants, antipsychotics, and selective serotonin reuptake inhibitors (SSRIs) are associated with decreased libido and erectile dysfunction in men.[39]

Thioridazine is associated with significantly lower LH and testosterone levels in men compared to other antipsychotics.[27] Table 28-2 lists other xenobiotics associated with sexual dysfunction.

Xenobiotics Used in the Treatment of Erectile Dysfunction

Intracavernosal Use

The three most common intracavernosal agents used for erectile dysfunction are papaverine, prostaglandin E_1 , and phentolamine. Papaverine is a benzylisoquinoline alkaloid derived from the poppy plant *Papaver somniferum* . It exerts its effects through nonselective inhibition of phosphodiesterase, leading to increased cAMP and cGMP levels and to subsequent cavernosal vasodilation. Papaverine was used for the treatment of cardiac and cerebral ischemia, but had limited efficacy. Presently, it is used as intracavernosal therapy for erectile dysfunction either alone or in conjunction with phentolamine. Systemic side effects include dizziness, nausea, vomiting, hepatotoxicity, lactic acidosis with oral administration, and cardiac dysrhythmias with intravenous use.

Intracavernosal administration is associated with penile fibrosis which is usually a dose-related phenomenon, although fibrosis can also occur with limited use.[43] More concerning is the development of priapism with papaverine use.

Anabolic steroids
Cyclic antidepressants
Anticholinergics[a]
Ethanol
Anticonvulsants

Lead
Antiestrogens
Lithium
Î±-Adrenergic antagonists
Monamine oxidase inhibitors[a]
Î²-Adrenergic antagonists[a]
Opioids (high dose)
Benzodiazepines
Oral contraceptives
Calcium channel blockers
Phenothiazines
Diuretics
Selective serotonin reuptake inhibitors
Cimetidine
Spironolactone

[a] Associated with erectile dysfunction.

TABLE 28-2. Xenobiotics Associated with Sexual Dysfunction (Particularly Diminished Libido and Impotence)

Prostaglandin E_1 (alprostadil) is a nonspecific agonist of prostaglandin receptors resulting in increased levels of intracavernosal cAMP, cavernosal smooth muscle relaxation, and penile erection. It is effective via intracavernosal administration as a single agent. Other preparations include an intraurethral preparation, which is less efficacious, and a topical gel formulation.[71] Penile fibrosis can occur, but the incidence is lower than with papaverine. Other adverse effects include penile pain, secondary to its effects as a nonspecific prostaglandin receptor agonist, and priapism.

Phentolamine is a competitive Î±-adrenergic antagonist at $Î±_1$ and $Î±_2$ receptors. It effects erection by inhibiting the normal resting adrenergic tone in cavernosal smooth muscle, thus allowing

increased arterial blood flow and erection. Intracavernosal use can cause systemic hypotension, reflex tachycardia, nasal congestion, and gastrointestinal upset. Penile fibrosis and priapism are also reported.

Oral Use

Phosphodiesterase 5 Inhibitors

Since the development of the phosphodiesterase 5 inhibitors, oral therapy has replaced intracavernosal injections as the mainstay for treatment of erectile dysfunction. Sildenafil was the first agent developed, followed by vardenafil and tadalafil. These medications have similar mechanisms of action but differ in their pharmacokinetics. Phosphodiesterase 5 inhibitors increase nitric oxide-induced cGMP concentrations by preventing phosphodiesterase breakdown of cGMP, enhancing nitric oxide-induced vasodilation to promote penile vascular relaxation and erection.[21]

After oral administration, sildenafil is rapidly absorbed, with a bioavailability of 40% and a median peak plasma concentration of 60 minutes. Its mean volume of distribution is 105 L, and its elimination half-life is 3â€“5 hours. Metabolism is primarily by the cytochrome P450 (CYP) 3A4 pathway, with some minor metabolic activity via the CYP2C9 pathway. Plasma concentrations of sildenafil are increased in patients older than age 65 years, as well as in patients with hepatic dysfunction or severe renal dysfunction (creatinine clearance <30 mL/min), and when used with CYP3A4 inhibitors (macrolide antibiotics, cimetidine, antifungal agents, protease inhibitors).[35]

Vardenafil has more selective inhibition of phosphodiesterase 5 enzymes and less inhibition of phosphodiesterase 6 enzymes compared to sildenafil. After oral administration, it has a 14% bioavailability, a volume of distribution of 208 L, a median peak

plasma concentration of 60 minutes, and an elimination half-life of 4â€“5 hours. The CYP3A4 pathway is the primary hepatic metabolic pathway with minor contributions from CYP3A5 and CYP2C9 enzymes.[14, 18] The primary metabolite, M1, has phosphodiesterase 5 inhibitory activity but is 4 times less potent than vardenafil.[18] As with sildenafil, vardenafil levels are increased in patients older than age 65 years, and in patients with hepatic dysfunction or severe renal dysfunction (creatinine clearance <30 mL/min), and when used with CYP3A4 inhibitors (macrolide antibiotics, cimetidine, antifungal agents, protease inhibitors).[83]

Tadalafil has a median peak plasma concentration of 2 hours and a mean elimination half-life of 17.5 hours. It is predominantly metabolized by CYP3A4 enzymes. Unlike sildenafil and vardenafil, plasma levels are not affected by age, hepatic dysfunction, renal dysfunction or CYP3A4 inhibitors. However, the FDA has issued recommendations to decrease the dosage of all phosphodiesterase 5 inhibitors if used in conjunction with atazanavir.[8]

The most common adverse effects of the phosphodiesterase 5 inhibitors are headache, flushing, dyspepsia, and rhinitis, which are related to phosphodiesterase 5 inhibitory effects on extracavernosal tissue.[70] Blurred vision, increased light perception and transient blue-greenâ€“tinged vision are also reported and are related to the weak phosphodiesterase 6 inhibition of sildenafil in the retina.[70] Vardenafil is associated with infrequent abnormal vision, such as haziness, but not color vision.[72] Blurred or color vision is not reported with tadalafil.

More serious adverse effects of sildenafil include myocardial infarction, when used alone or with nitrates, hypertrophic subaortic stenosis obstruction, priapism, and optic ischemia.[6, 55, 82, 142, 145] Tadalafil use is associated with anterior ischemic optic neuropathy.[19]

When taken alone, the vasodilatory effects of phosphodiesterase 5

inhibitors cause a modest decrease in systemic blood pressure. However, because of their mechanism of action via cGMP inhibition and vascular vasodilation, phosphodiesterase 5 inhibitors can have synergistic interactions with the vasodilatory effects of nitrates resulting in profound hypotension.[21 , 84] A study of healthy male volunteers taking sildenafil demonstrated significantly less tolerance to a glyceryl trinitrate infusion as compared to placebo.[157] Because of this interaction, patients with acute myocardial ischemic syndromes who are using phosphodiesterase 5 inhibitors should avoid taking organic nitrates.[35] Î±-Antagonists are also contraindicated for concurrent use with phosphodiesterase 5 inhibitors because of increased hypotensive effects.[84] Hypotension occurred in patients using vardenafil with terazosin and tamsulosin,[84] and in patients using tadalafil with doxazosin.[85] However, patients using tadalafil with tamsulosin did not develop hypotension.[85]

Yohimbine

Yohimbine, an indole alkylamine alkaloid from the West African yohimbe tree (*Corynanthe yohimbe*), is an $Î±_2$ -adrenergic antagonist with cholinergic activity used to treat erectile dysfunction and postural hypotension associated with anticholinergic drugs.[94] It is structurally similar to reserpine. Other names for yohimbine include Aphrodyne, corynine, hydroergotocin, quebrachine, and the street name â€œyo-yo.â€•[95] Its use in the treatment of impotence is based on the theory that erection is linked to cholinergic stimulation and $Î±_2$ -antagonism, resulting in an increase inflow and decrease outflow of blood to the penis. Although the agent Aphrodex, which contained 5 mg of yohimbine, 5 mg of methyltestosterone, and 5 mg of strychnine, improved performance in males with erectile failure,[101] its distribution was halted in 1973 because of safety concerns.[136]

Yohimbine can be obtained by prescription, but extracts are also available in â€œhealth foodâ€• products marketed as â€œvitalizing agents for men and women.â€•[47] Yohimbine can also be extracted from the Rauwolfia root.[60] The â€œtherapeuticâ€• dose is 2â€“6 mg 3 times daily. The drug is rapidly absorbed, with peak serum levels occurring in 45â€“60 minutes. The half-life is 36 minutes, and clearance is by hepatic metabolism without renal excretion.[121] Maximum pharmacologic effects occur 1â€“2 hours after ingestion, and effects persist for 3â€“4 hours.[95]

Because the erectile process involves various neurotransmitters, a single agent would be expected to only have a partial effect. In a double-blind study of 100 males with erectile failure treated with 18 mg/d of yohimbine, 42.6% of the treatment group and 27.6% of the placebo group reported some improvement in erectile function,

which was not statistically significant.[110] Another study that compared a higher dose of yohimbine and placebo in 82 males showed a statistically significant improvement with treatment.[148]

Adverse effects can occur with relatively low doses of yohimbine. Tachycardia, hypertension, mydriasis, diaphoresis, lacrimation, salivation, nausea, vomiting, and flushing can occur following intravenous administration.[78] In patients with bipolar disorder,[131] 10 mg of yohimbine can elicit manic symptoms and 15 mg/d is associated with bronchospasm[88] and a lupuslike syndrome.[137] A 16-year-old girl who ingested 250 mg of yohimbine powder, purchased for its purported aphrodisiac activity, developed an acute dissociative reaction with weakness, paresthesias, headache, nausea, palpitations, and chest pain. She also developed tachycardia, tachypnea, diaphoresis, tremors, and a rash. Her symptoms resolved without treatment after 36 hours.[95] Another report describes a 62-year-old man who ingested 200 mg of yohimbine and developed tachycardia, hypertension, and a brief

period of anxiety that resolved without treatment.[60] Symptomatic patients who ingest yohimbine should receive activated charcoal and should be observed until asymptomatic. Clonidine has been recommended for treatment of yohimbine's central and peripheral effects.[95] Î²-Adrenergic antagonists may attenuate some of the peripheral toxicity, but may also result in unopposed Î±$_1$ -adrenergic activity and worsening of hypertension, and should be avoided. Benzodiazepine administration may be sufficient for the treatment of agitation and sympathomimetic effects related to yohimbine.

Apomorphine

Sublingual apomorphine effects erection through activation of central dopaminergic pathways, most likely D_2 receptors in the paraventricular nucleus of the hypothalamus.[76] It reaches maximum plasma concentrations within 40â€“60 minutes after sublingual administration and is metabolized hepatically with a half-life of 2â€“3 hours.[5] Common adverse effects are nausea, headache, dizziness, and syncope. Unlike the phosphodiesterase 5 inhibitors, apomorphine is not associated with hypotension when used with antihypertensive medications, such as nitrates.

Priapism

Priapism is defined as a prolonged involuntary erection that is painful, unassociated with sexual stimulation, and can result in impotence. It most commonly occurs during the third and fourth decades of life and is caused by inflow of blood to the penis in excess of outflow. The corpora cavernosa become firm and the corpus spongiosum becomes flaccid. Intracavernosal pressures can exceed arterial systolic pressure, resulting in cell death. Priapism can occur from an imbalance in neural stimuli, interference with venous outflow, or as a result of xenobiotic-induced inhibition of penile detumescence. Î±-Adrenergic antagonist agents prevent

constriction of blood vessels supplying erectile tissue, resulting in priapism.[166] One of 10,000 patients taking trazodone develop priapism, which is thought to be related to its Î±-adrenergic antagonist effects.[136] A common cause of priapism is iatrogenic, resulting from the injection of papaverine for the treatment of impotence.[149] Other xenobiotics associated with xenobiotic-induced priapism include prazosin, labetalol, guanethidine, hydralazine, phenothiazines, and, rarely, androgens, anticoagulants, ethanol, marijuana, and cantharidin (Table 28-3).[81 , 149 , 166]

The goal in the treatment of priapism is detumescence with retention of potency. Initial therapy includes sedation with benzodiazepines, analgesia with opioids, ice packs, and early urologic consultation. Oral terbutaline (5â€“10 mg) is effective for prostaglandin E_1 -induced priapism and may be effective for other xenobiotic-induced priapism.[96 , 132] Aspiration and normal saline irrigation of the corpora cavernosa may be effective. If priapism occurs secondary to Î±-adrenergic antagonism, an Î±-adrenergic agonist (0.02 mg norepinephrine or 0.2 mg phenylephrine) diluted with 0.9% sodium chloride solution to 10 mL volume can be instilled by placing a 19-gauge butterfly needle into the corpora cavernosa. If the above measures fail, operative venous shunt placement may be required.[149 , 166]

Androgens
Cantharidin
Anticoagulants
Cocaine
Antihypertensives
Benzodiazepines
  Guanethidine
Ethanol
  Hydralazine
Marijuana

Labetalol
Papaverine
Phentolamine
Phosphodiesterase 5 inhibitors
Prazosin
Trazodone
Antipsychotics

TABLE 28-3. Xenobiotics Associated with Priapism

Female Fertility

The female reproductive system consists of the female gonadal organs and the respective hormonal system. Fertility encompasses the reproductive system, the process of oocyte fertilization, and gestation. Female infertility may result from changes in hormone levels, direct toxicity to the ovum, interference with the transport of the ovum, or inhibition of implantation of the ovum in the uterus. Women usually notice reproductive abnormalities more quickly than men, because menses may be affected, although infertility may occur while normal menses persist. Evaluation of female fertility is more difficult owing to the complexity of the systems involved and the inaccessibility of the female germ cell, but it is feasible and involves investigations of the anatomy and hormonal levels. The following is a discussion of oogenesis, xenobiotics that disrupt oogenesis, and xenobiotics that affect early embryo gestation.

Oogenesis

In contrast to men, women have a limited number of reproductive cells (ovarian follicles). Follicles are most numerous while the fetus is in utero, with the number decreasing to approximately 2

million at birth. By the time a woman reaches puberty, the majority of follicles have degenerated, leaving 300,000â€“400,000 ova, of which only about 400 will eventually produce mature ova during a woman's reproductive years. In contrast, men produce millions of spermatozoa a day. The process of oogenesis requires secretion of GnRH from the hypothalamus, resulting in production of LH and FSH from the pituitary, which are required for ovarian follicle maturation.[27] FSH induces early maturation by stimulating granulosa and thecal cell proliferation and estrogen production. LH is required for ovulation and for the formation of the corpus luteum. The corpus luteum continues estrogen production and produces progesterone, which stimulates the uterus to develop an endometrium receptive to any fertilized ovum. Successful ovulation requires not only hormone secretion but appropriate cyclic secretion as well.

Xenobiotics That Decrease Female Fertility

Antineoplastics

Alkylating agents are well described as causing oocyte destruction and disruption of the hypothalamicâ€“pituitaryâ€“ovarian axis in women. Ovarian failure with menstrual cycle disruptions and amenorrhea are reported with cyclophosphamide and busulphan as single agents.[27 , 155] Combination therapies with alkylating agents and vinca alkaloids are also reported to cause menstrual irregularities.

Hormonals

Exposure to diethylstilbestrol in utero rarely can lead to cervical and vaginal abnormalities in women.[27] Oral contraceptives can

rarely produce persistent infertility in women, following their discontinuation particularly in those women who are nulliparous. Prolonged infertility is more common with the use of the combined preparations as opposed to the use of sequential estrogen/progesterone contraceptives.[27] Medroxyprogesterone acetate depot administration is associated with transient ovulatory dysfunction of variable duration after cessation of therapy. These xenobiotics may affect the hypothalamicâ€“pituitary axis, gonadotropin release, or end-organ sensitivity to hormonal stimulation.

Psychotropics

As in men, all psychotropic agents can cause sexual dysfunction. MAOIs and tricyclic antidepressants are associated with the highest rates of sexual dysfunction, followed by antipsychotics and SSRIs.[39] These drug classes decrease libido and cause orgasmic dysfunction. Bupropion and nefazodone have the lowest rates of sexual dysfunction and are used to reverse SSRI-induced sexual dysfunction.[38 , 165] One study reported amenorrhea in 50% of women on thioridazine with return of menstruation 6 months after discontinuation.

Environmentals

Chlorinated hydrocarbons are a large group of chemicals that include polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethane (DDT), pentachlorophenol, and hexachlorocyclohexane. PCBs were widely used prior to the 1970s and often released into the environment, where they continue to exist and contaminate the food chain. Studies of the effect of PCBs on fertility are mixed. Some studies show no association with PCB exposure, whereas others show increased levels of PCBs in women with endometriosis. The same study showed increased levels of hexachlorocyclohexane and pentachlorophenol in women with

miscarriages and decreased conception rates with increasing DDT levels.[124]

Female Sexual Dysfunction

The National Health and Social Life Survey found that 43% of women in the United States (compared to 31% of men) reported having sexual dysfunction.[90] In 1999, a consensus panel of the American Foundation for Urologic Disease revised the classification of female sexual dysfunction into the following 4 categories: (a) sexual desire disorders, which include hypoactive sexual desire disorder and sexual aversion disorder; (b) sexual arousal disorder; (c) orgasmic disorder; and (d) sexual pain disorders, which include dyspareunia, vaginismus, and noncoital sexual pain disorder.[12] The organic etiologies of female sexual dysfunction parallel those of male sexual and erectile dysfunction: vasculogenic, neurogenic, musculogenic, psychogenic, endocrinologic, and xenobiotic-induced causes. The xenobiotics implicated in female sexual dysfunction are similar to the xenobiotics that decrease female fertility, with antihypertensives, antidepressants, and antipsychotics as the most frequent causes.[56]

Treatment for xenobiotic-induced female sexual dysfunction includes decreasing medication dosages, switching to alternate medications with less adverse effects on sexual function (ie, bupropion and nefazodone), temporary cessation of the medication (drug holiday), or adding another medication to stimulate sexual function. Bupropion alone was as effective as fluoxetine for the treatment of depression but with less sexual dysfunction,[41] and when used in conjunction with SSRIs, bupropion improved sexual function compared to SSRIs alone.[38] Sildenafil was successful for treating spinal cord-induced[144] and antidepressant-induced sexual dysfunction;[118] however, larger trials had mixed results with sildenafil for sexual arousal disorder.[13, 31] Sublingual apomorphine improved sexual function in women with hypoactive

sexual disorder.[30]

Most medical therapy for female sexual dysfunction is centered on hormonal agents, both estrogen and androgen supplementation. Estrogen replacement therapy is available in oral, dermal, vaginal ring, and topical cream formulations, either alone or in combination with progesterone.[154] Estrogen therapy is associated with a higher incidence of coronary disease, breast cancer, stroke, and venous thromboembolism. Androgen therapy includes testosterone, which is available in oral, dermal, and topical preparations, and dehydroepiandrosterone.[141] Adverse effects are weight gain, increased cholesterol, and androgenization.

Abortifacients

An abortifacient is defined as an agent that affects early embryonic gestation to induce abortion. These substances may act by flushing the zygote from the fallopian tube, blocking the uterine horn, inhibiting implantation, inducing fetal resorption, or by producing oxytocin-like activity that results in uterine irritation and contraction. Abortifacients may also indirectly affect pregnancy by altering hormonal levels through placental inhibition of human chorionic gonadotropin (hCG) or progesterone production, or through interference with progesterone receptors. In a US poison center study, 5 of 43 pregnant women who intentionally overdosed used known abortifacients, including quinine, misoprostol, methylergonovine, and oral contraceptives. Four of these patients developed vaginal bleeding and cramping, but no short-term (1â€“3 days) fetal demise was reported.[127] The use of abortifacients is more common in underdeveloped countries and by people without access to safer methods for termination or prevention of pregnancy.

Misoprostol is a synthetic prostaglandin E_1 methyl analog indicated for the prevention of gastric ulcers caused by nonsteroidal antiinflammatory drugs. It was approved for marketing in Brazil in

1985 and in the United States in 1988. The abortifacient properties of prostaglandins are well established,[100] and misoprostol can produce uterine contractions, uterine bleeding, and expulsion of the products of conception.[133] Common adverse effects are nausea, vomiting, diarrhea, abdominal pain, chills, shivering, and fever. In one case, overdose with 6000 Âµg of misoprostol resulted in abortion, hyperthermia, rhabdomyolysis, hypoxemia, and a metabolic acidosis.[67] Cases of congenital abnormalities such as scalp and skull defects, cranial nerve palsies, and limb defects such as talipes equinovarus are reported when misoprostol did not terminate pregnancy.[36] This drug has been extensively misused in Brazil to induce abortion.[40 , 44 , 126] In 1991, an estimated 10% of mothers giving birth at public hospitals in Rio de Janeiro were exposed to misoprostol.[44 , 126] The rate of successful pregnancy termination with this drug is 11â€“50%, and abortion can occur after amounts just above the recommended therapeutic dose.[86 , 133]

(Bristly starburâ€”whole plant)
Acanthospermum hispidum
Brazil
Preimplantation effects
Î±-Momorcharin (bitter melon)
Momordica charantia
China
Similar to trichosanthin
Pigeon peaâ€”fresh leaves
Cajanus cajan
Brazil
Preimplantation effects
Devil's claw
Ranunculus
South Africa
Similar to pennyroyal oil
Chinese angelica

Angelica polymorpha
â€”
Anticoagulant effects, photodermatitis
Ergotamines
Claviceps purpurea
â€”
Oxytocic
Justica adhatoda
Adhatoda vasica
India
100% abortifacient in rats
Lagenaria breviflora Robert
Lagenaria breviflora Robert
Nigeria
Antiimplantation, oxytocic
Lysol disinfectant
â€”
â€”
Death after intrauterine administration
Methotrexate
â€”
â€”
Medical use
Methylcytosine (Blue cohosh)
Caulophyllum thalictroides
â€”
Toxicity similar to nicotine
Horseradish tree
Moringa oleifera
India
100% abortifacient in rats
Prostaglandin E analog
Misoprostol
Brazil, US

Marketed as Cytotec for gastric ulcers
Pulegone (Pennyroyal oil)
Hedeoma pulegioides
â€”
Hepatotoxicity; *N* -acetylcysteine (NAC) may be effective
Quinine
Cinchona bark
â€”
Antimalarial
Rue
Ruta graveolens
Mexico
Preimplantation effects and oxytocic in animals
RU-486
Mifepristone
France, US
Marketed as an emergency contraceptive; administered with prostaglandins
Trichosanthin (compound Q) (snake gourd)
Trichosanthes kirilowii
China
Inhibits protein synthesis, â†“ hCG, â†“ progesterone

Xenobiotic Source	Country of Origin or Use	Miscellaneous/Toxicity

TABLE 28-4. Xenobiotics Used as Abortifacients

Mifepristone, or RU-486, an antiprogesterone used in Europe and the United States, is an effective abortifacient, especially when used in conjunction with a prostaglandin.[128, 135] RU-486 is a steroid compound with a 5-fold greater affinity for progesterone

receptors than progesterone. Upon complexing with these receptors, it causes downregulation of progesterone-dependent genes, decidual necrosis, cervical dilation, and consequent expulsion of the products of conception.[36] The sensitivity of the uterus to prostaglandins is also increased.[15] Adverse effects include excessive blood loss and fatigue, gynecomastia, alopecia, nausea, vomiting, and abdominal pain.[62, 73] Data on toxicity in overdose are not known.

Methotrexate is a folic acid analog that is used in conjunction with a prostaglandin in medical terminations of pregnancy. It competitively inhibits dihydrofolate reductase and decreases nucleic acid synthesis, which is necessary in rapidly dividing cells such as trophoblasts. Common adverse effects are nausea, vomiting, diarrhea, fever, and chills.[36] Large doses or decreased clearance of methotrexate can lead to clinical toxicity, which includes stomatitis and esophagitis, renal failure, and myelosuppression, and can be ameliorated with folinic acid administration. (See Chap. 52 for a more in-depth discussion of methotrexate toxicity and Antidotes in Depth: Folic Acid and Leucovorin [Folinic Acid].)

Many abortifacients are derived from plants and their extracts (Table 28-4). Not only are these agents toxic to the mother, but because many are ineffective in producing abortion, possible teratogenicity is a concern. Trichosanthin is an abortifacient protein extracted from the root of *Trichosanthes kirilowii*, a Chinese medicinal plant. The root is powdered and is used as a folk remedy to induce menstrual bleeding and to expel the fetus.[151] The active ingredient, trichosanthin, has abortifacient activity in animals and in humans when injected or applied intravaginally.[151] The mechanism is unknown, but may be related to inhibition of protein synthesis by preventing the incorporation of leucine.[151] Trichosanthin injures trophoblasts, and it may also inhibit hCG and progesterone production by the placenta.[151] Hypersensitivity occurs in some patients, limiting its clinical

usefulness.

Pennyroyal oil is a volatile oil extracted from the leaves of *Mentha pulegium* and *Hedeoma pulegioides* and contains the ketone pulegone (Chap. 43). Preparations also include a tablet, tea, essence of pennyroyal, and leaves. There are several reports of its use as an emmenagogue and illicit abortifacient. Pulegone depletes glutathione stores in the liver and is a direct hepatotoxin. The epoxide metabolite menthofuran may also contribute to hepatotoxicity. Fulminant hepatic failure can occur after ingestion of 2 ounces of pennyroyal oil.[3 , 10] Renal failure is also described (Chap. 42).[147] *N* -acetylcysteine has been successfully used to prevent pulegone-induced hepatotoxicity.[28]

Because of its oxytocic action, the cinchona alkaloid quinine has been used intravenously to induce labor in cases of fetal death.[113] It has also been used as an illicit abortifacient.[163 , 164] Because it is ineffective when ingested orally for this purpose, it may be taken in repeated doses leading to toxicity (Chap. 56).

Black cohosh root (*Cimicifuga racemosa*) extract is an herbal preparation used to induce abortion and primarily results in gastrointestinal toxicity after ingestion. Blue cohosh (*Caulophyllum thalictroides*) is also used and contains methylcytosine, which causes toxicities similar to nicotineâ€”nausea, vomiting, muscle paralysis, seizures, tachycardia, and hypotension.

Toxicity of Aphrodisiacs

Aphrodisiacs are defined as xenobiotics that heighten sexual desire, pleasure, and/or performance, and include xenobiotics from the plant, animal, and mineral kingdoms.[45] The search for an effective aphrodisiac has been ongoing for thousands of years. Ancient fertility cults used *Datura* , belladonna, and henbane as aphrodisiacs. Yohimbine has been used by African cultures to enhance sexual prowess, and mandrake was used in medieval

xenobiotics recommended include oysters, vitamin E, and ginseng. Because there are no measurable objective parameters, research in this area is lacking. Most published studies evaluating aphrodisiacs have been conducted in male rodents, and little information is available regarding humans.

Dopamine, nitric oxide, oxytocin, and adrenocorticotropic hormone (ACTH) all facilitate sexual behavior. Dopamine stimulates the forebrain and midbrain and leads to an increase in sexual response and arousal. In animals, dopamine agonists, such as apomorphine and quinpirole, have proerectile effects through stimulation of dopamine pathways, increasing nitric oxide in the paraventricular nucleus in the hypothalamus, and releasing oxytocin.[111] Other preparations tested for the treatment of impotence include bromocriptine,[2 , 20] glyceryl trinitrate,[112] zinc,[4] oxytocin,[93] and LH.[92] Endogenous opioids, Î³-aminobutyric acid (GABA), and norepinephrine are associated with decreased sexual behavior. Serotonin is generally inhibitory to sexual function, but the effects are dependent on the receptor subclass. 5-Hydroxytryptamine (5-HT)$_{1A}$ receptor stimulation inhibits erection, but facilitates ejaculation in rats, whereas 5-HT$_{2C}$ receptors facilitate male sexual behavior.[111] Various serotonergic drugs, including trazodone, nefazodone, bupropion, and clomipramine, are reported to improve sexual dysfunction.[136 , 165]

Lead

Some â€œaphrodisiacsâ€• in Asian countries contain lead and are associated with toxicity. In a British report, a 50-year-old man from Pakistan presented with anorexia, abdominal pain, and anemia with basophilic stippling. His whole-blood lead concentration was 96 Âµg/dL. He reported ingestion of a yellow-white powder provided to him by a traditional Asian practitioner

for the treatment of impotence, which contained 84% elemental lead by weight.[51] A 24-year-old man from Bangladesh presented to a London hospital with similar complaints and had a whole-blood lead concentration of 102 Âµg/dL after chronic ingestion of an aphrodisiac containing 46% lead.[23] Traditionally, aphrodisiacs from the Indian subcontinent contain silver and/or gold, but occasionally lead is substituted. The indications for chelation therapy are the same as in other cases of lead poisoning (Chap. 91).

Topical Agents

Spanish Fly

Spanish fly is cantharidin derived from crushed blister beetles (*Cantharis vesicatoria*) and is used to enhance sexual potency.[81] A 1% topical solution available for use in wart removal is also marketed in adult sex shops and by mail order as an aphrodisiac. Adverse effects are a consequence of the vesicant properties of the agent, and gastrointestinal, dermatologic, genitourinary, renal, cardiac, pulmonary, neurologic, and hematologic effects are all described (Chap. 115).

Following absorption, ingested cantharidin is bound to albumin and excreted by the kidney.[130] Symptoms generally occur 2â€“6 hours after ingestion. Gastrointestinal and genitourinary signs include dysuria, oral pain, dysphagia, nausea, hematemesis, and hematuria. Blistering of mucous membranes also occurs, and patients commonly develop hemorrhagic mucositis of the mouth, esophagus, and stomach. Fatal gastrointestinal hemorrhage has been reported, and the lethal dose varies from 10â€“80 mg in adults.[115 , 130] Blister formation in the urinary tract, tubular necrosis, and glomerular damage all result in gross hematuria, which can continue for 2 weeks after ingestion. Proteinuria is common, and death from acute tubular necrosis and renal failure

can occur.[150] Dermal exposure can result in blistering, ulceration, and systemic toxicity. Hemorrhage occurs in the ureters, bladder, and urethra, and hemorrhagic bullae may be noted in the bladder. Priapism, ovarian engorgement, and vaginal bleeding can also occur.[119] Sinus tachycardia is the most common cardiac manifestation of toxicity, but pericardial and subendocardial hemorrhage are also described. Patients may also develop dysrhythmias, ST-segment elevation, and T-wave changes.[119] Pulmonary effects are rare and include acute lung injury and bronchial hemorrhage. Disseminated intravascular coagulation occurs and may be caused by vesicant-related vascular injury. Neurologic symptoms are rare. No specific antidote is available and treatment is supportive. Cantharidin exposure should be considered in the differential diagnosis of unexplained hematuria or gastrointestinal hemorrhage.

Bufotoxin

â€œStone,â€• â€œlove stone,â€• â€œblack stone,â€• and â€œrock hardâ€• all refer to topical aphrodisiac preparations made from dried toad venom that contains bufalin, cinobufalin, cinobufagin, and other cardioactive steroids in the bufadienolide class. A 90-year-old man presented with bradycardia and a history of syncope after ingesting Yixin Wan, a nonprescription Chinese medication containing toad venom, ginseng, pearl, and musk.[87] Chan Su is a traditional Chinese medication produced from the venom of *Bufo bufo gargarizans* , which contains several cardioactive steroids, a topical anesthetic, and bufotenine.[24] Kyushin is another popular Asian traditional medication that contains dried toad venom. The cardioactive steroids have a similar structure and action to digoxin. Digoxin immunoassay may be positive after exposure to these agents, although the level may not correlate with toxicity. Four deaths were reported between 1993 and 1995 following ingestion of these topical aphrodisiacs. The patients presented with bradycardia and measurable digoxin

levels. Hyperkalemia also occurred. One patient was successfully treated with digoxin-specific Fab fragments.[25,26] An animal study evaluating the usefulness of digoxin-specific fragments in mice intoxicated with Chan Su demonstrated survival in 8 of 15 mice treated with digoxin-specific Fab, as compared with no survivors in the control group.[25] Digoxin-specific Fab (at least 10 vials) should be administered to any patient with a suspected cardioactive steroid overdose with hyperkalemia and/or dysrhythmia (see Chap. 62 and Antidotes in Depth: Digoxin-Specific Antibody Fragments [Fab]).

Inhaled Agents

Nitrites

Alkyl (amyl, butyl, and isobutyl) nitrites are aliphatic esters of nitrous acid and are yellow, highly volatile, sweet-smelling liquids administered by inhalation. Glass capsules typically contain 0.3 mL and are enclosed in a gauze jacket of woven absorbent covering that can be crushed and held to the nostrils. The capsules are called â€œpoppersâ€• because of the sound that is produced when they are broken.[75,99] The vasodilatory effects produced by inhalation of amyl nitrite were first described in 1859, and amyl nitrite was first used for the treatment of angina in 1867. Amyl nitrite was originally marketed as a prescription drug in 1937, but the FDA removed the requirement for a prescription in 1960. After 1960, nitrates replaced nitrites in the treatment of angina. Because abuse of inhaled nitrites became widespread in the 1960s, particularly by healthy young males, the FDA reinstated the prescription requirement for amyl nitrite in 1968.[75] Since 1968, isobutyl and butyl nitrite have been legally marketed as â€œroom deodorizersâ€• in bottles containing 10â€“30 mL.[66]

Amyl nitrite and other alkyl nitrites are especially popular

aphrodisiacs among men who have sex with other men. They are inhaled during foreplay to obtain a â€œhighâ€• and to produce anal sphincter relaxation, or just before orgasm to heighten and prolong the climax.[57] Butyl nitrite was popular among teens seeking a â€œhigh,â€• but the prevalence of usage among high school seniors decreased from 11.1% in 1979 to 1.6% in 2003.[80]

Nitrites are absorbed via the skin, lungs, mucus membranes, and the gastrointestinal tract. They are metabolized in the liver and excreted, partially unchanged, in the urine.[99] In mice, butyl nitrite undergoes rapid hydrolysis to nitrite ion and butyl alcohol. The half-life is 2â€“3 seconds, and metabolism is by first-order kinetics.[75] The relaxation of vascular smooth muscle results in potent vasodilation and hypotension. Blood pressure can decrease significantly within 30 seconds of inhalation. Inhalation of as little as 5 drops can result in hypotension and reflex tachycardia.[99] Cardiovascular collapse can occur, especially if nitrites are injected intravenously. Vasodilation of cerebral blood vessels results in increased intracranial pressure, and cerebral aneurysm rupture has been reported after amyl nitrite inhalation.[117]

A feeling of warmth and palpitations are frequently described after nitrite inhalation.[75] Headache, nausea, and syncope are also common. Nitrite use can be dangerous in patients with glaucoma due to a transient increase in intraocular pressure.[57] Nitrites can also cause methemoglobinemia (Chap. 122) which can be successfully treated with methylene blue.[53] Hemolytic anemia is also reported,[22 , 99] and is probably a result of the oxidizing effects of nitrites on hemoglobin. â€œPopper dermatitisâ€• is a characteristic rash that can be noted around the nose, lips, face, penis, and scrotum, and presents as erythematous, edematous, and crusted lesions.[57 , 98 , 99] It can have an appearance similar to that of impetigo and seborrheic dermatitis. The rash usually clears within 10 days, but reappears with repeat nitrite inhalation.[57] A generalized allergic dermatitis can also occur.[46]

The carcinogenic and immunosuppressive effects of amyl nitrite are not adequately tested in animals, although it is mutagenic with the Ames test.[54] There are some data to suggest that nitrites may be immunosuppressive in the setting of repeated viral antigenic stimulation.[66] It is postulated that this may contribute to the high frequency of Kaposi sarcoma in men who have sex with other men. In one study, amyl nitrite was the only xenobiotic that 100% of patients with Kaposi sarcoma reported using.[103] Concern for carcinogenicity associated with amyl nitrite has resulted in a recent decline in its use among men who have sex with other men.

Urinary System

The urinary system is composed of the kidneys, ureters, bladder, and urethra. Many xenobiotics are concentrated by the kidneys and eliminated in the urine. The effect of xenobiotics on the bladder and urine is discussed below. See Chap. 27 for further discussion on xenobiotics affecting the kidneys.

Bladder Anatomy and Physiology

The bladder is a hollow, muscular reservoir composed of two parts, the body and the neck, which, in adults, normally stores 350â€“450 mL of urine. A smooth muscle, the detrusor muscle, makes up the bulk of the body and contracts during urination. Urine from the ureters enters the bladder at the uppermost part of the trigone, an area in the posterior wall of the bladder, and leaves via the neck and the posterior urethra. Surrounding the neck and posterior urethra is smooth muscle interlaced with elastic tissue to form the internal sphincter. Sympathetic innervation from S2 to S4 of the sacral spinal cord to the internal sphincter maintains smooth muscle contraction. Distal to the internal sphincter is an area with voluntary skeletal muscle that forms the external sphincter.

The nerve supply and neurophysiology of urination involves interplay by the sympathetic and parasympathetic nervous systems (S2 to S4). Figure 28-1 illustrates the physiology of micturition. Norepinephrine is released by sympathetic postganglionic fibers. Î±-Adrenergic receptors predominate in the internal sphincter and the bladder neck, whereas Î²-adrenergic receptors supply the bladder wall. Stimulation of Î±- and Î²-adrenergic receptors results in internal sphincter contraction, increased bladder outlet resistance, and bladder filling, leading to urinary retention.[42] Parasympathetic pre- and postganglionic fibers release acetylcholine to M_2 and M_3 muscarinic receptors in the detrusor muscle. Stimulation of M_3 muscarinic receptors is responsible for detrusor muscle contraction and bladder emptying.[34] Conversely, anticholinergic drugs prevent bladder emptying and result in urinary retention.[32,33,37,59,65,109]

Urinary Abnormalities

Urinary incontinence is common as age increases and bladder size decreases, resulting in more frequent emptying. Early detrusor contraction, even with low bladder volumes, occurs more commonly in the elderly, causing a sense of urgency. There are many etiologies for urinary incontinence, including various xenobiotic exposures (Table 28-5). General or regional anesthesia, bladder instrumentation, and xenobiotics may produce bladder atony leading to incontinence.[37] Functional incontinence can also result from use of any xenobiotic that causes impaired cognition or decreased mobility, which is exemplified by the sedative-hypnotics and the opioids.[37] Pharmacologic agents used in the treatment of urinary incontinence

include the anticholinergics (tolterodine, oxybutynin, trospium chloride), imipramine, botulinum toxin A, and duloxetine. Duloxetine is a serotonin and norepinephrine reuptake inhibitor that acts centrally at the sacral cord pudendal motor nucleus to

stimulate urethral rhabdosphincter contraction.[50]

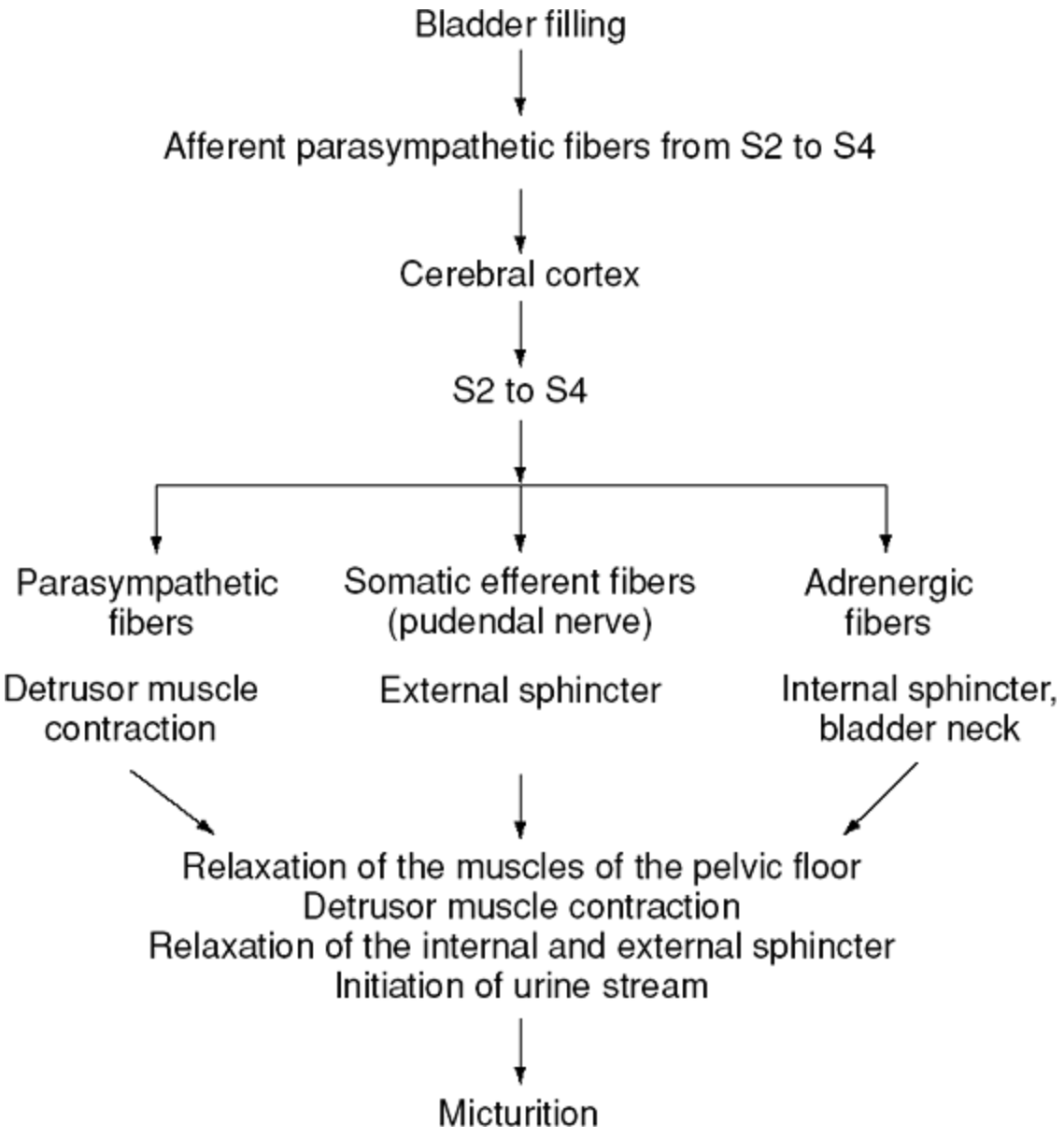

Figure 28-1. A schematic description of the physiology of micturition.

Î±-Adrenergic agonists
Increase internal sphincter tone; retention
Î±-Adrenergic antagonists

Decrease internal sphincter tone
Anticholinergics
Impair detrusor contraction; retention
Calcium channel blockers
Decrease detrusor contraction
Diuretics
Overflow (volume increase)
Opioids
Impair detrusor contraction; retention
Sedatives-hypnotics
Decrease sensorium; retention
Reprinted with permission from Chutka DS, Fleming KC, Evans MP, et al: Urinary incontinence in the elderly population. Mayo Clin Proc 1996;71:93â€“101.

Drug Action

TABLE 28-5. Xenobiotics that Cause Incontinence and Retention

Urinary retention can be obstructive, neurogenic, psychogenic, or pharmacologic in origin. Xenobiotics associated with urinary retention include sympathomimetics, anticholinergics, antidysrhythmics (quinidine, procainamide, disopyramide), antidepressants, antipsychotics, hormonal agents (progesterone, estrogen, testosterone), and muscle relaxants.[37, 59] In men older than age 50 years, benign prostatic hyperplasia is the most common cause of bladder outlet obstruction, leading to decreased urinary output and urinary retention. Treatment of benign prostatic hyperplasia consists of 5Î±-reductase inhibitors and Î±-adrenergic antagonists. 5Î±-Reductase inhibitors (finasteride, dutasteride) block the conversion of testosterone to dihydrotestosterone in order to decrease prostate volume.[106] The Î±-adrenergic antagonists (doxazosin, terazosin, alfuzosin,

tamsulosin) decrease urethral Î±-adrenergic contraction.[61]

Abnormalities in Urinalysis

Abnormalities of the urinalysis are often useful in identifying xenobiotic exposures. Color change or the presence of crystals may aid in diagnosis. The urinalysis in patients who ingest ethylene glycol often (but not always) reveals calcium oxalate or hippurate crystals. Calcium oxalate crystals are monohydrates (prism- or needlelike) or dihydrates (envelope-shaped). Hippurate crystals are needle shaped.[122] Crystalluria is present in 50% of cases of ethylene glycol poisoning (see Fig. 103-5). Hexagonal crystals are noted after massive primidone poisoning and result from precipitation of primidone in the urine.[152] Crystalluria is also described after therapeutic doses of salicylate, phenacetin, sulfonamide, and quinolones. After large ingestions, crystals can be seen with methotrexate, amoxicillin, cephalexin, ampicillin, and indinavir. Urine color is dependent on several factors, the xenobiotic, the pH, concentration, natural pigments, and length of time exposed to air.[69] Dilute urine secondary to diuretic use, diabetes mellitus, diabetes insipidus, or overhydration can appear colorless, whereas concentrated urine is usually orange. The presence of fluorescein, detected by illumination of the urine with a Wood lamp, suggests ethylene glycol (commercial antifreeze) ingestion, but this diagnostic test has poor sensitivity and specificity.[153] In a group of nonpoisoned children, all their urine samples had fluorescence when examined with a fluorometer, whereas physicians had a 61% sensitivity in detecting fluorescence in the same urine samples with a Wood lamp.[123] Table 28-6 notes other causes of colored urine.

Milky
- Chyle
- Lipids
- Pyuria

Reddish-Brown
- Anthraquinone
- Bilirubin
- Chloroquine
- Ibuprofen
- Levadopa
- Methyldopa
- Phenacetin
- Phenazopyridine
- Phenothiazines
- Phenytoin
- Porphyrins
- Trinitrophenol

Reddish-Orange
- Aminopyrine
- Aniline dyes
- Antipyrine
- Chlorzoxazone
- Doxorubicin
- Ibuprofen
- Mannose
- Phenacetin
- Phenazopyridine
- Phenothiazines
- Phenytoin
- Rifampin
- Salicylazosulfapyridine

Red
- Anthraquinones
- Beets
- Blackberries
- Eosin
- Erythrocytes
- Hemoglobin

- Myoglobin
- Porphyrins
- Rhubarb

Yellow-Brown
- Aloe
- Anthraquinones
- Chloroquine
- Fava beans
- Nitrofurantoin
- Primaquine
- Rhubarb
- Sulfamethoxazole

Yellow
- Fluorescein
- Phenacetin
- Quinacrine
- Riboflavin
- Santonin

Yellow-Orange
- Aminopyrine
- Anisindione
- Carrots
- Sulfasalazine
- Vitamin A
- Warfarin

Black
- Alcaptonuria
- Homogentisic acid
- Melanin
- *p*-Hydroxyphenylpyruvic acid

Brown-Black
- Cascara
- Iron
- Methyldopa

Phenylhydrazine
Senna

Greenish-Blue
Amitriptyline
Anthraquinones
Biliverdin
Chlorophyll breath mints
Flavin derivatives
Food Dye and Color Blue No. 1
Indicans
Indigo blue
Magnesium salicylate
Methylene blue
Phenol
Thymol

TABLE 28-6. Xenobiotics that Cause Colored Urine

There are multiple causes of hematuria.[102] It can be a result of xenobiotic interstitial nephritis, a condition distinguished by fever, rash, eosinophiluria, azotemia, and oliguria.[48] Hemorrhagic cystitis is a more frequent cause of hematuria and is associated with a number of xenobiotics. The clinical presentation of hemorrhagic cystitis includes hematuria, dysuria, and urinary frequency. Criteria for the diagnosis of hemorrhagic cystitis include a history of gross hematuria, laboratory findings of gross hematuria (>5 red blood cells [RBC]/high-power field [HPF]), platelet count >50,000/mm,[4] and a negative urine culture.[134] When in doubt, the diagnosis may be confirmed by cystoscopy, which reveals an inflamed, hyperemic, and sometimes ulcerated bladder mucosa.

Cyclophosphamide-related hemorrhagic cystitis was first described in 1959,[108] and is the best-documented type of drug-induced hemorrhagic cystitis.[63] As many as 46% of patients

receiving cyclophosphamide develop hemorrhagic cystitis.[52, 79, 86, 91] Acrolein, the causative agent, is a metabolite of cyclophosphamide that damages the urothelium when excreted. There is no sex or age predilection, and symptoms can occur months after exposure. Hemorrhagic cystitis is described after oral doses exceeding 100 g and after a single intravenous dose of cyclophosphamide.[146] Sloughing of the bladder mucosa occurs, and 5% of patients die from intractable hemorrhage.[74, 129] Patients at highest risk are those who are volume depleted, receive cyclophosphamide intravenously, or have previous or concomitant exposure to busulfan or radiotherapy.[108] Treatment with cyclophosphamide is also associated with a dose-related increase (9- to 45-fold) in the risk of subsequent bladder cancer (Chap. 52).[127, 146]

Prophylaxis against cyclophosphamide-induced hemorrhagic cystitis includes bladder catheterization and drainage, bladder irrigation, hydration, forced diuresis, and administration of oral sodium 2-mercaptoethane sulfonate (MESNA).[108] MESNA binds to acrolein in the urine to form an inert, nontoxic thioester, reducing the incidence of hemorrhagic cystitis by 85%.[146] Bladder irrigation with alum, silver nitrate, prostaglandins, and formalin[9] has also been used to treat cyclophosphamide-induced hemorrhagic cystitis.[108] In an animal model, pretreatment with hyperbaric oxygen reduces the incidence of hemorrhagic cystitis.[74] In severe cases, hypogastric artery ligation and/or cystectomy may be required to control bleeding.[74]

An outbreak of hemorrhagic cystitis occurred in workers in a packaging plant after exposure to chlordimeform, a formamidine insecticide used to control mites and insects on cotton. Nine workers developed abdominal pain, dysuria, urgency, and hematuria, with biopsy-proven hemorrhagic cystitis.[58] Eight young adults developed painful hematuria after consuming â€œbootlegâ€• methaqualone. The cause was orthotoluidine, a compound used in the synthesis of methaqualone, and the

symptoms occurred within 6 hours of ingestion.[68] Cases of hemorrhagic cystitis are also described with ticarcillin,[104] nafcillin, penicillin G, carbenicillin, piperacillin, isoniazid, indomethacin, tiaprofenic acid, and busulphan.[64 , 107 , 143]

Summary

Toxicologic evaluation of the reproductive system is challenging because reproduction is an intermittent phenomenon. Adverse effects from xenobiotic exposures to both the male and female reproductive systems may not be noticed until fertility is desired. Toxicants can affect the hormonal controls or the organs of gametogenesis. Sexual dysfunction, whether psychogenic or xenobiotic-induced, negatively impacts fertility. Agents used to treat sexual dysfunction, such as aphrodisiacs, can have adverse systemic effects. Adverse effects on the genitourinary tract are often overlooked when evaluating the toxicologic potential of various xenobiotics. Few physical findings, laboratory tests, or ancillary studies aid in diagnosis. A thorough history including past and present medications, illicit drug use, occupational and environmental exposures, and the use of herbal or alternative therapies is mandatory in the evaluation of patients with genitourinary complaints.

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Chapter 29
Dermatologic Principles

Dina Began

The skin shields internal organs from harmful xenobiotics in the environment and maintains internal organ integrity. The adult skin covers an average surface area of 2 m^2 .[10] Despite its outwardly simple structure and function, the skin is extraordinarily complex. When a xenobiotic exposure occurs, whether it is ingested, injected, or inhaled from an external source, the skin can express its effects. The basic principles of an adverse cutaneous reaction can be used to make relevant predictions, such as the physical and chemical properties of the xenobiotic and whether the effect of a response will be local or systemic. The clinician must obtain essential information as to the dose, timing, route, and location of exposure. Dermal exposures account for <10% of the cases and for approximately 1% of the fatalities reported to the American Association of Poison Control Centers (AAPCC) (Chap. 130). Dermatitis is among the most common occupational disorders. Where on the skin a xenobiotic acts histologically determines the morphology, the severity of the reaction pattern, and the overall clinical findings (Table 29-1). It should be noted, however, that

different xenobiotics may produce clinically similar skin changes and conversely that many xenobiotics may produce diverse dermal lesions.

Skin Anatomy and Physiology

The skin has three main anatomic components: the epidermis, the dermis, and the subcutis or hypodermis. The primary physiologic role of the epidermis, the most external layer of the skin, is to maintain water homeostasis and to establish immunologic surveillance. It is composed of five layers: the horny, transitional, granular, spinous, and basal layers (Fig. 29-1). The thin stratum corneum, or horny layer, is predominantly responsible for the protective function of the skin. Disruption or inadequate formation of the stratum corneum leads to a breakdown of this barrier function and many disease processes. The cells of the stratum corneum serve as a buffer to acidic and alkaline substances. Barrier function is also partly maintained by the granular layer. In this layer, there are Odland bodies, also known as membrane-coating granules, lamellar granules, and keratinosomes. The contents of these organelles provide a barrier to water loss while mediating stratum corneum cell cohesion.[12]

The stratum corneum is covered by a surface film composed of sebum emulsified with sweat and breakdown products from the horny layer.[1] The surface film functions as an external barrier to protect the entry of bacteria, virus, and fungi. The role of the surface film, however, is limited with regard to percutaneous absorption.[22] The major barrier molecules to percutaneous absorption in the skin are lipids called *ceramides* . Diseases characterized by dry skin, such as eczema, atopic dermatitis and psoriasis, are caused by decreased levels of ceramide in the stratum corneum which also allows increased xenobiotic penetration because of barrier degradation.[11] Similarly, hydrocarbon solvents, such as gasoline or methanol, or

detergents, commonly produce a â€œdefatting dermatitisâ€• by keratolysis or the dissolution of these surface lipids.

The degree of barrier function of the epidermis varies with its thickness as well. Differences in thickness are observed on different regions of the body. The epidermis varies from 1.5 mm on the glabrous surfaces (palms and soles) to 0.1 mm on the eyelids. The cells of the basal layer control the renewal of the epidermis. The basal layer contains stem cells and transient amplifying cells, which are the proliferative cells resulting in new epidermal formation that occurs every 59â€“75 days. As the basal cells migrate toward the skin surface they flatten, lose their nuclei, develop keratohyalin granules, and eventually develop into the horny layer. Patients with primary cutaneous diseases, such as psoriasis, have a significantly shortened epidermal renewal or turnover time resulting in a thicker epidermis (hyperkeratosis) and potentially less direct penetration of xenobiotics.[2] The basal layer is adjacent to the basement membrane zone and is also populated by melanocytes and Langerhans cells. Melanocytes contain melanin, which is the major chromophore in the skin that is responsible for absorbing ultraviolet and other light energies. They are also primarily responsible for skin pigmentation. The Langerhans cells are bone marrowâ€“derived cells with a primary role in immunosurveillance, including primary contact sensitization. Langerhans cells function in the recognition, uptake, processing, and presentation of antigens to previously sensitized T lymphocytes. Langerhans cells may also carry antigens via dermal lymphatics to regional lymph nodes.

The basement membrane zone, which consists of three layersâ€”the lamina lucida, the lamina densa, and the sublamina densaâ€”separates the epidermis from the dermis. It provides a site of attachment for keratinocytes and permits epidermalâ€“dermal interaction.

The dermis is deep to the epidermis and contains the adnexal

structures, blood vessels, and nerves. The dermis provides structural integrity as well as containing many important appendageal structures. The structural support is provided by both collagen and elastin fibers embedded in glycosaminoglycans, such as chondroitin A and hyaluronic acid. Mature dermis is predominantly composed of type I collagen. This collagen accounts for 70% of

the dry weight of the skin, whereas elastic fibers are equivalent to only 1â€“2% of the skin's dry weight. Several important cells, including fibroblasts and mast cells, are present in the dermis. Traversing the dermis are venules, capillaries, arterioles, nerves, and glandular structures.

Primary Cutaneous Lesions

Bulla: a circumscribed collection of free fluid more than 0.5 cm in diameter

Comedone: open and closed dilated pores (black heads and white heads)

Macule: a circumscribed flat variation of color that may be brown, blue, yellow, red, or hypopigmented (no thickness)

Nodule: a circumscribed elevation of â‰¥0.5 cm in diameter

Papule: an elevation of <0.5 cm in diameter

Plaque: a circumscribed elevation of more than 0.5 cm in diameter

Pustule: a circumscribed collection of leukocytes and free fluid that vary in size

Tumor: an elevation of greater than 0.5 cm in diameter

Vesicle: a circumscribed collection of free fluid up to 0.5 cm in diameter

Wheal: a firm edematous plaque resulting from infiltration of the dermis with fluid

Secondary Cutaneous Lesions

Erosion: a loss of the epidermis up to the full thickness of the epidermis but not through the basement membrane

Hypertrophy: a thickening of the skin

Lichenification: a secondary process with noted accentuation of skin surface markings

Scale: flaking that is separate from the original surface of a lesion

Scar: a thickened, often discolored, surface

Ulcer: a loss of full-thickness epidermis and papillary dermis, reticular dermis, or subcutis

TABLE 29-1. Dermatologic Diagnostic Descriptions of Lesions of the Skin

The arteriovenous framework of the skin consists of a deep plexus in the region of the subcutaneous dermal junction. From this deep plexus, smaller arterioles transverse upward to the junction of the reticular and papillary dermis, where they form the superficial plexus. Capillary-venules form superficial vascular loops that ascend into and descend from the dermal papillae. These communicating blood vessels provide channels in which xenobiotics exposed to the skin can be transported internally. In addition, they transport internally absorbed xenobiotics to the skin. These vessels also allow the cells of the immune system to be transported to the skin.

Parallel to the vasculature are cutaneous nerves, which serve the dual function of receiving sensory input and carrying sympathetically mediated autonomic stimuli that induce piloerection and sweating.[15]

The apocrine glands consist of secretory coils and intradermal ducts ending in the follicular canal. The secretory coil is located in the subcutis and consists of a large lumen surrounded by columnar to cuboidal cells with eosinophilic cytoplasm.[15] Apocrine glands, which are located in select areas of the body such as the axilla, produce secretions that are rendered odoriferous by cutaneous

bacterial flora.

The eccrine glands, in contrast, produce an isotonic to hypertonic secretion that is modified by the ducts and emerges on the skin surface as sweat. The eccrine unit consists of a secretory gland as well as intradermal and intraepidermal ducts. The coiled secretory gland is located in the area of the deep dermis and subcutis. Xenobiotics can be concentrated in the sweat with increased skin reactions at the sites of sweat secretion. Certain antineoplastic agents, such as cytarabine or bleomycin, directly damage the eccrine sweat glands, resulting in anhidrosis.

Sebaceous glands also reside in the dermis. They produce an oily, lipid-rich secretion that functions as an emollient for the hair and skin. The glands can be reservoirs of noxious environmental xenobiotics. Pilosebaceous follicles, which are present all over the body, consist of a hair shaft, hair follicle, sebaceous gland, sensory end organ, and erector pili. Certain halogenated aromatic chemicals, such as polychlorinated biphenyls (PCBs), dioxin, and 2,4-dichlorophenoxyacetic acid, are excreted in the sebum and cause hyperkeratosis of the follicular canal. This produces a syndrome, chloracne, that looks like acne vulgaris because of plugging of the ducts. Similar syndromes may result from exposure to brominated and iodinated compounds, known as bromoderma and ioderma, respectively.[34]

The hair follicle is divided into three portions. The lower portion of the hair follicle contains the bulb with matrix cells. These matrix cells are mitotically active with a rapid metabolic rate and often are the target of cytotoxic xenobiotics. The rate of growth and the type of hair are unique for different body sites. Hair growth proceeds through three distinct phases: the active prolonged growth phase (anagen phase) during which matrix cell mitotic activity is high; a short involutional phase (catagen phase); and a resting phase (telogen phase).[15] Understanding the phases and biochemical structure of hair growth is important because hair

growth can be used to identify clues regarding the timing and mechanism of a xenobiotic's action. For example, thallium toxicity results in alopecia 1â€“4 weeks after exposure. Within 4 days of exposure, a characteristic bandlike dark pigmentation is seen in the hair root. A hair mount observed using light microscopy will demonstrate tapered or bayonet anagen hair with black pigmentation at the base. (See ILTHALLIUM1 in the Image Library at http://www.goldfrankstoxicology.com) Seeing this anagen effect can reveal the timing of exposure. This effect is likely related to the structural similarity of thallium and potassium, allowing thallium to alter a number of potassium-mediated processes, including ligand formation with protein sulfhydryl groups which are present in human hair (Chap. 96).

The nail, which is often considered analogous to the hair, is also a continuously growing structure. Fingernails grow at average of 0.1 mm/d and toenails grow at about one-third that rate. The mitotically active cells of the nail matrix are subject to both traumatic and xenobiotic injury that affects the appearance and growth of the nail plate. Because nail growth is consistent, location of an abnormality in the plate can predict the timing of exposure, such as Mees lines (see ILMEESLINES in the Image Library).

Topical Toxicity

Exposure to any one of a myriad of industrial and environmental xenobiotics can result in skin â€œburns.â€• Although the majority of these xenobiotics injure the skin through chemical reactivity rather than thermal damage, the clinical appearances of the two are often identical. Injurious xenobiotics may act as oxidizing or reducing agents, corrosives, protoplasmic poisons, desiccants, or vesicants. Often an injury may initially appear to be mild or superficial with only faint erythema, blanching, or discoloration of the skin. Over the subsequent 24â€“36 hours there may be

progression to extensive necrosis of the skin and its underlying tissues.

Acids are water soluble and readily penetrate into the subcutaneous tissue. The damaged tissue coagulates and forms a thick

leathery eschar that limits the spread of the agent. The histopathologic finding following acid injury is termed *coagulative necrosis* . Alkali exposures characteristically produce a liquefactive necrosis, which allows continued penetration of the corrosive xenobiotic; consequently, dermal injury following alkali exposure is typically more severe than after an acid exposure of an equivalent magnitude.[8]

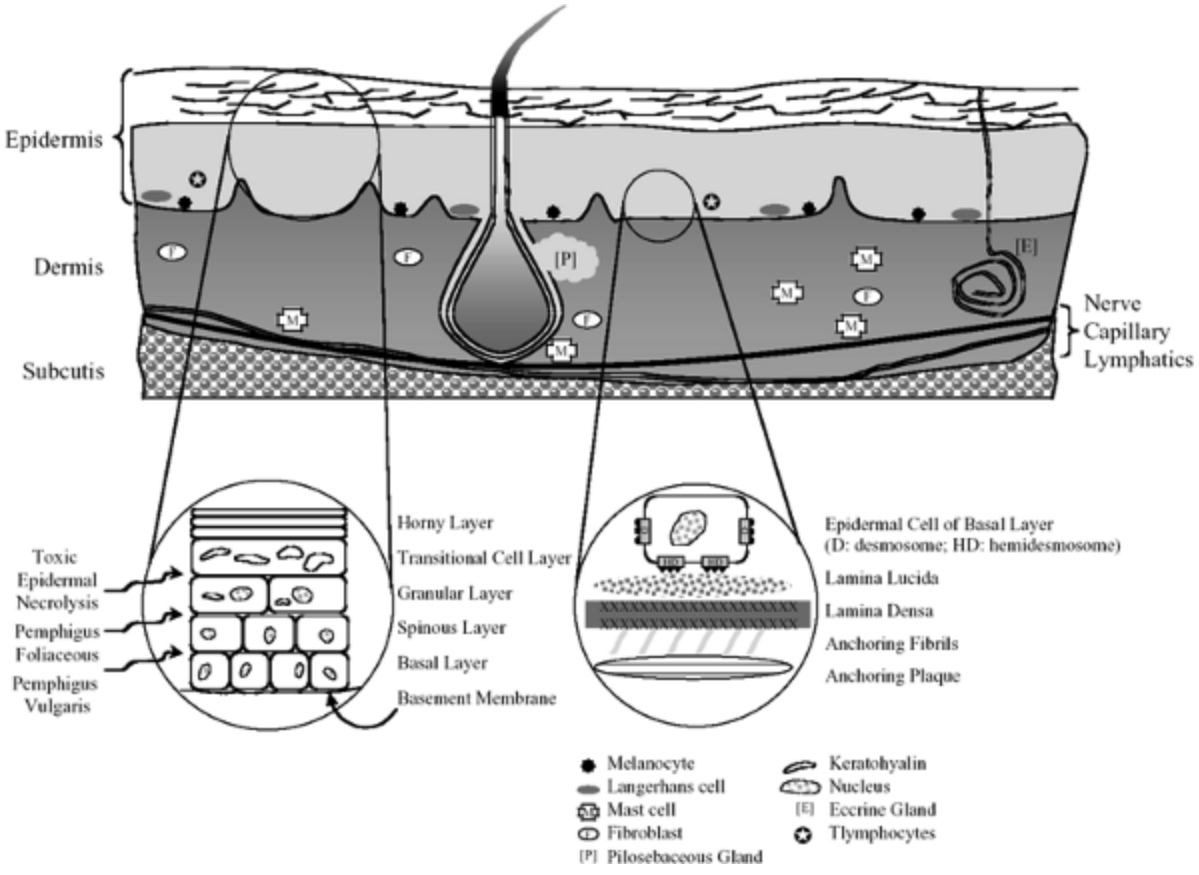

Figure 29-1. Skin histology and pathology. Intraepidermal cleavage sites in various drug-induced blistering diseases. In

pemphigus foliaceous, the cleavage is below or within the granular layer, whereas in pemphigus vulgaris, it is suprabasilar. This accounts for the differing types of blisters found in the two diseases.

Thermal damage can also be the result of a toxicologic exposure. For example, the exothermic reaction generated by the wetting of elemental phosphorus or sodium may result in a thermal burn. In these circumstances, the products of reactivityâ€”phosphoric acid and sodium hydroxideâ€”may produce secondary chemical injury. Alternatively, skin exposure to a rapidly expanding gas, such as nitrous oxide from a whipped cream cartridge or compressed liquefied nitrogen, or to frozen substances, such as dry ice, can produce a freezing injury, or frostbite.

Hydrocarbon-based solvents are typically liquids that are capable of dissolving nonâ€“water-soluble solutes.[8]

Absorption

In addition to producing topical injuries, many xenobiotics undergo percutaneous absorption by passive diffusion. Lipid solubility is the most important factor determining dermal absorption, although concentration, duration of exposure, molecular weight, and specific skin characteristics are also important determinants. Thus, although metal ions such as Hg^{+} have limited skin penetration, the addition of a methyl group, to form methylmercury, increases its lipophilicity and its systemic absorption. Dimethylmercury, formed by the addition of another methyl group, may produce life-threatening systemic effects with a minute amount applied to the skin (Chap. 92). Of importance is that the nonionized component of the weakly acidic hydrofluoric (HF) acid is able to penetrate deeply through the skin and even bone. The proton (H^{+}) and fluoride ion (F^{-}) are unable to penetrate the skin lipids because of their charged nature; however, once in the dermis, the HF acid

may ionize and cause both acid-induced tissue necrosis and fluoride-induced toxicity (Chap. 101).[5]

The vehicle of a xenobiotic may also influence absorption; indeed, transdermal drug-delivery systems are based on their ability to alter the skin partition coefficient through the use of an optimized vehicle. Similarly, through localized dermal occlusion, transdermal systems hydrate the skin and raise its temperature to increase the permeability. Despite these techniques to enhance drug delivery, transdermal systems still require that large amounts of drug be present externally to maximize the transcutaneous gradient.[31] Typically, much of the drug remains in the patch when it is discarded.

Percutaneous absorption may produce systemic, even life-threatening, toxicity. Morbidity and mortality are reported with the topical application of podophyllin, camphor, phenol, organic phosphorus insecticides, ethanol, organochlorines, nitrates, or salicylic acid. Children are particularly at risk for toxicities from percutaneous absorption because their skin is more penetrable than an adult's and specific anatomic sites, such as the face, often represent larger percentage of body surface areas than in the adult.[30] Furthermore, there is enhanced absorption on anatomic parts of the body with thinner skin, such as the mucous membranes, eyelids, and intertriginous areas (axillae, groin, inframammary, and intergluteal). Under certain circumstances, the stratum corneum may serve a depot function leading to continued systemic exposure despite apparent removal of the xenobiotic.[16]

Principles of Dermal Decontamination

On contact with xenobiotics, the skin should be thoroughly cleansed to prevent direct effects and systemic absorption. In general, a copious amount of water is the decontamination agent of choice for skin irrigation. Soap should be used when adherent

xenobiotics are involved. Following exposures to airborne xenobiotics, the mouth, nasal cavities, eyes, and ear canals should also be irrigated with appropriate solutions such as water or 0.9% NaCl. For nonambulatory patients, the decontamination process may need to be conducted using special collection stretchers if available.[7]

There are only a few situations in which water should not be used for skin decontamination. This includes contamination involving the reactive metallic forms of the alkali metals, sodium, potassium, lithium, cesium, and rubidium, which react with water to form strong bases. The dusts of pure magnesium, sulfur, strontium, titanium, uranium, yttrium, zinc, and zirconium will ignite or explode in contact with water. Thus, following exposure to these metals, any residual metal should be removed mechanically with forceps, gauze, or towels and stored in mineral oil. Phenol has a tendency to thicken and become difficult to remove following exposure to water. Suggestions for phenol decontamination include high-flow water or low-molecular-weight polyethylene glycol solution. Lime, or CaO, also thickens and forms $Ca(OH)_2$ following wetting.[7, 9]

Dermatologic Signs of Systemic Diseases

Cyanosis

Normal cutaneous and mucosal pigmentation is caused by several factors, one of which is the visualization of the capillary beds through the translucent dermis and epidermis. Cyanosis manifests as a blue or violaceous appearance of the skin and mucous membranes. It occurs when the light-absorbing characteristics of hemoglobin are altered either through hypoxia or by oxidation of its iron moiety to the ferric state to form methemoglobin (Chap.

122). The presence of the more deeply colored hemoglobin moiety within the dermal plexus results in cyanosis that is most pronounced on the skin surfaces with the least overlying tissue, such as the mucous membranes or fingernails.

Jaundice

Jaundice is typically a sign of hepatocellular failure or hemolysis and is caused by hyperbilirubinemia, a condition in which this yellow pigment deposits in the subcutaneous fat. A yellow discoloration of the skin can also occur in patients with hypercarotenemia, caused by an excessive consumption of either carrots or the vitamin A precursor carotene. True hyperbilirubinemia is differentiated from hypercarotenemia by the presence of scleral icterus in patients with the former which is absent in the latter. In addition, the cutaneous discoloration seen in hypercarotenemia can be removed by wiping the skin with an alcohol swab. Lycopenemia, a similar entity to carotenemia, is caused by the excessive consumption of tomatoes. Also, topical exposure to dinitrophenol or picric acid, stains from cigarette use, or inhalation of lycopene produces localized yellow discoloration of the skin.

Urticarial Drug Reactions

Urticarial drug reactions are characterized by transient, pruritic, edematous, pink papules, or wheals that arise in the dermis, which blanch on palpation and are frequently associated with central clearing. This reaction pattern is representative of a type I, or IgE-dependent, immune reaction and commonly occurs as part of clinical anaphylaxis. Widespread urticaria may occur following systemic absorption of an allergen or following a minimal localized exposure in patients highly sensitized to the allergen. Following limited exposure, a localized form of urticaria also may occur. Regardless of the specific clinical presentation, this reaction occurs

when immunologic recognition occurs between IgE molecules and a putative antigen triggering the immediate degranulation of mast cells, which are distributed along the dermal blood vessels, nerves, and appendages. The release of histamine, complements C3a and C5a, and other vasoactive mediators result in leakage of fluid from dermal capillaries as their endothelial cells contract. This produces the characteristic urticarial lesions described above. Activation of the nearby sensory neurons produces pruritus. Nonimmunologically mediated mast cell degranulation producing an identical urticarial syndrome may also occur, following exposure to various xenobiotics, including jellyfish or benzoic acid.

Pruritus is a common manifestation of urticarial reactions, but it may also be of nonimmunologic origin. Patients with hepatocellular disease frequently suffer from pruritus, which is mediated by the release of bile acids. In addition, in patients with chronic liver disease and obstructive jaundice, pruritus can be caused by central mechanisms, as suggested by elevated central nervous system (CNS) opioid peptide concentrations. Pruritus can also be caused by topical exposure to the urticating hairs of Tarantula spiders, spines of the stinging nettle plant (*Urtica* sp), or certain xenobiotics such as capsaicin.[14]

Xenobiotics also can evoke a type III immune reaction that causes mast cells to degranulate. The cellular inflammatory response to released chemotactic factors leads to increased vascular permeability.

Flushing

Vasodilation of the dermal arterioles leads to flushing. Flushing can occur following autonomically mediated vasodilation, as occurs with stress, anger, or exposure to heat, or it can be chemically induced by vasoactive xenobiotics. Those xenobiotics that cause histamine release through a type I hypersensitivity reaction are the most frequent cause of xenobiotic-induced flush. Histamine

poisoning itself, most frequently caused by the consumption of scombrotoxic fish, can cause flushing. Flushing after the consumption of ethanol is common in patients of Asian descent and is similar to that following ethanol consumption in patients exposed to disulfiram or similar agents (Chap. 77). The inability to efficiently metabolize acetaldehyde, the initial metabolite of ethanol, and its

increased production, results in the characteristic syndrome of vomiting, headache, and flushing. Niacin causes flushing through an arachidonic acidâ€“mediated pathway that may be inhibited by preingesting aspirin.[32] Vancomycin causes a transient bright red flushing that is mediated by histamine. It occurs during and immediately after rapid infusion, and is termed â€œred man syndrome.â€•

Skin Moisture

Xenobiotic-induced diaphoresis may be part of a physiologic response to heat generation or may be pharmacologically mediated following sympathomimetic xenobiotic use. The eccrine sweat glands are responsible for sweat production, and they are uniquely innervated by acetylcholine-containing neurons within the sympathetic nervous system. Because the postsynaptic receptor on the eccrine glands is muscarinic, most muscarinic agonists are capable of stimulating sweat production. The latter most commonly occurs following exposure to cholinesterase-inhibiting insecticides, such as organic phosphorus compounds, but it may also occur with direct-acting muscarinic agonists such as pilocarpine. Alternatively, antimuscarinic agents, such as atropine or diphenhydramine, reduce sweating and produce dry skin.

Metallic Pigmentations

Pigmentary changes can result from the deposition of fine metallic

particles. These particles can be ingested and carried to the skin by the blood, or may permeate the skin from topical applications. Argyria, a slate-colored pigmentation of the skin resulting from the systemic deposition of silver particles in the skin, can be localized or widespread. The discoloration tends to be most prominent in areas exposed to sunlight, probably secondary to the fact that silver stimulates melanocyte proliferation. (See ILARGYRIA1 in the Image Library.) Histologically, fine black granules are found in the basement membrane zone of the sweat glands, blood vessel walls, the dermoepidermal junction, and along the erector pili muscles (Chap. 95). Gold, which is used parenterally in the treatment of rheumatoid arthritis, can cause a blue or slate-gray pigmentation known as chrysiasis. The pigmentation is also accentuated in light-exposed areas but, unlike in argyria, sun-protected areas do not histologically demonstrate gold. Also, melanin is not increased in the areas of hyperpigmentation. The hyperpigmentation is probably secondary to the gold itself, but the cause of its distribution pattern remains unknown. Histologically, the gold is distributed in a perivascular pattern in the dermis with granules accentuated at the basement membrane zone of sweat glands.

Bismuth produces a characteristic oral finding of the metallic deposition in the gums known as bismuth lines. (See ILBISMUTH1 in the Image Library.) Arsenic, which is found in certain pesticides and in contaminated well water, causes cutaneous hyperpigmentation with areas of scattered hypopigmentation. Chronic lead poisoning can produce a characteristic â€œlead hueâ€• with pallor. Lead also deposits in the gums, causing the characteristic â€œlead line.â€• Iron can cause staining of the skin, resulting in pigmentation similar to that seen in tattoos.[13]

Specific Syndromes

The ability to describe lesions accurately is an important skill, as is the ability to recognize specific patterns. Such abilities help

clinicians in their approach to the patient with a rash. Several cutaneous reaction patterns account for the majority of clinical presentations occurring in patients with xenobiotic-induced dermatotoxicity (Table 29-2).

Toxic Epidermal Necrolysis and Related Syndromes

Toxic epidermal necrolysis (TEN) is a rare, life-threatening dermatologic emergency. Its incidence is estimated at 0.4â€“1.2 cases per 1 million population, and medications are causally implicated in 80â€“95% of the cases. The cutaneous reaction pattern is characterized by tenderness and erythema of the skin and mucosa, followed by extensive cutaneous and mucosal exfoliation.[28]

Classically, the eruption occurs within days of the exposure to the implicated substance and is preceded by malaise, headache, fever, myalgias, arthralgias, nausea, vomiting, diarrhea, chest pain, or cough. Initially, a macular erythema develops that subsequently becomes raised and morbilliform (â€œmeasles likeâ€•). The face, neck, and central trunk are usually the initial areas affected. The disease generally progresses to involve the extremities and the remainder of the body. Individual lesions are reminiscent of target lesions because of their dusky centers. The entire thickness of the epidermis, including the nails, becomes necrotic and may slough off. The mucosal surfaces of the lips, oropharynx, conjunctiva, vagina, urethra, and anus may show erythema and sloughing. A Nikolsky sign, consisting of sloughing of the epidermis when direct pressure is exerted on the skin lesion, may occur.[3] Although suggestive, the Nikolsky sign is not pathognomonic of TEN and occurs in a variety of other dermatoses, including pemphigus vulgaris. If the diagnosis is suspected, a biopsy should be performed and treatment initiated immediately. The histopathology typically shows partial- or full-thickness epidermal necrosis, with

subepidermal bullae with a sparse infiltrate, and vacuolization with numerous dyskeratotic keratinocytes along the dermoepidermal junction adjacent to the necrotic epidermis. Removal of the inciting agent and transfer to a burn center for sterile wound care are widely accepted initial management strategies. Although glucocorticoids are not generally recommended, there is emerging support for the use of immunosuppressive or immunomodulatory agents, such as intravenous immunoglobulins, cyclophosphamide, and cyclosporine. Reported mortality is as high as 30%, particularly in patients with gastrointestinal and tracheobronchial involvement.[28]

TEN is often considered to be the most severe manifestation of the spectrum of syndromes represented by erythema multiforme. Erythema multiforme is characterized by target-shaped, erythematous macules and patches on the palms and soles, as well as the trunk and extremities. The Nikolsky sign is absent. The etiology of recurrent erythema multiforme minor appears to be predominantly associated with recurrent herpes simplex virus infections. Contact sensitization to sulfonamides, phenytoin, antihistamines, many antibiotics, dinitrochlorobenzene (DNCB), diphenylcyclopropenone (DPCP), isopropyl-*p* -phenylenediamine (IPPD), rosewood, and urushiol can elicit erythema multiforme. The Stevens-Johnson syndrome is similarly considered to be an overlap reaction with erythema multiforme major when greater than 30% of body surface area is involved.

Blistering Reactions

Xenobiotic-related cutaneous blistering reactions may be clinically indistinguishable from autoimmune blistering reactions, such as pemphigus vulgaris or bullous pemphigoid. Certain topically

applied xenobiotics cause blistering by disrupting the anchoring filaments of basal cell desmosomes at the dermalâ€“epidermal

junction. In high concentrations, this can lead to necrosis of both skin and mucous membranes. Other xenobiotics cause a similar reaction pattern mediated by the production of antibody directed against the cells at the dermalâ€“epidermal junction.

Acneiform
Ethinyl estradiol
Psoralen
ACTH
Furosemide
Sulfanilamide
Amoxapine
Ketoconazole
Tetracyclines
Androgens
Methaqualone
Tolbutamide
Azathioprine
NSAIDs
Vinblastine
Bromides
Nitrogen mustard

Corticosteroids
Phenolphthalein
Photoirritant contact dermatitis
Danazol
Phenothiazines
Celery
Dantrolene
Phenytoin
Dispense blue 35
Halogenated hydrocarbons
Sulfonamides
Eosin

Iodides
Thiazides
Fig
Isoniazid

Fragrance materials
Lithium

Fixed drug eruptions
Lime
Oral contraceptives
Acetaminophen
Parsnip
Phenytoin
Allopurinol
Pitch

Barbiturates

Alopecia
Captopril

Toxic epidermal necrolysis
Anticoagulants
Carbamazepine
Allopurinol
Chemotherapeutics
Chloral hydrate
L-Asparaginase
Hormones
Chlordiazepoxide
Amoxapine
NSAIDs
Chlorpromazine
Bactrim
Phenytoin

Erythromycin
Mithramycin
Retinoids
D-Penicillamine
Nitrofurantoin
Selenium
Fiorinal
NSAIDs
Thallium
Gold
Penicillin

Griseofulvin
Phenytoin

Contact dermatitis

Lithium
Prazocin
Bacitracin
Phenacetin
Pyrimethamineâ€“sulfadoxine
Balsam of Peru
Phenolphthalein
Streptomycin
Benzocaine
Methaqualone
Sulfonamides
Carba mix
Metronidazole
Sulfasalazine
Catechol
Minocycline

Cobalt
Naproxen

Vasculitis
- Diazolidinyl urea
- NSAIDs
- Allopurinol
- Ethylenediamine dihydrochloride
- Oral contraceptives
- Cimetidine
- Formaldehyde
- Salicylates
- Gold
- Fragrance mix
- Sulindac
- Hydralazine
- Imidazolidinyl urea
- Levamisole
- Lanolin

Maculopapular reactions
- NSAIDs
- Methylchloroisothiazolinone/methylisothiazolinone
- Antibiotics
- Penicillin
- Anticonvulsants
- Phenytoin
- Neomycin sulfate
- Antihypertensive agents
- Propylthiouracil
- Nickel
- Antiinflammatory agents
- Quinidine
- *p*-Tert-butylphenol formaldehyde resin
- *p*-Phenylenediamine

Photosensitivity reactions

Vesiculobullous

Quaternium-15
Amiodarone
Amoxapine
Rosin (colophony)
Benoxaprofen
Barbiturates
Sesquiterpene lactones
Chlorpromazine
Captopril
Thimerosal
Ciprofloxacin
Carbon monoxide

Dacarbazine
Chemotherapeutic agents
Erythema multiforme
5-Fluorouracil
Dipyridamole
Antibiotics
Furosemide
Furosemide
Allopurinol
Griseofulvin
Griseofulvin
Barbiturates
Hydrochlorothiazide
Penicillamine
Carbamazepine
Hematoporphyrin
Penicillin
Cimetidine
Levofloxacin
Rifampin
Codeine

Nalidixic acid
Sulfonamides
Gold
Naproxen
Glutethimide
Piroxicam

TABLE 29-2. Xenobiotics Commonly Associated with Various Cutaneous Reaction Patterns

A number of medications, many of which contain a â€œthiol groupâ€• such as penicillamine and captopril, can induce either

pemphigus foliaceous, a superficial blistering disorder in which the blister is at the level of the stratum corneum, or pemphigus vulgaris, in which blistering occurs at the suprabasilar level (Fig. 29-1). Other xenobiotics produce the tense bullae that resemble bullous pemphigoid. Immunofluorescence studies might show epidermal intracellular immunoglobulin deposits at the dermalâ€“epidermal junction. Treatment options include immunosuppressive agents. The reaction may persist for up to 6 months after the offending agent is withdrawn.

â€œComa bullaeâ€• are flaccid bullae that occur occasionally in patients with sedative-hypnotic overdoses, particularly phenobarbital, or carbon monoxide poisoning. (See ILBARBBLISTERS in the Image Library.) Although these blisters are thought to result from pressure-induced epidermal necrosis, they occasionally occur in nonâ€“pressure-dependent areas, suggesting a systemic mechanism. An intraepidermal or subepidermal blister may occur. There is accompanying eccrine duct and gland necrosis.

Bullous Drug Eruptions

Multiple, large, ill-defined, dull, purplish-livid patches sometimes accompanied by large flaccid blisters characterize these eruptions. Typical locations include acral extremities, genitals, and intertriginous sites, and the process may be confused with TEN if widely confluent. However, bullous drug eruptions spare the patient's mucous membranes. This reaction pattern is generally not life-threatening. Bullous fixed-drug reactions result from the ingestion of a variety of medications such as angiotensin-converting enzyme inhibitors and a variety of antibiotics.

Drug-Induced Hypersensitivity Syndrome

The skin may be involved with systemic drug-induced immunologic diseases. The hypersensitivity syndromes are characterized by erythroderma and facial and periorbital edema, and are typically accompanied by high fever, elevated hepatic aminotransferases, lymphadenopathy, and peripheral eosinophilia. The syndrome typically occurs 2â€“7 weeks after starting therapy with an anticonvulsant (Chap. 47) or a sulfa-based drug. (See ILANTICONVULSANTS in the Image Library.) Management of this syndrome is supportive following elimination of the offending substance.[20 , 33]

Exfoliative Erythrodermas

Exfoliative erythrodermic eruptions can result from any xenobiotic and is characterized by widespread erythema and scale with the potential for multisystem organ failure. The process may persist for months. Such patients with exfoliative erythrodermas require aggressive fluid and electrolyte repletion and nutritional support. Boric acid toxicity causes a bright red eruption (â€œlobster skinâ€•), followed usually within 1â€“3 days by a generalized exfoliation. The mechanism of toxicity is unknown.

Vasculitis

Hypersensitivity vasculitis is characterized by purpuric, nonblanching macules that usually become raised and palpable. The purpura tends to occur predominantly on gravity-dependent areas, including the lower extremities, feet, and buttocks. Sometimes the reaction pattern can have edematous purpuric wheals (urticarial vasculitis), hemorrhagic bullae, or ulcerations. The underlying cytopathology consistently shows a leukocytoclastic vasculitis, which is characterized by fibrin deposition in the vessel walls and a perivascular infiltrate with intact and fragmented neutrophils which appear as black dots, known as nuclear dust, visible only by electron microscopy. This reaction pattern may be limited to the skin, or may be more serious and involve other organ systems, particularly the kidneys, joints, liver, lungs, and brain. The purpura results from circulating immune complexes, which form as a result of a hypersensitivity to a xenobiotic.

Purpura

Purpura is the multifocal extravasation of blood into the skin or mucous membranes. Ecchymoses are, therefore, considered to be purpuric lesions. Cytotoxic agents that either diffusely suppress the bone marrow, or specifically depress platelet counts below $30{,}000/mm^3$, predispose to intradermal hemorrhage, resulting in petechiae or purpuric macules. Xenobiotics that interfere with platelet aggregation, such as, aspirin, clopidogrel, ticlopidine, and valproic acid, may cause purpura. Anticoagulants, such as heparin and coumarin, may also result in purpura (Chaps. 24 and 57).

Coumarin Necrosis

Skin necrosis from coumarin may occur from day 3 to day 10 after the initiation of treatment. The necrosis is secondary to thrombus formation in vessels of the dermis and subcutaneous fat. There

may be blisters, ecchymosis, ulcers, and massive subcutaneous necrosis, usually in areas of abundant subcutaneous fat, such as the breasts, buttocks, abdomen, thighs, and calves. It may be associated with protein C or S deficiency and anticardiolipin antibody syndrome, as well as Leiden V factor mutations.[21]

Contact Dermatitis

When a xenobiotic contacts the skin, it can result in either an allergic contact dermatitis or an irritant dermatitis. Contact dermatitis is characterized by inflammation of the skin with spongiosis (intercellular edema) of the epidermis that results from the interaction of a xenobiotic with the skin. Erythema, induration, pruritus, or blistering may be noted on areas in direct contact with the xenobiotic, while the remaining areas are spared.

Allergic contact dermatitis fits into the classic delayed hypersensitivity, or type IV, immunologic reaction. The development of this reaction requires prior sensitization to an allergen, which, in most cases, acts as a hapten by binding with an endogenous molecule that is then presented to an appropriate immunologic T cell. Upon reexposure, the hapten diffuses to the Langerhans cell, is chemically altered, bound to an HLA-DR, and the complex is expressed on the Langerhans cell surface. This complex interacts with primed T cells either in the skin or lymph nodes, causing the Langerhans cells to make interleukin-1 and the activated T cells to make interleukin-2 and interferon-Î³. This subsequently activates the keratinocytes to produce cytokines and eicosanoids that activate mast cells and macrophages, leading to an inflammatory response (Fig. 29-2).[17 , 18]

Many allergens are associated with contact dermatitis; a complete list is beyond the scope of this chapter. Among the most common sensitizers are urushiol (poison ivy) (see ILPOISONIVY in the Image Library), sesquiterpene lactone (ragweed), and tuliposide A (tulip bulbs). Metals, particularly nickel, are commonly implicated

in contact dermatitis. Several industrial chemicals, such as the thiurams (rubber) and urea formaldehyde resins (plastics), account for the majority of occupational contact dermatitis.

Medications, particularly topical medications such as neomycin, commonly cause contact dermatitis.

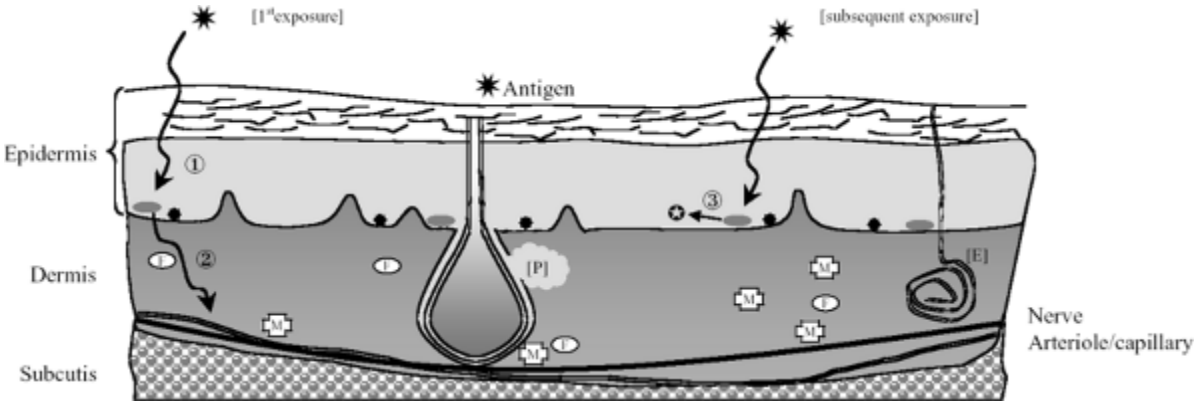

Figure 29-2. Contact dermatitis. (1) Causative chemical, typically a hapten of <500 daltons, diffuses through stratum corneum and binds to receptor on Langerhans cell. (2) The antigen is processed with HLA-DR receptor site, presented to T-helper lymphocytes, and carried through the lymphatics to regional lymph nodes. There it undergoes the sensitization phase by producing memory, effector, and suppressor T lymphocytes. (3) On reexposure to the same, or to a cross-reactive antigen, the Langerhans cell represents the antigen to T lymphocytes, which are now sensitized. This initiates an inflammatory process that appears as indurated, scaly patches. (See Figure 29-1 for symbol legend.)

Irritant dermatitis, while clinically indistinguishable, results from direct damage to the skin and does not require prior antigen sensitization. Still, the inflammatory response to the initial mild insult is the cause of the majority of the damage. Irritant xenobiotics include acids, bases, solvents, and detergents, many of which, in their concentrated form or following prolonged

exposure, can cause direct cellular injury. The specific site of damage varies with the chemical nature of the xenobiotic. Many xenobiotics can affect the lipid membrane of the keratinocyte, whereas others can diffuse through the membrane, injuring the lysosomes, mitochondria, or nuclear components. When the cell membrane is injured, phospholipases are activated and affect the release of arachidonic acid and the synthesis of eicosanoids. The second-messenger system is then activated, leading to the expression of genes and the synthesis of various cell surface molecules and cytokines. Interleukin-1 is secreted, which can activate T cells directly and indirectly by stimulation of granulocyte-macrophage colony-stimulating factor (GM-CSF) production.

Photosensitivity Reactions

Photosensitivity drug reactions are adverse reactions to nonionizing radiation, particularly to ultraviolet A (320â€“400 nm) and less often to ultraviolet B (280â€“320 nm). There are five types of acute photosensitivity reactions: polymorphous light eruption, subacute cutaneous lupus erythematosus, drug-induced phototoxicity, solar urticaria, and photoallergy.[19] There are generally two types of reaction patterns: phototoxic and photoallergic. Phototoxic drug reactions occur within 24 hours of the first dose and are dose-related. The clinical findings include erythema and edema in a light-exposed distribution, and resemble an exaggerated sunburn that can last for days to weeks. Photoallergic reactions occur less commonly, may occur following even small exposures, and are characterized by lichenoid papules or eczematous changes on exposed areas. Photoallergic reactions can be diagnosed by the use of patch tests. Both phototoxic and photoallergic reactions are managed with symptomatic therapy, including topical or, if needed, systemic corticosteroids. The patient should be advised to avoid sun exposure or wear a sunscreen that blocks both ultraviolet A and ultraviolet B with a

sun protection factor (SPF) of 15 or greater and is *para* -aminobenzoic acid (PABA) free.

Scleroderma-like Reactions

A number of environmental chemicals are associated with a localized or diffuse scleroderma-like reactions. Sclerodermatous changes refer to a tightened indurated surface change of the skin. These typically occur on the face, hands, forearms, and trunk. This may be accompanied by facial telangiectasias and Raynaud syndrome. Raynaud syndrome consists of skin color changes of white, red, and blue, accompanied by intense pain with exposure to cold, and can cause acral ulcerations, if untreated. The fibrotic process usually does not remit with removal of the external stimulus. The association of scleroderma-like reactions with polyvinyl chloride manufacture is likely related to exposure to vinyl chloride monomer. (See ILVINYLCHLORIDE in the Image Library.) Similar reports of this syndrome are associated with exposure to trichloroethylene and perchloroethylene, which are structurally similar to vinyl chloride.

Widespread cutaneous sclerosis, in patients exposed to imported rapeseed oil mixed with an aniline denaturant, occurred in Spain and became known as the â€œtoxic oil syndrome.â€• A similar syndrome, following ingestion of impure L-tryptophan as a dietary supplement, resulted in the eosinophilia-myalgia syndrome, which is characterized by myalgia, edema, arthralgias, alopecia, urticaria, mucinous yellow papules, and erythematous plaques.[6 , 24]

Hair

Xenobiotics that produce anagen effluvium, hair loss of those hairs in the anagen stage of the cycle, produce rapid hair loss, whereas those causing telogen effluvium might not produce hair loss for

weeks. Anagen toxicity is the most common mechanism and

occurs with chemotherapeutics and thallium exposures.[26] Many antineoplastic drugs reduce the mitotic activity of the rapidly dividing hair matrix cells, leading to the formation of a thin shaft that breaks easily. Thallium, a toxin classically associated with hair loss, causes alopecia by two mechanisms. Thallium distributes intracellularly, like potassium, inhibiting mitochondrial oxidative phosphorylation, thereby disrupting protein synthesis. In addition, by binding sulfhydryl groups, thallium also inhibits the normal incorporation of cysteine into keratin. Selenium may produce alopecia by similar mechanisms. Soluble barium salts, such as barium sulfide, are applied topically as a depilatory to produce localized hair loss. The mechanism of hair loss is undefined.

Nails

Nail findings may serve as important clues to xenobiotic exposures that have occurred recently or in the remote past. Matrix keratinization leads to the formation of the nail plate. This keratinization is programmed and occurs uniformly in a scheduled pattern. The observed changes in nails, such as Mees lines and Beau lines, can be used to predict the timing of a toxic exposure because of the reliability of rate of growth of the nails. Arsenic poisonings can accurately be dated by the position of growth of the Mees line, as nails grow approximately at an average rate of 0.1 mm/d. Thallium also causes Mees lines.[23] It should be noted that many xenobiotics, including radiation and chemotherapeutic agents, as well as starvation, cause these lines; they are nonspecific findings.

Summary

The integument is constantly exposed to xenobiotics. Whether the exposure occurs via ingestion, airborne, or topical routes, reactive

dermatoses may ensue. Prompt attention and diagnosis is imperative in treating such exposures. The skin, hair, and nails may provide invaluable clues as to the route and nature of the xenobiotic agent. With a careful history, clinical examination, and appropriate biopsy, the etiology and nature of the reaction can be ascertained and treated in a timely and an effective manner.

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Chapter 30
Reproductive and Perinatal Principle

Jeffrey S. Fine

Reproductive and perinatal principles in toxicology derive from many area basic science and are applied to many aspects of clinical practice. This cl reviews several principles of reproductive medicine that have implications toxicology: the physiology of pregnancy and placental xenobiotic transfer, effects of xenobiotics on the developing fetus and the neonate, and the management of overdose in the pregnant woman.

One of the most dramatic effects of exposure to a xenobiotic during preg the birth of a child with congenital malformations. Teratology, the study defects, has principally been concerned with the study of physical malfor A broader view of teratology includes â€œdevelopmentalâ€• teratogensâ€”agents that induce structural malformations, metabolic or physiologic dysfunction, or psychological or behavioral alterations or defic the offspring, either at or after birth.[216] Only 4â€“6% of birth defects are related to known pharmaceuticals or occupational and environmental exposures.[31 , 216]

Reproductive effects of xenobiotics may occur before conception. Female cells are formed in utero; adverse effects from xenobiotic exposure can

theoretically occur from the time of a woman's own intrauterine developm the end of her reproductive years. An example of a xenobiotic that had b teratogenic and reproductive effects is diethylstilbestrol (DES), which cau vaginal and/or cervical adenocarcinoma in some women who had been ex to DES in utero and also had effects on fertility and pregnancy outcome.[1]

Men generally receive less attention with respect to reproductive risks. M gametes are formed after puberty; only from that time on are they susce to xenobiotic injury. An example of a toxin affecting male reproduction is dibromochloropropane, which reduces spermatogenesis and, consequentl fertility. In general, much less is known about the paternal contribution t teratogenesis.[266]

Occupational exposures to xenobiotics are potentially important but often defined. In 2004, it was estimated that there were 41 million women of reproductive age in the workforce.[181] Although approximately 90,000 ch are used commercially in the United States, only a few thousand industria pharmaceutic agents have been specifically evaluated for reproductive to Many xenobiotics have teratogenic effects when tested in animal models, relatively few well-defined human teratogens have been identified (Table).[224] Thus, most tested xenobiotics do not appear to pre-sent a human teratogenic risk, but most xenobiotics have not been tested. Some of the presumed safe xenobiotics may have other reproductive, nonteratogenic toxicities. Several excellent reviews and online resources are available.[79 216 , 224]

Another type of xenobiotic exposure for a pregnant woman is the intentio overdose. Although a xenobiotic taken in overdose may have direct toxici the fetus, fetal toxicity frequently results from maternal pulmonary and/o hemodynamic compromise, such as hypoxia or shock, further emphasizing critical nature of the maternalâ€“fetal dyad.

Xenobiotic exposures before and during pregnancy can have effects thro gestation and may extend into and beyond the newborn period. In additio effects of medication administration in the perinatal period, and the speci of delivering xenobiotics to an infant via the breast milk, deserve special consideration.

Physiologic Changes During Pregnancy tha affect Drug Distribution

Many physical and physiologic changes that occur during pregnancy affec absorption and distribution of xenobiotics in the pregnant woman and consequently affect the amount of xenobiotics delivered to the fetus.[103] ,

During pregnancy there is delayed gastric emptying, decreased gastroint (GI) motility, and increased transit time through the GI tract. These char result in delayed but more complete GI absorption of xenobiotics and, consequently, lower peak plasma concentrations. Because blood flow to th and mucous membranes is increased, absorption from dermal exposure m increased. Similarly, absorption of inhaled xenobiotics may be increased of increased tidal volume and decreased residual lung volume.

Amiodarone

Transient neonatal hypothyroidism, with or without goiter; hyperthyroidis Amiodarone contains 39% iodine by weight. Small to moderate risk from weeks to term for thyroid dysfunction.

Androgens (eg, methylsteroidtestosterone, danazol)

Virilization of the female external genitalia: clitoromegaly, labioscrotal fu Effects are dose dependent. Stimulates growth of sex-steroid, receptorâ€“containing tissue.

Effects are dose dependent. Stimulates growth of sex-steroidtestosterone receptorâ€“containing tissue.

Growth retardation, cleft palate, microphthalmia, hypoplastic ovaries, clo corneas, renal agenesis, malformations of digits, cardiac defects, other anomalies

A 10â€“50% malformation rate, depending on the agent. Cyclophospham induced damage requires cytochrome P450 oxidation.

Aminopterin, methotrexate (amethopterin)

Hydro/microcephaly; meningoencephalocele; anencephaly; abnormal cra ossification; cerebral hypoplasia; growth retardation; eye, ear, and nose malformations; cleft palate; malformed extremities/fingers; reduction in

derivatives of first branchial arch; developmental delay[254]

These folate antagonists inhibit dihydrofolate reductase. High rate of malformations. Methotrexate is used to terminate ectopic pregnancies.

Angiotensin-converting enzyme inhibitors

Fetal/neonatal death, prematurity, oligohydramnios, neonatal anuria, IUG secondary skull hypoplasia, limb contractures, pulmonary hypoplasia

Does not interfere with organogenesis. Significant risk of effects related t chronic fetal hypotension during second/third trimester. If used during ea pregnancy, can be switched during first trimester.[31]

Carbamazepine

Upslanting palpebral fissures, epicanthal folds, short nose with long philt fingernail hypoplasia, anticondevelopmental delay, NTD[110]

Risk unquantified, but may be significant for minor anomalies. Risk is inc in setting of therapy with multiple anticon-vulsants, particularly valproic Mechanism may involve an epoxide intermediate. A 1% risk for NTD. Hig folate, although unproven, is recommended to try to prevent NTD. Increa of perinatal/neonatal bleeding related to deficiency of vitamin K-depende clotting factors, requires vitamin K prophylaxis and therapy.

Carbon monoxide

Cerebral atrophy, mental retardation, microcephaly, convulsions, spastic disorders, intrauterine/death

With severe maternal poisoning, high risk for neurologic sequelae; no inc risk in mild exposures.

Cocaine

IUGR, microcephaly, neurobehavioral abnormalities, vascular disruptive phenomenon (limb amputation, cerebral infarction, visceral/urinary tract abnormalities)

Vascular disruptive effects because of decreased uterine blood flow and f vascular effects from first trimester through the end of pregnancy. Risk f major disruptive effects is low.

Corticosteroids

Cleft palate, decreased birth weight (up to 9%) and head circumference (4%)

Low risk. Most information related to prednisone or methylprednisolone.

Coumadin	
Fetal warfarin syndrome: nasal hypoplasia, chondrodysplasia punctata, brachydactyly, skull defects, abnormal ears, malformed eyes, CNS malformations, microcephaly, hydrocephalus, skeletal deformities, menta retardation, spasticity	
A 10%â€“25% risk of malformation for first-trimester exposure, 3% risk hemorrhage, 8% risk of stillbirth. Bleeding is an unlikely explanation for produced in the first trimester. CNS defects may occur during second/thi trimesters and may be related to bleeding.[108] ,[253]	
Diazepam	
Cleft palate, other anomalies	
Controversial association, probably low risk.[32] ,[62] ,[79] Risk may extend to benzodiazepines. Also risk for neonatal sedation or withdrawal following maternal use near delivery.	
Diethylstilbestrol (DES)	
Female offspring: vaginal adenosis, clear cell carcinoma, irregular mense reduced pregnancy rates, increased rate of preterm deliveries, increased perinatal mortality and spontaneous abortion	
Male offspring: epididymal cysts, cryptorchidism, hypogonadism, diminish spermatogenesis	
A synthetic nonsteroidal estrogen that stimulates estrogen-receptorâ€“c tissue and may cause misplaced genital tissue with propensity to develop	
A 40â€“70% risk of morphologic changes in vaginal epithelium. Risk of carcinoma approximately 1/1000 for exposure before the 18th week. Mos patients exposed to DES in utero can conceive and deliver normal childre	
Ethanol	
Fetal alcohol syndrome (FAS): pre-/postnatal growth retardation, mental retardation, fine motor dysfunction, hyperactivity, microcephaly, maxillar hypoplasia, short palpebral fissures, hypoplastic philtrum, thinned upper joint, digit anomalies	
FAS in 4% of offspring of alcoholic women consuming ethanol above 2 g/l oz/d) over the first trimester. There may be a threshold for effects, but a dose has not been identified. Can see partial expression or other congeni anomalies (see text). Other effects: increased incidence of spontaneous	

abortion, premature delivery, and stillbirth; neonatal withdrawal.

Fluconazole

Brachycephaly, abnormal facies, abnormal calvarial development, cleft p femoral bowing, thin ribs and long bones, arthrogryposis, and congenital disease

Risk related to high dose (400â€“800 mg/d), chronic, parenteral use. Sin 150-mg oral dose probably safe.

Indomethacin

Premature closure of the ductus arteriosus; in premature infants, oligohydramnios, anuria, intestinal ischemia

NSAIDs generally labeled as category B. However, there is concern when after 34 weeks' gestation and for more than 48 hours and/or immediately to delivery. Risk may extend to other NSAIDs.

Iodine and iodinecontaining products

Thyroid hypoplasia after the 8th week of development

High doses of radioiodine isotopes can additionally produce cell death and mitotic delay. Tissue and organ-specific damage is dependent on the spe radioisotope, dose, distribution, metabolism, and localization.

Lead

Lithium carbonate

Lower scores on developmental tests

Ebstein anomaly

Higher risk when maternal lead is >10 g/dL. Low risk.

Methimazole

Aplasia cutis, skull hypoplasia, dystrophic nails, nipple abnormalities, hyp hyperthyroidism

Small risk of anomalies or goiter with first-trimester exposure. Hypothyr risk after 10 weeks' gestation.

Methylmercury, mercuric sulfide

Normal appearance at birth; cerebral palsyâ€“like syndrome after several months; microcephaly, mental retardation, cerebellar symptoms, eye/der anomalies

Inhibits enzymes, particularly those with sulfhydryl groups. Of 220 babies following the Minamata Bay exposure, 13 had severe disease. Mothers of

affected babies ingested 9â€“27 ppm mercury; greater risk with ingestion 6â€“8 months' gestation. In acute poisoning, the fetus is 4â€“10 times m sensitive than an adult. Pathologically, there is atrophy and hypoplasia of brain cortex and abnormalities in cytoarchitecture.[93] ,[259]

Methylene blue (intraamniotic injection)

Intestinal atresia, hemolytic anemia, neonatal jaundice

This xenobiotic was used to identify a twin.

Misoprostol

Vascular disruptive phenomena (eg, limb reduction defects); Moebius syn (paralysis of 6th and 7th facial nerves)

Synthetic prostaglandin E1 analog. Effects mostly observed in women aft unsuccessful attempts to induce abortion.

Oxazolidine-2,4-diones (trimethadione, paramethadione)

Fetal trimethadione syndrome: V-shaped eyebrows, low-set ears with an folded helix, high-arched palate, irregular teeth, CNS anomalies, severe developmental delay, cardiovascular, genitourinary, and other anomalies

An 83% risk of at least one major malformation with any exposure; 32% Characteristic facial features are associated with chronic exposure.

Penicillamine

Cutis laxa, hyperflexibility of joints

Copper chelatorâ€”copper deficiency inhibits collagen synthesis/ maturatio case reports; low risk.

Phenytoin

Fetal hydantoin syndrome: microcephaly, mental retardation, cleft lip/pa hypoplastic nails/phalanges, characteristic facesâ€”low nasal bridge, inn epicanthal folds, ptosis, strabismus, hypertelorism, low-set ears, wide m

Phenytoin has a direct effect on cell membranes and on folate and vitamin metabolism. May reduce the availability of retinoic acid derivatives or alte genetic expression of retinoic acid.

Epoxide intermediate may play a role in teratogenesis. Effects seen with exposure. A 5â€“10% risk of typical syndrome, 30% risk of partial syndr

Risks confounded by those associated with epilepsy itself and use of othe anticonvulsants. Increased risk of perinatal and neonatal bleeding related deficiency of vitamin K-dependent clotting factors requires vitamin K pro

and therapy. Possible increased risk of developing tumors, in particular, neuroblastoma, although absolute risk is very low.

Polychlorinated biphenyls

Cola-colored children; pigmentation of gums, nails, and groin; hypoplasti deformed nails; IUGR; abnormal skull calcifications

Cytotoxic agent. Body residue can affect subsequent offspring for up to 4 after exposure. Most cases followed high consumption of PCB-contaminate oil; 4â€“20% of offspring were affected.

Progestins (eg, ethisterone, norethindrone)

Masculinization of female external genitalia

Progestogens are converted into androgens or may have weak androgenic activity. Stimulates or interferes with sex-steroid receptors. Effects occur after exposure to high doses of some testosterone-derived progestins and be at the rate of 1% of those exposed. Oral contraceptives containing the agents are not thought to present teratogenic risk, despite their category designation.

Quinine Radiation, ionizing

Hypoplasia of 8th nerve, deafness, abortion Microcephaly, mental retarda eye anomalies, growth retardation, visceral malformations

Effects related to high doses used as abortifacients.

Significant doses of radiation from diagnostic or therapeutic sources prod death and mitotic delay. There is no measurable risk with X-ray exposures rads or less at any stage of pregnancy.[22] ,[30]

Retinoids (isotretinoin, etretinate, high-dose vitamin A)

Spontaneous abortions; micro-/hydrocephalus; deformities of cranium, e face, heart, limbs, liver

Retinoids can cause direct cytotoxicity and alter apoptosis. Neural crest c particularly sensitive. For isotretinoin, 38% risk of malformations; 80% a malformations. Effects are associated with vitamin A doses of 25,000â€“ U/d. Exposures below 10,000 U/d present no risk to fetus. Topical retinoi not considered a reproductive risk.[239]

Smoking

Placental lesions, IUGR, increased perinatal mortality, increased risk of SIDS77,129,227,[260]

Effects related to a combination of vasoconstriction (nicotine effect), hyp secondary to hypoperfusion, CO, and CN, and altered development of ne and neural pathways.212,[230]

Streptomycin

Hearing loss

Rare reports. A low-risk phenomenon that could be associated with long- maternal therapy during pregnancy.

Tetracycline

Yellow, gray-brown, or brown staining of deciduous teeth, hypoplastic toc enamel

Effects seen after 4 months of gestation, because tetracyclines must inte with calcified tissue. Effects occur in 50% of fetuses exposed to tetracycli in 12.5% of fetuses exposed to oxytetracycline.

Thalidomide

Limb phocomelia, amelia, hypoplasia, congenital heart defects, renal malformations, cryptorchidism, abducens paralysis, deafness, microtia, a Approximately 20% risk for exposure during days 34â€“50 of gestation.

Trimethoprim

NTD, oral clefts, hypospadias, and cardiovascular defects

Approximately 1% risk of NTD for first-trimester exposure. Mechanism is acid inhibition.

Valproic acid

Lumbosacral spina bifida with meningomyelocele; CNS defects, microcepl cardiac defects; narrow face with high forehead, epicanthal folds, broad, nasal bridge with short nose, long philtrum with a thin vermilion border; thin fingers and toes

Risk for spina bifida is approximately 1%, but the risk for dysmorphic fac be greater. The mechanism of teratogenicity is unknown. Possible explar include interference with glutathione, folate, or zinc metabolism, or regul intracellular pH. Risk is confounded by those risks associated with epileps or use of other agents.

Vitamin D

Possible association with supravalvular aortic stenosis, elfin facies, and r retardation

Large doses of vitamin D may disrupt cellular calcium regulation. Genetic susceptibility may play a role.

IUGR = intrauterine growth retardation; NSAID = nonsteroidal antiinflam drug; NTD = neural tube defect.

Adapted from Brent RL: Environmental causes of human congenital malformations: The pediatrician's role in dealing with these complex clini problems caused by a multiplicity of environmental and genetic factors. Pediatrics 2004;113:957â€“968; Nulman I, Atanackovic G, Koren G: Tera drugs and chemicals in humans. In: Koren G, ed: Maternalâ€“Fetal Toxico Clinician's Guide, 3rd ed. New York, Marcel Dekker, 2001, pp. 57â€“72; a Polifka JE, Friedman JM: Medical genetics: 1. Clinical teratology in the age genomics. CMAJ 2002;167:265â€“273.

Xenobiotic	Reported Effects	Comments

TABLE 30-1. Known and Possible Human Teratogens

P.466

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An increased free xenobiotic concentration in the pregnant woman can be by several factors, including decreased plasma albumin, increased bindin competition, and decreased hepatic biotransformation, during the later st pregnancy. Fat stores increase during the early stages of pregnancy; free acids are released during the later stages and, with them, xenobiotics tha have accumulated in the lipid compartment. The increased concentration fatty acids can compete with circulating free xenobiotic for binding sites albumin.

Other factors may lead to decreased free xenobiotic concentrations. Early pregnancy, increased fat stores, as well as the increased plasma and extracellular fluid volume, lead to a greater volume of distribution. Incre renal blood flow and glomerular filtration may result in increased renal elimination.

Cardiac output increases throughout pregnancy, with the placenta receivir

gradually increasing proportion of total blood volume. Xenobiotic delivery placenta may therefore increase over the course of pregnancy.

These processes interact dynamically, and it is difficult to predict their ne effect. The concentrations of many xenobiotics, such as lithium, gentamic carbamazepine, decrease during pregnancy, even if the administered dose changed.[143]

Although this is not specifically related to the physiologic changes occurr during pregnancy, the fetus may be exposed to xenobiotics that accumula adipose tissue before pregnancy. For example, typical retinoid malformat were seen in a baby born to a woman whose pregnancy began 1 year afte discontinued use of the xenobiotic etretinate (retinoic acid).[130]

Xenobiotic Exposure in Pregnant Women

Exposure to xenobiotics during pregnancy is common. Between 30 and 80 pregnant women take xenobiotics sometime during pregnancyâ€”primarily analgesics, antipyretics, antimicrobials, and antiemetics, as well as vitam caffeine, ethanol, and nicotine.[25 , 37 , 49 , 56 , 158 , 207 , 208] Some pregn women use medications to treat chronic disease; others use medications unknowingly, prior to the recognition that they are pregnant.

Pharmaceutical manufacturers are required by law to label their products respect to use in pregnancy, according to standards promulgated by the U and Drug Administration (FDA) (Table 30-2).[248] Similar classification sys have been developed in Sweden and Australia.[6 , 198 , 214] The original int the US regulations was to inform practitioners about the nature of the av evidence regarding risk in pregnancy; however, the general impression is the categories refer to teratogenic risk.[220] In this the FDA grading system been criticized for conveying an impression of a hierarchy of harmful effe of equivalence of risk within any category.[61 , 78 , 198 , 221] For example, US system, a category C medication is generally considered more danger than a category B medication in pregnancy, even though category C is th default category for medications about which there is little or no specific information available, and for which the risk is unknown. Approximately 9

medications are classified as category C.[141]

There is significant discordance between the useâ€“pregnancy labeling an teratogenic risk, as determined by clinical teratologists,[141] and the FDA s has been criticized for being too conservative.[78] Manufacturers may label medications as category X even when there is only limited information associating the medication with any adverse fetal or neonatal effects. For example, oral contraceptives generally carry a category X classification, e though they are not considered teratogenic. Certain agents with a categor classification may cause problems only at certain times during pregnancy medications that are classified as category D or X may only have a very l of teratogenicity or other adverse effect, and exposure to these agents, e during the first trimester, may not be a sufficient indication to terminate pregnancy. Specific current information on individual xenobiotics can be from

local and regional teratogen information services[124] and published books, [216 , 225] some of which also have online versions.[118 , 242] Motherisk is a Canadian program that uses specific information to advise women about actual risk to them of using a particular medication or xenobiotic in a cur planned pregnancy.[170 , 172]

A
No known risk
Multiple vitamins
Controlled studies show no risk. Adequate, well-controlled studies in pregnant women do not demonstrate a risk to the fetus and if animal stu exist, they do not demonstrate a risk.
B
Unlikely risk
Acetaminophen, penicillin
No evidence of risk in humans. Either animal studies show risk but hu studies do not, or if no adequate human studies have been done, animal show no risk.
C

Unknown risk
Albuterol
Risk cannot be ruled out. Animal studies may or may not show risk, bu human studies do not exist. However, benefits may justify the potential c unknown risk.
D
Known risk, but benefit may outweigh risk
Tetracycline
Positive evidence of risk. Investigational or postmarketing data or hum studies show risk to the fetus. Nevertheless, potential benefits may outw potential risk; for example, if the drug is needed in a life-threatening sit or serious disease for which safer drugs cannot be used or are ineffective
X
Known risk but risk significantlying outweighs benefit
Isotretinoin
Contraindicated in pregnancy. Studies in animals or humans or invest or postmarketing reports have shown fetal risk that clearly outweighs any possible benefit to the patient.
[a] Based on US Food and Drug Administration. Specific requirements on c and format of labeling for human prescription drugs. 21 CFR Ch. I (4â€“1 ed.) $ 201.57.

Category	Risk to Human Fetus	Example(s)	Basis

TABLE 30-2. FDA Use-in-Pregnancy Ratings[a]

The FDA is revising the approach to labeling medications, as well as the themselves. However, the questions raised during the revision process ar extraordinarily complex; for example: How should animal data in general evaluated? How should animal data be extrapolated to humans? How shou teratogenic risk be defined and quantified for any particular xenobiotic? H should the risk of not treating a particular disease be compared with the using a particular medication to treat that disease? How should any of thi information be communicated to practitioners and the public?[221]

Although most women are concerned about the teratogenic effects of medications, in utero exposure to therapeutic medications can have other pharmacologic effects on the newborn infant, such as hyperbilirubinemia withdrawal reactions.[32, 58, 170]

Estimates of substance use in pregnancy vary tremendously, depending o geographic location, practice environment, patient population, and screer method.[42, 132] Among a large national sample screened for xenobiotic us during pregnancy, 20% of pregnant women smoked, 20% drank ethanol, used marijuana, 0.5% used cocaine, 0.1% used methadone, and fewer th 0.1% used heroin. Women tend to decrease their exposure to xenobiotics they know they are pregnant.[26, 104, 107]

Placental Regulation of Xenobiotic Transfer the Fetus

With respect to the transfer of xenobiotics from mother to fetus, the plac functions like other lipoprotein membranes. Most xenobiotics enter the fe circulation by passive diffusion down a concentration gradient across the placental membranes. The characteristics of a substance that favor this p diffusion are low molecular weight, lipid solubility, neutral polarity, and lo protein binding.[176] Polar molecules and ions may be transported through interstitial pores.[245]

Xenobiotics with a molecular weight (MW) greater than 1000 Da do not d passively across the placenta, and this characteristic is used to therapeut advantage. For example, warfarin (MW 1000 Da) easily crosses the placer causes specific fetal malformations.[253] However, heparin (MW 20,000 Da) is too large to cross the placenta, is not teratogenic and, consequently, is preferred anticoagulant during pregnancy. Most therapeutic medications molecular weights between 250 and 400 Da and easily cross the placenta example, thiopental is highly lipid soluble and crosses the placenta rapidl plasma levels reach maternal levels within a few minutes. Muscle relaxan as vecuronium are more polar and cross the placenta slowly.[64]

Although the state of ionization is a limiting factor for diffusion, some hig

charged compounds can still diffuse across the placenta. Valproic acid (pK is nearly completely ionized at physiologic pH, yet there is rapid equilibra across the placental membrane. The small amount of xenobiotic that exist the nonionized form rapidly crosses the placenta; as equilibrium is reest a new, small amount of nonionized xenobiotic becomes available for diffu

Fetal blood pH changes during gestation. Embryonic intracellular pH is hig relative to the pregnant woman. During this developmental stage, weak a will diffuse across the placenta to the embryo and remain there because â€œion trapping.â€• Many teratogens, such as valproate, trimethadione, phenytoin, thalidomide, warfarin, and isotretinoin, are weak acids. Althou trapping does not explain the mechanism of teratogenesis, it may explain xenobiotics accumulate in an embryo. Late in gestation the fetal blood is 0.15 pH units more acidic than the mother's blood; this may permit weak xenobiotics to concentrate in the fetus during this period.[176]

The relative concentrations of protein binding sites in the pregnant woma fetus also have an impact on the extent of xenobiotic transfer to the fetu maternal free fatty acid concentrations increase near term, these fatty ac displace xenobiotics such as valproic acid or diazepam from maternal pro binding sites and make more free xenobiotic available for transfer to the Fetal albumin concentrations increase during gestation and exceed mater albumin concentrations by term. Because the fetus does not have high concentrations of free fatty acids to compete for protein binding sites, th sites are available for binding the xenobiotics. At birth, when neonatal fre acid levels increase 2- to 3-fold, they displace stored xenobiotic from the protein. In the cases of valproic acid and diazepam, the elevated concen of free xenobiotic have adverse effects on the newborn infant.[84 , 105 , 17

The placenta may also affect xenobiotic presentation to the fetus by ion and xenobiotic metabolism. The placenta blocks the transfer of some pos charged ions such as cadmium and mercury,[93] and may even accumulate This barrier does not necessarily protect the fetus, however, because the heavy metal ions interfere with normal placental function and may lead to placental necrosis and subsequent fetal death.[169]

The placenta contains xenobiotic-metabolizing enzymes capable of perfor both phase I and phase II reactions (Chaps. 9 and 26). However, the concentration of biotransforming enzymes in the placenta is significantly than that in the liver, and it is unlikely that the level of enzymatic activity protective for the fetus. Moreover, the fetus may be exposed to reactive intermediates that form during these processes. On the other hand, glut may also be present in the placenta and detoxify some of these reactive intermediates.[111]

Placental transfer of xenobiotics can have a positive effect when it provid therapy. For example, if a fetus is found to have supraventricular tachyca atrial flutter, digoxin can be given to the mother in order to treat the bab [205]

Effects of Xenobiotics on the Developing Organism

A basic premise of teratogenicity is that the particular toxic effects of a xenobiotic are determined by the organism's stage of development.[29 , 22] Although the fertilized ovum is generally thought to be resistant to toxic before implantation,[29] xenobiotics in the fallopian or uterine secretions m prevent implantation of the embryo. Xenobiotic exposure leading to cell lo chromosomal abnormalities may also lead to a spontaneous abortion, pos even before pregnancy has been detected. If the preimplantation embryo survives a xenobiotic exposure, the functional cells usually proceed to no development.[222] Teratogens that act in such a manner elicit an â€œall-o responseâ€•; that is, the exposed embryo will either die or go on to nor development.

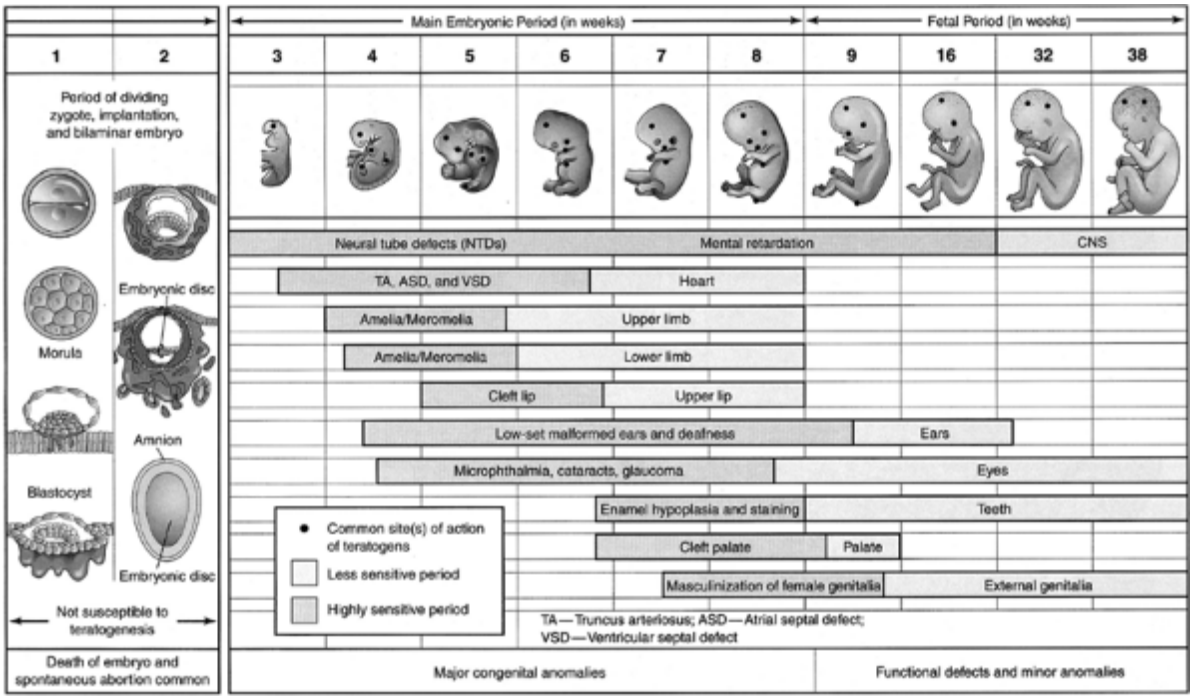

Figure 30-1. Critical periods of fetal development. *(Modified with permis from Moore KL, Persaud TVN: The Developing Human: Clinically Oriented Embryology, 7th ed. Philadelphia, WB Saunders, 2003, p. 520.)*

Teratogens generally behave according to a doseâ€“response curve; there threshold dose below which no effects occur and as the dose of the terat increases above the threshold, the magnitude of the effect increases. The might be the number of offspring that die or suffer malformations or the or severity of malformations. Strictly, teratogenic effects are those that c doses that do not cause maternal toxicity because maternal toxicity itself be responsible for an observed adverse or teratogenic effect on the deve organism.[29]

Organogenesis occurs during the embryonic stage of development betwee 18 and 60 of gestation. Most gross malformations are determined before although genitourinary and craniofacial anomalies occur later.[29] The perio susceptibility to teratogenic effects varies for each organ system (Fig. 30 For instance, the palate has a very short period of sensitivity, lasting approximately 3 weeks, whereas the central nervous system (CNS) rema susceptible throughout gestation.[29]

Theoretically, knowing the exact time of teratogen exposure during gesta would allow prediction of a teratogenic effect; this is true in animal mode where dose and time can be strictly controlled. It is also true for thalidor where different limb anomalies are specifically related to exposures on p days of gestation.[222] In many clinical situations, relating teratogenicity to particular xenobiotic exposure is difficult: Because the exact time of con is unknown, the exact time of exposure is unknown, both for xenobiotics administered intermittently and chronically.

During the fetal period, formed organs continue their cellular differentiati grow to functional maturity. Exposure to toxic agents such as cigarettes this period generally leads to growth retardation. Teratogenic malformatic death may still occur as a result of disruption or destruction of growing c as has been the result of exposure to the angiotensin-converting enzyme inhibitors during the second and third trimesters.[20]

Another concern during the fetal period is the initiation of carcinogenesis Significant cellular replication and proliferation lead to a dramatic growth of the organism. At the same time, when the fetus is exposed to xenobio development of biotransformation systems may expose the organism to metabolites that might initiate tumor formation. Some tumors, such as neuroblastoma, appear early in postnatal life, suggesting a prenatal origir pregnant rats given ethylnitrosourea during the embryonic period, lethal teratogenic effects occur.[193] If ethylnitrosourea is administered during th period, there is an increased incidence of tumors in the offspring. Clear c vaginal and cervical adenocarcinomas are seen in the female offspring of exposed to DES during pregnancy.[23]

Mechanisms of Teratogenesis

Cytotoxicity is one mechanism of teratogenesis and is the characteristic r exposure to alkylating or antineoplastic agents. Aminopterin, for example inhibits dihydrofolate reductase activity and leads to suppression of mitos cell death. If exposure to a cytotoxic agent occurs very early in developn

the conceptus may die, whereas sublethal exposure during organogenesis result in maldevelopment of particular structures. There is evidence that following cell death, the remaining cells in an affected region may try to the damage caused by the missing cellular elements. This â€œrestorative growthâ€• may lead to uncoordinated growth and exacerbate the origina malformation.

In the case of the cytotoxic agents, the mechanism of action is understoc although it is not always clear why particular agents affect particular str With other agents, the structural effects have a clearer relationship to the action. For instance, when glucocorticoids are administered in large doses some experimental animals during the period of organogenesis, malforma the palate occur. Glucocorticoid receptors are found in high concentrations palate of the developing mouse embryo.[188] Corticosteroid exposure can a cause cleft palate in humans at a low frequency.[183 , 225]

Caloric deficiency is not considered teratogenic during the period of organogenesis. However, specific nutritional or vitamin deficiencies can b teratogenic; an increased incidence of neural tube defects is seen with fo deficiency, and the incidence has been reduced following the use of folate supplementation before and during pregnancy.[142] Ethanol affects the fetu directly and indirectly. The craniofacial malformations seen in the fetal a syndrome probably result from the effects of ethanol during the period of organogenesis. Growth retardation may result from direct effects of ethar fetal growth, or from indirect effects resulting from ethanol-induced mate nutritional deficiencies.

Management of Acute Poisoning in the Pregnant Woman

Suicide and suicide attempts during pregnancy are uncommon. Each year number of women die during pregnancy or the postpartum period; 1â€“5% these pregnancy-related deaths may be the result of suicide. Between 2 a 12% of women who attempt or commit suicide may be pregnant.[119 , 186] Reported reasons for these suicide attempts include loss of a lover, econ

crisis, prior loss of children, and unwanted pregnancy and desire for an abortion.[53, 139, 262] In one series, 12% of ingestions were attempts to terminate pregnancy[186] (Chap. 28).

Medication ingestion is a common method of attempting suicide during pregnancy. Analgesics, vitamins, iron, antibiotics, and psychotropic med account for 50â€“79% of the reported ingestions by pregnant women.[186] These medications are frequently prescribed for, and used by, pregnant w

Managing any acute overdose during pregnancy provokes discussion of s questions. Is the general management different? Do altered metabolism a pharmacokinetics increase (or decrease) the woman's risk of morbidity or mortality from a medication overdose? Is the fetus at risk of poisoning fro maternal overdose? Is there a teratogenic risk to the fetus from an acute overdose or poisoning? Is the use of an antidote contraindicated, or shou be modified? When should a potentially viable fetus be emergently deliver prevent toxicity? When should termination of a pregnancy be recommend

As described above, physiologic changes during pregnancy affect pharmacokinetics; xenobiotics taken in overdose also have unpredictable toxicokinetics. In any significant overdose during pregnancy, pregnancy-alterations in pharmacokinetics are unlikely to protect the woman from significant morbidity or mortality.

Although a single high-dose exposure to a xenobiotic during the period of organogenesis might seem analogous to an experimental model to induce teratogenesis, most xenobiotics ingested as a single acute overdose do n induce physical deformities. Anticonvulsant agents are teratogenic and ma ingested in toxic doses, but their teratogenicity is probably related more chronic exposure. Ethanol teratogenicity may be related to binge drinking, single binge is unlikely to have significant effects. Acute acetaminophen intoxication in the first trimester may lead to an increased risk of sponta abortion,[196] suggesting a teratogenic effect similar to the all-or-none res described earlier. In general, however, it is extremely difficult to associat teratogenicity with a particular xenobiotic exposure following a single cas report. There is, for example, a report of multiple severe congenital malformations in the stillborn fetus of a woman who overdosed on isoniaz

during the 12th week of pregnancy.[136] However, because the backgrounc incidence of congenital malformations is 3â€“6%, it is almost impossible determine for a single case whether a particular xenobiotic exposure is th etiology of any observed malformations.[54] It is very unlikely that the sma of possible teratogenesis would ever lead to a recommendation for termi of pregnancy after an acute overdose of most xenobiotics.

In general, any condition that leads to a severe metabolic derangement in pregnant woman is likely to have an adverse impact on the developing fe Therefore, the management of overdose in a pregnant woman usually foll principles outlined in Chap. 4 , with close attention paid to the airway, oxygenation, and hemodynamic stability. The use of naloxone or dextrose not been specifically assessed in pregnancy, but should be guided by the considerations raised in managing the nonpregnant patient with alteration respiratory or neurologic function. Opioid-induced respiratory failure in th pregnant patient will lead to fetal hypoxia and adverse effects; opioid wi in a

pregnant woman, whether induced by abstinence or the use of naloxone, adversely affect the fetus or the pregnancy. Consideration of the benefits risks of the use of naloxone for an opioid-poisoned woman in respiratory or coma suggests that reduced morbidity, for both mother and fetus, may achieved by the use of carefully titrated doses of naloxone to minimize th likelihood of maternal withdrawal (see Chap. 38 and Antidotes in Depth: Antagonists).

Gastrointestinal decontamination is frequently a part of the early manage acute poisoning in the nonpregnant patient. Gastric lavage is not specific contraindicated for the pregnant patient; the usual concerns about protec airway apply to the pregnant patient. Even though the syrup of ipecac is longer recommended as a standard therapy for the management of inges pregnancy was previously considered a relative contraindication to its use because vomiting increases both intrathoracic and intraabdominal pressu

There is no specific contraindication to the use of activated charcoal in a pregnant woman. There may be a specific role for whole-bowel irrigation

management of several xenobiotic exposures, particularly in the treatmen iron overdose in pregnancy. The use of polyethylene glycol is safe in preg women.[178]

When considering the use of antidotes, the primary concern should be for health of the pregnant woman. Almost all antidotal agents are designated pregnancy-risk category C; that is, there is little specific information to g their use. Ethanol is labeled as category D (positive evidence of risk), alt this is presumably related to chronic use throughout pregnancy, not as an antidote. Fomepizole, which has replaced ethanol as the preferred antidot toxic alcohol poisoning, is labeled as category C. Pyridoxine and thiamine category A medications; *N* -acetylcysteine, magnesium, glucagon, and na are category B medications.

Thus far, there are no reports of adverse effects on the fetus from antido treatment of a poisoned pregnant woman. Conversely, in at least one cas withholding deferoxamine therapy may have contributed to the death of b woman and her fetus.[154 , 238] In the hypothetical case of a pregnant wor poisoned with a toxic alcohol for whom fomepizole is not available, the us ethanol is essential until hemodialysis can be performed, especially outsid the first trimester, although there are no data to predict outcome. In mos cases, the physician will need to weigh the short-term toxicity of high se ethanol concentrations against the unknown risk of fomepizole.

Acetaminophen

Acetaminophen is the most common analgesic and antipyretic agent used pregnancy and is one of the most common xenobiotics ingested in overdo during pregnancy.[164 , 196] There are two published series, as well as a n of individual reports, totaling more than 100 cases of acute acetaminoph overdose during all trimesters of pregnancy. In the two large series repr 112 acute and chronic overdoses, 33 patients had serum acetaminophen concentrations in the toxic range.[164 , 196] These studies, in addition to th reports described below, demonstrate that most pregnant women recover an acetaminophen ingestion without adverse effects to themselves or the babies.

In the two large series of acetaminophen overdose during pregnancy,[164] of 28 women who overdosed in the first trimester and continued their pr experienced spontaneous abortions, most within 2 weeks of the ingestion. 8 women, 5 had toxic serum acetaminophen concentrations; 1 woman re -acetylcysteine (NAC) within 8 hours, and 4 received NAC between 12 and hours after ingestion. In one of these cases there was both maternal and death. Five patients with toxic serum acetaminophen concentrations and nontoxic serum concentrations delivered healthy term newborns. Ten wom elective terminations of pregnancy.

The 2 large series include 32 second-trimester acute overdoses.[164 , 196] women who had nontoxic serum acetaminophen concentrations had spon abortionsâ€”one had symptoms of a threatened abortion several days prio the overdose, and the second was assaulted the day before the overdose aborted the next day. Six women with toxic serum acetaminophen conce delivered full-term healthy infants; 19 women with nontoxic serum concentrations delivered full-term babies, and 1 woman with a nontoxic s concentration delivered a premature infant 2 months after the overdose. women had elective terminations of pregnancy.

There are 3 case reports of women with acute overdoses in the second t One woman who overdosed at 15.5 weeks of gestation had a toxic serum acetaminophen concentration, was treated with intravenous NAC beginnin hours after the ingestion, and developed hepatotoxicity. She had a spont rupture of membranes at 31 weeks and delivered a male infant at 32 wee One woman who overdosed at 16 weeks had a toxic serum acetaminophe concentration, was treated with NAC within 8 hours, and did not develop hepatotoxicity.[201] She delivered a normal female infant at term. One wom overdosed at 20 weeks, received intravenous NAC starting some time bet and 18 hours after ingestion, and developed hepatotoxicity. She had labo induced at 41 weeks because of weight loss and delivered a male infant.[2 infant was irritable and developed hyperbilirubinemia, both of which reso after phototherapy.

The 2 large series described above included 39 third-trimester overdoses [196] Twelve women had toxic serum acetaminophen concentrations: 8 del

healthy term infants, 2 women who had no evidence of hepatotoxicity de premature infants 2 days after the overdose, 1 woman with hepatotoxicit delivered a moderately ill premature infant at 32 weeks of gestation, and woman with severe hepatotoxicity delivered a stillborn infant with hepatic necrosis at 33 weeks of gestation (Table 30-3). Twenty-seven women ha nontoxic serum acetaminophen concentrations; 2 delivered premature infa of whom had respiratory distress), and 25 delivered full-term infants. Of full-term infants, 1 developed a withdrawal syndrome, 1 developed pylori stenosis, and 3 had physical anomalies. Altogether, in these 2 series, 6 o women with third-trimester overdoses had premature delivery, usually wi to 3 days of the overdose.

In addition to the large series described, there are 11 case reports of thi trimester acetaminophen overdoses (Table 30-3). Three additional third- trimester cases are briefly described; 2 women had an acute overdose and a chronic overdose. All 3 women had toxic serum acetaminophen concen were treated with NAC, and delivered healthy infants while receiving NAC There are also several case reports of adverse pregnancy outcome in the of chronic use of acetaminophen, or acute overdose in the setting to othe chronic substance use.[41 , 100 , 127 , 148 , 196] It is difficult to interpret th reports with respect to specific acetaminophen effect because of the con of chronic disease, chronic use, or use of additional medications or subst

27
0 (36 h)
1226 (36 h)
ND
No
C/S for fetal distress. Infant: mild respiratory distress syndrome.
[80]

27â€“28
56 (16 h)
6226 (96 h)
ND
Yes

Ingestion over 24 h. No fetal movements at presentation. PO NAC started h. Induced labor at 4 d. Infant: stillborn with diffuse hepatic necrosis. He APAP 250 Âµg/g.
90

29
160 (10 h)
4300 (50 h)
76 (16 h, cord)
No
Ingestion of aspirin, caffeine, and quinine, followed 17 h later by APAP. Presented in labor. Treated with oral methionine. Spontaneous delivery at Infant: moderate hyaline membrane disease. Peak AST 86 (cord). Four w blood exchange transfusions. Discharge home at 54 d of life. Died at 106 apparent cause.
135

31
40 (26)
13320 (60 h)
41 (27)
Yes
APAP only, C/S for fetal distress 1 h after initial maternal evaluation. Inf birth weight was 1620 g. Apgars 0, 0, 1.[b] Infant died at 34 h of life. Moth at 34 h post ingestion. No autopsy of mother or child.
251

32
448 (12 h)
5269 (48 h)
0 (84 h, cord)
No
IV NAC started at 12 h. Induced delivery at 84 h. Infant: transient hypoglycemia, mild respiratory distress, mild jaundice. Peak AST 56 (day life).
264

33

135 (28 h)
6237 (66 h)
330 (3 d, cord)
Yes
Oral NAC at 12 h. Fetal death at 2 d, spontaneous delivery at 3 d. Infant: stillborn with diffuse hepatic necrosis.
196

36
280 (3â€“4 h)
Normal
217 (6â€“7 h, cord)
No
Ingestion of APAP, ethanol, barbiturates. Elective C/S at 6â€“7 h. Infant: volume exchange transfusion at 18 h. Discharge at 40 d, â€œcot deathâ€ 157 d.
200

36
200 (5 h)
25 (24 h)
ND
No
Oral NAC (? time). Infant: spontaneous delivery 6 weeks after ingestion. neonatal course.
38

38
216 (4 h)
Normal
13 (17 h, cord)
No
NAC (? route). Infant: normal neonatal course.
126

210

â€œTermâ€•
147 (9 h)

28 (9 h)
133 (9 h, 4 h of life)
No
Infant PT 44 at 4 h of life. IV NAC. No problems. AST 86 at 4 h of life.
15

Term?
89 (11 h)
326 (35 h)
144 (11 h, 4 h of life)
No
Mother presented in labor at 6 h. Infant received IV NAC at 4 h of life. AS
4 h of life.
213

APAP = acetaminophen; AST= aspartate aminotransferase; C/S = cesarea section; IV = intravenous; NAC = *N* -acetylcysteine; ND = not done or no reported; PO = oral; PT = prothrombin time.
[a] Time after maternal ingestion.
[b] Apgars are at 1, 5 and 10 minutes.

	Maternal		Infant		
Gestational Age (weeks)	APAP Level (Âµg/mL) (time[a])	AST Peak (IU/L) (time[a])	APAP Level (Âµg/mL) (time[a])	Hepato-toxicity (Yes/No)	Commen

TABLE 30-3. Reported Cases of Third-Trimester Acetaminophe Overdose

Acetaminophen is a FDA use-in-pregnancy category B medication; at recommended doses, it is considered safe for use during pregnancy. How overdose, it may put the developing organism at risk. As the third-trimes cases described above demonstrate, acetaminophen crosses the placenta

reach the developing fetus. The clinical series[164, 196] suggest that there some increased risk of spontaneous abortion after overdose during the fi trimester. There is also a question about whether overdose during the fir trimester can lead to late sequelae, for instance, premature labor.

Some experimental work may help to explain early pregnancy loss after overdose. Acetaminophen prevented the development of preimplantation cell stage) mouse embryos in culture, an effect that was not associated v alterations in glutathione concentrations,[133] and also led to abnormal ne development in cultured rat embryos.[234] These data suggest that acetan may be directly toxic to the immature organism. However, other work re that similar embryotoxic effects were associated with reductions in gluta concentrations[258] and that *N* -acetyl-*p* -benzoquinoneimine (NAPQI) prod nonspecific toxicity when added to the rat embryo culture medium.[234]

The fetal liver has some ability to metabolize acetaminophen to a reactive intermediate in vitro. Cytochrome P450 (CYP) activity was detected in int hepatocytes, as well as in microsomal fractions isolated from the livers of fetuses aborted between 18 and 23 weeks of gestation.[203] Fetal CYP activ only 10% of the activity of hepatocytes isolated from adults without cere activity selected as kidney donors; fetal CYP activity increased with incre gestational age. In 2 clinical cases, cysteine and mercapturate conjugates identified in newborns exposed to acetaminophen in utero, suggesting tha fetus and neonate can metabolize acetaminophen through the CYP system data suggest that the fetus in utero and the neonate can generate a toxic metabolite; the clinical cases suggest that the fetal liver is susceptible to

This CYP activity has not been further characterized. However, CYP2E1, o the cytochromes responsible for acetaminophen metabolism, is present in fetal tissues as early as 16 weeks of gestation.[167] CYP3A4 and CYP1A2 ar involved in acetaminophen metabolism, but are not present in fetal liver. is a functional fetal form of the CYP3 family, but its metabolic activity wit respect to acetaminophen has not been studied.[91]

The most difficult questions relate to management of overdose during the trimester. Can acetaminophen overdose lead to premature labor even if a

pregnant woman does not have a toxic serum concentration or develop hepatotoxicity? Should a woman be emergently delivered following overd Does NAC treatment of the mother help the fetus? What is the appropriat treatment of a neonate exposed to acetaminophen in utero?

The clinical cases may help with at least the last two questions (see Table). Six women, all less than 36 weeks of gestation, developed hepatotoxic infants died in utero with evidence of severe hepatotoxicity, although wha in utero postmortem changes may have had on serum acetaminophen concentrations or liver pathology is unclear. One infant died on the secon of life with hepatotoxicity. The other 3 infants experienced problems ass with prematurity but did not develop obvious hepatotoxicity. One of these an exchange transfusion, and had an unexplained death at 3 months of a women, all at 36 or more weeks of gestation, did not develop hepatotoxi One infant had an exchange transfusion and did not develop hepatotoxicit died a â€œcot deathâ€• at 5 months of age. One infant received IV NAC had a transient elevation of aspartate aminotransferase (AST) and prothr time. Two infants were not treated; both did well, although 1 had a trans elevation of AST. One infant was born 6 weeks after the overdose and wa normal.

Severe maternal hepatoxicity that is associated with any sign of fetal dist an indication for urgent delivery. Although a fetus with prolonged exposur acetaminophen in utero is at risk of developing severe hepatotoxicity, not risk infants are affected. What role gestational age, maternal disease stat other maternal factors may play is unknown. Although there are insufficie data to suggest that acetaminophen overdose per se is an indication for delivery, there may be an indication for urgent delivery when the matern serum acetaminophen concentration is in the toxic range but hepatotoxici not yet developed.[241] Significant acetaminophen overdose with or withou hepatotoxicity can precipitate premature spontaneous labor, and even wo with nontoxic serum concentrations may be at a slightly increased risk.

In 2 cases, exchange transfusion was employed to treat the exposed neo both cases, the acetaminophen half-life was prolonged, and in neither cas this affected by the transfusion. Disturbingly, these 2 infants had unexpl

deaths at several months of age. There is insufficient information on whic base a recommendation regarding exchange transfusion as therapy for p exposure.

The pregnant woman with acute toxic acetaminophen ingestion should be with *N* -acetylcysteine (see Chap. 34 and Antidotes in Depth: *N* -Acetylcy). This is therapy to treat the mother. Although maternal hepatoxicity or NAC therapy may be associated with fetal toxicity,[196] there is insufficient information to indicate that prevention of maternal toxicity will prevent f toxicity in either the first or the third trimester. NAC was found in cord b after administration to 4 mothers before delivery,[100] although NAC did nc the sheep placenta in vivo[223] or the perfused human placenta in vitro.[104] NAC does cross the placenta, whether it prevents fetal hepatotoxicity is because not all exposed fetuses develop hepatotoxicity.

In 4 third-trimester cases where the mothers overdosed at or after 36 we gestation and did not develop hepatotoxicity, the infants did well. One in received NAC. There are anecdotal reports of infants who received NAC postnatally and did well. Current theory suggests that infants and young are less likely than teenagers or adults to develop hepatoxicity after acetaminophen overdose because of immature CYP activity and increased sulfation activity. It is intriguing to consider that this metabolic protectior extend to the newborn exposed to acetaminophen in utero. It also makes difficult to know to what extent postnatal NAC therapy for the prenatally newborn might prevent toxicity. Although there are no reported cases, it seem that the premature newborn exposed in utero is the best candidate postnatal NAC therapy.

Iron

Iron is another common ingestant during pregnancy; maternal toxicity is generally greater than fetal toxicity. In 2 reported cases, normal babies delivered although the mothers died.[182, 194] In another case, the mother severe iron toxicity with acidosis, shock, renal failure, and disseminated intravascular coagulation but was not treated with deferoxamine because concerns about its teratogenic risks. Instead, the mother received an exc

transfusion followed 45 minutes later by a spontaneous abortion of the 1 fetus.[154, 238] Neonatal and cord blood iron concentrations were not eleva several cases, pregnant women who had signs and symptoms of iron pois and elevated serum iron concentrations were treated with deferoxamine a subsequently delivered normal babies.[24, 116, 128, 190, 217, 247]

Although the placenta transports iron to the fetus efficiently,[171] it also b the transfer of large quantities of iron. In a sheep model of iron poisoning a small amount of iron was transferred across the placenta despite signif elevated serum iron levels.[52]

Deferoxamine is an effective antidote for iron poisoning (see Chap. 40 an Antidotes in Depth: Deferoxamine), but it is reported to be an animal te that causes skeletal deformities and abnormalities of ossification (FDA cla pregnancy risk). An animal model observed similar effects, but only with of deferoxamine that caused maternal toxicity.[27] Experimentally, in sheep transfer of deferoxamine across the placenta was demonstrated;[52] therefo reported fetal effects may be secondary to chelation of essential nutrients as trace metals) on the maternal side of the placenta.[241]

In clinical case reports of iron overdose for which deferoxamine was used have been no adverse effects on the fetus, although most have been eith second- or third-trimester poisonings.[24, 116, 128, 182, 190, 217, 247] In series of 49 patients with iron poisoning during pregnancy, few of the pa exhibited any clinical toxicity other than vomiting and diarrhea; 25 receiv deferoxamine, most by the oral route.[163] One woman with a first-trimest overdose, 8 women with second-trimester overdoses, and 12 women with trimester overdoses were treated with deferoxamine and subsequently d full-term infants. One infant whose mother overdosed at 30 weeks of ges had webbed fingers on one hand. One woman overdosed at 20 weeks, ha minimal clinical toxicity, received deferoxamine, and delivered a 2.5-kg n infant at 34 weeks. One woman with a first-trimester overdose and 2 wor with second-trimester overdoses elected to terminate their pregnancies.

Further support for the safe use of deferoxamine in pregnancy is the exp with its use for pregnant women with thalassemia. For many years Defer has been administered as part of the therapy for posttransfusion iron ov

without adverse effects.[229]

Deferoxamine is probably safe for use in pregnant women. Considering th potentially fatal nature of severe iron poisoning, deferoxamine should be administered when signs and symptoms indicate significant poisoning.

Iron overdose may be one of the few specific indications for whole-bowel irrigation because iron is not adsorbed to activated charcoal (see Antidote Depth: Activated Charcoal). A case report demonstrated elimination of p fragments following treatment of a pregnant woman with whole-bowel irrigation.[249]

Carbon Monoxide

Carbon monoxide is the leading cause of poisoning fatalities in the United In contrast to iron and most other xenobiotics, when pregnant women are exposed to carbon monoxide, the fetus may be at greater risk of toxicity the woman herself. There are reports of both the mother and fetus dying, mother surviving but the fetus dying, and both the mother and fetus surv but with adverse neonatal outcome, primarily brain damage resembling th following severe cerebral ischemia.[39 , 51 , 121 , 144 , 155 , 180 , 249 , 265 S clinical effects have also been observed in animal models.[63 , 85 , 145

The case literature suggests increased risk of poor fetal outcome with cli severe maternal poisoning or significantly elevated carboxyhemoglobin le , [180] Women with minimal symptoms and/or low levels of carboxyhemogl have a low risk of fetal toxicity, but a lower limit of exposure without effe not been specifically defined.[125]

In animal models, under physiologic conditions, the fetus has a carboxyhemoglobin concentration 10â€“15% higher than the mother. Afte exposure to carbon monoxide, the fetus achieves peak carboxyhemoglobi 58% higher than those achieved by the mother at steady state, and the t peak level is also delayed compared to the mother. Similarly, the elimina carbon monoxide occurs more slowly in the fetus than in the mother.[96 , One case report describes such a phenomenon: after 1 hour of suppleme

oxygen, the maternal carboxyhemoglobin was 7% and the fetal carboxyhemoglobin was 61% at the time of death in utero.[69]

Carbon monoxide leads to fetal hypoxia by several mechanisms: (a) mat carboxyhemoglobin leads to a decrease in the oxygen content of materna and therefore, less oxygen is delivered across the placenta to the fetus, normally has an arterial PO_2 of only 20â€“30 mm Hg; (b) fetal carboxyhemoglobin causes a decrease in fetal PO_2 ; (c) carbon monoxide the oxyhemoglobin dissociation curve to the left and decreases the releas oxygen to the fetal tissues (an exacerbation of the physiologic left shift f with normal fetal hemoglobin); and (d) carbon monoxide may inhibit cyt oxidase or other mitochondrial functions (Chap. 120).

The treatment for severe carbon monoxide poisoning is hyperbaric oxyge therapy (HBO) (see Chap. 120 and Antidotes in Depth: Hyperbaric Oxyge There are questions about the use of HBO in pregnant women because ar models suggest HBO adversely effects the embryo or fetus.[73 , 168 , 215 , applicability of the animal models to humans is difficult to assess; many o animal models employed hyperbaric conditions of greater pressures and than those clinically employed for humans.

HBO has been used therapeutically for carbon monoxide poisoning in pre with good results reported, although there are limited data on the long-te follow-up of the children.[34 , 72 , 81 , 88 , 97 , 125 , 250] One large series re 44 women who were exposed to carbon monoxide during pregnancy and treated with HBO, regardless of clinical severity or gestational age: 33 ha births; 1 had a premature delivery 22 weeks after HBO, during an episod maternal fever; 2 had spontaneous miscarriages (one 12 hours after sev poisoning and one 15 days after mild poisoning); 1 delivered a child with syndrome; 1 had an elective abortion; and 6 were lost to follow-up.[69] Unfortunately, details regarding trimester of exposure, maternal carboxyhemoglobin level, and severity of symptoms are not available, ma difficult to interpret the reported outcomes. Although HBO appears safe f pregnant women and seems to present little risk to the fetus, it is not cle whether HBO prevents carbon monoxide-related fetal toxicity for those at Carbon monoxide can have a severe impact on fetal health and developm

and, as noted above, the maternal carboxyhemoglobin level may not acc reflect the fetal carboxyhemoglobin level.

HBO should be considered for any pregnant woman exposed to carbon m especially for a woman with an elevated serum carboxyhemoglobin conc or any evidence of fetal distress. If HBO therapy is not available, 100% o should be administered to the mother for a period of time five times long the time needed for the maternal carboxyhemoglobin to return to the nor range.

Substance Use During Pregnancy

One of the most complex areas of toxicology deals with issues of substan during pregnancy, and its effects on the woman, on the pregnancy itself, fetal and postnatal development. This section reviews of some of the imp aspects of this topic.

Clinical research in the area of substance use during pregnancy is very d to perform. With the increased use of cocaine during the latter half of the and 1990s, there was great interest in determining the effects of cocaine during pregnancy. As research in this area progresses, many of the critic methodologic issues related to substance use research are highlighted.[74, 138, 179, 268]

Substance-using women often have multiple risk factors for adverse preg outcomes, such as low socioeconomic status, polysubstance use, ethanol cigarette use, sexually transmitted diseases, AIDS, malnutrition, and lack prenatal care. Lack of prenatal care is highly correlated with premature b and smoking is associated with spontaneous abortion, growth retardation, sudden infant death syndrome (SIDS).[115, 260] Other factors not specifica related to substance use such as age, race, gravidity, and prior pregnanc effect pregnancy outcome. Each of these factors represents a significant potential confounding variable when the effects of a particular agent such cocaine or marijuana are evaluated during pregnancy and must be contro in research design. Many of these factors are also significant confounders evaluation of postnatal growth and development.

There may be bias in the selection of study subjects. For example, if all t patients are selected from an inner-city hospital obstetric service, there i potential for overestimating the effects of the xenobiotic being studied. I cohorts are followed over a long time, study subjects are frequently lost follow-up. Are the ones who continue more motivated, or do they have m problems that need attention?

Categorizing patients into substance-use groups is difficult. Self-reporting substance use is frequently unreliable or inaccurate, and making determ about the nature, frequency, quantity (dose),

or timing (with respect to gestation) of xenobiotic exposure is difficult. E substance users frequently use multiple xenobiotics, it may be difficult to categorize subjects into particular xenobiotic-use groups, and patients us different xenobiotics may be grouped together. In fact, there may be no xenobiotic-free control groups.

When urine drug screens are used to identify substance users, there is a probability of false negatives because drug screens reflect only recent use factor is particularly important because substance use tends to decrease pregnancy, and a negative urine drug screen in the third trimester or at may fail to identify a woman who was using xenobiotics early in pregnanc Testing for xenobiotics in hair or meconium may improve the accuracy of analysis with regard to the entire pregnancy.[121 , 137]

Another bias involves selection of infants who are exposed to xenobiotics Evaluating newborns who are â€œat risk,â€• show signs of withdrawal, c positive urine drug screens will miss some exposed infants. When researc concerns the neurobehavioral development of children exposed in utero t substances, it is important that the examiners performing the evaluation blinded to the infants' xenobiotic exposure category.

Finally, there may be a bias against publishing research that shows a neg no significant effect.[122]

Ethanol

Chronic ethanol use during pregnancy produces a constellation of fetal e The most severe effects are seen in the fetal alcohol syndrome (FAS), wh characterized by (a) intrauterine or postnatal growth retardation, (b) me retardation or behavioral abnormalities, and (c) facial dysmorphogenesis, particularly microcephaly, short palpebral fissures, epicanthal folds, max hypoplasia, cleft palate, hypoplastic philtrum, and micrognathia.[108] A chil be diagnosed with FAS even when a history of regular gestational alcohol cannot be confirmed.

In an attempt to formalize diagnostic criteria for FAS and other gestation alcohol-related effects, the Institute of Medicine has proposed some add descriptors.[236] Partial FAS is applied to a child with some of the characte facial features and with either growth retardation, neurodevelopmental abnormalities, or other behavioral problems. Alcohol-related birth defects congenital anomalies other than the characteristic facial features describe above, such as cleft palate, which are sometimes seen with regular gesta alcohol use. Alcohol-related neurodevelopmental disorder describes neurodevelopmental abnormalities or other behavioral problems, which a sometimes seen with regular gestational alcohol use.

Differential expression of the syndrome may reflect the effects of differer ethanol doses at critical periods specific for particular effects. The cranio anomalies probably represent teratogenic effects during organogenesis, some central nervous system abnormalities and growth retardation may from adverse effects later in gestation.

The fully expressed syndrome may be related to consumption of the equi of 2â€“3 ounces of 100% ethanol (4â€“6 â€œstandardâ€• drinks of hard per day throughout pregnancy,[236] although binge drinking (at least 5 sta drinks per occasion), with a significantly elevated peak blood ethanol concentration, may be more important.[3 , 152] Approximately 20% of wom consume some ethanol during pregnancy;[175] only 1â€“2% consume 4 or drinks each day. In this regard, it might be more appropriate to attribute fetal alcohol syndromes described above to alcoholism, or chronic regular frequent binging, rather than to any level of gestational ethanol exposure matter how little or how infrequent.[3 , 4] Even so, a no-effect level for eth

has not been defined, and a safe level of ethanol use in pregnancy has no determined.[109]

The incidence of FAS is 0.5â€“3 per 1000 live births; 4% of women who heavily may give birth to children with FAS.[2 , 160] This means that severa hundred children with FAS and several thousand with fetal alcohol effects born each year; ethanol use is considered the leading preventable cause mental retardation in this country.[236] Although the primary determinant o and its effects is the level of maternal ethanol consumption, there is som evidence that paternal ethanol exposure may play a contributing role.[1]

Other effects of ethanol use during pregnancy include an increased incide spontaneous abortion, premature deliveries, and stillbirths,[50 , 140] neona ethanol withdrawal,[50] and possibly carcinogenesis.[117] Infants may be irri hypertonic and may have problems with habituation and arousal. Long-te behavioral and intellectual effects include decreased IQ, learning disabilit memory deficits, speech and language disorders, hyperactivity, and dysfunctional behavior in school.[159 , 237]

Brain autopsies of children with FAS demonstrate malformations of gray a white matter, a failure of certain regions (eg, the corpus callosum) to dev failure of certain cells (eg, cerebellar astrocytes) to migrate, and a tende tissue in certain regions to die. The mechanisms of ethanol-induced teratogenesis are not fully elucidated.[19 , 92] Much of the work in animals focused on the developing nervous system, where ethanol adversely affe nerve cell growth, differentiation, and migration, particularly in areas of neocortex, hippocampus, sensory nucleus, and cerebellum.[67 , 89]

Several mechanisms are potential contributors to ethanol's effects.[87] Eth interferes with a number of different growth factors which may affect ne migration and development.[261] In addition, ethanol interferes with the development and function of both serotonin and *N* -methyl-D-aspartate (receptors. Ethanol, or its metabolite acetaldehyde, may also cause necros certain cells directly or through the generation of free radicals and exces apoptosis.[48 , 94] In particular, craniofacial abnormalities may be related t apoptosis of neural crest cells, through the formation of free radicals, a deficiency of retinoic acid, or the altered expression of homeobox genes

regulate growth and development.

One integrative model of ethanol induced teratogenesis proposes that sociobehavioral risk factors, such as drinking behavior, smoking behavior, socioeconomic status, and cultural/ethnic influences, create provocative conditions, such as high peak blood ethanol concentrations, circulating to constituents, and undernutrition. These provocative factors exacerbate fe vulnerability to potential teratogenic mechanisms, such as ethanol-relate hypoxia or free radical-induced cell damage.[5]

Opioids

Opioid dependency remains a significant cause of both maternal and neo morbidity. Approximately 0.2% of pregnant women may use heroin or methadone, and up to 75,000 babies per year may be exposed to opioids, utero.[175] Pregnant opioid users are at increased risk for many medical complications of pregnancy, such as hepatitis, sepsis, endocarditis, sexua transmitted diseases, and AIDS, and may be at increased risk for obstetr complications, such as miscarriage, premature delivery, or stillbirth.[74,8] of

the obstetric complications may be related to associated risk factors in a to the opioid use.

The most common effect of maternal opioid use is on fetal growth.[86,268] is an increased incidence of low birth weight in babies born to opioid-usir mothers, compared to controls, and the effect is greater for heroin than t methadone. Women who receive low-dose methadone and good prenatal have birth outcomes similar to nonusers, but they are at increased risk fo pregnancy-related complications.[74]

The most significant acute neonatal complication of opioid use during pre is the neonatal withdrawal syndrome (NWS), characterized by hyperirrita gastrointestinal dysfunction, respiratory distress, and vague autonomic symptoms, including yawning, sneezing, mottling, and fever (Table 30-4 Myoclonic jerks or seizures may also signify neurologic irritability. Withd

infants are recognizable by their extreme jitteriness, despite efforts at consolation; ecchymoses and contusions may be found on the tips of thei fingers or toes, as a result of trauma from striking the sides of the bassi From 60 to 90% of opioid-exposed offspring will show some signs of withdrawal.[74]

Some of the manifestations of the neonatal withdrawal syndrome may be by enhanced Î±-adrenergic activity in the locus ceruleus. Firing of neuron this region of the brain leads to such NWS-like behaviors as wakefulness tremorsâ€”effects that are inhibited by opioid agonists. Chronic opioid administration leads to tolerance, as well as an increased number of $Î±_2$ adrenergic receptors. Presumably, withdrawal of opioids causes increasec stimulation of a large number of receptors in this region, leading to clinic of withdrawal.

Opioid withdrawal symptoms typically occur within 2 weeks of birth. Hero withdrawal usually occurs within the first 24 hours; however, methadone withdrawal may be delayed because it has a larger volume of distribution slower metabolism in the neonate, and therefore an increased half-life. Methadone withdrawal occurs when the plasma concentration falls below mg/mL.[204] The onset and severity of symptoms may be related to whethe heroin, methadone, or both were used; how much was used chronically; much was used near the time of delivery; the character of the labor; whe analgesic or anesthetic agents were used; and the maturity, nutrition, an medical condition of the neonate.[57] Acute neonatal withdrawal symptoms generally last from days to weeks, but some symptoms may persist for months.[10]

- Exaggerated Moro reflex
- Dehydration
- Frequent yawning and sneezing
- Diarrhea
- High-pitched crying
- Poor feeding
- Hyperactive deep tendon reflexes
- Poor weight gain

Increased muscle tone
Uncoordinated and constant
Increased wakefulness
sucking
Irritability
Vomiting
Seizures
Autonomic signs
Tremors
Fever
Increased sweating
Mottling
Nasal stuffiness
Temperature instability

Reproduced with permission from the Committee on Drugs. Neonatal drug withdrawal. Pediatrics 1998;101:1079â€“1088.

Neurologic excitability Gastrointestinal dysfunction

TABLE 30-4. Signs and Symptoms of Neonatal Opioid Withdrawal

From 5â€“7% of babies showing signs of withdrawal experience seizures, generally by 10 days after birth.[95] Seizures may be more likely after me withdrawal than after heroin withdrawal.[267] These seizures do not neces predispose to idiopathic epilepsy; in one small study, children who had withdrawal seizures were normal at 1-year follow-up.[60]

Treatment of withdrawal begins with provision of a comforting environme swaddling or tightly wrapping the infant, minimal handling or stimulation, demand feeding. More severe symptoms may require pharmacologic ther One way of determining the need for therapy is the application of a seve scoring scale. In general, babies who are extremely irritable, have feedin difficulties, diarrhea, or significant tremors, or are crying continuously, a candidates for pharmacologic therapy.[10 , 112]

Opioid agonists such as morphine, methadone, tincture of opium and par

and sedative-hypnotic agents such as diazepam and phenobarbital have l used to treat withdrawal symptoms.[10, 112] Tincture of opium, diluted to dose of 0.4 mg/mL of morphine equivalent, may be the preferred agent l it is a pure opioid agonist, and the formulation has no additives. Howeve are few well-controlled trials evaluating the relative efficacy of the differ agents.[243]

Opioid agonists may be more effective at preventing withdrawal seizures heroin or methadone than from phenobarbital or diazepam.[95, 113] Howev sedative-hypnotic agents are commonly used by heroin users or adults maintained on methadone, and sedative-hypnotic withdrawal seizures ma contribute to the overall neonatal abstinence symptomatology. In this se there may be a role for phenobarbital. Because oral administration of phenobarbital may delay achieving a therapeutic level, parenteral admin may be required.

Infants of opioid-using mothers are at increased risk for SIDS compared controls.[114, 115] The relative risk is 3.6 for methadone and 2.3 for heroi mechanism may be related to a decreased medullary responsiveness to C the effect may be related to some condition of the postnatal environment [252]

Although young children born to opioid users do not seem to have signifi differences in behavior compared to controls, older children have increas learning problems and school dysfunction particularly related to behavior difficulties.[268]

Cocaine

Approximately 1% of pregnant women in the United States use cocaine s time during their pregnancy.[175] The rate may be as high as 15% in certa populations,[55] and it is estimated that more than 100,000 infants born in United States each year may be exposed to cocaine in utero.[42] The consequences of cocaine use during pregnancy have been extensively reviewed.[99, 102, 187]

The most commonly reported obstetric complications of gestational cocai

are abruptio placentae, premature delivery, and intrauterine growth reta Significant perinatal problems include seizures, cerebral infarctions, and CNS effects.[46, 187] A meta-analysis of studies published before 1989 cor that adverse effects on head circumference, gestational age, and birth w that had been attributed to the maternal use of cocaine during pregnancy related to polysubstance use, but not necessarily to cocaine.[147] In this a no increased risk of abruptio placentae was demonstrated. However, later which tried to control for polysubstance use although not always for smok ethanol use, suggested that there were significant effects of

gestational cocaine use on intrauterine growth and prematurity.[120, 187, The incidence of abruptio placentae may also be significant when related acute use.[226] It seems that good prenatal care can mitigate many of the effects of cocaine.[149, 195, 268]

Significant congenital malformations have been reported among some inf who were exposed to cocaine in utero, specifically genitourinary malform cardiovascular malformations, and limb-reduction defects.[36, 79] In one l population-based study, there was no increase in the incidence of malformations.[156]

Animal models have also identified teratogenic effects of in utero cocaine exposure. Decreased maternal and fetal weight gain and an increased fre of fetal resorption were demonstrated in rats;[71] sporadic physical anoma have also been observed.[47] Teratogenic effects similar to those observed humans were reported in mice: bony defects of the skull, cryptorchidism, hydronephrosis, ileal atresia, cardiac defects, limb deformities, and eye abnormalities.[75, 150, 151, 165] Cocaine caused hemorrhage, edema, and subsequently, limb-reduction defects in rats when administered during midgestation in the postorganogenic period.[255]

The perinatal effects of cocaine are probably mediated through a vascular mechanism. Cocaine administration in the pregnant ovine model causes increased uterine vascular resistance, decreased uterine blood flow, incre fetal heart rate and arterial blood pressure, and decreased fetal PO_2 and content.[14, 263] Similar effects have been seen in rats.[184] Fetal hypoxia r

cause rupture of fetal blood vessels and infarction in developing organ sy such as the genitourinary system[45 , 165 , 231] or the CNS.[44 , 59 , 256] Hyperthermia or direct effects of cocaine in the fetus may exacerbate the effects.[28] Limb-reduction defects similar to those attributed to cocaine ha been produced after mechanical clamping of the uterine vessels.[28 , 257] A developing concept is that following vasospasm and ischemia, reperfusion with the generation of oxygen free radicals and subsequent injury.[263 , 26

Despite the reported malformations and a possible mechanism, neither th human epidemiology, nor the effects observed in animal models, suggest specific teratogenic syndrome. The risk of a significant malformation from prenatal cocaine exposure is low, but the effect, if one occurs, may be se [, 65 , 79]

One of the greatest concerns about prenatal cocaine exposure is the pote adverse effect on the developing child, and this is an intensive area of epidemiologic research. The most common findings in early infancy are la state and autonomic regulation, decreased alertness and orientation, and abnormal reflexes, tone, and motor maturity; however, many studies sho effect.[70] For some children, these effects may manifest in later infancy as difficulty with information processing and learning. However, preliminary evidence suggests that, for school-age children, any observed cognitive may be more related to the home environment than to prenatal cocaine exposure, even for those children who showed some of the typical neona behaviors.[43 , 76 , 246] Nonetheless, there is also evidence of impairment modulating attention and impulsivity, which makes handling unfamiliar, c and stressful tasks more difficult,[162] and these effects are also observed animal models of prenatal cocaine exposure.[65 , 232] Cohorts of children e to cocaine in utero are now older and in school, and studies of developme behavior are in progress.

The mechanism of neurotoxicity has not been specifically elucidated. As described above, for many of the maternal and fetal physical defects, coc may have direct toxicity, or effects may be mediated through hypoxia or free radicals. Because cocaine interferes with neurotransmitter reuptake, likely that cocaine also disrupts normal neural ontogeny by interfering wit

trophic functions of neurotransmitters on the developing brain.[153, 161]

Breast-Feeding

In the United States, breast-feeding is the recommended method of infan nutrition because it offers nutritional, immunologic, and psychological be Many women use prescription and nonprescription medications while brea feeding, and are concerned about the possible ill effects on the infant of medications in the breast milk. This concern extends to the possible expo the infant to occupational and environmental xenobiotics via breast milk.[2] The response to many of these concerns can be determined by the answe following question: Does the risk to an infant from a xenobiotic exposure breast milk exceed the benefit of being breast-fed?[134]

Pharmacokinetic factors determine the amount of xenobiotic available for transfer from maternal plasma into breast milk; only free xenobiotic can the mammary alveolar membrane. Most xenobiotics are transported by p diffusion. A few xenobiotics, such as ethanol and lithium, are transported through aqueous-filled pores. The factors that determine how well a chen diffuses across the membrane are similar to those for other biologic mem such as the placenta: molecular weight, lipid solubility, and degree of io

Large-molecular-weight compounds, such as heparin or insulin, will not p breast milk. Lipid solubility is important not only for diffusion but also for xenobiotic accumulation in breast milk, because breast milk is rich in fat, especially breast milk that is produced in the postcolostral period (3â€“4 postpartum). With a pH near 7.0, breast milk is slightly more acidic than Consequently, weak acids in plasma exist largely as ionized molecules an cannot be easily transported into milk. Conversely, weak bases exist in p largely as nonionized molecules and are available for transport into breas Once in the breast milk, ionization of the weak base occurs, and the chen concentrated as a result of ion trapping. In other words, weak bases may concentrate in breast milk. Sulfacetamide (pK_a 5.4, a weak acid) has a concentration in plasma 10 times its concentration in breast milk, whereа sulfanilamide (pK_a 10.4, a weak base) is found in equal concentrations in plasma and breast milk.[134]

The net effect of these physiologic processes is expressed in the milk-to- (M/P) ratio. Xenobiotics with higher M/P ratios have relatively greater concentrations in breast milk. The M/P ratio does not, however, reflect th absolute concentration of a xenobiotic in the breast milk, and a xenobiotic high M/P *ratio* is not necessarily found at a high *concentration* in the bre For example, morphine has an M/P ratio of 2.46 (is concentrated in breas but only 0.4% of a maternal dose is excreted into the breast milk.[13] In g for most pharmaceuticals, approximately 1â€“2% of the maternally adm dose is presented to the infant in breast milk.[134]

The M/P ratio has several limitations. It does not account for differences xenobiotic concentration that may result from (a) repeat or chronic dosing breast-feeding at different times relative to maternal medication dosing, differences in milk production during the day or even during a particular feeding session, (d) the time postpartum (days, weeks, or months) when measurement is made, and (e) maternal disease.

While being cognizant of the limitations, a spot breast milk xenobiotic concentration or a concentration estimate based on the M/P ratio allows a simplistic estimation of the quantity of xenobiotic to which an infant is e assuming a constant breast-milk concentration:

Infant dose = Breast-milk concentration Ã— amount consumed

The effect of this dose on the infant depends on the bioavailability of the xenobiotic in breast milk, the pharmacokinetic parameters that determine xenobiotic levels in the infant, and the infant's receptor sensitivity to the xenobiotic. These parameters are often different in neonates than in adul may lead to xenobiotic accumulation; generally, absorption is greater, bu metabolism and clearance are reduced.[7] These effects are exaggerated in premature infants.[191 , 199] The amount of most xenobiotics delivered to in breast milk is adequately metabolized and eliminated.[134]

Many of the considerations above are theoretical, and the number of spe contraindicated xenobiotics is quite small.[11] Published guidelines on the advisability of breast-feeding during periods of maternal therapy are ger

based on the expected effects of full doses in the infant or on case report adverse occurrences. Interestingly, when the reports of adverse effects w reviewed, 37% of cases were in infants younger than 2 weeks old, 63% w infants younger than 1 month old, and 78% were in infants younger than months old; 18% were in infants 2 to 6 months old; and only 4% were in older than 6 months.[12] It seems, therefore, that adverse effects are most to be observed in the first few weeks of life, when an infant's metabolic is only 20â€“40% that of an adult.[7]

Every few years the American Academy of Pediatrics (AAP) publishes recommendations regarding breast-feeding in the setting of xenobiotic e In the latest revision, the AAP continues to discourage the use of xenobio such as cocaine or heroin during the breast-feeding period because of dir effects on the baby, as well as detrimental effects on the physical and en health of the mother and on the caregiving environment.[11] Although etha not specifically contraindicated for the breast-feeding mother, decreased production and adverse effects in the infant are noted with maternal consumption of large amounts of ethanol.[134]

The AAP recommends the temporary cessation of breast-feeding when the mother is exposed to metronidazole, an in vitro mutagen, or to certain radiopharmaceuticals, specifically isotopes of copper, gallium, indium, iod sodium, and technetium. In these cases, breast milk can be collected and before medication use for later feeding to the baby. Breast-feeding is res when the milk is no longer radioactive, generally 1 to 3 days for most of isotopes mentioned except gallium, after which radioactivity may be prese 2 weeks. Metronidazole can be administered as a single 2-g dose, allowin breast-feeding to be discontinued for only 12 to 24 hours.[134]

Although there are few data demonstrating specific effects, the AAP sugg caution with regard to breast-feeding while using sedative-hypnotic, antidepressant, and antipsychotic medications. These medications modula neurotransmitters in the CNS, which can adversely effect the developing system.

For most xenobiotics, a risk-to-benefit analysis must be made. For examp lithium is transferred in breast milk and may lead to measurable, althoug

subtherapeutic, serum concentrations in the breast-fed infant. Although t effects of such exposure to lithium are unknown, many practitioners belie the benefit of treating a mother's bipolar illness outweighs the potential r the infant.[134 , 218]

Similarly, the breast-fed infant of a woman who smokes is exposed to nic and other tobacco constituents, both by inhalation and via breast milk. A this child may be at increased risk for respiratory illness as a result of ex to tobacco smoke, some of the risk may be reduced by breast feeding.[11]

Many xenobiotics, including pharmaceuticals, foods, and environmental a have been found in breast milk, and Table 30-5 lists some of their effects addition to the effects listed, there may be a small increased risk of carcinogenicity associated with exposure to some environmental xenobio through breast milk.[202]

In most cases, women do not need to stop breast-feeding while using pharmaceuticals, such as most common antibiotics. However, â€œcompatibilityâ€• with breast-feeding is generally based on a lack of reported adverse effects, which may reflect limited clinical experience wit particular xenobiotic in breast-feeding patients. Therefore, in the setting limited information, exposure to a xenobiotic through breast milk should regarded as a small potential risk, and the infant should receive appropri medical follow-up. Not all â€œcompatibleâ€• medications are safe in all situations. For instance, phenobarbital can produce CNS depression in an if the mother's serum concentration is in the high therapeutic or supratherapeutic range, which often occurs while dosage adjustments are made. Such a concentration may or may not produce CNS depression in t mother. Nalidixic acid, nitrofurantoin, sulfapyridine, and sulfisoxazole, al generally safe, can cause hemolysis in a breast-fed infant with glucose-6- phosphate dehydrogenase deficiency.

Decisions on breast-feeding should be made with the informed involvemer the woman, her physicians, and, when necessary, a consultant with speci expertise in this field. Guidelines are available from several sources.[21 , 3 170]

Toxicologic Problems in the Neonate

Approximately 8% of all medication doses administered in neonatal inten care units (NICU) may be up to 10 times greater or lesser than the dose ordered.[174] As many as 30% of newborns in NICUs may sustain adverse effects, some of which may be life-threatening or fatal.[13] Physiologic dif between adults and newborn infants affect xenobiotic absorption, distribu and metabolism;[7 , 191] these pharmacokinetic differences account for sor cases of xenobiotic toxicity seen in the newborn infant.

GI absorption of xenobiotics in the neonate is generally slower than in ac [191] This delay may be related to decreased gastric acid secretion, decrea gastric emptying and transit time, and decreased pancreatic enzyme acti The GI environment of the newborn and young infant may allow the grow *Clostridium botulinum* and the subsequent development of infantile botul (Chap. 46). Infantile botulism has been reported in infants several weeks age.[101 , 244]

Although it is uncommon, cutaneous absorption of xenobiotics may be a r toxic exposure in the newborn.[68 , 211] Aniline dyes used for marking diap absorbed, causing methemoglobin-emia,[211] and contaminated diapers we responsible for one epidemic of mercury poisoning.[16] The absorption of hexachlorophene antiseptic wash has led to neurotoxicity with marked vacuolization of myelin seen microscopically.[131 , 157 , 228] The dermal application of antiseptic ethanol has caused hemorrhagic necrosis of the s

some premature infants. Iodine antiseptics have led to hypothyroidism in newborns.[40] An increased potential for absorption and toxicity has followe application of corticosteroids[82 , 209] and boric acid[66] to the skin of childr cutaneous disorders.

Use with Caution
5-Aminosalicylic acid
Diarrhea

Acebutolol, atenolol, nadolol, sotalol, timolol
Hypotension, bradycardia, tachypnea, cyanosis
Amiodarone
Possible hypothyroidism
Aspirin
Metabolic acidosis; may affect platelet function; rash
Bromocriptine
Suppresses lactation
Chloramphenicol
Potential risk for aplastic anemia or gray-baby syndrome[134]
Chlorpromazine
Galactorrhea in mother; drowsiness and lethargy in infant; decline in developmental scores
Cimetidine
Possible antiandrogenic effects[134]
Clemastine
Drowsiness, irritability, refusal to feed, high-pitched cry, meningismus
Clofazimine
Possible increased skin pigmentation
Cyclophosphamide, cyclosporine, doxorubicin, methotrexate
Neutropenia, thrombocytopenia, possible immune suppression; unknown on growth or association with carcinogenesis
Ergotamine
Vomiting, diarrhea, seizures; may inhibit prolactin secretion and lactatior
Fluoxetine
Colic, irritability, feeding and sleeping disorders, slow weight gain
Haloperidol
Decline in developmental scores
Lamotrigine
Potential therapeutic serum concentrations in infant
Lithium
Subtherapeutic concentrations in infant
Metronidazole, tinidazole
In vitro mutagen

Phenindione
Risk of hemorrhage
Phenobarbital
Sedation in exposed infants; withdrawal after weaning from phenobarbita containing milk; methemoglobinemia
Primidone
Sedation, feeding problems
Sulfapyridine, sulfisoxazole
Caution in infant with jaundice or G6PD deficiency and in ill, stressed, or premature infant
Sulfasalazine
Bloody diarrhea
Tetracycline
May cause staining of infant teeth after prolonged maternal use[134]
Thiouracil, methimazole
May cause thyroid suppression and goiter[134]

Use Is Compatible with Breast-feeding Despite Known Effect
Ethanol
Large doses: decreased milk ejection reflex; infant: drowsiness, diaphore decreased growth and weight gain
Bendroflumethiazide
Suppresses lactation
Caffeine
Irritability, poor sleeping pattern (no effect with usual amount of caffeina beverages)
Carbimazole
Goiter
Chloral hydrate
Sleepiness
Chlorthalidone
Excreted slowly
Contraceptive pills with estrogen/progesterone
Rare breast enlargement; decrease in milk production and protein conten

confirmed in several studies)
Danthron
Increased bowel activity
Dexbrompheniramine maleate with *d* -isoephedrine
Crying, irritability, poor sleeping pattern
Estradiol
Withdrawal vaginal bleeding
Indomethacin
Seizure
Iodine topical
Odor of iodine on infant's skin
Iodine, iodides
Goiter
Methyprylon
Drowsiness
Nalidixic acid
Hemolysis in infant with G6PD deficiency
Nitrofurantoin
Hemolysis in infant with G6PD deficiency
Phenytoin
Methemoglobinemia
Theophylline
Irritability

Specific Risk Categories
Aspartame
Caution if mother has phenylketonuria
Chocolate (theobromine)
Irritability or increased bowel activity if mother consumes large amounts
Fava beans
Hemolysis in infant with G6PD deficiency
Hexachlorobenzene
Skin rash, diarrhea, vomiting, dark urine, neurotoxicity, death
Lead

Possible neurotoxicity
Methylmercury, mercury
Possible neurodevelopmental toxicity
Polyhalogenated biphenyls
Lack of endurance, hypotonia, sullen expressionless facies
Silicone
Esophageal dysmotility
Tetrachloroethylene
Obstructive jaundice, dark urine
Vegetarian diet
Vitamin B_{12} deficiency
Adapted with permission from American Academy of Pediatrics, Committee Drugs: The transfer of drugs and other chemicals into human milk. Pedia 2001;108:776â€“789.

Xenobiotic Effect

TABLE 30-5. Xenobiotics Associated with Effects on Some Nurs Infants

Other routes of exposure have led to clinical poisoning. Several children aspirated talcum powder and died.[33, 173] Inhalation of mercury from inc thermometers may be a potential risk.[9] One child died following the opht instillation of cyclopentolate hydrochloride.[18]

Because of differences in total body water and fat compared to the adult, distribution of absorbed xenobiotics may differ in neonates. Water repres 80% of body weight in a full-term baby, compared to 60% in an adult. Approximately 20% of a term baby's body weight is fat, compared to only a premature baby. The increased volume of water means that the volume distribution for some water-soluble xenobiotics, such as theophylline or phenobarbital, is increased.

Protein binding of xenobiotics is reduced in newborns compared to adults: serum concentration of proteins is lower, there are fewer receptor sites t become saturated at lower xenobiotic concentrations, and binding sites h

decreased binding affinity.[191] Protein binding has potential relevance with respect to bilirubin, an endogenous metabolite that at very high concent can cause kernicterus; bilirubin competes with exogenously administered xenobiotics for protein binding sites. In vitro, certain xenobiotics, such as sulfonamides and ceftriaxone, displace bilirubin from protein receptor sit which might increase the risk of kernicterus, although this has not been demonstrated. Conversely, bilirubin may itself displace other xenobiotics, as phenobarbital or phenytoin, leading to increased plasma xenobiotic concentrations.

Newborn infants have decreased hepatic metabolic capacity compared to which may lead to xenobiotic toxicity. For instance, the newborn has limi ability to oxidize xenobiotics, so theophylline is metabolized primarily to active metabolite caffeine instead of methylxanthine and 1,3-dimethyluric which are the primary inactive metabolites in the adult. In addition, imm of the CYP system leads to increased elimination half-lives of xenobiotics phenytoin, phenobarbital, and theophylline.

Two syndromes related to immature metabolic function are described. Th â€œgasping baby syndrome,â€• characterized by gasping respirations, metabolic acidosis, hypotension, central nervous system depression, con renal failure, and, occasionally, death, is attributed to high concentrations benzyl alcohol and benzoic acid in the plasma of affected infants.[8 , 35 , 8] Benzyl alcohol, a bacteriostatic agent, was added to intravenous flush so and accumulated in newborns after repetitive doses. The high concentrati benzoic acid could not be further metabolized to hippuric acid by the imm liver. Immature glucuronidation in the neonate is responsible for the â€œ baby syndromeâ€• following high doses of chloramphenicol (Chaps. 31 a).[98]

The umbilical vessels are a common site of vascular access in sick neona Because blood drains into the portal vein, it is possible that IV medicatio experience a â€œfirst-passâ€• effect, although whether this route of xe administration affects metabolism or clearance has not been well studied. renal functions, including glomerular filtration rate and tubular secretion, relatively immature at birth;[106] the glomerular filtration rate of the newb

approximately 30% of that of an adult. Xenobiotics such as aminoglycosi antibiotics and digoxin are excreted unchanged by the kidney and, theref depend on glomerular filtration for clearance. Dosing of these agents in t newborn must account for these differences.

Very little information is available to guide the clinician in the manageme xenobiotic poisoning in the newborn infant. Cutaneous absorption is prob already complete by the time toxicity is noted, although further exposure prevented. Gastrointestinal decontamination is not generally performed i neonates, and the neonate may be at increased risk of fluid, electrolyte, thermoregulatory problems following gastric lavage or the use of catharti agents. Multiple-dose activated charcoal was used in a 1.4-kg 2-week-old premature infant to treat theophylline poisoning. Hemodialysis, hemoper and exchange transfusion are used in neonates to treat xenobiotic toxicit (Chaps. 10 and 31).

Summary

The use of xenobiotics in the pregnant or breast-feeding woman is a com area of medical practice and presents the clinician with potentially difficu management decisions. This chapter highlights some of the important pr of xenobiotic effects in both the pregnant woman and the fetus. Appropri management of many of the potential problems will be facilitated by the coordinated efforts of obstetricians, perinatologists, neonatologists, pediatricians, and toxicologists.

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Chapter 31
Pediatric Principles

Jeffrey S. Fine

Because phone calls to poison centers regarding child exposures to poter xenobiotics are more frequent than those for any other age group, and b poisoning is a important cause of pediatric injury morbidity, pediatricians been active in helping to establish and promote the field of medical toxic as well as in supporting the need for and use of regional poison control c Although the basic approach to the medical management of toxicologic p outlined in Chap. 4 is generally applicable to both children and adults, th issues, such as abuse by poisoning, that are of particular concern regardi children and when special considerations may be appropriate. This chapte provides a pediatric perspective on the application of toxicologic principle

Epidemiology

To analyze the problem of pediatric poisoning, it is necessary to understa magnitude of the problem. When assessing the impact of a particular type injury such as poisoning, epidemiologists examine multiple parameters, su exposure, morbidity, mortality, and cost, to measure the injury's effects. parameters are difficult to measure accurately. An important source for

information on the extent and effects of poisoning exposures is the Amer Association of Poison Control Centers (AAPCC). Each year the AAPCC com standardized data collected from poison centers throughout the United S the 2003 annual review includes information submitted by 64 poison cent the following discussion, comments on AAPCC data refer to cumulative information from the last 5 published reports covering the years 1999 to (Chap. 130).

The AAPCC reports approximately 1.5 million potentially toxic exposures year for children and adolescents ages 0 to 19 years, and these pediatric exposures represent 67% of the reported exposures for all age groups. C younger than age 6 years account for 79% of all reported pediatric expos children between 6 and 12 years of age account for 10%, and adolescents 19 years of age account for 11% of reported pediatric exposures. Childre younger than age 6 years account for 53% of all reported pediatric and a poisoning exposures. Girls represent 47% of the reported poisoning expo among young children and 56% of the reported exposures among adoles

Almost 99% of the AAPCC-reported poisoning exposures in children youn than 6 years of age are unintentional. In contrast, only 51% of the repor adolescent poisoning exposures are unintentional; 45% of exposures are intentional, mostly the result of substance use or suicide attempts. This l frequency of suicidal intent has also been reported by others.[171] The rem 4% of adolescent exposures have miscellaneous causes, such as adverse reactions, or are unknown. These differences in the reason for exposure between young children and adolescents account for differences in the outcomes of these exposures (discussed below).

Approximately 11,000 exposures each year are classified as adverse drug reactions. These account for approximately 0.3% of exposures in children than 6 years of age and approximately 2% of exposures in older children adolescents.

Table 31-1 shows the leading causes of reported exposures in children ar adolescents. According to the AAPCC, approximately 56% of pediatric ex are to xenobiotics that are commonly found around the house, such as c products, cosmetics, plants, hydrocarbons, and insecticides, whereas

approximately 44% are to pharmaceutical agents. This is in contrast to hospitalizations and death rates the majority of which are accounted for l pharmaceutical xenobiotics.

Table 31-1 lists the most common reported *exposures* , but not all these products lead to serious morbidity and mortality (Table 31-2). For exam children frequently ingest cosmetic products, so the number of reported exposures is large, but cosmetics manufactured in the United States are nontoxic. For children younger than age 6 months, poisoning is unusual b result from the inadvertent administration of an incorrect drug or drug do a parent,[56] intentional administration of a drug by a parent or sibling,[15] , passive exposure, for instance, to the smoke of â€œcrackâ€• cocaine or phencyclidine.[13] , [70] , [115] , [148] , [178] Any poisoning in a child younger than year of age should be carefully evaluated for possible child abuse or negl (see below).[15]

Several characteristics associated with ingestions in toddlers differentiate from ingestions in adolescents or adults: (a) they are without suicidal int (b) there is usually only 1 xenobiotic involved; (c) the xenobiotics are us nontoxic; (d) the amount is usually small; and (e) toddlers usually preser evaluation within 1 hour after the ingestion or soon after the ingestion is discovered. As many as 30% of children who experience one ingestion wi experience a repeat ingestion.[77] Children who ingest poisons may also be risk for other types of injuries.[11] , [47] Adolescents may also be at risk for repeated ingestions.[57]

The peak age for childhood poisoning is between 1 and 3 years.[29] Uninter ingestion is unusual after age 5 years, although it can result from mistak consumption of a xenobiotic from a

mislabeled container.[24] Between the ages of 5 and 9 years, poisoning ma reflection of intrafamilial stress or suicidal intent. After age 9 years and adolescence, overdose or poisoning frequently results either from a suici gesture or attempt, or from an adverse effect while seeking drug-induced euphoria. Unintentional poisonings are largely preventable (Chap. 130).

Cosmetics/personal care
157,834
Analgesics
51,943
Cleaning substances
119,752
Cough/cold preparations
21,069
Analgesics
88,086
Antidepressants
18,007
Topical agents
78,419
Cleaning substances
17,795
Plants
69,655
Cosmetics/personal care
17,703
Cough/cold preparations
63,107
Stimulant/street drugs
15,151
Insecticides/pesticides/rodenticides
47,618
Sedative-hypnotic drugs
13,297
Vitamins
41,918
Antihistamines
12,637
Gastrointestinal preparations
35,357

Art/craft supplies
12,399
Antimicrobials
33,847
Plants
11,833
[a] See Chap. 130 for references and discussion.
[b] Does not include AAPCC categories â€œBites/envenomationsâ€• and â€œForeign bodies.â€•

Age <6 Years		Age 6â€“19 Years	
Category	Number of Exposures	Category	Number of Exposure

TABLE 31-1. Average Annual Xenobiotic Exposures Reported to AAPCC (1999â€“2003)[a, b]

Because many children are exposed to nontoxic xenobiotics or to nontoxi amounts of toxic xenobiotics, it is not surprising that the relative number children and adolescents who suffer significant morbidity is small (Table However, because there are millions of exposures each year, the number children and adolescents reported by the AAPCC who suffer at least mode effects is approximately 33,000 per year. Fifty-six percent of these serio poisoned children are adolescents.

Alcohols
53
2
9
7
3
2
10
3
Analgesic agents

119
5
8
7
29
24
78
26
Anticonvulsants
106
5
4
3
4
3
4
1
Antidepressants/antipsychotics
182
8
9
7
4
3
36
12
Bites/envenomations
100
4
0
0
5
4
1

0
Carbon monoxide
42
2
18
15
17
14
10
3
Cardiovascular agents
182
8
7
6
5
4
7
2
Cleaning agents/chemicals
297
13
10
8
3
2
8
3
Cough/cold/antihistamine
92
4
8
7
12

10
12
4
Hydrocarbons
168
7
5
4
13
11
30
10
Insecticides/pesticides/rodenticides
123
5
7
6
6
5
2
1
Iron
52
2
7
6
1
1
0
0
Sedative-hypnotic agents
151
7
0

0
2
2
7
2
Stimulant/street drugs
84
4
1
1
4
3
78
26
Theophylline
38
2
3
2
1
1
1
0
Other
481
21
26
21
13
11
21
7
Totals
2270

122

109

283

[a] Data from Litovitz T, Manoguerra A: Comparison of pediatric poisoning hazards: An analysis of 3.8 million exposure incidents. Pediatrics 1992;89:999â€“1106.
[b] Data from AAPCC 1999â€“2003.
[c] Major effect = life-threatening signs and symptoms.
[d] The AAPCC does not report specific outcomes, other than death, by age individual agents; consequently, the number of major effects cannot be calculated.

	<6 Years Old				13â€“ Years	
Category	Reported MajorEffects[a],[c] Number	%	Reported Deaths[a] Number	%	Reported Deaths 1999â€“2003[b],[d] Number	%	Report Death 1999â€“ [d] Number

TABLE 31-2. Xenobiotics Responsible for Significant Pediatri Poisoning Morbidity and Mortality

Although the AAPCC is not the only source for epidemiologic data, there i detailed information available anywhere on poisoning morbidity. Estimates the rate of emergency department visits for poisoning and overdose are approximately 300â€“840 per 100,000 for children younger than 5 years and 290â€“360 per 100,000 for adolescents.[29, 48, 55, 108, 168] It has b estimated that between 100,000 and 170,000 children are seen in emerg

departments each year for poison-related injuries, and that between 10 a 20% are hospitalized.[28 , 108] Reported rates of hospitalization for young children range from 40â€“170 per 100,000.[30 , 48 , 57 , 131 , 171]

Following exposure to xenobiotics, adolescents are more frequently hosp than children.[57] However, it is unclear whether this reflects medical hospitalization for management of the poisoning or psychiatric hospitaliz The peak age for hospitalizing

young children exposed to xenobiotics is between 1 and 3 years, reflectin peak age of exposure. Hospitalized children younger than age 2 years are commonly exposed to nonpharmaceutical xenobiotics, whereas children o than age 2 years and adolescents are more commonly exposed to pharmaceuticals.[48 , 57 , 171]

0â€“5
98.90
1
0.1
0.002
6â€“12
96.75
3
0.2
0.005
13â€“19
88.96
10
1
0.04
All children and adolescents 0â€“19
97.79
2
0.2
0.007

[a] See Chap. 130 for references and discussion.

[b] Minor = minimal signs and symptoms, often not requiring therapy; moc = more pronounced, prolonged, or systemic signs and symptoms, often requiring therapy; major = life-threatening signs and symptoms.

	Effects (% of Reported Exposures)[b]			
Age (years)	Minor or None	Moderate	Major	Death

TABLE 31-3. Outcome of Reported Pediatric Xenobiotic Exposu (1999â€“2003)[a]

Although the AAPCC reports outcome related to age, it does not generally stratify outcome with regard to age and xenobiotic. In one earlier multiye review, the AAPCC reported those xenobiotics causing the greatest numbe major and fatal effects in children younger than 6 years old.[100] Table 31- the xenobiotics that cause significant morbidity and mortality. Other repo hospitalized patients, primarily from the United States or Western Europe describe a similar distribution of agents causing significant morbidity.[30 , 183] However, there are some differences in other international reports. In Australia, for instance, quinine, digoxin, and eucalyptus oil were significa causes of hospitalization, whereas in India, kerosene was the leading cau poisoning-related hospitalizations.[27 , 66 , 114]

Poison-related deaths represent approximately 2.5% of annual childhood adolescent deaths from unintentional injury.[118] The AAPCC reported 508 in children younger than 6 years of age from 1983â€“2003, an average o 24 per year. These deaths represent 3.6% of the reported poisoning fata for all age groups for those years and a 94% decrease from a high of 456 1959.[29] This dramatic decrease in poisoning mortality may be the result improved poisoning prevention (eg, child-resistant closures) and improve medical care, or may reflect a decrease in reporting (discussed later; see 130).

Thirty-four percent of the AAPCC-reported childhood fatalities result from unintentional ingestions, 18% are from environmental exposures such as

monoxide poisoning, and 25% are caused by medication errors and adver reactions; the remaining 23% have miscellaneous causes or are unknown. contrast, 42% of AAPCC-reported adolescent fatalities are the result of s and 35% follow substance use; only 3% are related to environmental exp and only 4% are caused by medication errors and adverse reactions.

Although the AAPCC data provide a remarkable amount of epidemiologic information, there are questions about the accuracy of the data.[68, 69, 1 comparison to the AAPCC, the National Center for Health Statistics report that for the years 1999â€“2001, the most recent dataset available, there 220 poison-related deaths for children younger than 5 years old, 225 for children ages 5â€“14 years, and 1706 for adolescents ages 15â€“19 year For the same years, the AAPCC reported 70 deaths for children younger t age 6 years, 18 for children ages 6â€“12 years, and 167 for adolescents 13â€“19 years. It is difficult to compare these two datasets directly beca they are organized very differently, but the differences in the raw numbe dramatic.

The most serious concern when considering the reported numbers of pois is that many significant poisonings are not reported to poison centers. Fo instance, physicians managing â€œcommonâ€• toxicologic problems may feel the need for the assistance of a local or regional poison center and m feel compelled to participate in the reporting process. Therapeutic misadventures may also go unreported. In Rhode Island, only 45 of 369 poisoning deaths were reported to the regional poison center (Chap. 130

The most notable difference between the toxins listed in Table 31-2 and from the 1960s and 1970s is that salicylates are no longer a leading caus reported poisoning morbidity and mortality.[35, 40] This change may be re to federal regulations requiring child-resistant closures as well as to the decreased availability of aspirin at home for use in children following the recognition of its association with Reye syndrome (Chap. 35).[17, 75, 116

There are some significant etiologic differences in Table 31-2 between ch and adolescents, particularly with regard to the lethality of agents. The l three categories of xenobiotics for children are analgesic agents, carbon monoxide, and hydrocarbons, which account for 53% of all reported pois

deaths. The top three categories for adolescents are analgesic agents, stimulants/street drugs, and antidepressants (mostly tricyclic antidepres accounting for 61% of reported poisoning deaths. Importantly, the hydrc deaths in young children generally result from unintentional aspiration, b almost all the hydrocarbon deaths in adolescents are related to abuse of hydrocarbons such as trichloroethane or chlorofluorocarbons.

Poisoning also has an economic cost. Charges for hospitalized patients ra from $2000â€“$10,000, depending on length of stay and outcome.[84, 164] In a large economic analysis of the cost of injury in the United States, th estimated average lifetime cost was $495 per child and $10,839 per ado or young adult injured or killed by poisoning.[131]

Behavioral, Environmental, and Physical Issues

A simplistic approach to childhood poisonings is that unobserved toddlers exploring their environment inadvertently ingest toxins. This approach ig the complex interplay of factors that may contribute to some pediatric ingestions.

One approach to understanding injury causation, in general, that can be to poisoning, uses an infectious disease-like model.[67] According to this n there are three interacting factors: host, agent, and environment. These interact during three phases: preinjury, injury, and postinjury. The factor themselves contribute to the likelihood, nature, and magnitude of, as well the host response to, an injury.

In the case of a toddler ingestion, the host is a child of a particular age, certain developmental abilities and a certain temperament. The agent is a particular toxin, at a particular dose, with a particular likelihood of causir injury. The environment is usually the home with the additional particular regarding storage practices or supervision. These environmental factors a discussed below.

During the preinjury phase, there is an interaction of the host, agent, and environment. Under the proper circumstances, an injury can occur. Modi of these factors can lead to prevention of an injury. For example, if a 2-y child finds 2 pills on a bedside table, there is a fair chance the child will the tablets. However, if these pills are stored out of reach of the child, th ingestion can be prevented.

The injury phase covers both the ingestion and the initial pathophysiologi response. Again, the particular factors determine the nature and extent o injury. Continuing the above example, if the 2 pills are 325-mg acetamin tablets, the ingestion will not lead to injury. However, if the pills are 0.2- clonidine tablets, there is a high likelihood of toxicity.

The postinjury phase is concerned both with the ongoing host response a medical management of the poisoning. In this phase, it would be determi whether the 2-year-old child with a clonidine ingestion manifests signs of toxicity, such as coma or hypotension; whether the child requires treatm with activated charcoal, fluid, or naloxone; and whether the child require hospital admission.

This paradigm is only a model; it is often difficult to examine any individu factor independently and the relative contribution of these factors is not defined. Nonetheless, consideration of the individual factors of host, agen environment allows us to focus on several relevant aspects of pediatric poisoning.

Childhood and adolescence are times of tremendous growth and development.[184] Some of these physical and social changes place children teenagers at increased risk for poisonings. By 7 months of age, an infant up can pivot in order to grab an object; by 9â€“10 months of age, most can creep and crawl; by 15 months of age, most toddlers are walking qui competently and eagerly exploring. Between 9 and 12 months of age, a c developing a skillful pincer grasp with the thumb and forefinger, that allo child to pick up small objects. Throughout this period, one of the child's sensory experiences is sucking on or gumming objects that are placed in mouth. Thus, the combination of three developmental skillsâ€”the ability move around the home and go beyond the immediate view of a guardian,

ability to pick up and manipulate small objects, and the tendency of child put things in their mouthsâ€”places them at risk for both foreign-body aspiration and poisoning.

As children develop socially, they desire to become more like their parent they tend to imitate behaviors, such as taking medicine or using mouthw Children are taught that medicine is good for them when they are sick. M children's medicines are sweetened and flavored to make them more pal and many parents inappropriately encourage their children to take medici telling them â€œit tastes like candy.â€• Children have been observed â€œmaking teaâ€• from plants or â€œmaking pizzaâ€• with mushrooms the yard.[24]

As children become more mobile, agile, and curious, xenobiotics that wer previously outside their reach now become accessible, even when stored some difficult-to-reach places. There is some evidence to suggest that pa underestimate the developmental skills of their children.[47] The meaning o term â€œunintentionalâ€• with respect to childhood poisoning should als reconsideredâ€”the toddler quite purposefully intends to get to a pill and but the child does *not* intend to injure himself.

Some of the reasons why a child wants to ingest a pill are because it is t looks like candy or food, the parent takes pills, and taking medicine is considered good for health. These reasons may not be sufficient to explai a child does something that the child knows should not be done. Another of childhood poisoning that must be considered is the interaction between child's temperament and the child's social environment.

Many authors have tried to identify psychosocial predictors for childhood poisoning in general, and for repeat poisoning in particular.[20 , 49 , 79 , 16 many as 30% of children may have repeat episodes of ingestions, frequer the same xenobiotic. Certain risk factors have been identified for single a repeated episodes of childhood poisoning, such as hyperactivity, impulsiv taking behavior, rebelliousness, or negativistic attitude. Other factors see be associated more with the parents, such as medical illness, depression, social isolation. Finally, a stressful environment or major social problem also be a contributing factor.[154 , 160] It is not difficult to imagine a situat

when a parent is depressed, uses antidepressant medication that is kept a bedside, and cannot give adequate attention to a demanding child. In a b attention, or as an expression of anger or frustration, the child ingests so the parent's medication.

With regard to the agent, there are a number of issues that affect the pr and injury phases. It was stated above that modification of any one of th interacting factors of host, agent, or environment can potentially prevent reduce the severity of injury. In this regard, if household products of low toxicity are available around the house, the likelihood of injury is reduced of these products is ingested. For example, less-toxic rodenticides such a warfarin have replaced many more toxic ones such as thallium or sodium monofluoroacetate. Relatively nontoxic paradichlorobenzene mothballs ha largely replaced relatively more toxic camphor-containing mothballs.

It may also be possible to reduce the likelihood of ingestion by making a xenobiotic unpalatable. Denatonium benzoate (Bitrex), an aversive bitter agent, is added to some liquid chemicals such as windshield washer fluid antifreeze, with the expectation that this will prevent unintentional poiso Some trials show that older children respond negatively to these agents b that younger children may ingest 1â€“2 teaspoonfuls of a xenobiotic befo responding to the bitter flavor.[18 , 154] This is an important consideration because even this small an amount of a xenobiotic such as methanol can toxic (see below). The actual usefulness of the bittering agent denatoniur benzoate in poison prevention is largely unstudied.[139]

The problem of unintentional ingestions is compounded by poison â€œloo alikesâ€•; that is, xenobiotics that resemble candy or food products.[50] (ILLOOKALIKE in the Image Library at http://www.goldfrankstoxicology.co Some common examples are ferrous sulfate tablets that look like M&M ca prenatal vitamins that resemble Good and Plenty candies, and fuel oils th come in cans that resemble soft drink containers. Many shampoos and dishwashing detergents are given lemon or strawberry scents and have p of fruits on the labels. Children are not always capable of distinguishing â€œlook-alikesâ€• from real candies, fruits, and sodas, and may be attr to bright colors, pleasant smells, and appealing packages. Eliminating the

â€œlook-alikesâ€• might prevent some unintentional ingestions.

Probably the most significant change to the physical aspect of the agent been packaging of pharmaceuticals and some other xenobiotics with child resistant closures mandated by the Poison Prevention Packaging Act of 19 (Chap. 130). This legislation is credited with a significant reduction in morbidity and mortality related to poisoning from aspirin and other regul products, although this analysis has been challenged.[137 , 173] Child-resist

closures have reduced the number of toxic exposures to kerosene in Sout Africa.[92]

Nonetheless, problems with child-resistant closures include pharmaceutic being dispensed in nonresistant containers, child-resistant containers not properly closed, and medicines being left out of the child-resistant contai use.[28 , 157] Seventy percent of potentially toxic pharmaceuticals may be nonâ€“child-resistant or in improperly functioning child-resistant contain Several studies have identified poor functioning of the closures when ther sticky liquid or pill residue around the top or in the screw threads of the resistant container.[77 , 84 , 182]

Although child-resistant containers are a significant deterrent to unintent ingestions in toddlers, they are not completely effective, and even withou problems noted, some children can open them. A sense of security assoc with these closures may lead some parents to be less compulsive regardi storage of the containers. It has been recommended that a double barrier instituted, such as a unit-dose dispenser within a child-resistant container blister pack, for a few pharmaceuticals associated with a large number of significant poisonings (eg, iron and antidepressant agents).[84]

In fact, in 1997 the Food and Drug Administration (FDA) issued a regulati package products with 30 mg or more of elemental iron per tablet in unit packages such as blister packs.[1] The intent of this regulation was to redu likelihood of childhood iron poisoning. Over the past decade the number o childhood iron ingestions has declined significantly, although whether any decrease is specifically related to the packaging changes is unknown. This was overturned in 2003, when it was determined that the FDA did not hav

statutory authority to regulate a drug for the purpose of poison preventic will be unfortunate if there is an increase in the number of iron poisonings result of these statutory changes.

A discussion of containers and storage naturally leads to a consideration third factor in the injury-causation model discussed above, the environm which is particularly important in the preinjury and the injury phases. Approximately 80% of childhood pharmaceutical ingestions occur at home remainder occur at the homes of grandparents, other relatives, and friend medicine usually belongs either to the child or to the mother, although a significant number of medications, both at home and away from home, b to a grandparent.[77 , 99] Grandparents, other relatives, and family friends without children at home may not receive or keep medications in child-re containers and may not be attentive to safe-storage practices.

Medications are frequently kept in the kitchen or bedroom while they are used.[77 , 182] In the kitchen, medications are stored in the refrigerator, or table, or on the counter, and in the bedroom, medications are left on a c or bedside table. A mother's purse is another location where medications commonly found. Interestingly, there are no significant differences in the storage practices in the homes of children who ingest and those who do n ingest medicines, so storage practices alone cannot be used to predict th likelihood of childhood poisoning.[159 , 182]

One important caveat relates to the storage of nonpharmaceutical xenob particularly those in liquid form, such as pesticides, hydrocarbons, and s hydroxide. These types of xenobiotics should never be transferred for sto to familiar household containers, such as food jars or wine or soda bottle children and adults have been exposed to xenobiotics, such as sodium hydroxide and potassium cyanide, stored in bottles in the refrigerator.[169]

History of the Ingestion

The appropriate management of any poisoned patient is influenced by the history of the exposure. Parents or guardians who are not abusing childre generally provide information to the fullest extent possible. As a rule, in

case of children, the xenobiotic and time of ingestion are known. The nun pills, or the volume of liquid ingested, may not be as accurate. Clues to t amount ingested are the number of pills or volume of liquid in a bottle be and after an ingestion, the number of pills set out on the night table, or t area of a spot of liquid after a spill. When symptoms are suggestive of poisoning, but the history is inadequate, information about possible expo outside of the home, such as with a babysitter, grandparent, friend, or o relative, should be obtained because approximately 15% of childhood poisonings occur outside the home.[77 , 125]

In contrast, suicidal adolescents may be unreliable when relating the hist an ingestion. When caring for these patients, the clinician must use the h provided but should remain skeptical about the reported type and number xenobiotics ingested, as well as the time of ingestion.

In cases in which a child may be the victim of abuse, or intentionally pois by a caretaker, the healthcare provider must ensure that (a) the history o poisoning remains consistent over time and among those people providing details of the event, (b) the child's clinical presentation is consistent with history of the poisoning, and (c) the reported actions are consistent with child's developmental level.

Gastrointestinal Decontamination

Chapter 8 is devoted to a complete discussion of gastrointestinal decontamination. This section reiterates and emphasizes only a few impo points.

As described above, children generally ingest small quantities of single a For most of these ingestions, gastric emptying is unnecessary. Some exa of nontoxic ingestions are eating a crayon or the leaf of a jade plant, lick cap of a household bleach container, or swallowing 2 adult-strength acetaminophen tablets.

Orogastric lavage is the preferred method of gastric emptying when indic for most serious ingestions. Small children can generally tolerate orogast lavage with a large-bore 28-French or 34-French tube; however, the sma

â€œlarge-boreâ€• tubes may not be effective for removing large pills or fragments from the stomach of a small child. Placement of an orogastric t an unpleasant and frightening procedure for an infant or small child. Ther often some local trauma related to tube placement and, rarely, there can more serious injury, such as esophageal perforation. Also, many children during placement of an orogastric tube. The use of orogastric lavage shou limited to cases in which the risk of serious poisoning is high, in which th likelihood of benefit is at least moderate, and in which the likely risk of i to the child is small. This procedure should never be used as a form of punishment. To use orogastric lavage safely in a child with a diminished g reflex or depressed level of consciousness, the trachea should be intubate protect the airway.

At one time, administration of syrup of ipecac to poisoned patients was considered a primary emergency intervention. However, the AAPCC repor the use of syrup of ipecac for case management

declined from 13% in 1983 to 0.4% in 2003. This is not surprising, becau syrup of ipecac is contraindicated in cases where there is, or is likely to b hemodynamic instability, seizures, or a depressed level of consciousness, likely effects of almost any serious poisoning. In addition, although syrup ipecac is highly effective at making children vomit, the efficacy of prever morbidity after an ingestion is questionable.

Even though syrup of ipecac was used infrequently in the emergency department management of poisonings, it was, until recently, being advo for use at home at the direction of a poison center in order to prevent an unnecessary evaluation in an emergency department. However, in 2003, American Academy of Pediatrics came out against the availability and use ipecac at home, and in 2004, the American Academy of Clinical Toxicology the European Association of Poison Control Centres and Clinical Toxicolog came out against the general use of syrup of ipecac for the management poisoning.[4 , 6] The reasons for the new recommendations include (a) the unpleasantness of the therapy, (b) its rare side effects, (c) its unproven usefulness, (d) its administration when not indicated or when no therapy indicated because of lack of consultation with a poison center, (e) its abu

potential, and (f) its interference with and complication of subsequent emergency department evaluation.

Notwithstanding the position statements, some toxicologists believe there rationale for home use under specific limited circumstances.[136] Thus, ther still be a very limited role for the use of syrup of ipecac in the manageme particular cases (see Chap. 8 and Antidotes in Depth: Syrup of Ipecac).

Activated charcoal is a current mainstay of poison treatment.[3, 33] Childr generally will not drink activated charcoal willingly. Some children can be coaxed to do so if the activated charcoal is disguised in a baby bottle or drink container or sweetened with juice or sorbitol.[179] A nasogastric or orogastric tube may have to be inserted to administer activated charcoal. can be a small-bore tube because it is not intended for lavage, although smaller the bore, the more difficult it is to administer the thick slurry of activated charcoal. Placement of the tube, the presence of activated char the stomach, the effects of the xenobiotic, or the previous use of an eme may make the child vomit, making aspiration of activated charcoal or sto contents a risk. For activated charcoal to be used safely in a patient who comatose and who does not have a gag reflex, the trachea should be intu and the airway protected. Even activated charcoal alone is unnecessary fo nontoxic ingestion.

Activated charcoal is available for home use.[93, 163] Administration of ac charcoal at home or by prehospital personnel allows for administration significantly earlier than can be achieved after arrival and evaluation in t emergency department.[36, 163] Although it would seem to have potential as home therapy, activated charcoal is unpalatable, quite messy, and not always available, with the result that it has not achieved widespread use home.[120, 136] It is also unclear how well parents can administer activate charcoal at home.[146, 147, 162] Whether the earlier administration of act charcoal would affect outcome is unknown. If activated charcoal is to rep syrup of ipecac for home therapy, it will require a substantial reeducation on the part of pediatricians, toxicologists, and pharmacists.

Methods of Enhanced Elimination

For consequential poisoning with xenobiotics such as methanol, ethylene salicylates, lithium, and theophylline, either hemodialysis or charcoal hemoperfusion is the optimal technique to enhance elimination, depending the particular toxin. These techniques can be performed on newborns or infants in specially equipped centers with dedicated personnel. The prima limiting factor is the ability to obtain vascular access.[16 , 44 , 46 , 170] How even large centers that routinely do pediatric hemodialysis may not be ab manage the very small infant. There is a report of the use of peritoneal for the treatment of alcohol intoxication in a child,[65] but this technique is generally recommended.

Exchange transfusion is a technique that is occasionally used to enhance elimination. This technique might be useful when multiple-dose activated charcoal cannot be administered, the xenobiotic is poorly adsorbed to ch or access to specialized pediatric hemodialysis or hemoperfusion is not re available. Exchange transfusion has been used successfully for poisoning salicylates[45 , 107] and theophylline.[12 , 122 , 152] Another drug for which exchange transfusion may be a therapeutic alternative is chloral hydrate.

Xenobiotics that May be Toxic or Fatal in S Quantities

When children ingest small quantities of toxic xenobiotics, they potentiall ingest large doses relative to their small size. There are a number of xenobiotics that can cause significant toxicity or even death with as little pill or 1 teaspoonful.[10 , 97] Table 31-4 lists these xenobiotics.

Xenobiotics that May have Delayed Toxicity Children

There are several xenobiotics that warrant particular concern because th effects may be significantly delayed. Classic examples are atropine-diphenoxylate (Lomotil)[21 , 38 , 109] and antidiabetics such as glipizide.[63 , 166] Both of these xenobiotics can cause serious morbidity with initial sym

or recurrence of symptoms, delayed by as much as 24 hours after ingest

Children who have or may have ingested Lomotil or oral antidiabetic ager should be admitted for observation and monitoring, even if they are asymptomatic, because effects may not become apparent for 24 hours (C 38 and 48).

Antidiabetics (sulfonylurea agents)
Antihistamines
Benzocaine
Î²-Adrenergic antagonists (sustained release)
Calcium channel blockers (sustained release)
Camphor
Clonidine
Diphenoxylate/atropine (Lomotil)
Methanol/ethylene glycol
Methylsalicylate
Opioids (methadone, codeine, OxyContin)
Phenothiazines
Quinine/chloroquine
Theophylline

TABLE 31-4. Xenobiotics that Can Cause Severe Toxicity to an Ir After a Small Dose

With the advent of new modified-release formulations of calcium channel blockers and Î²-adrenergic receptor antagonists, concern for delayed tox has been extended to other drugs.

Xenobiotics that have Unusual or Idiosync Reactions in Children

Benzyl Alcohol: Gasping Syndrome

Benzyl alcohol is a preservative added to liquid pharmaceutical preparati for small-volume medications administered to adults, the benzyl alcohol is quite safe (Chap. 53). At toxic doses, benzyl alcohol can cause respira failure, vasodilation, hypotension, convulsions, and paralysis. Intravenous solutions containing benzyl alcohol were implicated as the cause of the â€œgasping syndromeâ€• in sick newbornsâ€”severe metabolic acidosis, encephalopathy, respiratory depression, and gasping.[5] The association wa made when infants with this syndrome were found to have elevated levels benzoic acid and hippuric acid, metabolites of benzyl alcohol.[26 , 58] Benzy alcohol is metabolized by the conjugation of benzoic acid with glycine to hippuric acid. This pathway may not be functional in premature infants. E alcohol administration has also been associated with kernicterus and intraventricular hemorrhage in premature infants.[72 , 78] Although benzyl has been removed from many of the medications used for neonates, there still preparations that may contain this agent.[177]

Imidazolines/Clonidine: CNS Effects

Imidazolines such as tetrahydrozoline, oxymetazoline, xylometazoline, ar naphazoline are nonprescription sympathomimetic agents used as nasal decongestants and conjunctival vasoconstrictors (Chap. 50). Clonidine is imidazoline derivative used as an antihypertensive agent (Chap. 60). In children, these agents can cause central nervous system depression, res depression, bradycardia, miosis, and hypotension.[9 , 106 , 180] The presum mechanism of action is through stimulation of central $\hat{I}\pm_2$ -adrenergic and imidazole receptors. Although naloxone has been reported to reverse som the CNS effects of clonidine, there are no reports of its successful use wit other imidazoline agents (Chap. 60).

Ethanol: Hypoglycemia

Ethanol is the primary component of alcoholic beverages, as well as a ma constituent of many liquid preparations, such as mouthwash, vanilla flav and perfume. Besides its well-known sedative-hypnotic effects, ethanol intoxication in children is associated with hypoglycemia.[37 , 96 , 104 , 174]

Ethanol-induced hypoglycemia can cause seizures and may exacerbate th CNS effects induced by ethanol intoxication. Hypoglycemia results from t inhibition of gluconeogenesis in the setting of alcohol intoxication. There not seem to be a blood alcohol concentration threshold for the developme hypoglycemia, which has been reported with blood alcohol concentrations as 20 mg/dL (Chaps. 48 and 75).[37]

Chloramphenicol: Gray Baby Syndrome

Chloramphenicol is a broad-spectrum antibiotic that has been used in pe because of its activity against *Haemophilus influenzae.* It has largely bee replaced by other antibiotics in the United States because of its associati aplastic anemia. When administered at high doses, chloramphenicol can the â€œgray baby syndromeâ€• â€”abdominal distension, vomiting, meta acidosis, progressive pallid cyanosis, irregular respirations, hypothermia, hypotension, and vasomotor collapse. Although these effects occur primar premature newborn infants, they can also occur in older children and adu (Chap. 54).

Gray baby syndrome is associated with serum concentrations greater thar mg/L. Increased chloramphenicol levels may result from (a) inadequate conjugation of chloramphenicol with glucuronic acid because of inadequat activity of glucuronyl transferase in the newborn liver and (b) decreased elimination of unconjugated chloramphenicol. The exact mechanism of to is unknown; there is speculation that free radicals produced during the metabolism of chloramphenicol may interfere with mitochondrial function

Medication Errors

Ever since the publication of the Institute of Medicine's report in 1999, increasing attention has been paid to the issue of medical errors in medi Although most of the research regarding medication errors has focused o adults (Chap. 134), this problem also affects children. Subsequent remar this section are generally limited to the pediatric literature.

In the 2003 AAPCC report, there were approximately 115,000 poison cen

calls related to therapeutic errors in children and adolescents, or approx 7% of all calls; 1139, or approximately 2% of these errors, are described â€œiatrogenic.â€• During the last 5 years of AAPCC reports, there were of 34 deaths attributed to therapeutic errors, representing 7% of all deatl children and adolescents. Although only 5% of the reported calls about y children were related to therapeutic errors, approximately 19% of the re deaths were related to therapeutic errors. This is in contrast to adolescer whom 9% of the calls but only 2% of the reported deaths were related to therapeutic errors.

Medication errors can occur at any phase of a process that includes orde order transcription, pharmacy dispensing, preparation and administration medication, and monitoring of medication effects. In fact, the same type errors can usually occur at different points in the process. Table 31-5 list types of errors that can occur, and Table 31-6 provides some examples o errors.

Most of the analyses of medication errors have occurred in inpatient sett The reported frequencies of medication errors vary widelyâ€”from 0.47 to of written orders and from 0.51 to 157/1000 patient-days.[51, 73, 80, 82] The variance largely depends on whether the definition of â€œerrorâ€• d does not include prescribing errors, regardless of whether or not they are corrected, and whether potential, or only actual, adverse drug events are included. The reported frequencies also vary depending on whether there active case finding or whether there is only voluntary reporting.

In a 2001 study of pediatric inpatients where orders were actively monitc a 6-week period, 5.7% of 10,778 prescriptions had errors in the order for medication, transcription of the order, dispensing or administration of the medication, or monitoring of medication effects (56/100 admissions, 157 patient-days);[82] 1.1% had the *potential* to cause an adverse effect (10/1 admissions, 29/1000 patient-days). Eighty-four percent of the errors occ during the ordering or transcription phase, so most

of the errors were intercepted and corrected before drug administration. were 26 true adverse drug events; only 5 were considered preventable e

(0.05%, 0.52/100 admissions, 1.8/1000 patient-days). Although the ove error rate was similar to that reported by the same group in a study of a the rate of errors with the *potential* to cause harm was three times great 41% of the errors with the potential to cause harm were not intercepted.

1.
Wrong patientâ€”someone else's drug
2.
Wrong drug

a.
Wrong individual drug

b.
Wrong formulation

c.
Known allergy

d.
Known drugâ€“drug interactions

e.
Wrong indication

f.
Contraindication

g.
Expired

h.
Deteriorated
3.
Wrong dose

a.
Miscalculation

i.
Decimal point error

ii.
Wrong formula

iii.
Right formula using wrong dose, frequency, units, weight

iv.
Pound/kilogram confusion

v.
Mg/Âµg units confusion

vi.
Dilution error

b.
Appropriate individual dose divided into multiple doses

c.
Total daily dose for an individual dose

d.
Wrong IV infusion rate

e.
Measuring error
4.
Wrong route
5.
Wrong frequency

a.
Increased/decreased dosing interval

b.
Omitted/delayed/added dose

c.
Delay/failure to supply
6.
Transcription errors
7.
Documentation (order, prescription, transcription, logs)

a.
Illegible

b.
Incomplete/missing information (weight, signature, maximum daily dose, date)
8.
Monitoring
9.
Miscellaneous

a.
Wrong label

b.
Wrong information/advice

c.
Failure to detect error

d.
Breast milk exposure
Based on Kaushal R, Bates DW, Landrigan C, et al: Medication errors and adverse drug events in pediatric inpatients. JAMA 2001;285:2114â€“212(Lesar TS: Errors in the use of medication dosage equations. Arch Pediatr Adolesc Med 1998;152:340â€“344; and Wilson DG, McArtney RG, Newcor RG, et al: Medication errors in paediatric practice: Insights from a contin quality improvement approach. Eur J Pediatr 1998;157:769â€“774.

TABLE 31-5. Medication Errors

Generally, error rates are higher in intensive care units where the sickest patients are cared for; these patients often receive multiple medications complex administration regimens.[51, 73, 82, 129, 144, 172, 181] Results to those from inpatient settings have been reported from pediatric emerg departments.[90, 150]

The studies cited above suggest that the *frequency* of significant errors t lead to significant adverse drug events is low; however, even a low frequ applied to a large population of patients can result in a large number of patients. The most important outcome of the analysis would be to try to the number of errors in order to reduce the number of adverse drug ever

1. Wrong drug. In one nursery, an epidemic mimicking neonatal sepsis caused when racemic epinephrine was inadvertently administered inst

vitamin E because both drugs were manufactured by the same compa distributed in nearly identical bottles, and stored near each other insi nursery refrigerator.[161]

2. Wrong drug formulation. Acetaminophen suppositories (120 mg) w ordered for a toddler, but adult-strength suppositories (650 mg) were distributed and administered every 4 hours. The child developed hepatotoxicity requiring hospitalization and therapy (Chap. 34).
3. Wrong dose. A 1-kg premature infant required sedation for a diagnc study. A high dose of chloral hydrate, 100 mg/kg, was miscalculated t g (1000 mg) instead of 100 mg. The child had a cardiopulmonary arre died. When drugs require milligram-per-kilogram dosing, it is easy to decimal mistakes in the calculation or in the transcription.
4. Wrong dose/wrong route. A recommendation was made to treat a with penicillin G benzathine, 50,000 U/kg IM. The recommendation w transcribed as â€œpenicillin G 50,000 units/kg.â€• The order was handwritten as â€œBenzathine Pen G 150,000 U IMâ€• but was misr misinterpreted as 1,500,000 U IV. The patient had a cardiopulmonary and died.[158]
5. Wrong dose. A patient had the dose of cyclosporine changed from 1(to 7 mg twice daily. The child received 70 mg (0.7 mL of solution) in of 7 mg (0.07 mL). When the prescription was refilled, the parents re a 5-mL syringe to use instead of a 1-mL syringe they had used previ

TABLE 31-6. Examples of Medication Errors

The causes of medication errors are numerous, varied, and complex; they organizational, environmental, and personal, and include such factors as of training, knowledge level, competence, time of day, workload, staff interactions, communications, number of distractions or interruptions, lev ambient noise, perceived levels of authority, drug formulation, drug pack etc. (Chap. 134).[39 , 53 , 60 , 86 , 175]

There are several reasons why children may be at increased risk of being exposed to a medication error: (a) Someone other than the child adminis

the medication, so at least with respect to oral formulations, there is littl opportunity to prevent or limit drug administration; (b) a young child car warn practitioners about possible problems such as allergies; (3) a young cannot inform practitioners when he or she is experiencing side effects; (pediatric medication ordering and administration frequently requires dose calculations; (5) inexperienced practitioners may be uncomfortable with pediatric dosing or related calculations; (6) incorrect measurement of liq preparations or dilution of concentrated stock solutions may still result in small volume that is not perceived as obviously incorrect.[31, 42, 60]

The most common error attributed to physicians is prescription of an inc dose, particularly in children, where almost every prescription requires a determination of weight and calculation of the dose.[82, 91, 95] In addition the mg/kg dose may vary depending on the age of the patient or the clin indication. Although pediatric doses are generally determined on a mg/kg if the weight is recorded in pounds and this weight is used in the calculat there will be a built-in 2-fold error. Calculation errors also occur when dr preparation requires dilution of a concentrated stock solution or special compounding. Further confusion can arise when *mg* is written or interpret *mL* or *mcg* in a calculation.

When an extra zero is added or a required zero is omitted from calculatic written or verbal prescriptions, or in dispensed and administered medicat 10-fold error occurs. These large errors are common and result in signific under- or overdosing; 10-fold

errors have been reported in testing scenarios, case series, and case rep [42, 62, 87, 88, 91, 117, 129, 133, 141, 144, 156, 158] These errors are particular concern because the risk of toxicity generally increases with significant overdose.

Because the causes of medication error are numerous and complex, the to the problem must be multifaceted and interdisciplinary. The approach t problem is contained within the field of human factors research and pote requires changes in individual factors such as knowledge, environmental such as interruptions, and system problems such as how medications are

ordered, stocked, and dispensed (Chap. 134).[86 , 165 , 175]

The most commonly recommended solutions to reduce the frequency of medication errors are computerized physician order entry (CPOE) with cl decision support systems, ward-based clinical pharmacists, and improved communication among physicians, nurses, and pharmacists.[81 , 94 , 135 , its simplest form, CPOE eliminates errors related to legibility. Decision su adds the ability to check the prescription against age, weight, dose, aller drugâ€“drug interactions, etc. It cannot prevent ordering the wrong drug, there is still a need for education and human oversight. In the study cite above, it was estimated that these 3 solutions would have prevented mor 90% of the potential errors,[52] and two clinical trials suggest that CPOE decreases medication prescribing errors.[85 , 126]

It will still be some years before all inpatient medication orders and outp prescriptions are transmitted electronically. Until that time, it will be nec to ensure that prescriptions are written legibly and correctly. The Joint Commission for the Accreditation of Hospital Organizations (JCAHO) and other groups have made a number of recommendations to reduce errors i medication ordering (Table 134-2).

Standardized tests of the math skills necessary to calculate doses and administer medications have demonstrated deficiencies in both nursing ar physician groups.[14 , 19 , 119 , 123 , 127 , 140 , 145] These kinds of tests may way to identify practitioners at risk for making calculation errors, highligl areas in need of remediation, and serve as an ongoing educational tool.

As described above, there may be an increased risk of medication errors critical care areas because of severity of illness and intensity of medicati therapy. In many cases, such as during resuscitations, critically ill patien require immediate therapy, verbal orders are common, and there is often insufficient time to carefully review all of the particulars related to medic ordering and administration.[91 , 124]

Critical care areas, including the emergency department, might benefit fr having precalculated dosing charts available for resuscitation medications for other commonly prescribed medications; this is a recommendation of

American Heart Association.[7] Many units have developed their own dosing schemes. Commercial products such as the Broselow-Luten system are al available and have been shown to reduce the number of medication errors least in simulated resuscitation scenarios.[101 , 102 and 103 , 151]

The previous discussion has been almost exclusively related to hospital-b medication use, although significant errors also can happen in the outpat setting.

Antipyretic medications are among the most frequently recommended medications for children. Although significant toxicity following unintentio toddler ingestions is rare, administration of multiple supratherapeutic dos acetaminophen is not uncommon and can cause significant hepatotoxicity

In fact, many parents have significant difficulty both calculating the appr dose of acetaminophen and measuring out the appropriate amount once calculated, despite having received appropriate instructions and graduate or oral-dosing syringes.[64 , 105 , 111 , 155] The most commonly used meas device is also the most inaccurate; the household teaspoon is not standa for volume and can easily be confused with a household tablespoon.[105] Although graduated syringes are considered the most accurate of the me instruments available and are recommended by the American Academy of Pediatrics for young children, acetaminophen and ibuprofen elixirs are ty packaged with a graduated cup for administration. Color-coded or prema syringes may be one way to ensure accuracy of parental medication dosi

Intentional Poisoning and Child Abuse

Intentional poisoning of children is an unusual, though significant, form o abuse. There are several types of intentional poisoning, some of which d pathologic characteristics of the caretaker: (1) undifferentiated child abu neglect, or impulsive acts under stress; (2) factitious illness (MÃ¼nchaus syndrome by proxy); (3) overt parental psychosis; (4) altruistic motivatio bizarre childrearing practices; and (5) the Medea complex, or the vengefu killing of a child out of spite for one's spouse.[15 , 167]

Intentional poisoning is rarely suspected unless the patient dies and an a

is performed, a wide-ranging drug screen is ordered, or the history is biz enough to raise suspicions. In many cases where children were later foun be poisoned, the initial diagnoses were sepsis, meningitis, seizures, intra hemorrhage, gastroenteritis, apnea, apparent life-threatening events, or metabolic derangements.[15] In addition to many pharmaceutical agents, s pepper, water, caffeine, ethylene glycol, herbs, plants, and traditional re have been used to poison children.[15 , 43] Although the death rate from unintentional poisoning in childhood is much less than 1%, the death rate inflicted poisoning may be as high as 20â€“30%.[15 , 43 , 167]

Intentional poisoning may be associated with other abuse; approximately of poisoned children may have evidence of physical abuse.[15 , 43] Of child presenting to the emergency department after presumed unintentional poisoning, 36% had previous emergency department visits for trauma, 7% poisoning, 6% for both trauma and poisoning, and 1.4% for failure to thr the time of the visit, only 7% were evaluated for possible abuse, and 2.7 were considered neglected.[15] These data do not prove an association bet poisoning and physical trauma; however, in some children, repeat episode trauma and/or poisoning may be a manifestation of significant intrafamili stress. Healthcare providers must remain vigilant to the possibility that a presumed unintentional poisoning may have been inflicted, especially in t setting of a repeat ingestion or when there have been previous evaluation trauma.

Substance abuse by a parent or guardian may play a role in unintentional intentional poisoning of children. Children have been intoxicated with coca phencyclidine by passive inhalation,[13 , 70 , 115 , 148 , 178] unintentional ingestion,[83 , 134] and rectal adminstration,[130] as well as through breast m Children have been given doses of alcohol, methadone, and other xenobio order to quiet them or to prevent withdrawal.[40 , 71 , 132] There are report babysitters blowing marijuana smoke into babies' faces to â€œget them highâ€• or to quiet them.[149]

Factitious illness (Munchausen syndrome by proxy [MSBP]) is a condition which a parent, usually the mother, fabricates a history

of a nonexistent disease in a child or creates the signs and symptoms of in a child.[112, 113, 143] This is usually a manifestation of the parent's co psychiatric illness, which may include Munchausen syndrome itself.[22, 61] may be only a fine line separating MSBP from an intentional poisoning wi intent to harm or kill a child. Regardless of the specific intent, this condit considered a form of child abuse.

A child's fabricated illness can lead to multiple medical evaluations by m physicians, frequent hospitalizations, unnecessary surgery and diagnostic testing, unnecessary prescribing and administration of medication, and, occasionally, the death of the child. Administration of exogenous drugs is frequently the mechanism of creating a particular set of signs and sympt Agents that have been used to create factitious illness include analgesics antidepressants, insulin, syrup of ipecac, Lomotil, phenothiazines, sedati hypnotics, warfarin, phenolphthalein, and hydrocarbons.[142] Several warn signals may suggest a diagnosis of MSBP (Table 31-7).

In one illustrative case of MSBP, a 29-month-old boy with a previous hist appendectomy was hospitalized multiple times for vomiting, diarrhea, an dehydration.[59] Evaluation included multiple laboratory evaluations of bloo stool, a gastric pH probe, CT, MRI, endoscopy, and upper GI series. On t fourth admission, a small bowel obstruction was identified, and the child lysis of adhesions. Nonetheless, symptoms recurred every 2â€“4 months, necessitating hospitalization. The child failed to thrive and required a nasoduodenal tube for feeding, which frequently became dislodged. The went on to have a jejunostomy tube and a permanent central venous cat placed. Eighteen months after his initial presentation, the child presented congestive heart failure with evidence of cardiomyopathy. A urine screen identified emetine and cephaline, components of syrup of ipecac. The chi recovered, was removed from his home to protective custody, and remai asymptomatic while receiving a regular diet.

Siblings of children being poisoned may also suffer or have suffered from factitious illness. In addition, significant psychiatric illness is manifested victim, the parents, and the siblings.[23, 110]

1. A persistent or recurrent illness that cannot be explained.
2. The history of disease or results of diagnostic tests are inconsistent w general health and appearance of the child.
3. The signs and symptoms cause the clinician to remark, â€œI've never anything like this before!â€•
4. The signs and symptoms do not occur when the child is separated fro parent.
5. The parent is particularly attentive and refuses to leave the child's b even for a few minutes.
6. The parent develops particularly close relations with hospital staff.
7. The parent seems less worried than the physician about the child's condition.
8. Treatments are not toleratedâ€”intravenous lines fall out frequently, prescribed medications lead to vomiting.
9. The proposed diagnosis is a rare disease.
10. â€œSeizuresâ€• are unwitnessed by medical staff and reportedly do respond to any treatment.
11. The parent has a complicated medical or psychiatric history.
12. The parent is or was associated with the healthcare field.

Adapted with permission from Meadow R: Munchausen syndrome by proxy Dis Child 1982;57:92â€“98.

TABLE 31-7. Factitious Illness (Munchausen Syndrome by Prox Suggestive Characteristics in Clinical Situations

Child abuse or neglect is part of the differential diagnosis in any case of childhood poisoning. Intentional poisoning should be considered for (a) an â€œingestionâ€• in a child younger than 1 year of age; (b) a case with a confusing history or presentation; (c) a child with a previous poisoning or whose siblings have been previously evaluated for poisoning; (d) a child w previous presentation for a rare or unexplained medical condition; (e) a with apnea, unexplained seizures, or an apparent life-threatening event; massive ingestion by a small child; (g) an ingestion of multiple xenobiotics small child; (h) an exposure to substances of abuse; (i) an intoxication w

xenobiotic to which a child could or would not have access; (j) â€œaccid ingestionsâ€• in the school-age child; (k) a history of previous trauma, abuse, or neglect; or (l) sudden infant death syndrome or an unexplained death.[15 , 71]

These considerations of child abuse notwithstanding, rare diseases do oc One child's rare, inherited metabolic disorder, methyl malonic acidemia, misdiagnosed as ethylene glycol poisoning because the chromatographic appearance of the metabolite propionic acid was similar to that of ethyler glycol.[153]

Summary

Children are frequently exposed to potentially toxic xenobiotics; fortunat most childhood exposures are ingestions of nonpoisonous xenobiotics or nontoxic quantities of potentially toxic xenobiotics. When a child sustains significant toxic exposure, management follows general toxicologic princi Although most childhood exposures are unintentional, the clinician should alert to the possibility of the intentional poisoning of a child with pharmaceutical or household agents.

The normal development of children puts them at risk for unintentional ingestions. A chaotic home environment or a disorganized social structure compound these risks. Small size puts a child at increased risk for medic dosing and dispensing errors, and their immature metabolic processes ma to unexpected toxicity from pharmaceutical agents.

Toxicologists should encourage parents to provide as safe a home enviro as possible to prevent unintentional ingestions, and must encourage practitioners to exercise special vigilance when administering medications children.

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Chapter 32
Geriatric Principles

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The population in developed countries is aging steadily. In the United States, those older than 65 years of age comprise not only an increasing proportion of the population at large (12%), but an increasing proportion of patients seen in medical practices. Patients older than 65 years of age account for 43% of emergency department visits and 48% of all critical care admissions from emergency departments.[64]

Although the elderly account for only a small minority of toxicologic exposures, once exposed, they have the highest mortality rate. Among exposures reported to poison control centers in 2003, the fatality ratio (number of cases divided by number of deaths) increased with age and is highest among people 80 years of age and older.[79] The American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System (TESS) data may underestimate the serious consequences for elderly people exposed to toxic substances. First, there is a lack of

recognition of drug toxicity in the elderly.[3] Because of pharmacokinetic and pharmacodynamic changes that occur as one ages, a â€œstandardâ€• medication dose thought to be therapeutic may produce an unexpected serious effect. The presentation of toxicity may be atypical. Falls, a common presentation in the elderly, may be a presenting sign of drug toxicity; if the patient is cognitively impaired and the fall is unwitnessed, the immediate consequences of the fall may be adequately addressed, but the xenobiotic causing it may not,[39,56,58] because drug overdoses can result in focal neurologic deficits that may be attributed solely to structural cerebrovascular or cardiovascular disease, without identifying the toxicologic etiology.[69] Table 32-1 lists the drugs most commonly responsible for toxicity in the elderly.

The presentation of drug toxicity may be delayed in the elderly. Drugs with long half-lives may not reach a steady state and, hence, not achieve peak action until many days after the drug therapy is initiated. In some older patients, the active metabolite of flurazepam, desalkylflurazepam, has a half-life of up to 100 hours or longer, which requires days to achieve a steady state. When peak effects are delayed in this way, drug toxicity can easily be mistaken for nondrug-related illness.

Suicide and Intentional Poisonings

The risk of suicide by all methods increases steadily with age, particularly among white men.[49,54] Although data for individual ethnic groups are sparse, white men have a substantially higher risk of suicide than their same-age cohorts among the African American population.[49,53,54] Although suicide is more common among men than among women, women are more likely to attempt suicide. The male-to-female ratio of suicide attempts narrows with increasing age, so that in the oldest age groups, men attempt suicide slightly more often than women, when all methods of

attempted suicide are considered (Chap. 18).[24]

In the United States, firearms are the most frequent means of death by suicide. Among men older than age 65 years, firearms account for 73% of completed suicides, whereas drug overdose accounts for only 3%; among women, drug overdose is nearly as frequent a cause of death as firearms, each accounting for approximately 25% of successful suicides. When death by inhalation is included, poison exposure surpasses gunshot wounds as a cause of death among elderly women.[49] Drug overdose is an important factor in suicide attempts by the elderly of both sexes.[24] In other countries, firearms are only rarely used to commit suicide at any age, with methods such as drug overdose and inhalation consequently comprising a much greater proportion than in the United States.[71]

Among the elderly, the pattern of medications responsible for suicidal deaths may be changing, as safer serotonin reuptake inhibitors (SSRIs) are increasingly prescribed for depression instead of tricyclic antidepressants (TCAs), which are more likely to be lethal in overdose.[11] In Sweden, the relative fatality ratio for benzodiazepines was reported to be correspondingly increasing. Overdose of benzodiazepines is rarely fatal unless it is accompanied by alcohol or another toxic ingestion or occurs in the presence of serious medical problems. However, when all deaths from benzodiazepines are examined, they probably occur more often in older adults.[19]

Unintentional Poisoning and Adverse Drug Events

An adverse drug event (ADE) is defined as â€œan injury resulting from medical intervention related to a drug.â€•[5] This definition encompasses events that result from both inappropriate use of medications, such as a prescribing error, and from appropriate

use. It may be challenging for the clinician to distinguish poisoning from ADEs in the elderly. Compared to younger adults, the elderly are at increased risk of unintentional poisoning as well as other drug events. Life-threatening reactions may occur with therapeutic doses; examples include the serotonin syndrome and the neuroleptic

malignant syndrome. Typically, the serotonin syndrome occurs when two or more drugs that increase serotonin activity are used concurrently,[48] a more likely occurrence among the elderly for whom multiple medications are commonly prescribed.[8]

TABLE 32-1. Drugs Most Commonly Responsible for Toxicity in the Elderly[a]

Anticholinergics
Anticoagulants
Antidepressants
Antipsychotics
Cardiovascular medications
Î²-Adrenergic antagonists
Calcium channel blockers
Digoxin
Magnesium-containing antacids
Magnesium- and phosphate-containing laxatives
Nonsteroidal antiinflammatory drugs
Opioids
Salicylates
Sedative-hypnotics

[a] Polypharmacy increases toxicity as a result of diverse drugâ€“drug interactions.

The serotonin syndrome and neuroleptic malignant syndrome are relatively unpredictable and can occur at any age. However, other severe ADEs are more likely to occur among the elderly and are potentially avoidable if patients are carefully monitored. Examples include severe bleeding as a result of nonsteroidal antiinflammatory agents, metformin-induced lactic acidosis,[35] and prolonged hypoglycemia from sulfonylureas.[51,67,68]

Although reported poisoning exposures among the elderly are much less frequent than among other age groups, the incidence of ADEs increases steadily with age.[8,44] Moreover, when they occur, they are more likely to be serious. Serious ADEs, defined as those resulting in death, hospitalization, prolongation of hospitalization, or permanent or serious disability, are most prevalent among people 85 years of age and older.[8]

Substance Abuse in the Elderly

Substance abuse declines with age, but is important to consider in relevant clinical circumstances. Alcohol is the most common substance of abuse in people older than age 65 years. Abuse of alcohol, or other xenobiotics, may be a continuation of long-term habits, but some older adults in their 60s and 70s may first begin to use and abuse drugs late in life.[36]

Substance abuse in late life is probably underrecognized. In one Illinois study of patients presenting to a trauma facility, only 5% of those age 65 years and older were tested for alcohol or other substances, whereas among those younger than age 65 years, 22% were tested for alcohol and 29% for other substances.[82] However, almost half of the elderly patients tested for alcohol were positive and 72% of those had a blood alcohol level of 80 mg/dL (the legal limit in the study state of Illinois) or above, results that were comparable to those of younger patients who were studied, 75% of whom tested positive. For any given amount

of alcohol ingested, the blood alcohol concentration of a person age 65 years or older is higher than that of a younger adult because of pharmacokinetic changes, as discussed below. Moreover, because of an age-associated diminished tolerance to alcohol, the impact on cognitive or motor function tends to be greater.

In the same study, 11% of elderly patients who were tested had positive urine toxicology screening results compared to 43% of tested younger adults. The most common substances detected in the elderly were benzodiazepines, opioids, and barbiturates, which, like alcohol, are more likely to impair older than younger adults. The failure to consider use of these drugs, whether illicit or prescription, may have serious consequences. When admitted to hospitals, if a careful drug history is not elicited, withdrawal from these substances may occur, be misdiagnosed and hence inappropriately managed.

Pharmacokinetics

Age-related pharmacokinetic changes occur in the elderly. The most important and consistent pharmacokinetic change that occurs with aging is a decrease in renal function. Glomerular filtration rate (GFR) declines, on the average, by 50% between the ages of 30 and 80 years.[17,62] The GFR cannot be accurately predicted by serum creatinine because muscle mass, the source of serum creatinine, declines with age; consequently, in late life, serum creatinine may not be elevated even when the GFR is significantly impaired.

Because it is impractical and often difficult to measure 24-hour creatinine clearance before instituting therapy with an essential, renally excreted drug, clinicians commonly estimate creatinine clearance using age-adjusted formulas or nomograms. Frequently applied formulas are fairly predictive of renal function when renal function is stable.[55] However, age-related declines in GFR are not

universal, and data from longitudinal studies suggest that as many as 33% of the el-derly do not experience this age-related decline.[47] Predictive formulas could significantly overestimate actual creatinine clearance in chronically ill, debilitated elderly, especially those with renal insufficiency.[42] Because muscle mass declines even in healthy aging, more research is required to determine if predictive formulas have sufficient accuracy in healthier groups of elderly.[63] For all of these reasons, it is difficult to accurately predict the renal elimination of drugs or drug metabolites in the elderly. A practical solution is to assume that renal function has declined and to exercise caution when prescribing maintenance doses of drugs with a narrow therapeutic-to-toxic ratio (Table 32-2). Failure to do so is an important cause of toxicity.[46]

TABLE 32-2. Drugs with Narrow Therapeutic-to-Toxic Ratios and Potential for Accumulation in the Presence of Diminished Renal Function

Antimicrobials
Aminoglycosides
Imipenem
Pyrazinamide
Vancomycin
Benzodiazepines with active metabolites
Chlordiazepoxide
Clorazepate
Diazepam
Flurazepam
Halazepam
Digoxin
Enoxaparin
Lithium

Meperidine (active metabolite: normeperidine)
Metformin
Procainamide (active metabolite: *N*-acetyl procainamide)
Salicylates

Controversy exists regarding the impact of age-related hepatic changes on drug elimination. Liver mass decreases with an associated decrease in hepatic blood flow,[80] which results in decreased efficiency of drug removal by hepatic extraction. Enzymatic processes are often unpredictable,[38] and there is considerable controversy over the extent to which advanced age alters the ability of drugs to undergo hepatic metabolism, particularly oxidative processes.[66] Hepatic conjugation does not decline significantly with age, so drugs such as temazepam and oxazepam that are metabolized by these processes do not have a prolonged elimination half-life. In contrast, drugs such as diazepam and flurazepam, which are metabolized by hepatic oxidative enzymes, are eliminated more slowly with age,[28] but decreased renal elimination of active metabolites may be the most important factor. Studies that consider cofactors that could affect hepatic enzymes, such as concurrent medications or cigarette smoking, or that determine isozyme genotype, may demonstrate that there is no age-related change in hepatic oxidative enzyme function.[6]

Unlike conjugated metabolites, which tend to be inactive, products of oxidative metabolism are often active. Because these active metabolites are generally excreted by the kidney, the presence of active drug may be markedly prolonged. Other changes in enzyme systems may occur late in life. For example, a decline in gastric alcohol dehydrogenase leads to increased peak effect of ethanol in the elderly.[59] Decline in this enzyme is attributed to the increased incidence of gastric atrophy with age. Whether age-related

changes occur in metabolic enzymes that are present in many organ systems, such as intestine, brain, and kidney, and what impact such changes have on drug disposition, are likely to become active areas of research.

Age-related alterations in body composition can affect drug disposition in later life (Table 32-3). For example, lean muscle mass and total body water decline and the fat-to-lean ratio increases with advancing age.[57] Thus, highly lipid-soluble drugs tend to have an increased volume of distribution (Vd). As a result, there may be a delay before steady state is reached, and peak effect and toxicity may occur later than expected. This mechanism may be an additional reason drugs such as diazepam and flurazepam have prolonged half-lives in otherwise healthy elderly patients. In contrast, drugs that distribute in water, such as ethanol, have a smaller Vd, which may partly account for the more rapid and more pronounced peak effect of ethanol in the elderly.

Protein reserve diminishes with age, as a consequence of decreased muscle mass and decreased protein synthesis.[60] Although serum albumin remains in the normal range in the healthy elderly,[10] patients in this age group are more likely to experience a rapid decrease in albumin levels when there is acute or chronic illness or when protein intake does not keep up with demand.[81] A decline in serum protein increases the free or active fraction of drugs that are otherwise highly protein bound. Free drug is able to travel more readily to the liver and kidney for metabolism or excretion, so a gradual change in the serum protein level is unlikely to lead to a change in the patient's response to the drug. However, these changes may be clinically important for interpreting serum levels of highly bound drugs. Clinical laboratories typically measure total drug levels which include both free and bound drug. Because most drug is bound, the reported value reflects mostly bound drug and therefore, the total drug concentration may be in the therapeutic range, even though the active unbound fraction is actually elevated. Phenytoin, which is

highly bound to albumin, serves as an illustrative example. If the serum level of phenytoin is reported as subtherapeutic, the physician might order a dose increase even though the free fraction of phenytoin actually is in the therapeutic range. With a dose increase, the free or active fraction of the drug may increase to toxic levels.

TABLE 32-3. Special Pharmacokinetic Considerations in the Elderly

	Young	Elderly	Consideration
Fat (% of body weight)	15	30 (â†‘)	â†‘Vd for drugs distributing to fat (amitriptyline, diazepam)
Intracellular water (% of body weight)	42	30 (â†“)	â†“Vd for water-soluble drugs
Muscle (% of body weight)	17	12 (â†“)	â†“Vd for drugs distributing into lean tissue (acetaminophen, caffeine, digoxin, ethanol)
Albumin (g/dL)	4	â†“ With acute or chronic	â†‘ Free levels of drugs if >90% bound to albumin,

		illness	especially in overdose; interpretation of serum concentration altered
Liver	Normal	â†“Size â†“Hepatic blood flow	Liver enzymes not predictive; drugs with high extraction may increase (propranolol, triazolam)
Kidney	Normal	â†“Renal blood flow â†“GFR â†“ Tubular secretion	Accumulation (lithium, aminoglycosides, *N*-acetyl procainamide, ACE inhibitors, cimetidine, digoxin

Modified with permission from Mayersohn M: Special pharmacokinetic considerations in the elderly. In: Evans WE, Schentag JJ, Justo WJ, eds: Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring, 3rd ed. Vancouver, WA, Applied Therapeutics, 1992, pp. 1â€“43; and Fox FJ, Auestad A: Geriatric emergency clinical pharmacology. Emerg Med Clin North Am 1990;8:221â€“239.

Basic drugs are not bound to albumin but to Î±-acid glycoprotein (AAG), an acute-phase reactant that tends to increase, rather than decrease, with age.[1] However, the increase attributed to age is most likely related to underlying disease. These unpredictable changes would be expected to have the reverse effect on the ratio of bound to unbound drug in any laboratory report.[59] The correlation between clinical effect and free drug levels requires further study because there may be complex factors involved, including alterations in Vd and specific tissue concentrations.

The contribution of gastrointestinal absorption to drug toxicity is unknown. Absorption declines modestly, if at all, with advancing age. However, age-related changes in the gastric mucosa may account for enzymatic changes, as demonstrated in the case of alcohol dehydrogenase, noted above.

Pharmacodynamics

Pharmacodynamic factors may also affect a patient's response to a particular drug. In general, age-related physiologic changes in target or nontarget organs lead to increased sensitivity to a given drug, although sensitivity to some drugs may also be decreased. For

example, there is evidence that Î²-adrenergic receptor sensitivity declines with aging, leading to a diminished response to both Î²-adrenergic agonists and antagonists.[14,76] However, clinical experience demonstrates that the elderly respond normally to drugs of this category in terms of therapeutic response, adverse effects, and toxicity.[23]

TABLE 32-4. Pathophysiologic Disorders Exacerbated by Drugs in the Elderly

Disorder	Drug	Possible Outcome
ADH secretion (increased)	Antipsychotics, SSRIs	Hyponatremia
Androgenic hormones (males, decreased)	Digoxin, spironolactone	Gynecomastia
Baroreceptor dysfunction, venous insufficiency	Antipsychotics, diuretics, tricyclic antidepressants	Orthostatic hypotension
Bladder dysfunction	Diuretics	Incontinence
Cardiac disease	Thiazolidinediones	Congestive heart failure
Dementia	Sedatives, anticholinergics, and many others	Confusion
Gastritis (atrophic)	NSAIDs, salicylates	Gastric hemorrhage
Immobility, cathartic bowel	Anticholinergics, opioids	Constipation

Nodal disease (sinus or AV)	Î²-Adrenergic antagonists, digoxin, diltiazem, verapamil	Bradycardia
Parkinson disease	Antipsychotics, metoclopramide	Parkinsonism
Prostatic hyperplasia	Anticholinergics, tricyclic antidepressants, disopyramide	Urinary retention
Thermoregulation, disordered	Antipsychotics	Hypo- or hyperthermia
Venous insufficiency	Calcium channel blockers, others	Edema

The observation of enhanced sensitivity to drugs is probably related to altered pharmacokinetics in many, if not most, cases.[29] Proving that enhanced sensitivity is related to altered pharmacodynamics would require demonstrating that the concentration of drug at the tissue site was not increased as the result of diminished elimination.[21] Regardless of the mechanism, it is important to recognize that the response to a given drug might be altered in specific ways among the elderly. These altered responses are probably caused less by chronologic aging and more by an increased prevalence of disease in the elderly.[29] Table 32-4 provides examples of pathophysiologic changes that frequently occur in the elderly and are unmasked by medications.

Adverse Drug Events

The likelihood of experiencing an ADE increases with the increasing number of drugs prescribed for a patient.[32] Geriatric patients take more prescription and nonprescription drugs than any patient group.[8,37] A complicated drug regimen reduces adherence, increases medication errors, and increases the risk of clinically important drug interactions. ADEs may occur as a consequence of drugâ€“drug interactions, but the relationship between the two phenomena is sometimes difficult to quantitate.[32]

Concurrent disease in target or nontarget organs also may alter the patient's sensitivity to a drug,[33] resulting in a serious ADE even when the patient is given a standard or previously used dose of the drug. Coexistent disease is often subclinical, and the patient's enhanced sensitivity may not be anticipated. A patient with subclinical Alzheimer disease whose cognitive function is overtly normal may acutely develop delirium or symptoms of dementia when given ordinary doses of drugs such as sedative-hypnotics and tricyclic antidepressants. Delirium is a medical emergency and an important cause of emergency department visits by the elderly.[33]

Another contributing factor is physician lack of knowledge about principles of geriatric therapeutics.[22] In a series of hospitalized patients, failure to consider advanced age was the most common factor associated with clinically important prescribing errors, and inattention to abnormal renal function was the second most important.[35] New drugs deemed safer than older agents may be problematic, and inattention to risk factors can lead to significant morbidity. For example, the hypnotic agent, zolpidem, was marketed as a safe alternative to benzodiazepines for the elderly. However, like benzodiazepines, zolpidem may cause confusion, memory loss, and falls, leading to hip fracture.[77,78] Another example is enoxaparin, which has more predictable pharmacokinetics than unfractionated heparin, and is associated

with a lower rate of bleeding. Therapeutic monitoring via antifactor Xa activity is cumbersome and not recommended except in unusual circumstances,[31] and therefore, enoxaparin may be perceived as more convenient as well as safer. However, enoxaparin is eliminated by the kidney and repeated doses lead to progressive increases in antifactor Xa activity when creatinine clearance is â‰¤30 mL/min,[13] a degree of renal insufficiency that is common in frail elderly patients, despite normal serum creatinine concentration. It is notable that most reported cases of serious, unexpected enoxaparin-induced bleeding occur in elderly patients who are receiving â€œstandard,â€• and not age appropriate, dosing.[50,74,75] In addition to inadequate prescribing methods, physicians often prescribe drugs deemed inappropriate in the elderly at any dose,[16] such as tricyclic antidepressants, long-acting benzodiazepines, and anticholinergic agents.[12]

Compounding the problem of lack of knowledge is the fact that new drugs are often inadequately studied in the elderly (see Chap. 133 for further details).[65,73] Reactions occurring in a small percentage of patients in a special subgroup can easily be missed during the initial investigations. Even when a substantial number of subjects older than age 60 years are studied, much smaller proportions of patients older than age 70 years may be included in clinical trials.[2,45] Thus, the adults at highest risk for many forms of drug toxicity are those least-often studied. Subjects undergoing drug testing are generally young adults and disease free, so pharmacokinetic profiles do not reflect patterns of drug disposition that are characteristic of geriatric patients. Pharmacokinetic testing may be limited to a one-time dose, and frequently the evaluation takes place over a short time. On average, approximately 5 half-lives of a drug are necessary to achieve steady-state drug levels. Thus a drug with a half-life of 24 hours might not reach a steady state for 5 days, and in the presence of prolonged elimination associated with age-related factors, a steady state might not be reached for substantially longer. As a result,

even if the elderly are included in a drug trial, the ultimate effect of that drug might not be noted during testing intervals that are frequently designed for younger patients.

Morbidity and mortality occurring in elderly patients as a result of specific drugs might be avoided if the responsible drugs were studied under the predictably high-risk conditions typically present in the elderly. For example, benoxaprofen, a long-acting nonsteroidal antiinflammatory agent, was responsible for cholestatic jaundice and death in several elderly patients. Following the drug's introduction there was a substantial delay before the jaundice and other serious drug-related toxicities were recognized. Another example is the antibiotic temafloxacin. Temafloxacin was available for only 3 months before it was withdrawn following 3 reported deaths and more than 300 cases of hypoglycemia, many of which occurred in elderly patients with diminished renal function.

If pharmacokinetic studies identify vulnerable subgroups, safe maximum doses could be recommended for specific populations at risk, theoretically limiting the risk for these individuals.[4] As a result of these problems, the Food and Drug Administration (FDA) now requires sponsors of new drug applications to present effectiveness and safety data for important demographic subgroups, including the elderly, in their FDA submission data.[18]

Drugs involved in serious drug interactions, such as digoxin, warfarin, and diuretics, are commonly prescribed in the elderly population. This situation is complicated by the fact that elderly patients often have multisystem disease and may visit several physicians, who prescribe medications without specific knowledge of, or attention to, the remainder of the patient's drug regimen, thereby increasing the risk of inappropriate drug combinations.[72]

Herbal preparations also may interact with prescription medications.[25,52] The use of herbal preparations has increased

substantially in recent years, particularly among patients with illnesses that afflict the elderly, such as cancer, dementia, and depression. Very few patients voluntarily report use of these or other nonprescribed therapies to their physicians, and too often the physician fails to inquire specifically about such â€œalternativeâ€• or â€œcomplementaryâ€• therapies. Drug interactions involving herbals also occur with nonprescription preparations such as dextromethorphan, a common component of cough medicine, and St. John's wort (hypericum), a heavily promoted herbal remedy for depression that can reduce warfarin sensitivity.[43] Ginkgo biloba, commonly taken for memory loss, inhibits platelet function[40] and has the potential to enhance bleeding tendency when used with warfarin.[20,61] Combinations of herbals and SSRIs have been reported to cause serotonin syndrome.[9,25] Poisonings and other problems related to herbal preparations are discussed further in Chap. 43.

The use of nonprescription pharmaceuticals may cause serious adverse effects. For example, excessive use of magnesium-containing preparations can cause severe toxicity, often in older individuals. Impaired renal clearance, decreased gastrointestinal motility, and other medical comorbidities are just 3 risk factors that potentiate magnesium toxicity in the elderly. The source of magnesium in these cases may include the cathartics magnesium hydroxide (â€œmilk of magnesiaâ€•) and magnesium citrate, antacid preparations, and magnesium sulfate (Epsom salts).[26] Virtually all of the most popular nonprescription medications[37] are more likely to produce problems in the elderly than in younger patients, including gastrointestinal bleeding (aspirin and other nonsteroidal antiinflammatory agents), enhanced warfarin sensitivity (cimetidine), confusion and urinary retention (anticholinergic antihistamines), and cardiovascular symptoms (pseudoephedrine).

Outdated and discontinued drugs are an additional problem for the elderly who often retain products in their homes for decades.

Patients may be unwilling to change, or successive physicians may continue to renew the prescription without sufficiently reevaluating the patient.

Other age-related factors can increase the risk of unintentional poisonings in geriatric patients: impaired vision, hearing, and memory may lead to misunderstanding or the inability to follow directions concerning the use of prescription and nonprescription drugs. Dementia is an important risk factor in unintentional poisonings. In addition to cognitive impairment, patients with dementia sometimes exhibit abnormal feeding behaviors, including ingestion of inappropriate substances.

Management

Management decisions must be made with the foregoing principles in mind. Gastrointestinal decontamination should proceed as in younger patients. Because constipation is a more frequent problem in the elderly, when multiple-dose activated charcoal is indicated, particular attention must be paid to gastrointestinal function and motility. The specific precautions and contraindications in the basic management of gastrointestinal decontamination detailed in Chap. 8 are particularly pertinent for the geriatric population.

The presence of clinical or subclinical heart failure or renal failure may increase the risk of fluid overload when sodium bicarbonate is used. In the elderly, hemodialysis or hemoperfusion may be indicated earlier in cases of lithium or theophylline poisoning, where elimination may be hampered by a decreased creatinine clearance or reduced endogenous clearance, respectively.

A problem that may go unrecognized in geriatric patients is the development of alcohol or drug withdrawal symptoms. Because elderly patients are typically not perceived as drug users, the physician may not be aware of the chronic use of prescribed benzodiazepines or opioid analgesics, and consequently might fail

to consider the possibility of substance withdrawal when unanticipated complications occur during the hospitalization.

Strategies to limit unintentional toxic exposures in elderly patients with cognitive or sensory impairment should be similar to those employed in young children, who are at high risk for ingesting toxic substances or pharmaceuticals prescribed for others in the household. The strategies should include the removal of potentially dangerous substances and unnecessary drugs from the el-derly patient's environment. The physician should request that the patient or caregiver bring all medications to the office in the original bottles and then limit the number of pills dispensed. It may be necessary to limit medications such as antidepressants to a 1-week supply or to choose alternative medications with a safer therapeutic toxic index ratio. Administration and control of the medications by directly observed therapy may, of necessity, become the responsibility of the caregiver rather than the patient.

Admission Criteria

When geriatric patients are evaluated in the emergency department for poisonings or serious ADEs, the need for hospital admission should be guided by concerns about the patient's frailty, weighed carefully against the known hazards of hospitalization for the elderly.[15]

The physician should be particularly alert to certain situations that might mandate admission: elder abuse or neglect, unresolved mental status changes, inadequate home care manifested

by unexplained falls or overdose of medications with prolonged durations of action.

When there is concern that the established caregivers at home are abusing the patient, the patient will require further observation, removal from the environment, and possibly hospitalization. Signs

of actual physical abuse may be more obvious than signs of neglect.[41] Vulnerable elderly who are physically disabled or cognitively impaired may be brought to the hospital because of presumed illness, but the source of the problem may actually be the caregiver. The caregiver, frequently a family member, may be depleting the patient's funds for personal use. Patients may become ill because funds were diverted from the purchase of food or because the patient's prescription drugs were sold on the street. More direct abuse may take the form of intentional poisoning of the patient by overdose of the patient's own prescription drugs.

Unresolved mental status changes may require close observation and hospitalization. Elderly patients who are confused or unable to walk are sometimes mistakenly assumed to be chronically impaired. However, incomplete explanation of an altered mental status or physical impairment should prompt careful inquiry into the patient's baseline functional status. Functional deterioration should not be assumed to be age related. Many very elderly patients are cognitively normal, physically robust, and independent in all activities of daily living.

Overdose with long-acting agents requires careful monitoring. Because duration of action of certain drugs may be markedly prolonged among geriatric patients, a higher degree of vigilance is required. A classic example is associated with the use of the sulfonylurea, chlorpropamide, which has a half-life of 24â€“72 hours or more and can cause protracted hypoglycemia. This drug is rarely used today, but observational studies suggest that severe hypoglycemia (glucose <50 mg/dL), in the presence of neurologic or cardiac symptoms, is more common with glyburide than with other commonly used sulfonylurea agents,[27,67] possibly because of an active, renally eliminated metabolite.[34] Although comparable to glipizide in ideal conditions,[7] renal failure or use of concurrent medications that could potentiate hypoglycemia might elevate risk. Hypoglycemia leading to serious morbidity or death is an

important drug-related problem among the elderly and occurs with virtually all sulfonylurea agents.[67]

Summary

Older patients may account for only a small fraction of poisoning victims, but when poisoned, they have the highest mortality rate. More importantly, the elderly are much more likely to experience serious adverse drug events as a consequence of appropriate or inappropriate use of medications. Attention to risk factors is essential in this vulnerable population. Important risk factors include pharmacokinetic and pharmacodynamic changes; the presence of overt or subclinical disease, including dementia; patient and physician error; suicide risk; complex therapeutic drug regimens; and a general lack of knowledge about the principles of geriatric prescribing.

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Chapter 33
Postmortem Toxicology

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Intravenous phenytoin is administered to a 25-year-old man with a history of seizures, who is maintained on phenytoin in order to achieve a therapeutic concentration. Eight minutes after the beginning of the infusion, the man experiences a bradydysrhythmia followed by asystole. The infusion is immediately discontinued and resuscitation is attempted, but is unsuccessful.

Postmortem toxicology is the study of the presence, distribution, and quantification of a xenobiotic after death. This information is used to account for physiologic effects of a xenobiotic at the time of death, through its quantification and distribution in the body at the time of autopsy. Several variables may cause changes in xenobiotic concentrations during the interval between the time of death and subsequent autopsy. Toxicologists and forensic pathologists are frequently asked to interpret postmortem xenobiotic concentrations and decide whether these substances

were incidental or contributory to the cause of death.

The development of the field of forensic toxicology, and the improvement of laboratory technology, now permits more refined identification and quantification of xenobiotics. The interpretation of postmortem xenobiotic concentrations and their significance, however, continues to evolve.

This chapter reviews factors affecting xenobiotic concentrations identified on autopsy and discusses an approach for interpreting postmortem toxicologic reports as they relate to cause and manner of death.[37,39,45,46 and 47,53,61,71,89]

History and Role of Medical Examiners

The relationship between antemortem xenobiotic exposures and death has been a subject of investigation for centuries. In 12th century England, an appointee of the royal court, eventually named the â€œcoroner,â€• was designated to record and identify causes of death.[65] In suspicious circumstances coroners investigated poisonings, but scientific methods were primitive and conclusions regarding such deaths were conjecture, at best.

By the mid-19th century, however, techniques for detecting certain compounds in postmortem tissue were developed and focused generally on identifying heavy metals as a cause of death in homicides.[40,65,69,86,91] At this time, coroners were still elected or appointed individuals with little or no medical training. However, with better laboratory techniques and autopsies performed by trained pathologists, the specialty of forensic medicine continued to develop. In late 19th century Massachusetts, trained pathologists, referred to as medical examiners, ultimately replaced the coroner system and were empowered by the state to investigate deaths (medicolegal autopsies).[65] Currently in the United States, legal jurisdiction of death investigations is the responsibility of either a coroner or a

medical examiner, depending on the state and/or county, with 19 states using medical examiner systems almost exclusively.[44]

The medicolegal autopsy is performed by a forensic pathologist who attempts to establish cause and manner of death (Table 33-1). â€œCause of deathâ€• is the physiologic agent or event necessary for death to occur. For example, the presence of cyanide in the toxicologic evaluation may be sufficient to establish cardiorespiratory arrest from cyanide poisoning. â€œManner of deathâ€• is an explanation of how the death occurred and broadly distinguishes natural from nonnatural (or violent) deaths. Nonnatural deaths, depending on the jurisdiction, can be divided into several categories (Table 33-2). With the identification of cyanide, the manner of death cannot be considered natural, because a poisoning is a â€œchemically traumaticâ€• (violent) event. The medical examiner must make the best determination of the manner of death based on available evidence.[91,98] An unintentional exposure may be classified as an â€œaccidentâ€• (a legal term for some unintentional nonnatural deaths), and intentional self-exposure may be classified as a â€œsuicide.â€• If the circumstances indicate an exposure as a consequence of the acts of another person, the manner of death is classified as a â€œhomicide.â€•

Determination of manner of death has important consequences. Homicide necessitates involvement of law enforcement officials for further investigation. Cases deemed suicide not only impact survivors psychologically, but also may nullify life-insurance payments; conversely, a case deemed an â€œaccidentâ€• may have a double-indemnity insurance clause. Assignment of financial responsibility for workplace disasters may be similarly affected when illicit drugs are identified in the postmortem specimens of involved workers.

Recognition of xenobiotic-related deaths also has significant public health consequences. The forensic pathologist may be the first to

identify and report critical information regarding fatal drug reactions, medication errors, or rapidly fatal epidemics associated with illicit drug use. In cases of occupational and environmental xenobiotic-related fatalities, interventions can be implemented to prevent subsequent morbidity and mortality. In addition, the pathologist describes gross and microscopic autopsy findings that may elucidate mechanisms of xenobiotic toxicity.

TABLE 33-1. Information Used by Forensic Pathologists

Autopsy
Evidence from scene
Laboratory investigations
Medical consultants
Available history
Medical records
Police reports
Interviews with contacts

Postmortem toxicologic techniques also can be used in other types of investigations. For example, when carboxyhemoglobin is identified in the burned human remains of an airplane crash, a cabin fire before descent is more probable than a fire on impact. This type of postmortem analysis is useful in reconstruction of events leading to the crash.[8,51,57]

The Toxicologic Investigation

Ordinarily, toxicologic samples are collected as part of a complete autopsy. In the hospital, when a death is assumed to be from natural causes, the hospital pathologist may perform an autopsy

with consent of the family. In the medicolegal investigation, however, the forensic pathologist determines the need for a complete or partial autopsy and has the jurisdiction to act on that determination with or without familial consent. Occasionally, only fluid samples need be obtained if a complete autopsy is either unnecessary or the family has legal or religious grounds for objection. The precise list of xenobiotics screened in postmortem samples varies greatly by jurisdiction. Large cities may routinely screen for hundreds of illicit, therapeutic, and environmental xenobiotics. Occasionally the suspicions of the medical examiner warrant special assays that are performed only upon request.

The sampling of fluid and tissue may be obtained minutes to years after death. The â€œpostmortem interval,â€• defined by the degree of bodily decomposition, can vary, depending on environmental conditions, such as ambient temperature, humidity, and immersion under water.[58] Samples may be collected from a body during advanced stages of decomposition, after exhumation from a grave, or after embalming.[7,41,70] Knowing the condition of the body at the time of sampling assists in interpreting toxicologic findings. These postmortem changes are reviewed below.

Decomposition and Postmortem Biochemical Changes

The first stage of decomposition is *autolysis* where endogenous enzymes are released and normal mechanisms maintaining cellular integrity fail.[52] Chemicals move across leaky cellular membranes down relative concentration gradients. Glycolysis continues in red blood cells until intracellular glucose is depleted, and then lactate is produced. Ultimately, intracellular ions and proteins are released into the blood, and tissue and blood acidemia develops (Table 33-3).[91]

TABLE 33-2. Categories of Manner of Death

Natural
Nonnatural
Homicide
Suicide
Accident
Therapeutic complication[a]
Undetermined

[a] Not all jurisdictions recognize therapeutic complication as a manner of death.

TABLE 33-3. Postmortem Biochemical Changes Over First 3 Days[a]

Increased	Decreased	Stable	Variable
Amino acids	Cl^-	BUN/creatinine (vitreous)	Lipids
Ammonia	Glucose	Cholinesterases	T_3
Ca^{2+}	Na^-	Cortisol(serum)	
Epinephrine	pH	Proteins (serum)	

Hepatic enzymes	T_4	Sulfates	
Insulin (especially right-heart blood)			
K^+			
Mg^{2+}			
[a] In refrigerated bodies.			

The next stage of decomposition is *putrefaction.* This involves digestion of tissue by bacterial organisms that typically originate in the bowel or respiratory system. Later, other organisms may be introduced by insects or other external sources. As the putrefactive process advances, skin and organ colors change, epithelial blebs may form and separate from the underlying dermis, and gases may accumulate, forming foul odors and bloating.[91]

If death occurs in a very warm, dry climate, such as a desert or a comparably arid environment, the body may desiccate so rapidly that putrefactive changes may not occur. This results in *mummification*, and produces a lightweight cadaver with a tight, dry skin enveloping a prominent bony skeleton.[91]

If the environment is very cold and devoid of oxygen, such as at great depths under water, putrefaction will be slowed. Anoxic decomposition of fatty tissues occurs, forming a white cheesy material known as *adipocere.*

Another phase of decomposition, *anthropophagia*, occurs in unprotected postmortem environments where insects or other animals feed on the remains.[91]

Most postmortem changes are temperature dependent with increased temperatures accelerating the process, and cooler temperatures retarding it. In general, morgue refrigerators achieve low enough temperatures (40Â°F; 22Â°C) to prevent further gross decomposition and associated postmortem changes.

Another process that alters natural decomposition is *embalming*, a process of chemically preserving tissues that can be performed in a variety of ways.[42,43] Typically, blood is drained through large vessel pumps, and an embalming fluid is injected intravascularly to perfuse and preserve the face and/or other tissues. Intracavitary spaces may be injected with the preserving substances, and solid organs may or may not be removed.

Samples used for Toxicologic Analysis

Unless the medical examiner is suspicious about a death, only standard autopsy samples will be taken from an otherwise intact body.[23,36,49,54,74,89] These typically include samples of blood, gastric

contents, bile, urine, and, occasionally, solid organs such as the liver or brain. Less commonly, vitreous humor is obtained for analysis (Table 33-4). If the decedent was hospitalized prior to death, antemortem specimens may also be available for evaluation and comparison. These specimen analyses are reviewed in greater detail below.

TABLE 33-4. Sampling Sites [16,21,24,36,49,91]

Routine	Infrequent	Uncommon
Bile	Bone	Antemortem blood
Blood	CSF	Extravasated blood
Brain	Fat	Extravasated fluid
Liver	Hair	Casket fluid
Gastric contents	Kidneys	Insect larvae
Urine	Lungs	Pupae casings
Vitreous humor	Muscle	Soil
	Nails	
	Skin	

Blood

Postmortem cell lysis prevents the reporting of plasma concentrations, and â€œbloodâ€• concentrations are reported instead. Intravascular blood from the subclavian or femoral vessels is a common source for toxicologic examination. In patients with a prolonged postmortem interval, or in cases where

intravascular blood is coagulated, right-heart blood may serve as a sample site. Usually just 1 site is sampled unless an unusual xenobiotic with nonuniform distribution is suspected of causing the death.

Other sources of blood are sometimes available to the forensic pathologist. These other sources include antemortem samples and, occasionally, extravasated blood, which is unlikely to undergo extensive metabolism. Intracranial clots, in particular, serve as useful comparative samples in patients with a prolonged survival period following exposure to a xenobiotic.

In advanced states of decomposition blood from the abdominal or thoracic cavities is less useful, as it can be contaminated by bacteria or other substances that may affect xenobiotic recovery and/or analysis.

Vitreous Humor

Because of the relatively avascular and acellular nature of the fluid, the vitreous humor is well protected from the early decompositional changes that typically occur in blood.[16,21,24] When bodies are immediately refrigerated, creatinine, blood urea nitrogen, and sodium can be reliably approximated from vitreous humor samples for up to 3 or 4 days. Potassium concentrations are less reliable, as cell lysis causes intracellular release. When vitreous glucose is elevated, hyperglycemia at the time of death can be assumed. A low vitreous glucose is inconclusive with regard to the antemortem serum glucose concentration. A low vitreous glucose may be a result of either antemortem hypoglycemia or postmortem glycolysis, even in the relatively avascular vitreous.

The aqueous content of the vitreous is normally higher than that of blood and may affect partitioning of certain water-soluble xenobiotics.

Urine

Urine may be available at autopsy and can reveal renally eliminated substances or their metabolites. Because the bladder serves as a reservoir in which metabolism is unlikely to occur, the concentrations of xenobiotics obtained at autopsy reflect antemortem urine concentrations. An isolated urine sample is of limited quantitative value, but may be useful when compared to other sample sites.

Gastric Contents

The gross contents of the stomach are inspected for color, odor, and the presence or absence of pill fragments, food particles, activated charcoal, and other foreign materials.[89] Typically, gastric concentrations of xenobiotics are reported as milligrams of substance per gram of total gastric contents. Xenobiotic-induced pylorospasm, diminished intestinal motility, or decreased splanchnic blood flow all may decrease gastric emptying and affect the quantitative values obtained from sampling different parts of the GI tract.

Solid Organs and Other Sources

Xenobiotic concentrations in solid organs such as liver or brain are usually reported as milligrams of substance per kilogram of tissue. Other tissue samples, including hair and nails, are used for thiol-avid agents such as metals. Rarely, tracheal aspirates of gases can be analyzed to confirm inhalational exposures. Pleural fluid analysis of postmortem xenobiotics typically yields qualitative results in decomposed bodies, as redistribution of xenobiotics from the stomach and intestines may occur.[30,81]

Other Sampling Sources

In an embalmed body, either the organs that remain, such as muscle tissue, or the embalming fluid can be used for analysis. Some countries regulate the contents of embalming fluid to specifically avoid confounding postmortem analysis. Most embalming fluid in the United States consists of formaldehyde, sodium borate, sodium nitrate, glycerin, and water. When a body is disinterred, soil samples are usually obtained from above and below the coffin site to permit identification of chemicals that may have leeched into or out of the body.

On rare occasion, cremated remains, often referred to as cremains, will be the only source of sampling available. Most metallic implants such as pacemakers are removed prior to cremation, and only dental remains, particulate matter, and, occasionally, calcified blood vessels are available for analysis.[4,97] In most cremations performed in the United States, the incineration process is followed by grinding remains to form a fine particulate matter.[97] The ability to extract xenobiotics from such samples is markedly limited at best, and there are few published data on the subject. A new technique to identify such heavy metals as lead from cremains has been described but is not routinely used at present.[4,97]

Entomotoxicology

In putrefied bodies and in bodies that have undergone anthropophagy, fluids and insect parts can be analyzed. Forensic entomologists collect samples of these insects from the remains and after taking into account the stage of insect life, environmental conditions, and season, can extrapolate the approximate time of death. The species *Calliphoridae*, or bluebottle fly, is attracted to unprotected remains by a very fine scent that develops in the body

within hours of death. The adult fly lays eggs on mucosal surfaces

or in open wounds. Once the eggs hatch, the larvae feed on the decomposing tissue. Larval samples can be examined for the presence of toxins. To achieve accurate analysis, these samples must be collected and preserved immediately, because living larvae can continue to metabolize certain xenobiotics. In another phase of their life cycle, the larvae undergo pupation, secreting a substance that encloses them into pupal casings until they hatch as adults. These casings are often found in the soil beneath the body. Some toxins have been identified in the casings even after the adult fly has emerged (Table 33-5).[79] A variety of other anthropophagic insect species may demonstrate the presence of xenobiotics;[1,38,56] this process of analysis is termed *entomotoxicology.*

TABLE 33-5. Xenobiotics Reported from Larvae and Pupae Casings[38,56,79,91]

Benzoylecognine
Cocaine
Heroin
Malathion
Mercury
Methamphetamine
Morphine
Nortriptyline
Oxazepam
Phenobarbital
Triazolam

TABLE 33-6. Considerations in Interpreting Postmortem Xenobiotic Concentrations

- Xenobiotic dependent
  - Pharmacokinetic considerations
    - State of absorption/distribution at time of death
    - Postmortem redistribution
    - Postmortem metabolism
  - Pharmacodynamic considerations
    - Expected clinical effects
    - Synergistic interactions
  - Postmortem xenobiotic stability during
    - Putrefaction
    - Preservation
- Decedent dependent
  - Comorbid conditions
  - Tolerance
  - Pharmacogenetic variability
- Autopsy dependent
  - Postmortem interval: state of preservation/decomposition
  - Previously undiagnosed conditions
  - Specimens sampled
  - Sample sites
  - Handling and preservation
- Other
  - Laboratory techniques
  - Evidence at scene
  - Previously published tissue concentrations

Interpretation of Postmortem

Toxicologic Results

Once fluid and tissue samples are collected and analyzed for the presence of xenobiotics, the process of interpreting the results begins. This complex task attempts to account for the clinical effects of a xenobiotic at the time of death by integrating medical history, autopsy findings, and toxicologic reports. Multiple confounding variables can affect the sample concentrations of xenobiotics from the time of death to that of the autopsy. Variables include the nature, metabolism, and distribution of the xenobiotic, the state of health of the decedent, and the techniques and findings of the autopsy (Tables 33-6 and 33-7).

Variables Relating to the Xenobiotic

Postmortem Redistribution

Xenobiotic blood concentration may be higher at autopsy than at the time of death if the agent undergoes significant postmortem redistribution.[50,73,96,103] Most often, redistribution occurs with substances that have large volumes of distribution and when decomposition results in release of intracellular xenobiotic into the extracellular compartment.[77] For example, amitriptyline may be released from tissue into the blood as autolysis progresses, resulting in a higher blood concentration at autopsy than at the time of death. If postmortem redistribution is not considered, xenobiotic concentrations obtained at autopsy may be misinterpreted as supratherapeutic or toxic, and the cause of death may be inappropriately attributed to this agent.

TABLE 33-7. Xenobiotic Stability and Laboratory Recovery[10,12,22,27,73,79,80,87]

- Quantitative recovery affected by preservatives
  As, Pb, Hg, Cu, Ag
  Cyanide
  Carbon monoxide
  Ethchlorvynol
  Nortriptyline (converted to amitriptyline in fixatives)
- Chemical stability in formalin

Stable	Labile
Succinylcholine	Desipramine
Phenobarbital	
Diazepam	
Phenytoin (30 days)	

- Chemical stability in putrefying liver

Stable	Labile
Acetaminophen	*o*,*p*-Aminophenols
Amitriptyline	Chlordiazepoxide
Barbiturates	Chlorpromazine
Chloroform	Clonazepam
Clemastine	Malathion

Dextropropoxyphene	Metronidazole
Diazepam	Nitrofurazone
Doxepin	Nitrazepam
Flurazepam	*p*-Nitrophenol
Glutethemide	Obidoxime
Hydrochlorothiazide	Perphenazine
Imipramine	Trifluoperazine
Lorazepam Methaqualone Morphine Nicotine Paraquat Pentachlorophenol Quinine Strychnine Vegetable alkaloids	

Postmortem Metabolism

Less commonly, xenobiotic concentration may fall secondary to postmortem metabolism. For example after death, cocaine continues to be degraded by blood cholinesterases, which are

stable in postmortem tissue. Unless blood is collected immediately after the time of death in tubes containing enzyme inhibitors such as sodium fluoride, the concentration of cocaine will continue to fall and the analysis will not accurately reflect the concentration of the drug at the time of death.[55,63,94] Specific information that is available regarding postmortem redistribution or metabolism should be considered and the toxicologic results interpreted accordingly.

State of Absorption and Distribution

Both in the living and deceased, the state of absorption, distribution, and other toxicokinetic principles affect the sampling concentration of a xenobiotic. For a xenobiotic with minimal postmortem metabolism or redistribution, the phase of absorption is suggested by the relative quantity of the agent in different fluids and solid organs. For example, a high concentration of xenobiotic pill fragments in the gastric contents, with progressively lower concentrations in the liver, blood, vitreous, and brain, suggests an early phase of absorption at the time of death. When an agent is orally administered and the tissue concentration is highest in the liver, the relationship suggests a postabsorption phase but a predistribution concentration. A concentration found to be highest in the urine suggests that the xenobiotic was in an elimination phase at the time of death. Although this approach has limitations, it may be important for correlating the state of absorption and the expected clinical course of the xenobiotic. Unfortunately, multiple samples may not always be available at the time of autopsy or the interpretation of reports, and opportunities for subsequent sampling are often limited.

Xenobiotic Stability

Xenobiotic stability refers to the ability of an agent to maintain its molecular integrity despite changes during decomposition of the

body, storage conditions, or the addition of preservatives.[5,13,15,84,92,100,101 and 102] Postmortem xenobiotic stability was assessed in homogenized liver tissue infused with various concentrations of xenobiotics.[92] The samples were allowed to putrefy outdoors, and sequential sampling of xenobiotic concentrations was performed. The xenobiotics that decreased in concentration as putrefaction progressed were considered â€œlabile,â€• whereas samples with a constant concentration were considered stable. The authors proposed that the chemical moieties of a xenobiotic determine its stability. For example, labile agents share the molecular configuration of an oxygen-nitrogen bond, thiono groups, or aminophenols. Conversely, chemical structures that enhance stability include single-bonded sulfur groups, carbon-oxygen and carbon-nitrogen bonds, as well as sulfur-oxygen and hydrogen-nitrogen bonds. Although not explicitly studied in otherwise intact, putrefying bodies, logically, a less-stable xenobiotic may be recovered in a lower concentration than the actual concentration at the time of death. This must be considered when information regarding stability is available and the body of the decedent is in an advanced stage of decomposition.

Xenobiotic Chemical Interactions

An artifact may result from a chemical interaction with a xenobiotic added during the postmortem period, such as embalming fluid.[35] In a study of xenobiotic-spiked blood and formalin in test tubes, amitriptyline was formed through methylation of nortriptyline.[26] Identification of amitriptyline, which was not present at the time of death, could confuse the interpretation of toxicologic analyses.

Expected Clinical Effects of the Xenobiotic

For a fatality to be attributed to a xenobiotic, the expected clinical

course of the exposure should be consistent with the autopsy findings. For example, what are the implications if a person is found dead 90 minutes after having been seen ingesting pills and a large concentration of acetaminophen is identified in both the gastric contents and blood, but not in other tissues of a person? Although suicidal intent (manner) may be supported by this finding, the onset of death within minutes is inconsistent with a fatality from an acetaminophen overdose. Thus, another cause of death must be sought. Interpretation of postmortem toxicology must also incorporate clinically relevant consequences of xenobiotic interactions. For example, the combined ingestion of phenobarbital and ethanol can cause fatal respiratory depression. Although neither may be fatal alone, their clinical synergy must be acknowledged during toxicologic interpretation.

Variables Related to the Decedent

Comorbid Conditions

The clinical response to a xenobiotic may be affected by acquired and inherited physiologic conditions that are not always identified on autopsy. A thorough medical history is important, and may assist in interpreting the clinical effects of a xenobiotic exposure. Similarly, certain clinical conditions may produce substances that interfere with postmortmen laboratory assays. For example, an individual with a critical illness may produce digoxin-like immunoreactive substances (DLIS) which can cross-react with the postmortem digoxin assay.[6] Without knowledge of DLIS production, the results may confound toxicologic analysis.

Tolerance

Tolerance is an acquired condition in which higher and higher xenobiotic concentrations are required to produce a given clinical effect. It is an important consideration for deaths in the presence

of opioids, ethanol, and sedative-hypnotic agents. For example, respiratory depression and death from methadone is easily diagnosed in an opioid-naive individual with a history of methadone exposure and methadone-positive postmortem samples. However, the same methadone concentrations in a patient on chronic methadone maintenace therapy will not produce the same outcome. Unfortunately, there are no biochemical or histologic markers on autopsy that can be used to predict clinically dangerous xenobiotic concentrations in tolerant individuals. Complex postmortem assays analyzing opioid receptors are not routinely used.[34] Postmortem assessment of tolerance ultimately depends on knowledge of the patient, pharmacokinetics of the agent, and the best judgment of the investigator.

Pharmacogenetics

There is genetic variability in the expression of certain metabolic enzymes. For example, pharmacogenetic differences in metabolic enzymes such as CYP2D6 predispose some individuals to fatal hypotension from the inability to metabolize debrisoquine. Such distinctions are not routinely identifiable on autopsy.[28]

Variables Relating to the Autopsy

State of Decomposition

In decedents with advanced stages of decomposition, xenobiotics can diffuse from depot compartments such as the stomach or bladder into adjacent tissues and blood vessels, or secondarily affecting their sample concentrations.[22,67,68,76,77 and 78]

During putrefaction, bacteria cause fermentation of endogenous carbohydrates, resulting in ethanol formation. In decedents

without gross evidence of putrefaction, especially those in cool,

dry environments, endogenous ethanol production is minimal.[17,18] With a longer postmortem interval or in an environment more conducive to ethanol production, the distinction between endogenous and exogenous sources of ethanol becomes more difficult. Multiple sample sites are often useful in making the distinction.[93]

Handling of the Body

Inappropriate handling of the body can result in artifacts.[83,85] In one reported case, methanol was detected in the vitreous humor of a decedent, postembalming.[12] The methanol was subsequently traced to a spray cleanser that likely settled on the surface of open eyes during washing of the body.

In the United States, preservatives containing metals are currently banned for use in embalming because they can contaminate subsequent evaluation for metal poisoning. Formalin may also affect stability or quantitative identification of some xenobiotics. When necessary, an analysis of embalming fluid used by the mortician, or soil sampling around disinterred bodies, can facilitate the toxicological investigation.[19]

Autopsy Findings

In many xenobiotic-related deaths, the anatomic findings are nonspecific.[99] In some cases, the autopsy reveals confirmatory or supportive findings. A large quantity of undigested pills in the stomach is consistent with an intentional overdose, and suicide can be considered. Centrilobular hepatic necrosis may be found in decedents with a history of acetaminophen overdose. The autopsy may reveal other findings such as coronary artery narrowing, chronic hypertension, renal abnormalities, or a clinically silent myocardial injury. Such information may be useful to assess the potential effects of a xenobiotic in a patient with previously undiagnosed conditions. In other cases, the absence of a chronic

condition may be strongly suggestive of a xenobiotic-related death. For example, a decedent with an autopsy finding of aortic dissection, in the absence of chronic hypertensive findings or other predisposing conditions, may suggest a xenobiotic-induced hypertensive crisis, as may occur from use of cocaine or other sympathomimetics.

Artifacts Related to Sampling Sites

Site-specific differences in postmortem xenobiotic blood concentrations are common.[33] For example, blood drawn from femoral vessels may have a low glucose because of postmortem glycolysis, but the glucose concentration of blood removed from the right-heart chambers may be high as a result of the release of liver glycogen stores. Hyperglycemic states are more reliably assessed from sampling of the vitreous humor. An elevated vitreous glucose concentration suggests antemortem hyperglycemia. The individual interpreting the toxicologic report must know the exact site sampled.[20,54]

Ideally, more than one site is available for comparison. Multiple blood samples are not often routinely obtained. The comparison of concentrations from different sites may reveal important information regarding the state of xenobiotic absorption at the time of death, and acute versus chronic exposure.[9,10 and 11,20,25,29,48,59,63,72,74,76,77,80,81 and 82,87,88,93,95]

Other Considerations

Published therapeutic, toxic, and fatal postmortem xenobiotic concentrations are available to aid in interpretation of postmortem specimens.[3,62] However, the conditions associated with reported concentrations do not necessarily permit comparisons with those concentrations in a particular case under investigation. Thus, these resources are valuable, but should be used mainly as guidelines and not accepted as absolute values that define fatal

toxic concentrations. Similarly, formulas available for assessing xenobiotic doses or concentrations in the living, are not usually applicable when analyzing postmortem samples.

Other Limitations

Although there are generalized standards of practice in forensic investigations, specimen collection and laboratory methodology may vary.[2,3] Some xenobiotic concentrations may be falsely elevated or depressed, depending on chosen methodology.[30,64] Descriptions of specific laboratory toxicology techniques are beyond the scope of this chapter, but these variables must also be given consideration in postmortem toxicologic interpretations. Other limitations may include the lack of information relating to the circumstances of death, and possible compromises in specimen handling that affect the proper chain of custody, required in forensic autopsies.

Summary

To accurately interpret postmortem toxicologic reports, it is essential to understand potential biochemical changes and the artifacts that affect postmortem sampling. Unfortunately, because of the complexity and variety of mitigating circumstances, there is no single resource that can systematically correlate postmortem xenobiotic blood and tissue concentrations to those at the actual time of death. Postmortem toxicology is an evolving discipline that may only permit the most likely truths associated with the xenobiotic identified and the circumstances in question.[14,31,66]

Progress in this field depends on the continued collaboration between treating physicians, medical and forensic toxicologists, and forensic pathologists.

Case Discussion

A complete medical history was reported to the medical examiner including the details of his general health, why he presented to the hospital, and what transpired immediately prior to, and during the cardiac arrest. The tubing and all remaining fluid in the phenytoin infusion was saved for analysis, and the laboratory was informed to save all samples of antemortem and perimortem blood obtained during the hospitalization.

The postmortem blood from the right subclavian vein revealed lidocaine 8 Âµg/mL and phenytoin 16 Âµg/mL, but lidocaine is not commonly used during bradycardic arrests. The toxicologist therefore requested a complete medical record to determine whether this medication was administered during an attempt to restore circulation. If it was so used, lidocaine could be excluded as a cause of cardiac arrest and treated as a therapeutic artifact. Alternatively, lidocaine toxicity might have caused a bradydysrhythmia. The volume of distribution of lidocaine is between 1 and 2 L/kg and undergoes limited postmortem redistribution. If the toxicologist remains uncertain about causation, the remainder of the intravenous infusion can be analyzed for the presence of lidocaine and the possibility of a medication error. As it turned out, the resuscitation resulted in a transient episode of ventricular fibrillation that was treated with successive defibrillation and the administration of boluses of lidocaine. The remaining 40 mL of the original phenytoin infusion contained only phenytoin in a propylene glycol diluent. The conclusion was reached that the postmortem lidocaine concentration

was likely a result of resuscitative efforts and in the absence of any other autopsy findings, the bradycardic arrest was likely caused by rapid infusion of propylene glycol, as the diluent used with intravenous phenytoin.

Additional Case Discussions

Case A

A 72-year-old male with a history of atrial fibrillation is found dead 1 hour after his last dose of digoxin. The autopsy, performed the following day, demonstrated an enlarged heart and findings consistent with chronic hypertension. The postmortem right-heart blood digoxin concentration was 5.6 ng/mL. How should these results be interpreted?

This high blood concentration may reflect either the early state of absorption or postmortem redistribution of digoxin. Alternatively, the individual may have suffered death from chronic digoxin toxicity. Sampling another site, such as the vitreous humor, becomes important to make the distinction. The vitreous concentration will likely reflect the chronic concentration of digoxin as it equilibrates with blood over a period of hours after ingestion. If the vitreous humor concentration is 0.9 ng/mL and the vitreous creatinine is 0.8 mg/dL, it is unlikely that chronic digoxin toxicity was responsible for the patient's death.

Case B

A 50-year-old man with diabetes is found in an advanced stage of decomposition in his apartment during a warm summer month. The vitreous humor is cloudy and has a glucose concentration of 5 mg/dL. Right-heart ethanol concentration is 40 mg/dL. How do you interpret these values?

Unlike elevations in vitreous glucose, low vitreous glucose is inconclusive with regard to the glycemic state at the time of death. Thus, low vitreous glucose is inconclusive in establishing antemortem hypoglycemia even if the postmortem interval was relatively brief and the vitreous sample, clear. The ethanol could have been consumed prior to death, or it could have been

generated during the postmortem interval, but usually does not rise above 50 mg/dL. An ethanol sample from the brain and bladder (if available) in which ethanol undergoes less fermentation would be useful to make the distinction. Regardless of the source of the ethanol, a level of 40 mg/dL is unlikely to have caused death alone, but may be useful if aspiration, unusual bodily position, or other sedative hypnotics were also identified at autopsy.

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Special Considerations: Organ Procurement from Poisoned Patients

Rama B. Rao

Xenobiotics can cause brain death because of the vulnerabilities of the central nervous system. With supportive care, however, such patients may be suitable candidates for organ donation.[8,26] Early identification of donors is critical, as the viability of transplantable tissue diminishes as duration of brain death progresses.[26] Timely identification may be further complicated by the presence of xenobiotics that mimic brain death (Tables SC-1 and SC-2).[3,5,24]

Protocols to establish brain death are reviewed elsewhere.[3,5,24] Once brain death is established, organ procurement personnel assist in obtaining familial consent, deciding which organs are most suitable for transplant, and maximizing physiologic support and perfusion until organ procurement occurs.[26]

Successful transplantation of organs is reported from poisoned donors associated with a multitude of xenobiotics (Table SC-3).[1,2,5,7,10,18,20,21,22 and 23] Although some xenobiotics, such as cyanide and carbon monoxide (CO), are highly toxic, transfer of

clinical poisoning to the organ recipient is not reported. This is likely a result of several factors, including xenobiotic metabolism, tissue redistribution or binding prior to procurement, as well as the means of handling organs during the transplantation process. For example, some xenobiotic clearance may occur in the myocardium during organ rinsing and cardiopulmonary bypass.[20] Furthermore, individual organs may not uniformly manifest toxicity in response to xenobiotic insults. For example, the heart of a CO-poisoned donor was examined after a transplantation failure from technical reasons. The myocardium did not demonstrate histologic signs of CO poisoning.[23]

TABLE SC-1. Conditions That Can Mimic Brain Death[3,5,24]

Guillain-BarrÃ© Syndrome
Hypoglycemia
Hypothermia
Poisonings
Amitriptyline
Bismuth salts
Inhaled anesthetics
Sedative hypnotics
Barbiturates
Benzodiazepines
Meprobamate
Chloral hydrate
Trichloroethylene
Pontine hemorrhage
Rabies
Tetrodotoxin

Probably more critical to transplantation success is adequate

tissue perfusion and well-maintained cellular morphology. For example, patients suffering brain death from acetaminophen poisoning are not suitable liver donors, given the specific destruction of hepatic cells. Alternatively, xenobiotics considered toxic to organ function by impairing enzymes have resulted in successful transplantation if the cellular structure is otherwise maintained. For example, a donor with cardioactive steroid poisoning did not preclude successful heart transplantation, even when the donor had a bradydysrhythmia, elevated serum digoxin concentration, and required cardiopul-monary resuscitation.[23] In another case, the liver of a patient poisoned with brodifacoum was transplanted after donor administration

of fresh-frozen plasma and vitamin K_1. The recipient's INR (international normalized ratio) after transplantation was 2 and corrected rapidly with supportive care. Recipient concentrations of brodifacoum were not reported and not clearly causative of the elevated INR.[20] In both the examples of brodifacoum and cardioactive steroids, the target of toxicity was enzymatic and the tissue morphology was otherwise minimally affected.

TABLE SC-2. Clinical Criteria for the Diagnosis of Brain Death

No alternative cause for the clinical condition (eg, hypothermia)
Poisoning not or no longer a consideration as the cause of the clinical condition
Coma: No motor responses to appropriate painful stimuli
Absence of brainstem reflexes
  Pupillary responses to light and pupils at midposition (4â€“6 mm)
  Corneal reflexes

Caloric (oculocephalic) responses
Gag reflex
Coughing in response to tracheal suctioning
Sucking and rooting reflexes
Apnea test
Respiratory drive at a $PaCO_2$ that is 60 mm Hg or 20 mm Hg above normal baseline values
Interval between 2 evaluations, according to patient's age

Term to 2 mo, 48 h	>1 yr to < 18 yr, 12h
> 2 mo to 1 yr, 24 h	â‰¥18 yr, interval optional
Confirmatory tests	
Term to 2 mo, 2 confirmatory tests	>1 yr to <18 yr, optional
>2 mo to 1 yr, 1 confirmatory test	â‰¥18 yr, optional

Confirmatory tests include:
Cerebral angiography
Electroencephalography
Cerebral scintigraphy
Transcranial Doppler ultrasonography

TABLE SC-3. Organs Transplanted After Donor Poisonings

Organ	Xenobiotics Identified
Cornea[a1,18,20,22]	Brodifacoum, cyanide
Heart[5,10,20,23]	Acetaminophen, benzodiazepines, Î²-adrenergic antagonists, brodifacoum, carbamazepine, carbon monoxide, clomethiazole, cyanide, digitalis, digoxin, ethanol, flurazepam, glyburide, insulin, meprobamate, methanol, organic phosphorus compounds, propoxyphene, thiocyanate
Kidney[a2,7,10,20,22]	Acetaminophen, brodifacoum, carbon monoxide, cyanide, ethylene glycol, methanol, tricyclic antidepressants
Liver[7,10]	Brodifacoum, carbon monoxide, cyanide, ethylene glycol, methanol, tricyclic antidepressants
Lung[4,10,20,21,22]	Brodifacoum, carbon monoxide, methanol
Pancreas[7,20]	Acetaminophen, brodifacoum, carbon monoxide, cyanide, ethylene glycol, methanol, tricyclic antidepressants

Skin[22]	Cyanide
[a]Can be cadaveric procurement.	

Most failures of transplant organs from poisoned donors are a result of rejection, sepsis, or technical reasons. The 1-year survival in recipients of transplant organs from poisoned donors approximates that of recipients of transplant organs from nonpoisoned donors, and in one series was reported at 75%.[7]

Ideally, a comprehensive international registry of transplant organs from poisoned donors will be established to improve understanding of transplanting organs from such patients. It appears that patients who suffer brain death from poisoning are potentially suitable donors when cellular infrastructure is preserved.[16,17,19,26] Consideration for organ procurement should not be limited by the xenobiotic itself.

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Chapter 34
Acetaminophen

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Kenneth E. Bizovi

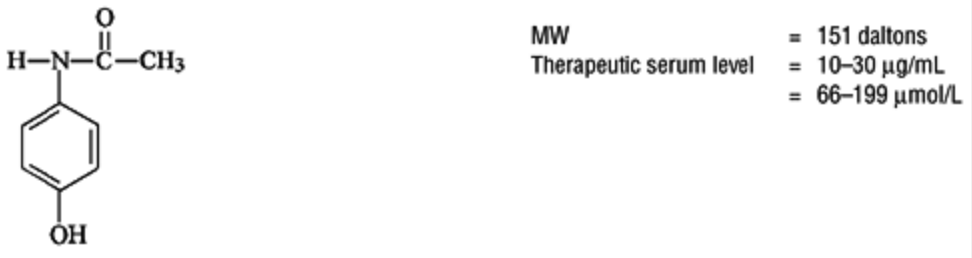


Figure. No Caption Available.

A 21-year-old woman was brought to the emergency department (ED) by her boyfriend when he learned that she ingested

approximately 30 (325-mg) acetaminophen tablets in an attempted suicide. He was unaware of any previous significant medical or psychiatric illness but reported that she was seen in another ED several days earlier for persistent headaches. He said that she did not abuse alcohol or any other drugs.

The patient was able to provide a history and admitted to taking approximately 30 tablets approximately 3 hours before coming to the hospital because she wanted to kill herself. Shortly after taking the tablets she developed a bad â€œstomach ache,â€• felt extremely nauseated, and vomited once. She denied taking any other medications or alcohol in the suicide attempt.

On physical examination the woman was diaphoretic and pale, and she appeared uncomfortable. Her vitals signs were blood pressure, 95/70 mm Hg; pulse, 100 beats/min; respiratory rate, 20 breaths/min; oral temperature, 98.6Â°F (37Â°C). Examination of the head, eyes, ears, nose, and throat was unremarkable. Her neck was supple, her lungs were clear, and the cardiac examination was within normal limits. Examination of the abdomen revealed only moderate midepigastric tenderness without peritoneal signs. Bowel sounds were normoactive. Cranial nerves were grossly intact and reflexes were 2+ bilaterally. She was oriented to time, place, and person.

The patient was given 50 g of oral activated charcoal along with 40 mL of 70% sorbitol. A 4-hour serum acetaminophen concentration was 215 Âµg/mL, and as a result the patient was treated with intravenous *N*-acetylcysteine (NAC) over 20 hours. The patient's aminotransferase concentrations remained normal, and after treatment was completed she was transferred to a psychiatric facility.

History and Epidemiology

Acetaminophen (*N*-acetyl-*p*-aminophenol [APAP]), a metabolite of phenacetin, was first used clinically in the United States in 1950. The well-known toxicity of phenacetin led to unfounded concerns about acetaminophen safety that delayed widespread acceptance of acetaminophen until the 1970s. Acetaminophen has since proved to be a remarkably safe drug at appropriate dosage, which has made acetaminophen the analgesic-antipyretic of choice in many circumstances. Acetaminophen is available alone in a myriad of single-agent dose formulations and delivery systems and in a variety of combinations with opioids, other analgesics, sedatives, decongestants, expectorants, and antihistamines.

The diversity and wide availability of acetaminophen products dictate that acetaminophen toxicity be considered not only after identified acetaminophen exposures but also after exposure to unknown or multiple drugs in settings of drug overdose, drug abuse, and therapeutic misadventures. The Toxic Exposure Surveillance System of the American Association of Poison Control Centers reports well over 100,000 calls to US poison centers each year resulting from potential acetaminophen exposures, and more hospitalizations are reported after acetaminophen overdose than after overdose of any other common pharmaceutic agent (Chap. 130).

Despite enormous experience with acetaminophen toxicity, many controversies and challenges are unresolved. In order to best understand the continuing evolution in approach to acetaminophen toxicity, it is critical to start with an analysis of certain fundamental principles and then to apply these principles to both typical and atypical presentations in which acetaminophen toxicity must be considered.

Pharmacology

Acetaminophen is an analgesic and antipyretic with weak peripheral antiinflammatory properties. Analgesic activity is

reported at a serum acetaminophen concentration ([APAP]) of 10 Âµg/mL and antipyretic activity at 4â€“18 Âµg/mL.

Antipyresis is mediated by central nervous system (CNS) inhibition of prostaglandin E_2 (PGE_2) synthesis via either direct inhibition of cyclooxygenase (COX)-2 or inhibition of membrane-associated PGE synthase.[10,93,104,148] PGE synthase inhibition may be a result of local reductions of glutathione concentrations initiated by conversion of APAP to reactive metabolites via the COX-2 enzyme.[104] Although binding and inhibition of COX-3 by APAP may have an antipyretic effect,[34,35,57] its clinical relevance remains unclear.[31,104]

The analgesic effect of acetaminophen is also mediated by its central inhibition of COX-2 and prostaglandin synthase and by possible indirect modulation of serotonergic pathways.[104] In animal models, several serotonin antagonists, as well as serotonin depletion, inhibit the analgesic effect of APAP.[2,30,192,193,230] This effect may be a result of decreased stimulation of serotonergic neurons from APAP-induced inhibition of prostaglandin synthesis.[104] Additional effects may be linked to indirect stimulation of descending opioid pathways.[212,213]

Although APAP functions as a central COX-2 inhibitor, it has mild peripheral antiinflammatory properties that are attributed to its mild inhibition of peripheral prostaglandin synthetase[96] and limited inhibition of peripheral COX.[64] APAP previously was considered a weak inhibitor of peripheral COX in general; however, its poor peripheral antiinflammatory properties more likely are the result of differences in receptor utilization (COX-1 and COX-2) in various cellular conditions.[103,104] In circumstances where peroxidase and arachidonic acid concentrations are low, such as in the CNS, prostaglandin is predominantly metabolized by COX-2,[178] and prostaglandin synthesis is blocked by APAP.[180] However, in peripheral inflammatory lesions, where peroxidase and arachidonic acid concentrations are elevated, COX-1 metabolism predominates,

and APAP is less effective in decreasing inflammation.[36,104,109]

Pharmacokinetics

Following oral ingestion, immediate-release acetaminophen is rapidly absorbed with a time to peak [APAP] of approximately 45 minutes.[4,77] Liquid acetaminophen has a time to peak of 30 minutes.[4,77] Extended-release acetaminophen has a time to peak of 1â€“2 hours but is almost entirely absorbed by 4 hours.[81] Time to peak is delayed by food[77] and coingestion of opioids or anticholinergic agents.[107,177] Oral bioavailability is 60â€“98%. Peak [APAP] after recommended dose ranges from 8â€“32 Âµg/mL. After administration of rectal suppositories in children, the time to peak [APAP] ranged from 107â€“288 minutes, with bioavailability of 30â€“40%. Peak [APAP] after single 20-mg/kg doses given rectally varied from 4.1â€“13.6 mg/L.[23] Acetaminophen has total protein binding of 10â€–30% that does not change in overdose.[167] APAP crosses both the placenta and the bloodâ€–brain barrier.[147]

First-pass metabolism removes 25% of a therapeutic dose. Once absorbed, approximately 90% of acetaminophen normally undergoes hepatic conjugation with glucuronide (40â€“67%) and sulfate (20â€–46%) to form inactive metabolites, which are eliminated in the urine.[231] A small fraction of unchanged acetaminophen (<5%) and other minor metabolites reaches the urine but is not thought to be clinically relevant.[204,231] The remaining fraction, which usually ranges from 5â€–15%, is oxidized by CYP2E1 (and, to a lesser extent, CYP3A4, CYP2A6 and CYP1A2),[114,159] resulting in the formation *N*-acetyl-*p*-benzoquinoneimine (NAPQI).[66] Glutathione quickly combines with NAPQI, and the resulting complex is converted to nontoxic cysteine or mercaptate conjugates, which are eliminated in the urine (Fig. 34-1).[166,173] The elimination half-life of acetaminophen is approximately 2â€–3 hours after a nontoxic dose[4,209] but may become prolonged in patients who develop hepatotoxicity.[209]

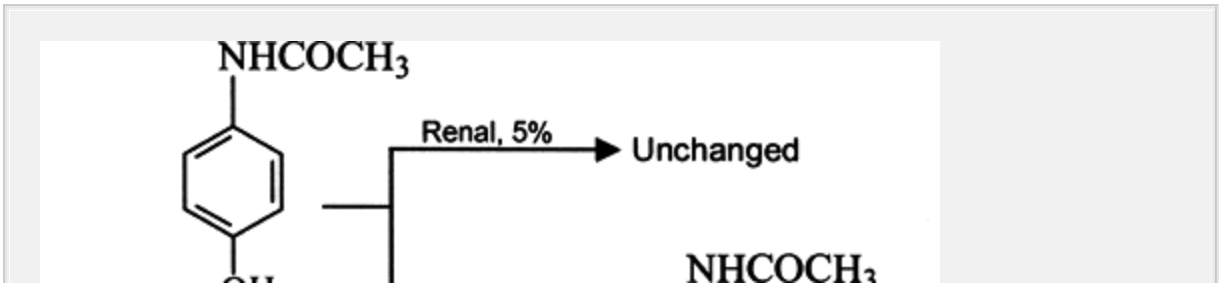
Biliary excretion is minimal, and breast milk contains <2% of the maternal dose.[184]

Toxicokinetics

Even after overdose, the majority of acetaminophen absorption occurs within 2 hours. Peak plasma concentrations generally occur within 4 hours, although later peaks are rarely documented in overdoses.[202,265] After clinically significant overdose, saturation of the normal nontoxic routes (sulfation) of metabolism becomes important in the development of toxicity.[200] The amount of NAPQI formed is increased out of proportion to the acetaminophen dose because maximal rates of sulfation are exceeded (see Fig. 34-1).[72] Glucuronidation, although initially believed to be saturatable, is likely only saturated in severely poisoned patients.[198] In addition to an increase in the formation of toxic metabolite, overall elimination is prolonged as normal metabolic systems become saturated.

An exact understanding of P450 metabolism, which is fundamental to assessing the relationship between ethanol or other

concomitant xenobiotic use and acetaminophen toxicity, continues to evolve. Evidence suggests that NAPQI production is largely the result of activity of the CYP2E1 enzyme following both therapeutic and supratherapeutic doses of APAP.[114,159] Contributions of CYP1A2, CYP3A4, and CYP2A6 to the production of NAPQI in humans are small and insignificant, but they may be variable depending on individual host factors and dosage.[114,188,214,262]



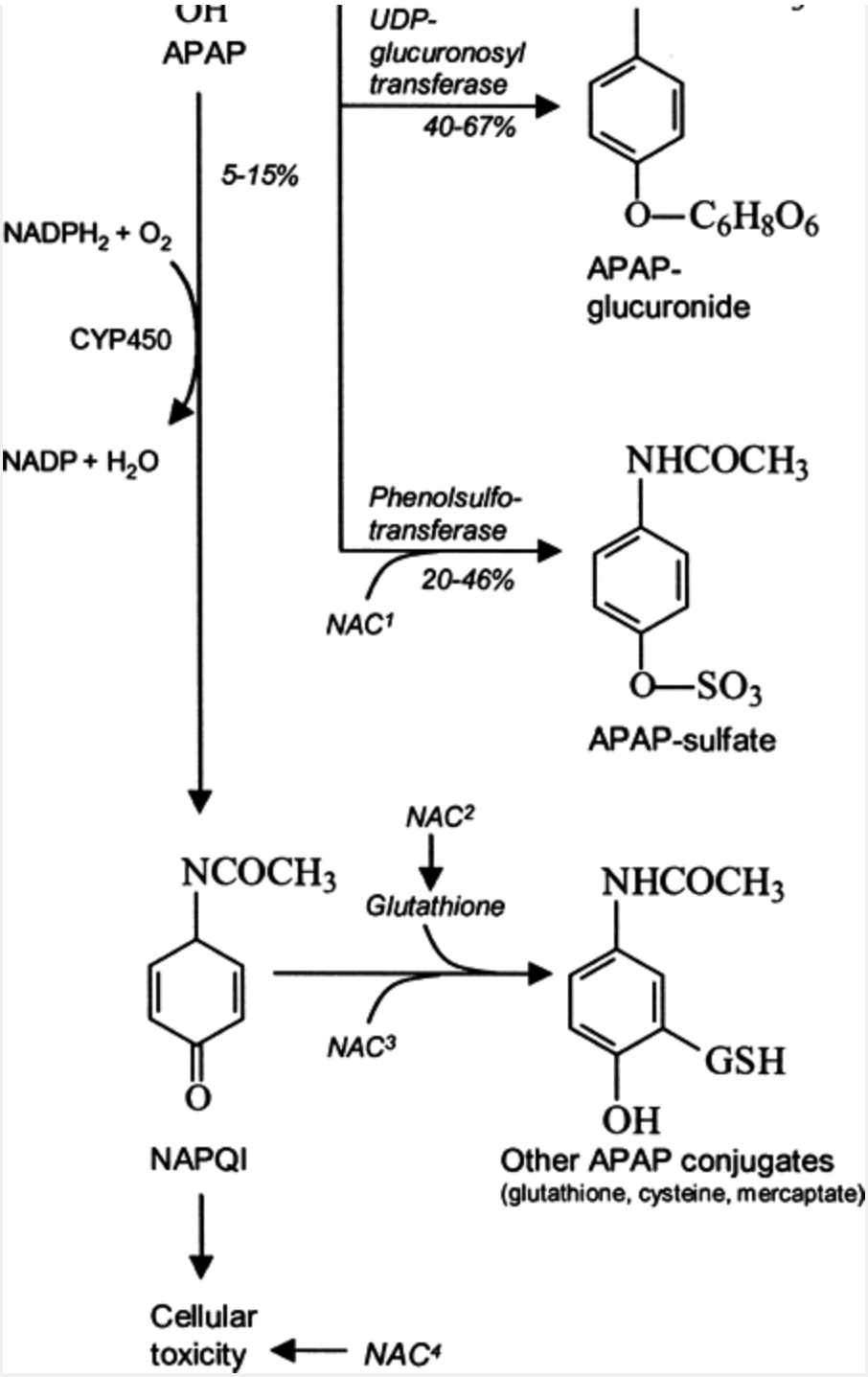


Figure 34-1. Important routes of acetaminophen metabolism in man and mechanisms of *N*-acetylcysteine (NAC) hepatoprotection. NAC[1] augments nontoxic sulfation. NAC[2] is a

glutathione (GSH) precursor. NAC[3] is a GSH substitute. NAC[4] improves multiorgan function during hepatic failure and possibly limits extent of hepatocyte injury. APAP = *N*-acetyl-*p*-aminophenol.

Pathophysiology

After the earliest reports,[70,257] a flurry of subsequent case reports, and the first reported series of acetaminophen toxicity,[154,209,210] an intensive research effort clarified the metabolic basis of both the pharmacologic safety and the toxicologic danger of acetaminophen (see Fig. 34-1).[125,171,172,196]

The safety of appropriate acetaminophen dosing results from the availability of electron donors such as reduced glutathione (GSH) and other thiol-containing compounds. After therapeutic acetaminophen dosing, GSH supply far exceeds that required to detoxify NAPQI, and no toxicity occurs. After overdose, the rate and quantity of NAPQI formation outstrip supply and regeneration of GSH, resulting in free NAPQI rapidly binding to hepatocyte constituents. In animal experiments of acetaminophen overdose, hepatic toxicity becomes evident only when hepatic GSH falls to â‰¤30% of baseline.[171] This affords acetaminophen a remarkably safe therapeutic index: A therapeutic acetaminophen dose is 10â€“15 mg/kg, whereas significant toxicity after a single acute overdose generally involves doses â‰¥150 mg/kg.[201]

Once NAPQI formation overwhelms the supply of thiol-containing compounds, it covalently binds and arylates critical cell proteins, inducing a series of events that result in cell death.[125] This covalent binding and arylation occurs rapidly after glutathione depletion and within hours of ingestion.[22,121,125,216] Once thought to be an irreversible process resulting directly from covalent binding of NAPQI, it now is clear that the events leading to cell

death are far more complex, and, most importantly, that the process can be prevented, interrupted, and even reversed after binding has occurred.[47,75,101,121,194,216]

Which, if any, single event is critical and commits the cell to death is unknown. NAPQI-induced oxidation of enzymes alters normal cell functions and impairs cell defenses against endogenous reactive oxygen species, resulting in further oxidation of vital proteins.[216,267] Selective arylation of critical cell proteins likely is more important than total covalent binding as a determinant of toxicity. Subsequent intracellular calcium dyshomeostasis[175,266] and lipid peroxidation[281] each has been demonstrated, but neither process is consistently required or sufficient to result in cell death.[45,106,110] Critical, possibly irreversible, events in cell death include DNA fragmentation[237] resulting from interactions with topoisomerase 2-Î±,[17] increases in mitochondrial permeability,[216] and mitochondrial injury,[78] but further work is required to reliably define the trigger(s) of acetaminophen-induced cell death. The final pathway of cell death may vary, with evidence for apoptosis early in APAP toxicity and direct necrosis later.[157,215] Macrophages, neutrophils, and inflammatory cells infiltrate after necrosis,[143] and destruction caused by secondary inflammation[295] and impairment of microcirculation[170] are demonstrated, although neither appears to be necessary for hepatic injury.[120,143,280]

Factors that may predispose patients to hepatotoxicity include increased frequency of acetaminophen dosing, prolonged duration of excessive dosing, increased capacity for CYP2E1 activation to NAPQI, decreased GSH availability, and decreased capacity for glucuronidation and sulfation. Potentially more important than the actual concentration of GSH or the activity of CYP2E1 is the balance of these two factors. Despite experimental evidence for all of the factors, clinical consideration of these factors is complex and controversial.

The pathophysiology of most organ dysfunction resulting from

acetaminophen toxicity results from the local formation of acetaminophen metabolites. Normally, most oxidative drug metabolism, and the majority of CYP2E1, is concentrated in hepatic zone III (centrilobular), and this zone is the first and the most profoundly affected by acetaminophen toxicity (Chap. 26). In more severe cases, necrosis may extend into zones I and II, destroying the entire liver parenchyma. In perhaps 25% of cases with significant elevated hepatic enzyme concentration, clinically evident renal injury also

occurs.[201] Evidence of mild renal injury may be evident even with little or no elevated aminotransferase concentrations after an acute overdose.[37] Renal CYP2E1 formation of NAPQI is the likely cause of acute proximal renal tubular necrosis after acute overdose;[43,87,117] however, several other nephrotoxic mechanisms are proposed.[113] Conversion of acetaminophen to nephrotoxic *p*-aminophenol[54] and renal conversion of hepatically derived acetaminophen-GSH,[174] both demonstrated in selected animal models, likely are not significant.[86,88,163] NAPQI formation via renal prostaglandin synthetase[274] or prostaglandin-mediated renal medullary ischemia[207] is also suspected of contributing to chronic analgesic nephropathy from acetaminophen alone or in combination with other analgesics.[97,217,229] Volume depletion and hepatorenal syndrome may be contributory cofactors.

Injury to other organs is rarely reported. Whether the etiology of these injuries is caused by local or circulating toxic metabolites is controversial. The mechanism causing myocardial damage, reported in some patients with acetaminophen-induced fulminant hepatic failure, is thought to be part of multisystem organ failure rather than being acetaminophen specific.[44,152] Pancreatic injury from acetaminophen, experimentally produced in mice, appears not to be the result of NAPQI formation,[94] and the paucity of human cases prevents analysis of the specific toxic mechanism. Glutathione depletion in rat brain[55] is suggested as a possible

cause of CNS effects of acetaminophen, but this finding is inconsistent,[21] and the mechanism of early manifestations of CNS depression associated only with massive acetaminophen overdoses is undefined. Similarly, an acetaminophen-induced metabolic acidosis may occur as an early manifestation after massive ingestion of APAP, typically in association with depression of mental status,[95,105,137,222,251] and may be a result of alterations in mitochondrial respiratory function.[51,91,253] The elevated anion gap acidosis may or may not be accompanied by lactic acidemia.

The remaining sequelae of severe toxicity are secondary effects of fulminant liver failure rather than direct acetaminophen effects, and the pathophysiology of these complex multisystem problems is well described.[144] The ability of NAC to ameliorate secondary multiorgan failure via extrahepatic mechanisms suggests that oxidation of vital thiols and loss of normal microvascular function are important components of secondary organ failure.[112]

Clinical Manifestations

Early recognition and treatment of patients with acetaminophen poisoning are essential in order to minimize morbidity and mortality. This task is made difficult by the lack of predictive clinical findings early in the course of acetaminophen poisoning, and clinicians should not be reassured by the absence of clinical symptoms shortly after ingestion. The first symptoms after acetaminophen overdose may be those of hepatic injury, which develop many hours after the ingestion when antidotal therapy will have diminished efficacy.

The clinical course of acute acetaminophen toxicity can be divided into four stages.[227] During *stage I* toxicity, hepatic injury has not yet occurred, and even patients who ultimately develop severe hepatotoxicity may be asymptomatic. Clinical findings, when present, are nonspecific and may include nausea, vomiting, malaise, pallor, and diaphoresis. Laboratory indices of liver

function are normal. In extremely rare cases of massive overdose, a decreased level of consciousness and metabolic acidosis may occur during this stage in the absence of signs or symptoms of hepatotoxicity.[95,137,222,251,293] These clinical findings should never be attributed to acetaminophen alone without thorough evaluation of other possible causes.

Stage II represents the onset of liver injury, which occurs in a fraction of those who overdose. When stage II occurs, onset is most common within 24 hours after ingestion but is nearly universal by 36 hours.[238] Symptoms and signs during stage II vary with the severity of liver injury but mimic other causes of hepatocellular injury such as infectious hepatitis. Aspartate aminotransferase (AST) is the most sensitive, widely available measure to detect the onset of hepatotoxicity, and AST abnormalities always precede evidence of actual liver dysfunction (prolonged prothrombin time [PT], elevated bilirubin concentration, hypoglycemia, and metabolic acidosis). Although uncommon, elevated AST concentrations may occur as early as 8â€“12 hours after ingestion in the most severely poisoned patients.[238] When discussing APAP, by convention *hepatotoxicity* is defined as a peak AST concentration >1000 IU/L. Although lower peak concentrations of AST represent some injury to hepatic tissue, they rarely have any clinical relevance.

Stage III, defined as the time of maximal hepatotoxicity, most commonly occurs between 72 and 96 hours after ingestion. The clinical manifestations of stage III include fulminant hepatic failure with encephalopathy, coma, or exsanguinating hemorrhage. Results of laboratory studies are variable: AST and alanine aminotransferase (ALT) concentrations >10,000 IU/L are common, even in patients without other evidence of liver failure. In fact, the highest reported ALT concentration caused by acetaminophen toxicity is >100,000 IU/L.[186] Much more important than the degree of aminotransferase concentration elevation, abnormalities of PT, bilirubin, glucose, lactate, and phosphate concentrations,

and pH indicate the degree of liver failure and are essential determinants of prognosis and treatment.

Fatalities from fulminant hepatic failure generally occur between 3 and 5 days after an acute overdose. Death results from either single or combined complications of multiorgan failure, including hemorrhage, acute respiratory distress syndrome, sepsis, and cerebral edema.[156] Patients who survive this period reach *stage IV*, defined as the recovery phase. Hepatic regeneration becomes complete in survivors. No cases of chronic hepatic dysfunction attributable solely to acetaminophen poisoning have been reported. The rate of recovery varies; in most cases, laboratory evaluation is normal by 5â€“7 days after an acute overdose. However, recovery may take much longer in severely poisoned patients, and histologic abnormalities may persist for months.[146,160,195]

Renal function abnormalities are rare overall[108,201] but occur in as many as 25% of patients with significant hepatotoxicity[69,208] and in >50% of those with hepatic failure.[156,285] Infrequently, mild renal insufficiency occurs without elevations in aminotransferase concentrations.[37] Renal abnormalities may be more common after sustained repeated excessive dosing.[203] When overt renal failure necessitating hemodialysis occurs, it nearly always does so among patients with marked hepatic injury.[53] In cases of acetaminophen-induced fulminant hepatic failure, the incidence of acute renal failure is nearly the same as among patients with hepatic failure of other causes.[285]

Serious clinical manifestations other than hepatic and renal injury are unusual. Electrocardiographic and histologic evidence of myocardial injury, first noted in early case reports,[63,190] is most often noted in patients with fulminant hepatic and multisystem failure, but never as an isolated problem.[152] Hyperamylasemia and pancreatitis[80,102] have been attributed to acetaminophen overdose

alone or in combination with ethanol abuse.[90] Clinical findings in these rare cases are typical of acute pancreatitis.

Diagnostic Testing

Assessing the Risk of Toxicity

Principles That Guide the Diagnostic Approach

Fatalities from acetaminophen overdose are common but preventable by timely diagnosis and treatment with NAC. At the same time, the overwhelming majority of acetaminophen exposures result in no toxicity. Therefore, an appropriate approach must avoid the enormous costs of unnecessary overtreatment while eliminating patient risk. To balance these seemingly divergent goals, the clinician must understand the basis for and sensitivity of current toxicity screening methods.

When considering risk determination, it is useful to separate different categories of acetaminophen exposure. There is an extensive body of experience and literature on acute overdose in typical circumstances, permitting a more systematic approach with demonstrated efficacy. For issues related to repeated excessive acetaminophen dosing, uncertain circumstances, patients with possible predisposition to toxicity, new acetaminophen formulations, and many other permutations, there is an important conceptual framework for decision making but little in the way of validated strategies. For these challenges, the central concepts and one approach are presented, with the understanding that they are dynamic and that more than one approach may have validity.

The clinician must rely solely upon the often unreliable ingestion history and measurement of [APAP] in the patient to assess the risk for subsequent toxicity and thus the need for treatment for

the following reasons: the amount and rate of NAPQI formation, the availability of hepatic GSH, the balance of NAPQI formation (CYP2E1 activity) and hepatic GSH supply, and the capacity for nontoxic metabolism are major determinants of toxicity.[169,225] Thus the ideal model for determining risk after acetaminophen overdose assesses each of these factors. At present, none of these measures is available to clinicians. The profile of urinary acetaminophen metabolites may reflect increased NAPQI formation,[72] but there is no indication that measurement is of any predictive value in any given case. Plasma GSH concentration can be measured but has an uncertain relationship to hepatic GSH availability.[246] Protein adducts, indicating binding of NAPQI to hepatocyte proteins, can be determined experimentally and are a marker of covalent binding[211,279] but are unlikely to prove useful as a screening measure. Because some degree of hepatocyte necrosis must precede the appearance of measurable serum adducts, the early warning value of the test is limited. Prior to actual hepatotoxicity, there are no reliable indirect measures of acetaminophen excess.

Risk Determination After Acute Overdose

Acute overdose usually is considered a single ingestion, although in fact many patients overdose incrementally over a brief period of time. For purposes of this discussion, an *acute overdose* is arbitrarily defined as one in which the entire ingestion occurs within a single 4-hour period. Figures of 7.5 g in an adult or 150 mg/kg in a child are widely disseminated as the lowest acute dose capable of causing toxicity.[7,151,201] These standards have stood the test of time as sensitive markers, but they are not based on human data and are quite conservative. Although there is wide interspecies variation in susceptibility to acetaminophen,[203] animal data suggest that a single dose of at least 15 g is required to cause consequential GSH depletion in a human adult.[173]

Higher dose cutoffs for consideration of risk would improve specificity; however, the value of improving specificity has not been weighed against the current, sensitive lower cutoff. In the face of an enormous variety of potential outliers, the near absence of screening failures almost certainly results from the use of these standards and of a very sensitive screening nomogram. The adult standard may be considered less controversial than that for children because massive ingestions, unreliable histories, and factors that might predispose to toxicity occur primarily in adults, justifying continued use of 7.5 g as a screening amount to avoid missing serious toxicity.

The dose history should be used in the assessment of risk only if there is reliable corroboration or direct evidence of validity. Therefore, dose estimates may be useful in determining risk in many cases of unintentional or therapeutic acetaminophen exposures, but this information is not sufficiently reliable in patients with attempted self-harm or drug abuse. When the history suggests possible risk, however, the reported dose is insufficient evidence on which to base treatment decisions; risk then should be assessed using determination of [APAP].

Interpretation of [APAP] after acute exposures is based on adaptation of the Rumack-Matthew nomogram (Fig. 34-2).[226] The original nomogram was based on the observation that untreated patients who subsequently developed AST or ALT concentrations >1000 IU/L could be separated from those who did not on the basis of the initial [APAP]. A nomogram was constructed that

plotted the ln [initial APAP] versus time since ingestion, and a discriminatory line was drawn to separate patients who developed hepatotoxicity from those who did not. The initial discriminatory line stretched from [APAP] of 300 Âµg/mL at 4 hours to 50 Âµg/mL at 12 hours but was lowered to between 200 Âµg/mL at 4 hours and 50 Âµg/mL at 12 hours after evaluation of additional patients.[225] The half-life of acetaminophen was not a factor in the

development of the nomogram, and the slope of the treatment line does not reflect any discriminatory APAP half-life or acetaminophen kinetics.[225] Although patients who develop hepatotoxicity tend to have half-lives greater than 4 hours,[206] use of a half-life to determine risk is not practical. At the time the nomogram was developed, acetaminophen absorption was known to be generally complete within 4 hours, so the nomogram does not begin until 4 hours after ingestion. The nomogram was later extrapolated to 24 hours using the same slope of the original nomogram line.[225]

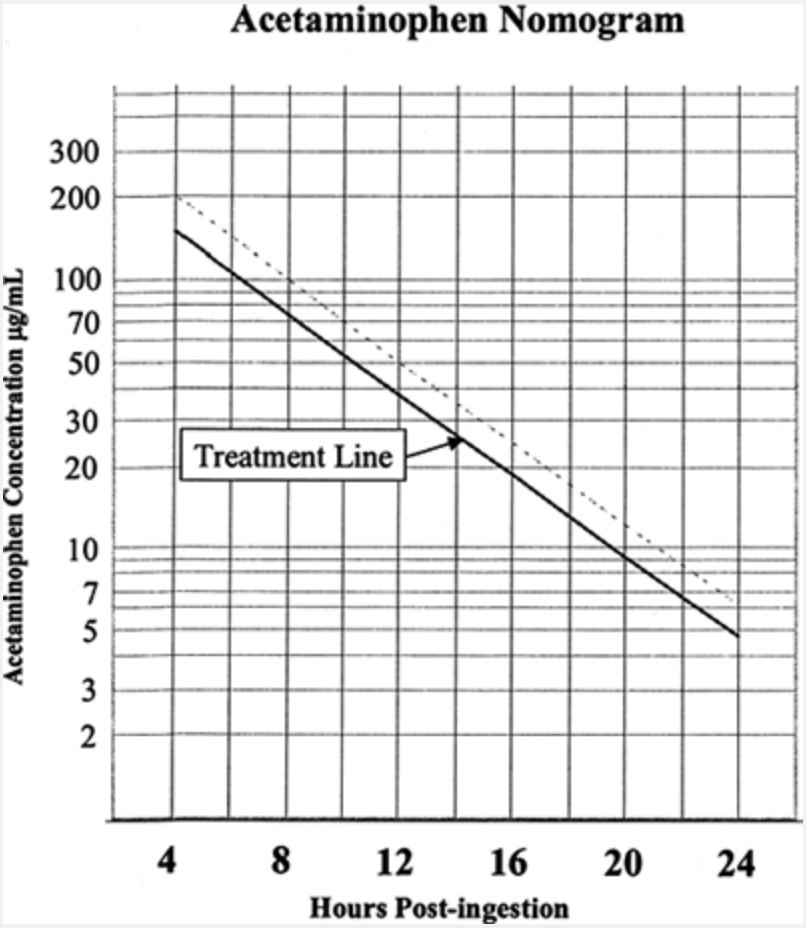


Figure 34-2. The Rumack-Matthew nomogram (reconstructed) for determining the risk of acetaminophen-induced

hepatoxicity following a single acute ingestion. Levels above the treatment line on the nomogram indicate the need for *N*-acetylcysteine therapy.

It is important to realize that the line was based on aminotransferase concentration elevation rather than on hepatic failure or death, and it was chosen to be very sensitive, with little regard to specificity. Without antidotal therapy, only 60% of those with an initial [APAP] above this original line will develop hepatotoxicity as defined by aminotransferase concentrations >1000 IU/L,[205] but the risk of hepatotoxicity is not the same for all such patients. Elevated aminotransferase concentration develops in virtually all untreated patients with [APAP] far above the line and serious hepatic dysfunction occurs frequently, whereas the incidence of hepatotoxicity among untreated cases with [APAP] immediately above the line is very low, and the risk of hepatic failure or death is far less.[201,205]

The original line is still used in the United Kingdom, Canada, Europe, Australia, and other locations. The line used in the United States runs parallel to the original but was arbitrarily lowered by 25% in order to add even greater sensitivity.[225,227] The lower line, subsequently referred to as the *treatment line*, starts at an [APAP] of 150 Âµg/mL at 4 hours postingestion; declines with a 4-hour half-life; and ends at 4.7 Âµg/mL, 24 hours after the overdose. The treatment line is one of the most sensitive screening tools used in medicine. The incidence of nomogram failures in the United States, using this line, is only 1â€“3% (depending on time to treatment) and most likely results predominately from inaccurate ingestion histories.[225] A vanishingly small number of anecdotal cases of nomogram failure involve special circumstances of increased risk,[59,162,179] questionable facts, or both.[241]

Cases of nomogram failure using the original line in the United

Kingdom are published. In some cases the patients described had no potentially predisposing factors,[46] and all had [APAP] above the *treatment line* and below the original line. Some authors suggest that the incidence of nomogram failures may be higher in the United Kingdom and recommend that the nomogram being used in the United Kingdom is not sensitive enough for patients with comorbid factors that potentially predispose to hepatotoxicity.[42,46,71,270] The validity of this observation is not adequately studied.

Based on these observations and more than 20 years of use, the treatment line should be considered an adequate screening device in nearly all cases and reliable when rigorously followed. When using the acetaminophen nomogram, it is essential to precisely define the time â€œwindowâ€• during which acetaminophen exposure occurred and, if the time is unknown, to use the earliest possible time as the time of ingestion. Using this approach, patients with [APAP] below the treatment line, even if only slightly so, do not require further evaluation or treatment for acute acetaminophen overdose. This also applies to most patients with factors that may predispose them to acetaminophen-induced hepatotoxicity. There appears to be adequate experience with acute acetaminophen overdose in the settings of potentially predisposing factors such as chronic alcohol abuse, chronic medication with CYP-inducing drugs, and inadequate nutrition to recommend that no special approach is required in such cases. Further study is needed to determine whether there are exceptions. Isolated case reports[179] suggest that chronic use of isoniazid, for example, may uniquely predispose patients to toxicity after acetaminophen overdose.[89,291]

The goal should be to determine [APAP] at the earliest point at which it will be meaningful in decision making. Measurement of [APAP] 4 hours after ingestion or as soon as possible thereafter is used to *confirm* risk of toxicity and thus the need to initiate NAC. There are no established guidelines for use of determinations

made less than 4 hours after ingestion, and because of variability in absorption such values will have less predictive value. Although it is optimal to start NAC therapy as soon as possible after confirmation of risk, most patients will have excellent outcomes if therapy is started earlier than 8 hours after the overdose.[243] Although this fact is not a license to delay the initiation of NAC treatment until 8 hours postingestion, it allows clinicians some leeway to wait for the laboratory results of [APAP] prior to starting therapy in patients in whom the history of ingestion suggests that concentration will fall below the treatment line. Factors that complicate diagnostic decision making after acute overdose include situations that prevent the return of an [APAP] measurement prior to 8 hours postingestion, inability to establish the time of ingestion, presentation more than 24 hours postingestion, and newer formulations of acetaminophen.

Only if the results of [APAP] determination cannot be obtained within 8 hours of the overdose should history alone be considered adequate to consider the patient at risk and as an indication to start NAC. In such cases, [APAP] still should be determined as soon as possible. The result, when it becomes available, should be interpreted according to the treatment line on the acetaminophen nomogram and NAC either continued or discontinued on the basis of this result. In the unusual circumstance where no determination of [APAP] can ever be obtained, evidence of possible risk by history alone is sufficient to initiate and complete a course of NAC therapy.

Early Measurement of [APAP]

Measurement of [APAP] between 1 and 4 hours after ingestion may be helpful only to exclude ingestion of APAP. If [APAP] is <10 Âµg/mL in this time frame, significant APAP overdose can be excluded. However, an [APAP] that is detectable between 1 and 4 hours cannot be interpreted and mandates a repeat [APAP] at 4

hours.

Determination of Risk When the Acetaminophen Nomogram is not Applicable

Risk Determined When Time of Ingestion Is Unknown

Another challenging variation on risk determination is the case where the time of ingestion simply cannot be determined. Although this is a common initial concern, it is unusual after thoughtful questioning of the patient, family, and others. It is almost always possible to at least establish a time window during which the exposure must have occurred and then use the earliest possible time as the time of ingestion for risk-determination purposes. If this time window cannot be established or is so broad that it encompasses a span of more than 24 hours, the following approach is suggested. Determine both [APAP] and AST concentration. If AST concentration is

elevated, regardless of [APAP], treat with NAC. If [APAP] is below the lower level of detection and AST concentration is normal, there is no evidence that subsequent consequential hepatic injury is possible and NAC is unnecessary. Although some authors speculate that subsequent liver injury could follow an interval during which [APAP] is negligible and AST concentration is normal, there are no documented cases of serious hepatotoxicity under these conditions. In all cases there has been either elevation of AST concentration and/or prolonged acetaminophen elimination resulting in a measurable [APAP] beyond 24 hours.

In the remaining cases in which the time of ingestion is completely unknown and [APAP] is detectable, it is prudent to assume that the

patient is at risk and to initiate treatment with NAC.

Risk Assessment After Extended-Release Acetaminophen

Previously, acetaminophen formulations were all immediate-release acetaminophen preparations, and exposures to these agents formed the basis for the nomogram and a successful diagnostic and therapeutic approach. An alternative extended-release formulation (Extended Relief Tylenol, Tylenol 8 Hour, Tylenol Arthritis Pain) consists of an outer 325-mg immediate-release acetaminophen dose and an inner 325-mg dose designed for delayed dissolution. These dissolution characteristics have given rise to concerns about whether the nomogram is an appropriate method for evaluating patients with suspected overdose of products containing this formulation.

The manufacturer initially recommended additional measurements of [APAP] if the 4-hour [APAP] was below the treatment line.[257] Treatment with NAC was recommended if the second value was above the treatment line. This approach was based on concern that an initial [APAP] below the line could be followed by a subsequent value above the line and place the patient at risk for hepatotoxicity. Critical evaluation of the available information confirms that such treatment line â€œcrossingâ€• is likely[56,271] in extended-release overdose and occurs in up to 10% of overdoses of immediate-release formulations.[49] However, despite intuitive concerns, there is no evidence of additional risk to the patient.

Reliance upon an initial [APAP] below the line that fails to detect a patient whose subsequent [APAP] is above the line is not the issue. What is important is whether reliance upon an initial [APAP] below the line would fail to detect a patient who subsequently might develop consequential liver injury. Although a single [APAP] will miss treatment line â€œcrossingâ€• because of limited early

absorption of acetaminophen and lack of late sustained elevations in [APAP],[56,81,252] such cases are very unlikely to place the patient at risk for toxicity. In addition, after ingestion of extended-release acetaminophen, absorption may be delayed but nevertheless is nearly complete at 4 hours.[56,81,252] The continued absorption likely will produce a 4-hour [APAP] that is higher than after ingestion of the same dose of immediate-release acetaminophen, making the treatment line more conservative than for immediate-release acetaminophen ingestions. Therefore, unless unusual circumstances are evident, a single [APAP] determination, plotted on the nomogram, should be adequate to exclude the need for antidotal therapy even after extended-release acetaminophen overdose. The validity of this conclusion requires ongoing evaluation, and any new type of extended-release acetaminophen formulation must be evaluated individually.

[APAP] Elimination Half-Life: Utility in Risk Assessment

Although it seems logical that the elimination half-life of acetaminophen would correlate with the risk of hepatotoxicity, serial [APAP] is not clinically useful in acute overdose for several reasons. First, even after massive overdose the half-life of acetaminophen is highly variable and may be less than 4 hours even in patients at risk for hepatotoxicity.[134] Second, the accuracy of determining a half-life using only two data points is variable because of the potential for multiplying inherent laboratory ranges in [APAP] testing. Finally, half-life testing adds little to the sensitivity of the nomogram. In one study, in order to equal the sensitivity of a single [APAP] plotted on the nomogram, a half-life cutoff of 2.5 hours or less would be necessary.[245]

Patients With Signs or Symptoms of Hepatic Injury After Acute Ingestion

Patients who present with signs or symptoms of hepatic injury after acute acetaminophen ingestion should be immediately started on NAC and measurements of AST concentration and [APAP] obtained. In patients with elevated AST concentration and [APAP] that is below the treatment line, the history should be reviewed with respect to the timing of ingestion and repeat excessive acetaminophen dosing. The patients should be thoroughly evaluated for causes of hepatic failure and for other causes of elevated AST concentration.

Risk Determination After Chronic Overdose Exposure

There are no well-established guidelines for risk determination after repeated acetaminophen exposures; nonetheless, careful interpretation of laboratory testing may make a relative risk assessment possible. In order to consider risk assessment after chronic APAP exposure, several factors must be considered. First, hepatotoxicity from repeated therapeutic dosing is remarkably rare given the extent of acetaminophen use. Second, therapeutic doses appear to be safe in most patients. Third, despite such patients representing only a small fraction of those using acetaminophen, nearly all reported cases of â€œchronicâ€• acetaminophen toxicity involve patients who ingested supratherapeutic doses and had factors that potentially predisposed them to acetaminophen-induced hepatic injury: infants with febrile illness who have received excessive dosing;[52,58,62,74,83,115,183,247,255] chronic alcohol users;[14,18,235,296] and patients taking CYP2E1-inducing medications chronically.[38,42] Short-term fasting is also suggested as a factor;[283] however, it is impossible to determine whether fasting was causal or was merely a marker of the severity of other associated conditions.

Conceptually, the groups that are at â€œhigh riskâ€• for hepatotoxicity after chronic overdosage of acetaminophen have

either potentially increased activity of CYP2E1, and therefore additional NAPQI formation, or decreased glutathione stores and turnover rate. However, these two risk factors cannot be taken in isolation because it is the balance of these two factors that determines the risk of hepatotoxicity. For example, malnourished patients have been theorized to be at high risk for hepatotoxicity after chronic overdosage of acetaminophen because of a decrease in glutathione stores.[283] However, evidence suggests that protein/calorie malnutrition leads to both decreased activity of CYP2E1[61] and decreased [GSH].[132] The interplay of these two factors in this and other conditions, and the impact on individual patients, is an important area of research.

Apart from these high-risk groups, the incidence of serious acetaminophen toxicity after repeated doses is negligible and appears to follow only massive dosing[68,145,153,161,278] or prolonged

excessive dosing.[20,38,41,68] Less serious hepatic abnormalities with atypical clinical or histologic features indicating other pathophysiologic mechanisms are reported at lower doses taken for months to years.[11,29,124]

The chronic ingestion of â€œmaximal therapeuticâ€• doses (4 g/d) in normal adults without the special circumstances appears to be safe. Several randomized controlled trials have used maximal therapeutic doses of APAP (4 g/d) in hundreds of patients over periods from 4 weeks to 2 years with no reported increase in adverse events or hepatic injury.[24,40,98,191,286] A short-term study of healthy patients given APAP 4, 6, and 8 g/d for 3 days found no alteration in APAP kinetics and no change in aminotransferases or creatinine.[99] Finally, several studies have evaluated recently abstaining chronic alcoholics administered APAP 4 g/d for 2â€“3 days without hepatotoxicity.[68,138]

Although recommended dosing of APAP appears to be safe, no

upper limit for safe repeated dosing has been established. Unlike acute dosing, not only is the total dose important but the interval between dosing and the duration of dosing also appears to be important. The interaction of an individual's CYP2E1 activity, and therefore NAPQI production, with the rate of glutathione turnover ideally should be considered as well but currently is not measurable. When interindividual variations such as CYP2E1 activity[100] and GSH supply and regeneration capacity[292] are considered, predicting the dose that will reach the critical threshold for development of toxicity becomes impossible.

Analysis is further complicated by the likelihood of unreliable information. A substantial proportion of cases of chronic toxicity involve parental dosing errors, iatrogenic errors, alcoholics, litigants in product liability cases, and other situations in which those providing the history may be unable or unwilling to accurately describe the dosing. Furthermore, because acetaminophen use is common after liver injury from alcoholism, acute infectious illnesses, and use of other medications with hepatotoxic potential, it is unclear in which cases acetaminophen is causative, contributory, or completely unrelated to hepatotoxicity. Analysis of these cases is further complicated because liver injury from any cause may lead to slowed metabolism and persistent elevation of [APAP]. Ultimately, resolution of this problem requires â€œgold standardâ€• laboratory markers of impending or actual acetaminophen-induced toxicity, but no such methods are yet available.

When there is concern about toxicity risk after repeated excessive acetaminophen dosing, several approaches are suggested. The goal should be to select patients at risk based on dosing history and other risk factors and then to use limited laboratory testing to determine the need for NAC. A logical screening laboratory evaluation consists of determination of [APAP] and AST concentration, with additional testing as indicated by these results and other clinical features. The objective is to identify the two

conditions that warrant NAC therapy: remaining acetaminophen yet to be metabolized and potentially serious liver injury. The predictive value of this approach depends almost entirely on proper selection of patients at risk.

Role of History and Physical Examination in Chronic Overdose

The first consideration when evaluating a patient with a history of repeated excessive acetaminophen dosing is the presence or absence of signs or symptoms of hepatotoxicity. Regardless of risk factors or dosing history, such findings should prompt treatment with NAC and laboratory evaluation. This is particularly important because most reported cases of serious toxicity after repeated dosing are symptomatic for more than 24 hours prior to diagnosis, and earlier diagnosis should improve outcome. In the asymptomatic patient, the next consideration should be the presence or absence of factors that potentially predispose the patient to toxicity. If no â€œhigh-riskâ€• factors are present, then asymptomatic adults who ingest 7.5 g or more in a 24-hour period should have laboratory evaluation. In fact, the adult dosing threshold for asymptomatic patients without potentially predisposing factors likely should be as high as 10â€“12 g in any 24-hour period, but a conservative approach is warranted.[68,155]

Despite the lack of verifiable data, logic and respect for anecdotal reports justify the use of a lower screening threshold in patients with potentially predisposing factors. Although some retrospective series and some reports from litigation suggest that toxicity can occur after recommended dosing,[233] this suggestion is not supported by other major studies or controlled trials with therapeutic and supratherapeutic APAP dosing.[24,40,68,98,99,138,191,286] Therefore, it is reasonable to use a history of a daily dose >4 g in adults or >90 mg/kg in children as a conservative cutoff for considering laboratory evaluation of

asymptomatic patients who are at *high risk.* The duration of dosing, any occurrence of large bolus dosing, presence of multiple potentially predisposing factors, and other features almost certainly affect risk, but until they can be adequately or quantitatively analyzed the lowest logical risk cutoff seems appropriate. These cutoff values (>4 g/d in adults and >90 mg/kg/d in children) are almost certainly substantially less than those required to cause toxicity,[155] but it is prudent to start from these sensitive cutoffs until better screening strategies are developed. This same approach should be used in patients who may be at high risk for hepatotoxicity from chronic overdosage of APAP, including chronic alcoholics, patients taking isoniazid, and infants and young children with febrile illnesses. Others deserving similar consideration include individuals with chronic malnutrition, AIDS, or other conditions that lead to GSH depletion.

Role of Laboratory Evaluation in Chronic Overdose

Using the strategy described here, patients with elevated AST concentrations are considered at risk, regardless of [APAP]. [APAP] is useful in patients with normal AST concentrations as a tool to determine only whether sufficient acetaminophen remains to lead to subsequent NAPQI formation and delayed hepatotoxicity. In some cases AST concentration is normal and [APAP] <10 Âµg/mL, obviating the need for NAC. Because no evidence in the literature or experience indicates that a patient with [APAP] <10 Âµg/mL and normal AST concentration developed consequential liver injury,[68] this value is appropriate as a sensitive cutoff to define the presence or absence of remaining acetaminophen. An alternative strategy that might increase specificity in reliable patients after repeated ingestions is to treat only patients with substantially elevated AST concentration (eg, 2 times normal) or elevated [APAP].[68] This strategy requires further study.

If AST concentration is normal, patients should be considered at risk if [APAP] is higher than expected. A definition of [APAP] that has a risk of hepatic injury is a concentration >10 Âµg/mL and higher than expected for an appropriate acetaminophen dose. After ingestion of a normal dose of acetaminophen, peak [APAP] should be <30 Âµg/mL 30â€“90 minutes after ingestion and <10 Âµg/mL 4â€“6 hours after ingestion. Patients who develop liver injury after chronic acetaminophen overdose should be evaluated and treated. Additional laboratory evaluation should include tests to assess hepatotoxicity and prognosis (creatinine, lactate, and phosphate concentrations, PT, and pH).

Determination of Risk Subgroups After Chronic Acetaminophen Exposure

Using a strategy that describes risk in a relative manner, we consider patients to be at *higher risk* in the following situations: AST concentration is more than twice normal even if the patient is asymptomatic; AST concentration is elevated and the patient is either symptomatic or [APAP] is >10 Âµg/mL; or [APAP] is higher than expected. In these cases, treatment with NAC is recommended. Patients who are asymptomatic and have less than expected [APAP] and a normal AST concentration or who have [APAP] <10 Âµg/mL and an AST concentration less than twice normal are considered *low risk.* Follow-up by telephone or by return visit in 24 hours is recommended for *low-risk* patients, who should be given discharge instructions to return immediately for any symptoms of hepatic injury such as nausea, vomiting, abdominal pain, and constitutional symptoms. Patients with normal AST concentration and [APAP] <10 Âµg/mL are at *minimal risk*, and NAC is not recommended. *Minimal-risk* patients should be instructed to return immediately if symptoms of hepatic injury arise. The theoretical patient with impending toxicity but without

signs or symptoms of toxicity, who might be missed by this approach, still can be detected in a timely manner by appropriate patient discharge instruction and follow-up.

Risk Determination After Acetaminophen Exposure in Children

Serious hepatotoxicity after acute overdose is less common in children than in adults, but whether this difference reflects relative hepatoprotection or merely results from differences in the characteristics of poisoning in children is unclear.[5] Serious hepatotoxicity or death after acute acetaminophen overdose is extremely rare in children.[9,27,150,224,258] When all cases with initial [APAP] above the treatment line are considered, the incidence of hepatotoxicity is lower in children younger than 5 years than in adults,[224] but there are insufficient documented pediatric cases with very high [APAP] or delays to NAC treatment to allow adequate comparison with adult data.

Among the several theories that have been advanced to explain the potential protection of children from acute acetaminophen-induced hepatotoxicity are the proportionately increased sulfation capacity[166] and glutathione supply in children;[140] however, no decrease in oxidation to NAPQI has been demonstrated in children,[273] and this proposed resistance remains controversial.

Although limited by methodology, studies advocate increasing the threshold acetaminophen dose requiring screening tests after pediatric acute overdose.[6,28] Similarly, because of the paucity of reported toxicity, some recommend screening children using the original, higher nomogram. Although both of these suggestions are statistically likely to be safe, currently we advocate continued use of 150 mg/kg as the risk-defining dose and use of the treatment line for [APAP] screening until valid data demonstrate that children are selectively protected or until accumulated experience with a

higher dose threshold for screening proves it to be safe.

Following excessive repeated acetaminophen dosing, there is no evidence that children are relatively protected. In fact, infants and children with acute febrile illnesses compose one of the few groups in which toxicity after repeated excessive dosing is well described.[52,58,62,74,83,115,116,183,219,247,255] Common sources of dosing errors include substitution of adult for pediatric preparations; substitution of drops (100 mg/mL) for elixir (32 mg/mL); overzealous dosing by amount or frequency in attempts to maximize effect; and failure to read the label and dose carefully.[5] It appears that age younger than 2 years is an independent risk factor for development of toxicity.[128] In almost all cases, the reported doses associated with toxicity are >150 mg/kg/d. Confounding factors make dose determination and acetaminophen attribution extremely difficult, particularly in reports of lesser dosing.

The frequency of toxicity after repeated excessive dosing in febrile children may simply reflect that these children constitute the most common setting for pediatric acetaminophen use and that children are at greater relative risk for excessive dosing because of their size. Although logically one can argue that inflammatory oxidant stress and short-term fasting during febrile infectious illnesses affect oxidative drug metabolism and decrease glutathione supply, these relationships are complex and not well defined. Of the reported cases of repeated excessive APAP dosing in children, hepatic injury likely was the result of infectious illness in some, acetaminophen in others, and both in still others.[3]

Risk Determination After Acetaminophen Exposure in Pregnancy

The initial risk of toxicity of a pregnant patient is similar to that of a nonpregnant patient, with a few exceptions. Little evidence

suggests that any alteration of the treatment line is necessary. In fact, there are no reported cases of fetal or maternal toxicity in women with [APAP] below the treatment line[164] or in those treated with NAC within 10 hours of an acute ingestion.[218] However, there is controversy in assessing the risk of fetal toxicity once the mother is determined to be at risk. In order to better understand the issues, a review of maternal-fetal physiology and pharmacokinetics related to APAP and NAC is necessary.

Acetaminophen is capable of crossing the human placenta,[12,147,182,220] and APAP may be present in concentrations that are similar to maternal serum concentrations within hours after ingestion.[12,182,220] Fetal metabolism of APAP probably is inefficient but is not completely understood. Fetal sulfation and oxidative metabolism of APAP are slower than in adults, and glucuronidation is undetectable until 23 weeks of gestation.[221] P450 enzymes that are capable of oxidizing APAP are present in the fetus as early as 18 weeks.[221] However, the activity of these enzymes is <10% that of adult enzymes at 18 weeks and increases to only 20% activity at 23 weeks.[221] How the opposing forces of decreased overall metabolism of APAP and decreased NAPQI formation impact fetal risk is unclear.

The mechanism of fetal risk in patients with [APAP] over the treatment line remains controversial. The degree of fetal toxicity that is attributable to fetal metabolism of APAP or to maternal illness is unclear. In clinical case series, the majority of pregnant women who overdose on APAP have uneventful pregnancies.[164,218] Pregnant women who develop APAP toxicity in the first trimester have an increased risk of spontaneous abortion,[218] and those who develop APAP toxicity in the third trimester have a potential risk of fetal hepatotoxicity because of fetal metabolism. However, reports of third-trimester fetal hepatotoxicity are rare[164,218] and are only associated with severe maternal toxicity.[218,277] The factors associated with poor fetal outcome after large APAP overdose are delayed treatment with NAC and early gestational age.

The decision to treat a pregnant woman with NAC requires consideration of what is known about the efficacy and beneficial effects as well as the adverse effects of NAC for both fetus and mother. There is every indication that NAC is both safe and

effective in treating the mother,[218] but there are inadequate data to evaluate efficacy in the fetus, although fetal outcome has generally been excellent after maternal treatment with oral NAC.[218] Given that NAC has been safely used in many pregnancies[164,218] and fetal mortality is linked to delays to treatment, NAC should be initiated in pregnant women whose [APAP] is over the treatment line. The necessary length of NAC therapy is difficult to determine. Although the 20-hour IV protocol probably is the most common NAC protocol used for pregnant women worldwide, there is a paucity of *published* experience with NAC treatment courses shorter than the oral 72-hour protocol.[164,218]

Ethanol and Risk Determination

The effects of ethanol on acetaminophen toxicity are complex and best described by clearly separating experimental animal data from actual human overdose experience, acute from chronic ethanol abuse, and single from repeated excessive acetaminophen dosing. Although not entirely consistent, most animal data indicate that simultaneous administration of ethanol with acetaminophen may be somewhat hepatoprotective,[263,269] presumably because ethanol competitively inhibits CYP2E1, preventing metabolism of acetaminophen to NAPQI. Chronic ethanol administration in animal models, however, increases the risk from acute acetaminophen dosing[149,235,269] on the basis of induced CYP2E1 metabolism of acetaminophen and/or decreased mitochondrial GSH supply or regeneration.[141,294] In humans who ingest APAP after recent abstinence from ethanol, NAPQI formation may increase by up to

22%.[261]

After acute acetaminophen overdose, these factors appear to be of little importance.[223,244,264] There is no evidence that chronic ethanol use should alter the approach after an APAP acute overdose. Because of the potential failure of the higher original nomogram to adequately screen alcoholics and those chronically taking P450 inducers, some authors suggest using a much lower standard.[59,71,270] However, there is only one reported case of nomogram â€œfailureâ€• in an alcoholic using the treatment line, and the actual events of the case are unclear.[59,241] Furthermore, unpublished data from a large series revealed no difference in incidence of hepatotoxicity among groups identified as chronic-acute (or acute-on-chronic ethanol users) and ethanol nonusers.[244] These observations indicate the treatment line is adequately sensitive for screening after an acute APAP overdose, regardless of the patient's pattern of ethanol use.

The relationship between chronic ethanol use and chronic APAP use is complex. Hepatotoxicity has been sporadically reported in patients with chronic ethanol abuse after repeated excessive acetaminophen dosing.[14,18,235,296] Complicating these reports are the clinical challenges of obtaining accurate histories in alcoholics, failure to exclude non-APAP causes of hepatotoxicity, and other factors. Evidence demonstrates minimal risk of hepatotoxicity in alcoholic patients who ingest therapeutic doses of APAP.[26,138] These trials were performed on recently abstaining alcoholics who theoretically have maximal CYP2E1 induction without inhibition of acute ethanol intake.[261] There was no increased risk of elevated AST concentration (although 40% of controls developed mildly elevated AST concentration <120 U/L) or hepatotoxicity in patients treated with APAP 4 g/day compared to the control group. Given the prevalence of both ethanol and acetaminophen use, further studies with the power to detect lower incidence of adverse effects are needed.

P450 Inducers and Risk Determination

Inducers of the P450 group of enzymes have long been theorized to increase the risk of toxicity from APAP because of a proportionally increased production of NAPQI.[226] A more refined knowledge of the hepatic enzyme systems has provided increasing evidence that enzyme induction of only specific subgroups of the P450 system is responsible for any increase in NAPQI production in humans.

Because APAP is metabolized to NAPQI largely by CYP2E1,[114,159] only induction of this enzyme is thought to increase the risk of hepatotoxicity. Ethanol and isoniazid are known inducers of CYP2E1 and hence may lead to increased NAPQI production during excessive chronic APAP use. As noted previously in the case of ethanol, there is no evidence that P450 inducers should alter the approach to acute ingestion of APAP, and the treatment line can be applied without modification for patients with acute overdoses of APAP who take these medications.

Several other medications, including phenytoin, carbamazepine, and phenobarbital, had been theorized to increase APAP toxicity because of nonspecific P450 induction activity. However, these medications do not induce CYP2E1 and, hence, are not expected to increase the risk of hepatotoxicity after APAP overdose. Evidence of any increased risk as a result of coingestion of phenytoin, carbamazepine, and phenobarbital has been inconclusive and largely based on animal data.[25,82,171,197] Clinical data, although scant, suggest that these medications are not factors that increase toxicity.[268]

Assessing Actual Toxicity: Critical Components of the Diagnostic Approach

Earlier protocols and guidelines recommended extensive and ongoing laboratory assessment after acetaminophen overdose.[151,227] Based on the pathophysiology and time course of toxicity, a simplified and far more cost-effective approach is logical.

Initial Testing

[APAP] should be measured in patients with acute acetaminophen overdose and no evident hepatotoxicity, but no other initial laboratory assessment is required. AST concentration should be measured in patients considered to be at risk for APAP toxicity according to the nomogram or history (in the case of repeated excessive dosing) or in those suspected of already having mild hepatotoxicity by history and physical examination. The first AST determination serves as a screen to detect preexistent hepatic dysfunction, which may indicate the patient requires closer monitoring. Also, as mentioned, AST determination serves as a key component of decision making after repeated excessive dosing and other unusual circumstances.

Unless evidence of serious hepatotoxicity is present, AST concentration is sufficient indication of hepatic conditions, and no additional testing is initially needed. Death of hepatocytes, resulting in release of measurable hepatic enzymes, precedes all cases of serious liver dysfunction. Even if abnormalities of other markers precede elevation of AST concentration, there is no evidence that their detection benefits the patient.[16] Mild renal toxicity may rarely occur without hepatotoxicity;[37] however, at least minimal elevation of AST concentration generally precedes evidence of clinically significant nephrotoxicity.[1,65] Exceptions are rare,[37,55,131,208] and routine screening of renal function in the absence of elevated AST concentration probably is unnecessary.

Acetaminophen overdose may lead to minor prolongation of PT even without causing hepatotoxicity.[284] This most commonly

occurs between 4 and 24 hours after ingestion and may be a result of

NAPQI-related inhibition of vitamin K-dependent Î³-carboxylation of factors II, VII, IX, and X.[260,284] These minor prolongations (resulting in PT that usually is less than twice control) are rarely clinically relevant, are not evidence of hepatotoxicity, and should not be used as prognostic factors or indications for NAC treatment. In fact, treatment with NAC may prolong PT[122,136] by interfering with the PT assay, by reversing an APAP/NAPQI effect,[260] or by direct NAC effects.[260] Clinical interpretation of these minor prolongations of PT is clouded by preexisting conditions, treatment with NAC, and laboratory error. Even in cases where PT is prolonged, if consequential liver injury does develop, elevation of AST concentration precedes serious liver dysfunction.

Ongoing Monitoring and Testing

If no initial elevation of AST concentration is noted, repeated AST determination aloneâ€”without other biochemical testingâ€”every 24 hours until completion of treatment is sufficient to exclude the development of hepatotoxicity. If elevated AST concentration is noted, then PT and creatinine concentration should be measured and repeated every 24 hours or more frequently if clinically indicated. Results of other liver tests, such as Î³-glutamyltransferase, alkaline phosphatase, lactic acid dehydrogenase, and bilirubin, which are useful when determining the etiology of liver abnormalities, will be abnormal in cases of serious acetaminophen-induced hepatotoxicity but provide little additional useful information if the etiology is certain.

If evidence of actual liver failure is noted, then careful monitoring of blood glucose, creatinine, phosphate, and lactate concentrations and acidâ€“base status are important in assessing extrahepatic organ toxicity and are vital in assessing hepatic function and the

patient's potential need for transplant (see Assessing Prognosis). In addition, meticulous bedside evaluation is necessary to detect and document vital signs, neurologic status, and evidence of bleeding. Many additional tests may be useful in the setting of liver failure, based on clinical condition and local protocols. Testing for other rare acetaminophen-associated conditions by electrocardiogram, lipase determination, or other studies should be performed on a case-by-case basis only.

Management

Limiting Gastrointestinal Absorption

In cases of very early presentation or coingestion of agents that delay gastrointestinal (GI) absorption, gastric emptying may be appropriate for some patients. In general, however, gastric emptying is not a consideration for patients with isolated acetaminophen overdose because of the very rapid GI absorption of acetaminophen and the availability of an effective antidote.

Administration of activated charcoal shortly after APAP ingestion appears to decrease the number of patients who have [APAP] above the treatment line.[48] Although activated charcoal is most effective when given within the first 1â€“2 hours after APAP ingestion, it may be reasonable to give activated charcoal any time prior to 4 hours postingestion as long as no contraindications exist. Significant concerns that activated charcoal may bind to orally administered NAC and decrease its effectiveness have been expressed, but these concerns are unfounded for several reasons.

In most cases, there should be no interaction because GI absorption of APAP is complete by 4 hours after ingestion, prognosis is determined by 4 hours after ingestion, and NAC typically is administered between 4 and 8 hours after ingestion. As a result, there generally is no difficulty separating the doses.

If delayed or repeated activated charcoal dosing is indicated because of suspected delayed absorption or because of coingestants, then a strategy using an IV NAC protocol should be strongly considered. Alternatively, if time (to start NAC) permits, separating oral NAC and activated charcoal doses by 1â€“2 hours is logical, as long as this timing can be accomplished safely. NAC is rapidly absorbed high in the GI tract and is unlikely to interact with activated charcoal if the doses are not administered simultaneously. However, NAC treatment should not be delayed by the activated charcoal dose because time to administration of NAC correlates with risk of hepatotoxicity.

In unusual cases, as a result of coingestants and timing of presentation, it may be important to administer NAC and activated charcoal simultaneously. To avoid any interaction, intravenous NAC should be used in these circumstances whenever possible. However, in cases where only oral NAC is available, the theoretical concern of an interaction probably is not clinically relevant. Although there is clear in vitro evidence of binding between activated charcoal and NAC[60,133,228,259] and volunteer data suggest that activated charcoal causes statistically significant decreases in NAC absorption,[85] there is no evidence that this interaction is clinically significant.[249]

Supportive Care

General supportive care consists primarily of controlling nausea and vomiting and managing the hepatic injury, renal dysfunction, and other manifestations. Treatment of these problems is based on general principles and is not acetaminophen dependent. Discussion of the management of liver failure is clearly beyond the scope of this chapter, but certain aspects deserve mention. Monitoring for and treatment of hypoglycemia as a result of liver failure are critical, as hypoglycemia is one of the most readily treatable of the life-threatening effects of liver failure. If adequate viable

hepatocytes are present, vitamin K may produce some improvement in coagulopathy; thus, trial dosing is logical as liver injury develops and as it resolves. Administration of fresh-frozen plasma (FFP) should be based on specific indications rather than PT alone.

One of the most important advances is use of prolonged NAC for treatment of fulminant hepatic failure. Parenteral NAC, other advances in supportive care, and successful liver transplantation programs appear to have substantially improved survival from APAP-related liver failure.[155]

Antidotal Therapy with NAC

Mechanism of Action of NAC

Conceptually, it is helpful to think of NAC as serving three distinct roles. During the metabolism of acetaminophen to NAPQI, NAC *prevents toxicity* by limiting the formation of NAPQI. More importantly, it *increases the capacity to detoxify* NAPQI that is formed (see Fig. 34-1). In fulminant hepatic failure, NAC *treats toxicity* through nonspecific mechanisms that preserve multiorgan function.

NAC prevents toxicity by serving as a glutathione precursor, leading to increased GSH availability.[139] NAC can also serve as a GSH substitute, combining with NAPQI and being converted to cysteine and mercaptate conjugates, just as GSH is converted.[50] NAC may also lead to increased substrate for nontoxic sulfation, allowing increased metabolism by this route and less metabolism by oxidation to NAPQI.[239] Each of these preventive mechanisms

must be in place early, and none is of benefit after NAPQI has initiated cell injury. Time is required to saturate nontoxic metabolism from excessive NAPQI, deplete GSH, and overcome GSH production; thus there is a window of opportunity after

exposure to an APAP overdose during which NAC can be initiated prior to the onset of liver injury, without any loss of efficacy. Based on large clinical trials, it appears that NAC efficacy is nearly complete as long as it is initiated within 8 hours of an acute overdose.[130,242,243] The efficacy of NAC almost certainly decreases with time even prior to 8 hours postingestion. Existing data support that short delays in NAC initiation, such as those that might result from GI decontamination (oral NAC only) or while awaiting results of [APAP] determination, pose little risk to the patient as long as NAC can be started within 8 hours of overdose. Despite this finding, however, the relationship between time to administration of NAC and the risk of hepatotoxicity should be considered a continuous variable,[250] with the risk of hepatotoxicity rising at some time near 8 hours postingestion. For this reason, NAC therapy should not be unnecessarily delayed until 8 hours if it can be safely administered earlier.[199]

Several observations illustrate the effectiveness of NAC by other mechanisms of action even after NAPQI formation and binding. NAC actually reverses NAPQI oxidation in both a mouse model[66] and an in vitro human hepatocyte model.[157] In a large clinical trial of the 18-dose oral NAC protocol,[244] the severity of hepatotoxicity among high-risk patients first treated with NAC between 16 and 24 hours after overdose was far less than had been observed in untreated historical controls or patients treated with the 20-hour IV NAC protocol.[205] More recent use of the 20-hour IV NAC protocol has suggested it also may be effective in treating late (16â€“24 hour after ingestion) APAP toxicity.[48] Other experimental work demonstrates that even after cell injury is initiated, late interventions could diminish hepatocyte injury.[47] Most significantly, a prospective, randomized trial found that even after fulminant hepatic failure was evident, starting IV NAC diminished the need for vasopressors and the incidences of cerebral edema and death.[129]

These dramatic findings were accompanied by a fascinating

observation: despite improved organ function and survival in the NAC-treated group, there was no apparent difference in the degree of hepatic injury. Elevations of enzyme concentration and prolongation of PT were equivalent in the two groups, suggesting that much of the benefit of NAC may not be derived from decreasing hepatic injury. Initial investigations supported this hypothesis, showing that oxygen delivery and utilization were enhanced by NAC.[76,112,248] Although this proposed mechanism of action has been challenged,[126,275,276] no subsequent studies have reevaluated or negated the impact of NAC on outcome.

Whether based on its nonspecific antioxidant effects, its ability to enhance GSH supply, or, more likely, its role in mediating microvascular tone, NAC improves function in several organs affected by multisystem failure.[67,76,272] As a result, NAC may be the agent of choice for cerebral edema after liver failure according to one study.[282] Even with aggressive hemodynamic treatment, hemodialysis, and use of widely available blood products, cerebral edema remains the most feared and most lethal manifestation of liver failure. In this setting, NAC may preserve cerebral blood flow and perfusion better than traditional therapies such as mannitol and hyperventilation, which may actually be detrimental.

Intravenous Versus Oral Administration

As with many issues related to acetaminophen toxicity, the choice of oral versus intravenous NAC is complex. Available information suggests each has advantages and disadvantages, and each may be more appropriate than the other in certain settings. Because no controlled side-by-side studies have compared IV and oral NAC, conclusions about relative benefit of each are largely speculative.

With the exception of established liver failure, for which only the intravenous route has been investigated, intravenous and oral NAC administration are equally efficacious in treating acetaminophen toxicity.[49,199] Initial concerns about the apparent superiority of

oral NAC over IV NAC when started 16â€“24 hours after overdose have been resolved by data showing equivalent results between the two protocols.[49] Any difference in outcome for these patients almost certainly is related to the duration and dose of NAC therapy rather than the route itself. The decision of which route to use should be dependent on the rate of side effects, safety, and ease of use and not efficacy.

Safety is the best understood of these issues. Oral NAC clearly has fewer severe side effects than IV NAC. Nausea and vomiting, sequelae of APAP ingestions, are typically present prior to NAC administration and occur in approximately half of patients treated with oral NAC. Diarrhea is prevalent, but there is no credible evidence of more serious complications resulting from oral NAC.[165] Reports of skin rash and unusual complications are rare.[176] In contrast, intravenous NAC is associated with a 17% rate of anaphylactoid reactions, most of which are mild but of which 1% are severe.[130] The anaphylactoid reactions, which typically are minor, include rash, flushing, vomiting, and bronchospasm,[13,130,240] but in rare instances they may lead to hypotension and death.[8,15,73,79,92,127,158,240,289] These reactions are attributed to both dose and concentration of NAC. However, although reaction rate may be decreased by using a more dilute NAC solution[127,130,289] and despite decreased adverse events after slowing NAC infusions in some studies,[49] prolongation of the loading infusion from 15 to 60 minutes did not decrease anaphylactoid rate significantly (from 18% to 14%) in one prospective study.[130] Minor reactions, such as rash, generally do not require treatment, rarely recur, and do not preclude administration of subsequent NAC doses.[13,240,289] Even when urticaria, angioedema, and respiratory symptoms develop, they usually are easily treated, and NAC can be subsequently restarted with a very low incidence of recurrence.[13] Although proper dosing of IV NAC is very safe, IV NAC nevertheless must be considered more dangerous than oral NAC because of the risk of dosing

errors. An additional safety concern with use of intravenous NAC is the potential problem associated with concomitant infusion of large volumes of free water to pediatric patients, in some instances leading to hyponatremic seizures.[254]

The main disadvantage of the oral formulation of NAC is the high rate of vomiting and the concern that vomiting may delay therapy.[199] Delays in administration of NAC are correlated with an increased risk of hepatotoxicity.[243] The intravenous route avoids an increased rate of vomiting in patients who typically are already nauseated and avoids the use of high-dose antiemetics that may alter mental status. Another potential disadvantage of oral NAC is that its absorption may be delayed up to 1 hour compared to IV NAC.[118] However, although short delays in delivery of NAC to the liver are probable in some instances, the equivalent rates of hepatotoxicity in patients treated with oral and IV NAC early after APAP ingestion[49,205,243] suggest the delays associated with the oral route may not be clinically relevant. Oral NAC doses may be difficult to administer to patients with alterations of mental status because of the risk of aspiration, so IV NAC offers a distinct advantage in these instances.

One theoretical, albeit unproven, advantage of oral NAC early in the course of toxicity is that direct delivery via the portal circulation yields a higher concentration of NAC ([NAC]) in the liver. Because of this first-pass clearance, oral NAC results in circulating [NAC] 20- to 30-fold lower than after IV dosing, suggesting that most oral NAC ended up in the liver.[32,118] However, elevated serum [NAC] may be an advantage of intravenous NAC administration when the liver is not the target organ of NAC, as with cerebral edema or in pregnancy.

Lower costs of care are emphasized as an advantage of oral NAC, particularly in the United States where the IV formulation is more expensive than the generic oral formulation.[142] Additional savings

include a potential reduction of inpatient costs related to IV care and monitoring. However, the shorter course of the IV NAC protocol (20 hours vs. 72 hours) significantly decreases the length of hospital stay and may significantly decrease the overall cost of care.

Historically, prior to the current intravenous formulation in the United States, the oral formulation had been used intravenously for years with an excellent safety profile[84,127,289] and without published evidence of infectious or febrile consequences.[33,84,127] This intravenous use of the oral formulation for this purpose is not generally recommended but is historically effective and may be necessary in cases where only the oral formulation is available and the patient has intractable vomiting or acetaminophen-induced hepatic failure.[142]

Specific Indications for IV NAC

In addition to decisions based on cost, duration, safety, and ease of use, three situations exist for which the available information suggests IV NAC is preferable to oral NAC: fulminant hepatic failure, inability to tolerate oral NAC, and acetaminophen poisoning in pregnancy. Each requires further study for validation, but all three seem well supported by current information.

Fulminant hepatic failure is an important indication for IV NAC. The choice of IV over oral NAC is based on several observations. Most importantly, IV is the only route that has been studied in liver failure. Oral NAC may prove effective but has not yet been demonstrated. Second, evidence that (some or all of) the benefit of NAC in liver failure is extrahepatic suggests that IV NAC is preferable. Intravenous NAC results in higher blood [NAC], which presumably leads to more NAC delivery to critical organs. Finally, concomitant GI bleeding, use of lactulose, and other factors make IV NAC more practical.

A more common indication for IV NAC use is for the patient with a

very high [APAP] who is approaching or is more than 8 hours from the time of ingestion and who is unable to tolerate oral NAC after a brief aggressive trial of antiemetic therapy. Use of IV NAC is logical to prevent further delays and resultant loss of NAC efficacy, even without proof that continued vomiting significantly limits NAC absorption.

The most controversial indication for IV NAC use is during pregnancy. Administration of IV NAC to the mother has the theoretical advantage of increased delivery to the fetus over oral NAC use. Intravenous administration circumvents first-pass metabolism, presumably exposing the fetal circulation to higher maternal serum concentrations with IV dosing. Some studies have suggested that placental transfer of NAC to the fetus is limited.[123,236] However, one case series found that [NAC] in cord or neonatal blood after oral maternal NAC administration equaled the [NAC] seen in patients treated with oral NAC.[119] Of course, equivalent serum [NAC] does not prove adequacy of therapy. Unlike the neonates studied, patients treated with oral NAC have extensive first-pass hepatic uptake prior to NAC entry into the serum where [NAC] was measured.[32,118] Whether serum [NAC] in the neonates studied reflects any significant hepatic NAC delivery is uncertain.

Duration of NAC Treatment

Known mechanisms of action and the observation that all studied durations of NAC are effective, when started within 8 hours,[49] suggest that all courses of treatment currently published are effective when NAC is used for its early preventive actions. All available information indicates the conceptual basis for discontinuing NAC should be the completion of acetaminophen metabolism and the absence or resolution of consequential liver injury.[135] Once these conditions can be assured, discontinuation of NAC therapy is appropriate. Results from use of the traditional 20-

hour IV NAC protocol,[205] 48-hour and 36-hour IV NAC protocols studied in the United States,[187,240] one oral 20-hour protocol,[290] and other â€œshort-courseâ€• dosing protocols[287,288] indicate that all therapies are safe and effective in patients treated within 8 hours of an acute ingestion.[256,288]

Regardless of the protocol initiated (20-hour IV, 72-hour oral, 48-hour IV, 36-hour IV), [APAP] and AST concentration should be measured at the completion of the course, and NAC therapy should be continued beyond the prescribed protocol time if there is evidence of significant liver injury (AST concentration greater than normal) or acetaminophen metabolism is incomplete ([APAP] >10 Âµg/mL). This likely will not be an issue in the vast majority of cases, as the aminotransferases of approximately half of all NAC-treated patients with [APAP] above the treatment line will remain <100 IU/L.[242] In addition, patients with late rises in AST concentration should be detected even when the 20-hour protocol is used, as the 20 hours is measured as infusion time and so is typically 26â€“28 hours after the ingestion. This time frame should be adequate to detect early elevations of AST concentration that lead to significant hepatotoxicity, although this theory has not been adequately tested.

Both the oral NAC data and the liver failure study seem to confirm the importance of longer duration of NAC when treating already established liver injury. The IV NAC dosing protocol that has proved beneficial in liver failure is the same initial dosing as the 20-hour IV protocol, but with the IV infusion continued until resolution of liver failure. These observations suggest that, rather than a single duration of therapy for all patients, it is appropriate to extend treatment protocols based on the clinical course of the patient.

Once NAC therapy is extended beyond a set-length protocol, the decision to discontinue therapy should be entirely based on the patient's condition. For patients who develop liver failure, IV NAC

is continued until PT is near normal and encephalopathy, if present, is resolved.[155] For patients without liver failure but with elevated AST concentration, NAC is often continued until all liver abnormalities resolve (AST concentration is decreasing and <1000 U/L).

Assessing Prognosis

The availability and success of liver transplantation after acetaminophen-induced liver failure create an important need for early prognostic assessment. Survival without transplantation is certain if AST concentration is normal at the time of NAC initiation.[243] However, although this method identifies patients at the lowest risk, no accurate means of identifying early in the course those who will not survive without transplant are available. Earlier reports described poor prognostic features that are sensitive but have inadequate specificity and are based on

findings that develop too late in the course of toxicity to be useful.[63] Efforts to determine earlier or more specific markers of poor prognosis have improved our understanding; however, accurate early prediction of the need for transplant remains one of the greatest challenges related to acetaminophen toxicity.

A method for predicting hepatic encephalopathy has been developed using the time until treatment with NAC, decrease in PT, and early thrombocytopenia as markers.[232] These data are used to determine the prognostic index and subsequently the probability of hepatic encephalopathy. Although not predictive of the need for transplant alone, this prognostic tool may be clinically useful to determine patients in need of transfer to specialty care units. Hepatic encephalopathy requires increased supportive care, monitoring for progression of liver failure, and assessment for liver transplantation.

One strategy for prognostication that uses a combination of clinical

features of fulminant hepatic failure is the *King's College Hospital criteria.* The single criterion of pH <7.30 after fluid and hemodynamic resuscitation or the combination of PT >100 seconds, creatinine >3.3 mg/dL, and grade III or IV encephalopathy is predictive of a patient who will die without transplant.[155,185] Any patient who meets or approaches these criteria should be considered for transplant.

Blood lactate concentration may be used as a single marker to predict the need for transplantation. A blood lactate concentration >3.5 mmol/L at a median of 55 hours after APAP ingestion or blood lactate concentration >3.0 mmol/L after fluid resuscitation was shown to be both a sensitive and a specific predictor of patient death without transplant.[19] Whether earlier blood lactate concentrations are predictive remains to be studied.

An Acute Physiology and Chronic Health Evaluation (APACHE) II score >15 in isolated APAP ingestions may be as specific as the above Kings College Hospital criteria and slightly more sensitive.[168] These criteria may be beneficial in determining whether to transfer a patient to a transplant center because the score is easily calculated, is sensitive, and is available within the first days of admission; however, confounders such as coingestants may decrease its utility.

Other prognostic strategies use only the coagulation profile in an attempt to simplify the approach and, more importantly, to allow earlier intervention. Using this approach, a markedly abnormal PT that continues to rise on the fourth day after overdose indicates a very poor prognosis.[111] In most cases, however, other criteria of poor prognosis are evident by that time. For earlier screening, other authors suggest that any patient with a PT in seconds that exceeds the number of hours since ingestion should be considered at extreme risk.[181] Attempts to correlate individual clotting factor concentrations or ratios show promise but appear to offer no benefit over the use of PT alone.[39,189]

Interpretation of PT must include awareness of therapy with vitamin K or FFP. Use of vitamin K does not confuse interpretation. Vitamin K therapy, if effective, implies that transplant may be unnecessary because viable liver remains. If vitamin K is ineffective, PT can be used as discussed in the previous paragraph. Transfusion of exogenous clotting factors, such as FFP, alters interpretation because improvement in PT may not indicate improvement in liver function. Depending on the volume of factors transfused, the subsequent decline in factors must be considered when interpreting PT values. The prognostic importance of monitoring PT in this setting suggests that FFP should be given only with evidence of bleeding, with risk of bleeding from known concomitant trauma, or prior to invasive procedures, and not based merely on the PT value. Since survivors regenerate normal liver, no long-term laboratory monitoring is indicated after return to adequate function is demonstrated.

Another approach to predicting poor prognosis uses the serum phosphate concentration at 48 hours after ingestion and may be particularly helpful in determining the need for transplant or transfer to a transplant center early in the course of APAP hepatotoxicity. A serum phosphate concentration >1.2 mmol/L (3.75 mg/dL) on day 2 (48â€“72 hours) was both sensitive and specific for predicting patients who either received a transplant or died[2,3,4] of APAP hepatotoxicity. The elevation in phosphate concentration correlates with early acidosis and renal impairment. The predictive value of this test is based on the concept that serum phosphate concentration increases with early renal impairment, whereas a liver with regenerative capacity uses the phosphate for regeneration of adenosine triphosphate and hepatocytes. In patients who lack hepatic regenerative capacity, the phosphate remains elevated.[2,3,4]

Summary

Several key concepts will help the clinician effectively manage acetaminophen exposures. When managing intentional overdoses, measurement of [APAP] should be considered part of the patient's initial evaluation. In cases where risk assessment for acetaminophen toxicity is merited, treatment with NAC should be initiated as soon as possible and ideally within 8 hours from the time of ingestion. IV NAC should be preferentially used in cases of fulminant hepatic failure or intractable vomiting and in pregnant patients. Otherwise, the efficacy of the oral and IV formulations should be considered the same. Patients who present after repeated excessive APAP dosing should be assessed for evidence of hepatic injury and for the possibility of ongoing production of NAPQI. Factors that potentially predispose patients to hepatotoxicity after repeated dosing should be taken into account when deciding which patients to assess further for hepatic injury.

Patients showing evidence of severe hepatotoxicity or hepatic encephalopathy and those at risk for fulminant hepatic failure may require admittance to the ICU. All of these patients require frequent neurologic checks, monitoring of vital signs, and additional and repeated laboratory studies. Consultations with a regional poison center, gastroenterologist (or hepatologist) consultant, and regional transplant center are important to guide treatment strategies and to coordinate transplantation when needed. Early psychiatric consultation can be helpful in assessing transplant eligibility. Absolute indications for transplantation vary and should be discussed early with the appropriate local transplant center, poison control center, and hepatologist(s).

Although our understanding of acetaminophen toxicity has advanced significantly and additional therapeutic modalities (primarily IV NAC) have become more widely available, many important challenges remain. Development of an entirely new method of toxicity screening to accurately determine the risk of toxicity in atypical patients, high-risk patients, and those who present after repeated excessive dosing of APAP is needed.

Ongoing study of antidotal therapy dosing protocols is needed to assess the validity of many assumptions. Most importantly, improved methods to determine the indication for liver transplantation early after APAP ingestion are desperately needed. These and other issues predict that further changes are likely. Hopefully, the principles and current strategies

presented in this chapter will serve as a strong foundation for these important future advances.

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Antidotes in Depth

N-Acetylcysteine

Mary Ann Howland

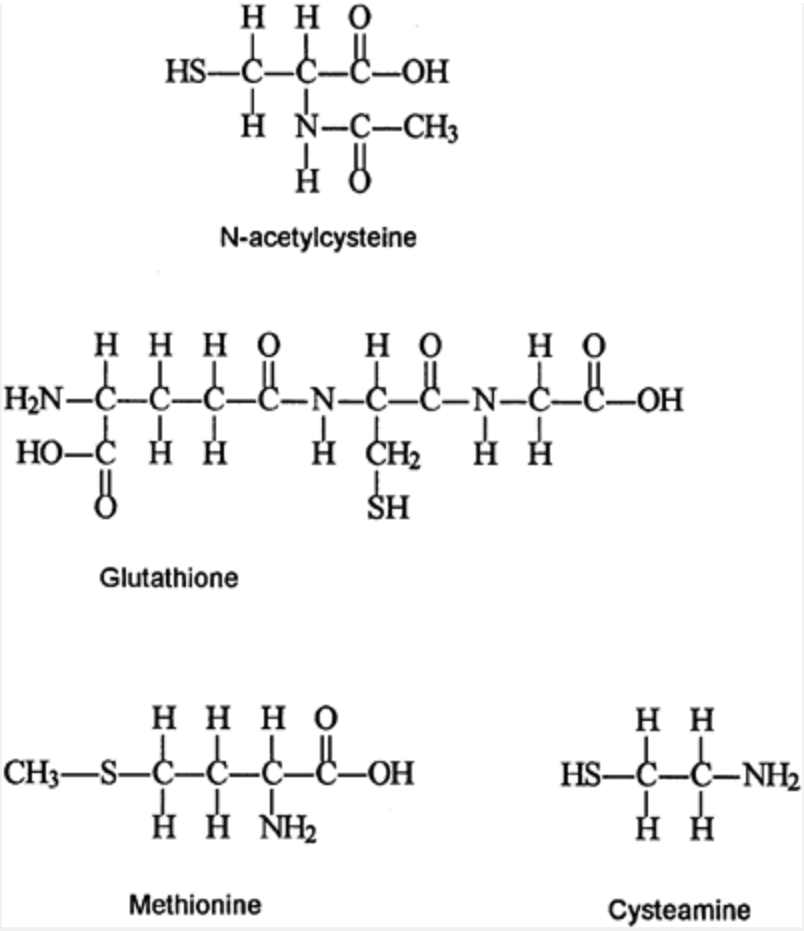

Figure. No Caption Available.

N-acetylcysteine (NAC) is the cornerstone of therapy for patients with potentially lethal acetaminophen overdose. If administered early in the course of exposure, NAC can prevent significant acetaminophen-induced toxicity. Later, it can ameliorate toxicity. NAC also has a role in limiting toxicity caused by glutathione depletion and free radical formation, such as from carbon tetrachloride, chloroform, pennyroyal oil, and possibly valproic acid.[17,25,26,93] Finally, NAC is useful in the management of fulminant hepatic failure caused by toxicologic and nontoxicologic etiologies. Its beneficial effects are also under investigation in

critically ill patients with a variety of stress-induced disorders,[46,83,90] perhaps in the prevention of further renal impairment in patients with chronic renal insufficiency administered a radiographic contrast agent, and in those with hepatorenal syndrome.[32,33,76,86] Furthermore, NAC is potentially beneficial following exposure to certain metals such as cobalt.[45]

History

Shortly after the first case of acetaminophen hepatotoxicity was reported, Mitchell and coworkers described a protective effect of glutathione.[52,73] Prescott et al.[59] first suggested the use of *N*-acetylcysteine (NAC) for acetaminophen poisoning in 1974. Early experiments demonstrated that NAC could prevent acetaminophen-induced toxicity in mice when treatment was initiated within 4.5 hours of ingestion and that the oral and intravenous (IV) routes were equally efficacious when treatment was initiated within 1 hour of ingestion.[58] Mitchell et al.,[52] Prescott et al.,[59,62] and Rumack and Peterson[74] performed human research with oral and IV NAC in the 1970s. The United States Food and Drug Administration approved oral NAC in 1985 and IV NAC in 2004.

Cysteamine, methionine, and NAC, which are all glutathione precursors or substitutes, have been used successfully to prevent hepatotoxicity, but cysteamine and methionine both produce more adverse effects than does NAC therapy, and methionine is less effective than NAC. Therefore, NAC has emerged as the preferred treatment.[63,78,87]

Background: Toxicology

Ninety percent of a therapeutic dose of acetaminophen is metabolized to nontoxic glucuronide (approximately 60%) and sulfate (approximately 30%) conjugates.[60] Only 4% is metabolized by the cytochrome P450 mixed-function oxidase system (3A4 at

low doses; 2E1 predominantly at high doses)[51] to the potentially toxic reactive intermediate *N*-acetyl-*p*-benzoquinoneimine (NAPQI). This intermediate is conjugated with glutathione to form nontoxic cysteine and mercapturic acid conjugates. After acetaminophen overdose, both the fraction and the total amount of drug undergoing P450 metabolism increase, leading to glutathione depletion, binding of the highly reactive intermediate, liberation of reactive oxygen and nitrogen species, and resultant centrilobular hepatic necrosis.[18,35,64] It is postulated that the ensuing oxidative stress causes mitochondrial and other damage to cardiac, pulmonary, and hepatic tissues (Chap. 12).[9,27,64,79] NAC is a thiol-containing compound that is deacetylated to cysteine, a thiol-containing amino acid that is used intracellularly in addition to the amino acids glycine and glutamate to synthesize glutathione.[72] The availability of cysteine becomes the rate-limiting step in the synthesis of glutathione, and NAC is effective in replenishing diminished supplies of cysteine.

Mechanism of Action

When administered shortly following acetaminophen ingestion, NAC acts to prevent toxicity. Later in the clinical course, NAC modifies the subsequent xenobiotic-induced inflammatory response. NAC effectively prevents acetaminophen-induced hepatotoxicity if it is administered before glutathione stores are depleted to 30% of normal. This level of depletion occurs approximately 8 hours after toxic acetaminophen ingestion.[62,70,81] NAC acts as a precursor for the synthesis of glutathione,[41] as a substrate for sulfation,[80] as an intracellular glutathione substitute by directly binding to NAPQI,[15] and by enhancing the reduction of NAPQI to *N*-acetyl-*p*-aminophenol (APAP).[41]

After NAPQI covalently binds to hepatocytes,[70] NAC modulates the subsequent cascade of inflammatory events in a variety of ways.[29] The inflammatory damage can occur in many tissues. Antioxidants

function as electron donors and are oxidized preferentially to relatively less reactive and destructive species.[9] Examples of endogenous antioxidants include vitamins C and E and reduced

glutathione. Glutathione protects cells against electrophilic compounds by acting as both a reducing agent and an antioxidant.[72] Glutathione replenishment may protect against further cell damage but is incapable of completely restoring damaged tissues. In this second stage, NAC may act directly as an antioxidant; act as a reservoir for thiol groups; increase nitric oxide synthase to improve blood flow by combining with nitric oxide to form the potent vasodilator *s*-nitrosothiol; increase formation of essential endogenous antioxidants such as glutathione; and increase substances depleted by the oxidant stress such as endothelium-derived relaxing factor.[23,29] In this manner NAC can modulate the oxidative stress and inflammatory cascade while improving oxygen delivery and extraction in extrahepatic organs such as the brain, heart, and kidney.[46,76,83]

Clinical Use

If the patient's history suggests an acute acetaminophen ingestion â‰¥150 mg/kg and the results of blood tests will not be available within 8 hours of ingestion or if the serum [APAP] falls on or above the treatment line on the Rumack-Matthews nomogram, NAC should be instituted expeditiously. Aspartate aminotransferase and APAP concentrations should be determined in adults with chronic overdoses who ingest more than the recommended maximum daily dose of 4 g or children who ingest more than 90 mg/kg/d and are at high risk (increased NAPQI formation or reduced glutathione stores). NAC should be administered when hepatotoxicity is manifest by symptoms or liver enzyme elevations (Chap. 34). Interpretation of acetaminophen concentrations in these chronic overdoses is difficult, and the acetaminophen nomogram can never be applied.

Some patients who are at increased risk for acute or chronic acetaminophen poisoning may require administration of NAC at a lower threshold. Unfortunately, this threshold is not yet defined. Glutathione-deficient patients who are malnourished, have chronic alcoholism, or are receiving CYP2E1-inducing agents such as isoniazid or ethanol may theoretically be at increased risk for acetaminophen toxicity.[12,30,42,81] However, an analysis of a small number of patients who received anticonvulsants or chronically ingested alcohol did not demonstrate these patients to be at risk independent of acetaminophen dose.[49,82] Also currently no data indicate the need to lower the threshold when evaluating a patient with hepatic enzyme abnormalities.[82]

Pharmacokinetics

When administered, NAC is present in plasma in the reduced or oxidized state and is either free or bound with other thiols such as NAC-cysteine. NAC is metabolized to many sulfur-containing compounds such as cysteine, glutathione, methionine, cystine, disulfides, and conjugates.[23,56,61] Thus the pharmacokinetic study of NAC is complex.

Oral NAC is rapidly absorbed, but the bioavailability is low (10â€“30%) because of significant first-pass metabolism.[23,61] NAC has a relatively small volume of distribution (0.5 L/kg), and protein binding is 83%. Serum concentrations after IV administration of an initial loading dose of 150 mg/kg over 15 minutes reach approximately 500 mg/L.[61] A steady-state plasma concentration of 35 mg/L (10â€“90 mg/L) is reached in approximately 12 hours with the standard IV protocol.[61] Its elimination half-life is 5.7 hours. Severe liver damage does not appear to affect NAC elimination.[61]

Conflicting in vitro[16,39,75] and in vivo[14,22,54,66] data regarding the concomitant use of activated charcoal suggest that the resultant

bioavailability of NAC is either decreased or unchanged. This interaction is of limited importance now that IV NAC is available.

Oral NAC is being studied as a potential chemopreventive agent. Pharmacokinetics and pharmacodynamics of oral NAC were determined in a phase I trial in 26 adult volunteers at risk for development of cancer or recurrent cancer.[56] Absorption of NAC is rapid, with a mean time to maximum peak concentration of 1.4 Â± 0.7 hours and a mean elimination half-life of 2.5 Â± 0.6 hours that is linear with increasing dose up to 3200 mg/m^2/d given as a single daily dose. Intersubject plasma NAC concentrations vary 10-fold from a maximum concentration of 1.7â€“20.8 mg/L at a dose of 800 mg/m^2/d. Chronic administration leads to a decrease in plasma concentrations from a C_{max} of 8.9 mg/L at the end of 1 month to 5.1 mg/L at the end of 6 months.[56]

Oral Versus Intravenous *N*-Acetylcysteine

Although these approaches have never been directly compared, they appear to confer equal protection when either is administered within 8 hours.[95]

The 20-hour IV NAC protocol is 150 mg/kg loading dose over 15 minutes, followed by an additional dose of 50 mg/kg over 4 hours and then 100 mg/kg over 16 hours for a total dose of 300 mg/kg. The 72-hour regimen is 140 mg/kg loading dose followed by 70 mg/kg for 17 additional doses for a total dose of 1330 mg/kg. Both protocols are effective in preventing hepatic damage when given within 8 hours of acetaminophen ingestion.[62] A 48-hour IV regimen studied in the United States appears to be superior to the 20-hour regimen when the first dose is delayed until 16â€“24 hours after ingestion.[81] The 72-hour oral NAC regimen also appears superior to the 20-hour IV NAC protocol when started 16â€“24 hours postingestion. Perhaps most patients who receive

their first dose of NAC within 8 hours require only the short course because the inflammatory cascade is not initiated, whereas patients whose treatment is delayed benefit from a longer course of therapy and the associated benefits of the antiinflammatory/antioxidant effects of NAC. Some authors recommend a 36-hour oral course in low-risk patients with careful evaluation and follow-up, but this recommendation has not been adequately studied.

Only the IV route has been studied in hepatic failure.[28,38] The IV route achieves higher serum concentrations than the oral route. It is unclear whether oral or IV dosing results in superior drug delivery to the liver and whether the higher hepatic concentrations enhance drug efficacy.[57] The oral route often produces vomiting and requires antiemetics to complete therapy, but it is not usually associated with other serious adverse effects. Theoretically higher serum concentrations may be helpful for extrahepatic effects, whereas the oral route might provide higher intrahepatic concentrations.

We now recommend IV NAC for all adult patients without asthma[4] or other contraindication to IV NAC and in whom an anaphylactoid reaction would not be devastating. In children who do not tolerate oral NAC, IV NAC may be acceptable. However, the appropriate dilution of IV NAC in children is problematic. Currently, the package insert only provides dosing information down to a patient weight of 40 kg.[1] Hyponatremia is possible and has

been reported in a 13-kg child receiving the adult IV dosing volume (1700 mL), leading those authors to suggest a final concentration of NAC of approximately 4% in 5% dextrose in water (D_5W) to avoid the administration of excess free water and the potential for hyponatremia.[85] However, the pH of Acetadote (acetylcysteine injection, Cumberland Pharmaceuticals, Nashville, TN) is adjusted close to neutral where NAC is stable, resulting in an osmolarity of approximately 2600 mOsm/L for the 20%

solution. Therefore sodium concentrations and fluid requirements must be meticulously monitored. A 2% final NAC concentration in D_5W of Acetadote is approximately 485 mOsm/L and may be more appropriate.

Use in Pregnancy and Neonates

Untreated acetaminophen toxicity is a far greater threat to the fetus than is NAC treatment.[68] The risk of not treating pregnant women almost certainly far exceeds any potential risk to the developing fetus if a toxic ingestion has occurred. Although an earlier sheep model suggested otherwise, human data demonstrate that NAC traverses the placenta and produces cord blood concentrations comparable to maternal blood concentrations.[34] NAC is Food and Drug Administration (FDA) Pregnancy Category B. Limited data exist with regard to the management of neonatal acetaminophen toxicity,[5,43,71,77] although IV and oral NAC have been used safely.[1,5] No adverse effects were observed when preterm newborns were treated with IV NAC[1] (Chaps. 30 and 34). The elimination half-life of NAC in preterm neonates was 11 hours compared to 5.6 hours in adults.[1] IV administration has the advantage of assuring adequate antidotal delivery. Oral administration in general is associated with necrotizing enterocolitis in neonates.

Other Uses (Nonâ€“Acetaminophen)

Diverse investigations of NAC as a treatment for a number of xenobiotics associated with free radical or reactive metabolite toxicity are reported. Some of these xenobiotics include chloroform, carbon tetrachloride, 1,2-dichloropropane, acrylonitrile, doxorubicin, and cyclophosphamide.[17,23,89,93]

NAC is under study as a chemopreventive agent against amatoxins cancer, lung injury, cardiac injury, radiographic contrast

exposure,[86] and malnutrition.[2,20,21,46,72,83,84] NAC has extracellular antimutagenic effects, enhances repair of nuclear DNA damaged by carcinogens, and inhibits malignant cell invasion and metastases.[21,55,65] Oral NAC added to prednisone and azathioprine preserves vital capacity in patients with idiopathic pulmonary fibrosis.[21a]

Rescue NAC therapy is being studied with high-dose acetaminophen (â‰¤20 g/m^2) in patients with advanced malignancies.[40] Use of NAC in these settings may further enhance our understanding of the beneficial effects of NAC in both the early and late phases of acetaminophen poisoning.

Adverse Effects and Safety Issues

Oral NAC may cause nausea, vomiting, flatus, diarrhea, gastroesophageal reflux, and dysgeusia; generalized urticaria occurs rarely. Anaphylactoid reactions described after IV NAC dosing[3,10,11,19,24,31,48,50,61,67,88,91] are not noted after oral therapy and may be related to rate, concentration, or high serum NAC concentrations.[8,61]

Administration of oral NAC via the IV route produced cutaneous reactions in 4 of 76 patients and a generalized anaphylactoid reaction in 1 patient. None of these patients developed adverse hemodynamic effects.[94]

The IV route assures delivery, but rate-related anaphylactoid reactions are possible. Although the package insert for Acetadote recommends infusing the loading dose over 15 minutes, many authors, including ourselves, believe that infusion over 1 hour reduces the potential for life-threatening anaphylactoid reactions.[48] The manufacturer categorizes the number of anaphylactoid reactions occurring in 109 patients receiving the 15-minute loading dose as mild 6%, moderate 10%, and severe 1%.[1] Although similar findings are listed for the 60-minute loading dose

infusion, problems with study design cast doubt on these findings.[1,96] Of the adverse events occurring in more than 2000 patients who received IV NAC, vasodilation, rash, and pruritus account for approximately 10%, hypotension 4%, bronchospasm 6%, and angioedema 8%.[1]

If angioedema or an anaphylactoid reaction characterized by hypotension, shortness of breath, or wheezing, flushing, or erythema occurs, NAC should be stopped and standard symptomatic therapy instituted. Once the reaction resolves, NAC can be carefully readministered after 1 hour assuming NAC is still indicated. If the reaction persists or worsens, discontinue IV NAC and consider switching to oral NAC. Adverse reactions confined to flushing and erythema usually are transient, and NAC can be continued with meticulous monitoring for systemic symptoms that indicate the need to stop the NAC. Urticaria can be managed with diphenhydramine with the same precautions.[7]

Iatrogenic overdoses with IV NAC have resulted in comparable adverse events.[3,6,50] IV NAC decreases clotting factors and increases the prothrombin time in healthy volunteers and overdose patients without hepatic damage.[36,47,53,92] This effect occurs within the first hour, stabilizes after 16 hours of continuous IV NAC, and rapidly returns to normal when the infusion is stopped.[36] Because the prothrombin time is used as a marker of the severity of toxicity and is one of the criteria for transplantation, this adverse effect of NAC should always be considered when evaluating the patient's condition. An elevated prothrombin time without other indicators of hepatic damage probably is related to the NAC.

Dosing

The manufacturer recommends a loading dose of 150 mg/kg in 200 mL of D_5W (for adults) infused over 15 minutes, followed by a first maintenance dose of 50 mg/kg in 500 mL D_5W (for adults) infused

over 4 hours followed by a second maintenance dose of 100 mg/kg in 1000 mL D_5W (for adults) infused over 16 hours. We recommend infusing the loading dose over 60 minutes.

The appropriate dilution of IV NAC in children is problematic. Currently, the package insert only provides dosing information down to a patient weight of 40 kg.[1] Because of issues with osmolarity, sodium concentrations, and fluid requirements, meticulous monitoring is required. A 2% final NAC concentration in D_5W is approximately 485 mOsm/L and may be acceptable until further information becomes available.

When NAC is administered orally, the patient should receive a 140-mg/kg loading dose either orally or by enteral tube. Starting 4 hours after the loading dose, 70 mg/kg should be given every 4 hours for an additional 17 doses. The solution should be diluted to 5% with a soft drink to enhance palatability. If any dose is vomited

within 1 hour of administration, the dose should be repeated[44] or IV delivery used. Antiemetics (such as metoclopramide or a serotonin antagonist) should be used to ensure absorption. If the acetaminophen concentration is above the nomogram line, the standard approach is to administer 72 hours of therapy. Shorter courses may be acceptable (Chap. 34).

If hepatic failure intervenes, IV NAC should be administered at a dose of 150 mg/kg in D_5W infused over 24 hours and continued until the patient has a normal mental status (or recovers from hepatic encephalopathy),[29] the patient's international normalized ratio (INR) becomes <2.0,[69] or the patient receives a liver transplant.[13,28,38] Before the FDA approval of Acetadote, NAC approved for oral administration was administered by the IV route, often while using a 0.22-Âµm filter as a delivery precaution.[37,94] We would no longer recommend this practice except under unique circumstances.

Availability

Acetadote (NAC) is available as a 20% concentration in 30-mL single dose vials designed for dilution prior to IV administration. NAC for oral administration is available in 10-mL vials of 10% and 20% for oral administration.

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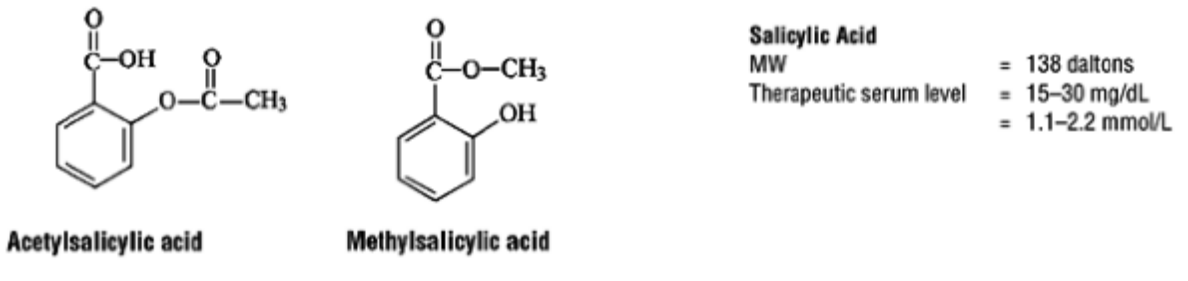
Chapter 35
Salicylates

Neal E. Flomenbaum



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Case

A 22-year-old woman came to the emergency department

complaining of abdominal pain, nausea, and vomiting. She had a history of depression but stated that she currently was not being treated by a psychiatrist or taking any psychiatric medications. Upon further questioning, the patient said that 6 hours earlier she had been severely depressed and had ingested at least half a bottle of aspirin tablets in a suicide attempt, after which she vomited once. She denied tinnitus but said that she was short of breath. She denied significant past medical or surgical problems.

On physical examination, the patient appeared to be well developed, well nourished, and diaphoretic. Vital signs were: blood pressure, 120/60 mm Hg; pulse, 110 beats/min; respiratory rate, 30 breaths/min; rectal temperature, 100.2Â°F (37.9Â°C). Examination of the head, eyes, ears, nose, and throat was unremarkable. The neck was supple, and there was no jugular venous distension. The chest was clear to auscultation and percussion. Cardiac examination revealed normal heart sounds and no murmurs, rubs, or gallops. Bowel sounds were normal, but the abdomen was diffusely tender, without guarding; stools were negative for occult blood. There was no clubbing, cyanosis, or edema. The patient was alert and fully oriented. No cranial nerve abnormalities were noted; deep tendon reflexes were intact and symmetric with plantar flexion of the toes; motor and sensory testing was normal.

An intravenous catheter was inserted. Blood was drawn and sent for determination of blood urea nitrogen (BUN), glucose, and electrolyte concentrations, complete blood count, coagulation studies, and salicylate and acetaminophen concentrations. Cardiac monitoring was instituted, and an arterial blood gas (ABG) specimen was obtained from the patient prior to administering supplemental oxygen. A Foley catheter was inserted, and a bedside ferric chloride test of the urine was positive. With the patient in the left lateral decubitus position, orogastric lavage was performed using a 40-French lavage tube. After food and particulate matter were recovered and a total of 2 L of fluid instilled and removed, the lavage fluid was clear. Sixty grams of activated charcoal in a slurry of water and 60 g sorbitol were

administered next, after which the lavage tube was removed.

The initial laboratory data revealed urine pH 5.5; specific gravity 1.025; 1+ protein; 2+ ketones; no red blood cells or white blood cells. ABG values on room air were: pH 7.51; PCO_2 11 mm Hg; PO_2 134 mm Hg. Serum electrolytes were Na^+ 144 mEq/L; K^+ 3.8 mEq/L; HCO_3^- 8 mEq/L; Cl^- 98 mEq/L; BUN 23 mg/dL; creatinine 0.9 mg/dL; glucose 88 mg/dL; calcium 9.6 mg/dL. Urine pregnancy test was negative.

A bolus of 88 mEq sodium bicarbonate was administered, and a bicarbonate drip consisting of 132 mEq sodium bicarbonate in 1 L of 5% dextrose in water (D_5W) was started at a rate of 250 mL/h. Potassium replacement was initiated.

After 2.5 hours, the patient's pulse had increased to 140 beats/min, and her blood pressure had dropped to 106/64 mm Hg. Although the salicylate concentration was not yet available, a nephrology consultation was requested. Fluid rates were increased, and a second dose of activated charcoal was administered. A repeat ABG determination revealed pH 7.48; PCO_2 13.9 mm Hg; PO_2 116 mm Hg.

Approximately 1 hour later (4 hours after presentation), a third ABG analysis on room air revealed pH 7.44; PCO_2 14 mm Hg; PO_2

93 mm Hg. At this time, the initial salicylate concentration was reported to be 107 mg/dL, and the acetaminophen concentration was negative. Arrangements for hemodialysis were made. Another ABG determination on room air 30 minutes later revealed pH 7.37; PCO_2 24 mm Hg; PO_2 64 mm Hg. At this time, rales could be auscultated at both bases. The bicarbonate infusion was reduced to 125 mL/h, and a third dose of activated charcoal was administered.

The patient became agitated shortly thereafter. A fifth ABG determination on 4 L nasal O_2 revealed pH 7.20; PCO_2 46 mm Hg; PO_2 92 mm Hg. ABG determination was immediately repeated, and the results were pH 7.10; PCO_2 63 mm Hg; PO_2 80 mm Hg.

Because of her rapidly deteriorating condition, the patient was intubated and hyperventilated, but her systolic blood pressure fell to 80 mm Hg by palpation and did not respond to a fluid bolus of 1 L of 0.9% sodium chloride solution. Postintubation ABG determination revealed pH 6.90; PCO_2 41 mm Hg; PO_2 182 mm Hg. Ventilation was increased, a second bolus of 88 mEq bicarbonate was administered, and an intravenous dopamine infusion was started. Systolic blood pressure was maintained at approximately 100 mm Hg while hemodialysis was started in the medical intensive care unit.

After 4 hours of hemodialysis, the patient's salicylate concentration was 22 mg/dL, and her ABG was pH 7.42; PCO_2 36 mm Hg; PO_2 190 mm Hg. Eight hours following hemodialysis completion, the patient appeared to be significantly improved clinically. A psychiatric consultation was obtained the next day. Three days later the patient was transferred to the psychiatric service from which she was later discharged home. One week after discharge, the patient returned to her job.

Epidemiology

Between 1999 and 2003 the number of analgesic exposures in the United States annually reported by the American Association of Poison Control Centers (AAPCC)/Toxic Exposure Surveillance System (TESS) increased from 214,066 to 269,982. During that same period, the number of analgesic-related deaths increased from 340 to 656 (Chap. 130). Since 2000, â€œanalgesicsâ€• has consistently ranked first among both the substances most frequently involved in human exposures and the substances responsible for the largest number of deaths. Of the analgesic-related deaths reported, acetaminophen, alone or in combination, accounts for slightly more than 50%, and aspirin, alone or in combination, accounts for approximately 12.6% (somewhat less than a decade ago). If â€œaspirin, alone or in combination with other analgesicsâ€• were listed as a separate category, it would be the seventh or eighth most common cause of

death from toxic exposures recorded by AAPCC/TESS.

Safety packaging, increasing use of nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen, or other alternatives to aspirin for adults, and use of acetaminophen instead of aspirin for children to avoid Reye syndrome[10,59] have contributed to the decreased incidence of unintentional salicylate poisoning. On the other hand, the historic widespread availability of salicylate preparations without prescription, the increasing confusion regarding specific ingredients suggested by product names and brand names, and the toxicity caused by small increments in salicylate dosage when used chronically make salicylate poisoning a common and sometimes fatal occurrence.[64]

Over the past 2 decades, popular brand and product names previously associated exclusively with salicylates or acetaminophen have been applied to other analgesic-containing products. For example, the names Alka-Seltzer, Anacin, and Excedrin, which once were used exclusively for salicylate-containing products, now are used as brand names for products containing aspirin, acetaminophen, or both. Bayer, a company once associated exclusively with aspirin, now markets, in addition to its aspirin products, a line of products called Bayer Select, which contains ibuprofen or acetaminophen. Clinicians should be aware that parents and healthcare providers seeking to use acetaminophen for children with viral illnesses to avoid Reye syndrome may inadvertently select a product containing aspirin either alone or in combination with acetaminophen, and an overdose in this setting might involve aspirin.[23] Another source of confusion associated with salicylate toxicity concerns correct dosage: Terminology such as grains and milligrams, and â€œbaby,â€• â€œchildren's,â€• â€œjunior,â€• and â€œadultâ€• aspirin are confusing and often misinterpreted. Maximum doses of aspirin should never be based on age range; instead, doses should always be based on body weight.

Unintentional salicylate toxicity may occur in patients who are

unaware that fixed-dose cold preparations often contain aspirin and then ingest additional aspirin tablets. Another popular medication, Pepto Bismol, or bismuth subsalicylate, contains 8.7 mg of salicylic acid/mL[38] and travelers using large quantities (200â€“300 mL) of this antidiarrheal may expose themselves to high doses of salicylates.

Salicylate poisoning, particularly in children but also in adults, may result from the extensive application of salicylate-containing ointments, keratolytic agents, or other agents containing methyl salicylate (oil of wintergreen).[16] Liniments and products used in hot vaporizers contain high concentrations of methyl salicylate (up to 30% in liniments and 100% oil of wintergreen). The intentional or unintentional *ingestion* of such topicals is usually disastrous: approximately 1â€“2 teaspoons (5â€“10 mL) of methyl salicylate can be lethal for a young child.[20] In Hong Kong, medicated oils containing methyl salicylate accounted for 48% of acute salicylate poisoning cases treated in one hospital.[20]

Salicylates continue to be used frequently as antipyretics for children in developing countries. In one study in Kenya, 94% of 250 mothers who purchased drugs for a febrile child purchased nonprescription drugs containing salicylates and 21% administered a dose exceeding the recommended maximum daily dose. More than one salicylate preparation was given to 27% of children, of whom 35% received a dose higher than the recommended maximum.[34]

Serious adolescent and adult salicylate poisonings frequently result from suicide attempts. Even in this setting rapid diagnosis and appropriate therapy initiated quickly may reduce mortality. However, overdose management recommendations written and distributed by pharmaceutical companies may contain inadequate, misleading, or dangerous advice for managing salicylate overdoses, as demonstrated by a published report from Canada.[17] Salicylism must be considered in all patients who have neurologic abnormalities, tachypnea, acidâ€“base disorders, and acute lung injury (ALI),

particularly in older patients and children and adults who are candidates for chronic iatrogenic salicylate poisoning.

Pharmacokinetics of Salicylates

There are 2 types of salicylic acid esters: phenolic esters (eg, aspirin) and carboxylic acid esters, including methyl salicylate, phenyl salicylate, and glycosalicylate.[27] Most of the studies of salicylate metabolism in the literature involve the phenolic ester aspirin or acetylsalicylic acid.[27]

Therapeutic Doses of Aspirin

Ingested salicylates in the form of aspirin tablets are rapidly absorbed from the stomach. The pK_a of aspirin is 3.5, and approximately 50% of salicylates is nonionized in the acid stomach.[27,54,105] Absorption of salicylates may be less efficient in the small bowel because of its higher pH but occurs rapidly there as well because of the large surface area of the small bowel[82] and because the increase in pH increases the solubility of salicylates and dissolution of tablets.[101] The dosage form of salicylates (effervescent, enteric-coated) often influences the absorption rate.[98,102,120] Delayed absorption of enteric-coated aspirin may result from salicylate-induced pylorospasm, pyloric stenosis,[49,102] gastric outlet obstruction,[106] or bezoar formation.[13,98] Protein-binding abnormalities, urine and plasma pH variations, and delayed absorption all influence the maximum salicylate concentrations and the rates of decline.[82,98]

After ingestion of therapeutic doses of immediate-release salicylates, significant plasma concentrations are achieved in 30 minutes, and maximum concentrations are often attained in less than 1 hour.[27] The volume of distribution is 0.2 L/kg, and 80â€“90% is protein bound. Salicylates are conjugated with glycine and glucuronides in

the liver and eliminated by the kidneys. Approximately 10% of salicylates is excreted in the urine as free salicylic acid, 75% as salicyluric acid, 10% as salicylic phenolic glucuronides, 5% as acylglucuronides, and 1% as gentisic acid.[101] More than 30% of ingested salicylate may be eliminated as free salicylic acid in alkaline urine and as little as 2% in acidic urine.[101,116] Free salicylic acid is filtered through the glomerulus, reabsorbed from the proximal tubules, and secreted from the proximal tubules; salicylic acid elimination is dependent on urine pH and serum concentration. Salicylate conjugates (glycine and glucuronides) are filtered and secreted by the proximal tubules; salicylate conjugates are not reabsorbed across renal tubular cells because of poor lipid solubility and the amount eliminated is dependent on glomerular filtration rate and proximal tube secretion but not urine pH.

Neither age nor gender appeared to affect the absorption rate and plasma clearance of an acute 900-mg dose of aspirin,[82] and systemic availability of salicylate appears to be unaffected by aging alone. An increase in the apparent volume of distribution, a decrease in maximum plasma salicylate acid concentration, and a significant decrease in renal salicyluric acid clearance with age were observed in 22 men 30â€“85 years of age after a 600-mg oral dose of sodium salicylate. Nevertheless, the authors concluded that age alone does not have a major influence on salicylate deposition in healthy adult men.[1]

To achieve an antiinflammatory effect for chronic conditions such as rheumatoid arthritis, salicylates typically have been prescribed in doses of approximately two regular strength (325 mg Ã— 2 = 650 mg) aspirin tablets every 4 hours. The goal of such dosing is to achieve blood salicylate concentrations of 15â€“30 mg/dL, which is considered the therapeutic range.[73] Concentrations higher than 30 mg/dL are associated with signs and symptoms of toxicity. The Food and Drug Administration Advisory Panel on Internal Analgesic and Antirheumatic Products recommends that the maximum adult maintenance dose of aspirin for a 70-kg person not exceed 3900 mg

in 24 hours for more than 10 days. No more than 650 mg should be given every 4 hours, except for the initial dose, which should not exceed 1000 mg.

Toxicokinetics

In overdosage, peak serum concentrations may not be reached for 4â€“6 hours or longer. There is a decrease in protein (albumin) binding from 90% at therapeutic concentrations to less than 75% at toxic concentrations.[2,14,35] The apparent volume of distribution simultaneously increases from 0.2 L/kg at low concentrations to more than 0.3 L/kg (possibly as high as 0.5 L/kg) at higher concentrations.[75,109] Salicylates also have substantially longer apparent half-lives at toxic concentrations than at therapeutic concentrations, varying from 2â€“4 hours at therapeutic concentrations to as long as 20 hours at toxic concentrations.[29,74] As the concentration of salicylates increase, 2 of the 5 pathways of eliminationâ€”those for salicyluric acid and the salicylic phenolic glucuronideâ€”become saturated and exhibit zero-order kinetics. As a result of this saturation, overall salicylate elimination changes from first-order kinetics to zero-order kinetics.[72] Figure 35-1 illustrates the main features of salicylate metabolism. (Pharmacokinetics and toxicokinetics are discussed in Chap. 9). Finally, the pH of salicylic acid offers a unique opportunity to increase elimination by alkalinizing the urine (see â€œIncreasing Salicylate Elimination by Urine Alkalinizationâ€”â€˜Ion Trappingâ€™?â€•).

Topical salicylates used as keratolytics or liniments are rarely responsible for salicylate poisoning when used in the intended manner, as absorption through normal skin is very slow.[16] After 30 minutes of contact time, only 1.5â€“2.0% of a dose is absorbed, and even after 10 hours of contact with methylsalicylate, only 12â€“20% of the salicylates is systemically absorbed.[16,100] (Fig. 35-1 shows methylsalicylate metabolism). Although heat, occlusive dressings, young age, inflammation, and psoriasis all increase salicylate

absorption, the real danger of salicylate toxicity caused by salicylate-containing topicals results from its intentional or unintentional *ingestion*.[21] Methylsalicylate is rapidly absorbed from the gastrointestinal tract and much, but not all, of the ester is rapidly hydrolyzed to free salicylates. Onset of symptoms usually occurs within 2 hours of ingestion.[21] When ingested, 1 mL of 98% methylsalicylate is as potent as 1.4 g of acetylsalicylic acid. In a 10-kg child, the minimum toxic salicylate dose of approximately 150 mg/kg body weight can almost be achieved with 1 mL of oil of wintergreen, which results in 140 mg/kg of salicylates (Chap. 31).

Pharmacology

The glycoside salicin was extracted from the willow bark and used as an antipyretic beginning in the early 1800s, but acetylsalicylic acid was first synthesized and commercially introduced as aspirin by Bayer in 1899.[101] Aspirin and other salicylates are analgesics, antiinflammatories, and antipyretics, a combination of traits shared by all medications of varying structures known as â€œnonsteroidal antiinflammatory drugsâ€• (NSAIDs). Most of the beneficial effects of NSAIDs result from their ability to inhibit cyclooxygenase (COX), the enzyme that enables the synthesis of prostaglandins, which in turn mediate inflammation and fever. Independent of their effects on prostaglandins, salicylates and other NSAIDs may also directly inhibit neutrophils, contributing to their antiinflammatory effects. The type of pain for which salicylates and NSAIDs are purportedly most effective in treating is the pain that accompanies inflammation and tissue injury. Such pain is elicited by prostaglandins, which are liberated by bradykinin and cytokines. Fever is also mediated by cytokines such as interleukin (IL)-Î², IL-6, Î± and Î² interferons, and tumor necrosis factor-Î±, all of which increase synthesis of prostaglandin E_2.[101]

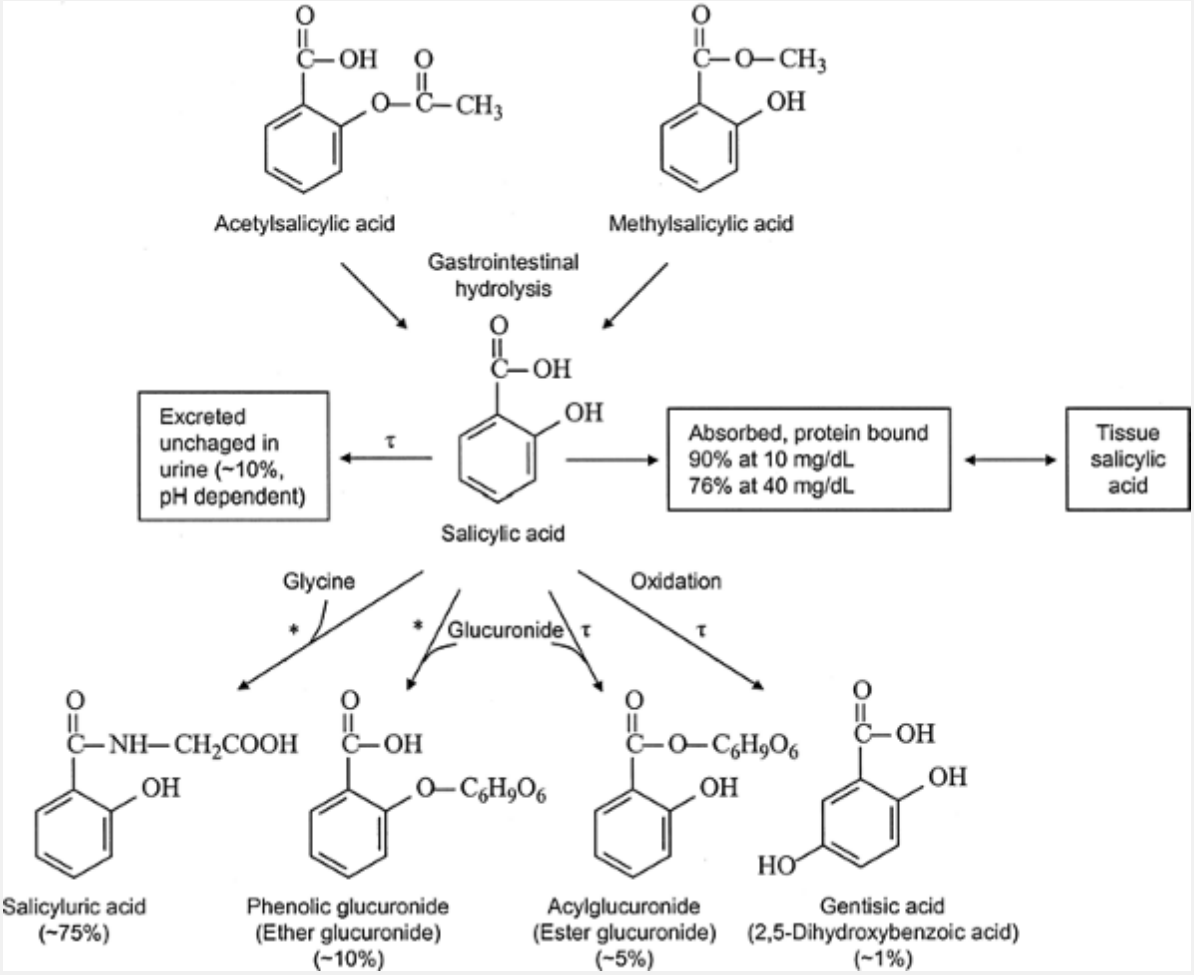

Figure 35-1. Salicylate metabolism. At excessive doses, the d mechanisms of salicylic acid metabolism are overloaded, leading to increased tissue binding, decreased protein binding, and increased excretion of unconjugated salicylic acid. * = Michaelis-Menten kinetics; Ï„ = first-order kinetics.

Because platelets cannot regenerate COX, a daily dose of as little as 40 mg of aspirin inhibits COX for the 8- to 11-day life of the platelet.[101] Frequent aspirin use appears to reduce the incidence of colon cancer, but the reason is not clear.

Adverse effects of aspirin and some NSAIDs include gastrointestinal ulcerations and bleeding, interference with platelet adherence,[99] and a variety of metabolic and organ-specific effects described below in â€œGastrointestinal Effects.â€ •[101]

Pathophysiology

Acidâ€“Base Disturbances Caused by Salicylate Poisoning: Differences Between Adult and Pediatric Patterns

Salicylates stimulate the respiratory center in the brainstem, leading to hyperventilation and respiratory alkalosis.[113] In addition, salicylates are weak acids and in toxic concentrations replace 2â€“3 mEq per liter of plasma bicarbonate. Impaired renal function resulting from salicylate toxicity leads to accumulation of sulfuric and phosphoric acids, both strong acids.[101] Salicylates interfere with the Krebs cycle, which limits production of adenosine triphosphate (ATP),[62] and salicylates uncouple oxidative phosphorylation, which causes accumulation of pyruvic and lactic acids and generates large amounts of heat.[68] Salicylate-induced increased fatty acid metabolism generates ketone bodies: Î²-hydroxybutyric acid, acetoacetic acid, and acetone. The net result of all of these metabolic processes is a wide anion gap metabolic acidosis (Chaps. 17 and 103). A significant part of this metabolic acidosis is a ketoacidosis.

Although metabolic acidosis begins with the earliest stages of toxicity, a primary respiratory alkalosis predominates initially. At the time an adult patient typically presents to the hospital after a substantial acute salicylate overdose, this mixed respiratory alkalosis and metabolic acidosis is discernible by arterial blood gas (ABG) and serum electrolyte analysis.[45] It is important to understand that the respiratory alkalosis of salicylate poisoning is not merely compensatory for the metabolic acidosis (or vice versa), but that

adults acutely poisoned by salicylates characteristically present with 2 primary acidâ€“base disturbances.[45]

By the time children typically present to the hospital after salicylate poisoning, the predominant respiratory alkalosis that initially characterizes *adult* salicylate poisoning may be missed because the metabolic acidosis may already be significant.[46,110] Ultimately, a respiratory acidosis may replace the initial respiratory alkalosis

that is seen so typically early after adult salicylate poisonings. Possible reasons for not seeing a predominant respiratory alkalosis in children are that they may present later, the exposure to salicylates per body weight in children may be much larger, or children do not respond to salicylate poisoning with the same degree of sustained hyperventilation or hyperpnea as do adults. The typical acidotic presentation of a seriously poisoned child led some investigators in the past to incorrectly suggest that pediatric salicylate poisoning produces only a metabolic acidosis. Although some children present with a mixed acidâ€“base disturbance and a normal pH after a significant salicylate ingestion, most such children present with acidemia.[46]

Mixed respiratory alkalosis and metabolic acidosis is found in the majority of adults with serum salicylate concentrations <40 mg/dL[45] and respiratory alkalosis initially predominates. This pattern is so characteristic of adult salicylate poisoning that any salicylate-poisoned adult who presents early with a respiratory *acidosis* almost certainly has either salicylate-induced ALI (formerly called salicylate-induced pulmonary edema [SIPE]), central nervous system (CNS) depression from a mixed overdose, or severe fatigue from the strenuous exercise of hyperventilating for a prolonged period. Mixed xenobiotic overdoses in the adult population are fairly common, as demonstrated by the findings of one study that one third of patients with a presumed primary salicylate overdose had taken other xenobiotics;[45] benzodiazepines, barbiturates, alcohol, and cyclic antidepressants all appear to blunt the centrally induced

hyperventilatory response to salicylates, resulting in either an actual respiratory acidosis (PCO_2 >40 mm Hg) or a metabolic acidosis without the appropriate respiratory compensation (PCO_2 <40 mm Hg, but inappropriately high for the concomitant pH). The combination of metabolic *and* respiratory acidosis from salicylate poisoning in an adult resulting in severe and worsening acidemia indicates an exceedingly grave prognosis and almost invariably is a preterminal event.[92]

Glucose Metabolism

Salicylate poisoning appears to produce a discordance between plasma and cerebrospinal fluid (CSF) glucose concentrations. Despite normal plasma glucose, CSF glucose concentration fell 33% in salicylate-poisoned mice compared to controls.[114] In other words, the rate of CSF glucose use exceeded the rate of supply, even in the presence of normal serum glucose concentration. There was also a marked increase in oxygen consumption in mice, even with low salicylate concentrations.[52] A case report of refractory hypoglycemia secondary to poisoning from topical salicylate absorption underscores the problems of glucose metabolism caused by salicylates.[96]

Hepatic Effects

Salicylate-poisoned mice had a marked decrease in glycogen and a dramatic increase in lactate compared to controls[52] as increased glycolysis apparently compensates in part for the uncoupling of oxidative phosphorylation.[80] In humans, the increased metabolic demands resulting from salicylate poisoning stimulate peripheral use of glucose and fat with resultant hypoglycemia and ketosis. Salicylates reduce lipogenesis by blocking the incorporation of acetate into free fatty acids, inhibiting epinephrine-stimulated lipolysis in fat cells and displacing long-chain fatty acids from human plasma proteins. All of these effects lead to increased entry of fatty acids into muscle and liver and to their oxidation inside. As a result,

the concentrations of *plasma* free fatty acids, phospholipids, and cholesterol decrease. Ketone body oxidation is increased.[101]

Salicylate-induced hepatitis occurred in children who were being treated with high (average concentration, 30.9 mg/dL) or chronic doses of salicylates for rheumatic fever and juvenile rheumatoid arthritis.[48,76,104]

Another form of liver disease associated with salicylates, also primarily seen in children, is Reye syndrome, which is characterized by nausea, vomiting, hypoglycemia, elevated concentrations of liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT)], fatty infiltration of the liver, and coma following a viral illness, usually influenza or varicella.[7,10] Although the nature of the link between Reye syndrome and salicylates has never been fully elucidated, the existence of such a link is fairly certain. The mean serum salicylate concentration in biopsy-proven Reye syndrome was 12.3 mg/dL, and the mean serum salicylate concentration in patients who died of or survived Reye syndrome with neurologic deficits was 15 mg/dL.[23,87]

Further evidence of a causal relationship between salicylate use for a viral illness and Reye syndrome is suggested by the finding that the incidence of Reye syndrome has fallen steadily concomitantly with the decreased use of salicylates in children.[10,97,117] From December 1980 through November 1991, 1207 cases of Reye syndrome were reported in the United States in patients younger than 18 years, with a peak incidence of 555 cases in 1980. Between 1994 and 1997, no more than 2 cases each year were reported.[10] However, the problem has not completely disappeared, as evidenced by 2 fatal cases reported in 2003.[12,23] In one case, a 3-year-old boy who presented in 1999 with signs of Reye syndrome had an initial salicylate concentration of 3.9 mg/dL.[12] In the case of a 10-year-old girl who presented in 2002, the *reported* amount of aspirin that she had knowingly ingested was two 325-mg tablets, which did not correlate with the serum salicylate concentration of 16 mg/dL obtained on

admission to the hospital 3 days later. The discrepancy may have resulted from confusion between brand or product labeling or an inability to accurately determine the contents of the nonprescription medications used.[23]

Neurologic Effects

Toxic doses of salicylates first stimulate and then depress the CNS. Confusion, dizziness, delirium, psychosis, and then ultimately stupor and coma may occur.[101]

Otolaryngologic Effects

The pattern of salicylate-induced auditory sensorineural alterations is different than the pattern characterizing other ototoxic drugs.[18] Tinnitus, loss of absolute acoustic sensitivity, and alterations of perceived sounds are the 3 effects resulting from exposure to large doses of salicylates.[18] Tinnitus followed by mild to moderate reversible hearing loss typically occurs with serum salicylate concentrations of 20â€“45 mg/dL or higher.[15,18,84] Occasionally investigators have questioned whether salicylate ototoxicity can be used as an indicator of serum salicylate concentration, only to note that some patients with therapeutic concentrations of salicylates complained of tinnitus and many with higher or toxic concentrations had no tinnitus. In a study of 94 patients with salicylate concentrations >30 mg/dL on one or more occasions, the majority (55%) had no tinnitus, which only correlated with blood salicylate concentrations in 30%, although audiologic testing results usually were abnormal regardless of the presence or absence of tinnitus. The authors concluded that symptomatic ototoxicity is

too nonspecific and too insensitive to serve as an indicator of serum salicylate concentrations.[47]

The mechanism of ototoxicity is not completely understood but

appears to be multifactorial. Inhibition of COX by salicylates prevents prostaglandin synthesis, which interferes with the Na^+-K^+-adenosine triphosphatase (ATPase) pump in the stria vascularis and the vasoconstriction decreases cochlear blood flow[15,19,36,61] Membrane permeability changes cause a loss of outer hair cell turgor in the organ of Corti, which may impair otoacoustic emissions.[94,95] For a more complete description of the pathophysiology of salicylate-induced ototoxicity and sensorineural alterations and comparisons to the patterns of other ototoxic xenobiotics, see Chap. 21.

Pulmonary Effects

When a patient with salicylate poisoning presents with the clinical and radiographic manifestations of pulmonary edema or ALI, major etiologies that must be considered include aspiration pneumonitis, viral and bacterial infections, postictal and neurogenic ALI, and salicylate-induced ALI (formerly known as salicylate-induced pulmonary edema [SIPE] or noncardiogenic pulmonary edema)[57,63] (Chap. 22).

Many different causes of ALI result in increased pulmonary capillary permeability and subsequent exudation of high-protein edema fluid into the interstitial or alveolar spaces. Severe traumatic CNS injuries and elevation of intracranial pressure may be responsible for a form of â€œcentralâ€• ALI (formerly called postictal pulmonary edema).[58] Hypothalamic lesions from trauma, increased intracranial pressure, or salicylate poisoning may be the critical factor, with resultant adrenergic overactivity producing a shift of blood from the systemic to the pulmonary circulation, loss of left ventricular compliance with left atrial and pulmonary capillary hypertension, and subsequent pulmonary edema (Chap. 22).

In 111 consecutive patients with peak salicylate concentrations >30 mg/dL, ALI occurred in 35% of patients older than 30 years of age and none of the 55 patients younger than 16 years of age. Risk factors for developing ALI included cigarette smoking, chronic

salicylate ingestion, and presence of neurologic symptoms on admission. The average arterial blood pH was 7.37 Â± 0.022 in the 6 adult patients with ALI and 7.46 Â± 0.010 in the 30 adults without ALI. There was no significant difference in salicylate concentrations, which were approximately 57 mg/dL in both groups.[118] In a 2-year review of all salicylate deaths in Ontario, Canada, 51 patients were studied, with autopsies performed in 39. The autopsies revealed that 59% had pulmonary pathology. The presence of pulmonary pathology, mostly â€œpulmonary edema,â€• was significantly associated with therapy for >4 hours.[79]

Although the exact mechanism for ALI is obscure, hypoxia may be an important factor.[56,57] Hypoxia can result in pulmonary arterial hypertension and a local release of vasoactive substances. Severe salicylate poisoning has been identified as a distinct cause of ALI in children and in adults.[41]

Gastrointestinal Effects

Gastrointestinal manifestations of salicylate use include nausea and vomiting, which probably result from local gastric irritation at lower doses and from stimulation of the medullary chemoreceptor trigger zone at higher doses (27 mg/dL).[101] Hemorrhagic gastritis, decreased gastric motility, and pylorospasm also result from the direct gastric irritant effects of salicylates.[102] The effects appear more pronounced or consequential in the elderly.[64]

Renal Effects

The kidneys clearly play a major role in the handling and excretion of salicylates, and many believe in turn that salicylates are significantly nephrotoxic, but the majority of studies and experimental evidence do not strongly support this notion.[26,37,88] Most of the adverse renal effects historically associated with salicylates occurred with use of combination products such as aspirinâ€“phenacetinâ€“caffeine (APC)

tablets and appear to have been due mostly to the nonsalicylate ingredient(s), that is, phenacetin,[37] or to a synergistic effect contributed to by salicylates. The synergistic nephrotoxicity of aspirin and acetaminophen results from the effects of each on depleting glutathione.[33,89,121] Renal papillary necrosis (RPN) and chronic interstitial nephritis initially characterized by reduced tubular function and reduced concentrating ability are rarely seen in adults using aspirin or salicylates unless they have chronic illnesses that already compromise renal function.

Although extremely high doses of aspirin have produced RPN experimentally in 1 rat species, RPN has not been demonstrated following excessive doses of aspirin alone in humans or other species, or after lesser doses of aspirin in other rats.[26] Similarly, neither chronic nephrotoxicity nor an increased risk of end-stage renal disease (ESRD) from long-term use of aspirin alone has been demonstrated in humans, with the exception of 1 case control series demonstrating a low but statistically significant risk of ESRD. In adults with preexisting glomerulonephritis, cirrhosis, or chronic renal insufficiency and in children with congestive heart failure, short-term therapeutic doses of aspirin may precipitate reversible acute renal failure, possibly because of inhibition of the vasodilatory prostaglandins necessary to maintain renal blood flow in these conditions.[26] In healthy adults, however, short-term therapeutic doses of aspirin do not adversely affect creatinine clearance, urine volume, or sodium and potassium clearance. Aspirin doses >300 mg/kg can cause acute renal failure, and chronic aspirin poisoning can cause reversible or irreversible acute renal failure associated with a pseudosepsis syndrome.[26]

Hematologic Effects

Hematologic effects of salicylate poisoning include hypoprothrombinemia and platelet dysfunction.[44] Anemia in patients who chronically abuse salicylates may be a result of the effects of

both platelet dysfunction and gastric mucosal barrier breakdown (gastrointestinal bleeding),[44] particularly in the elderly.[6,25] Hemolysis is unusual, and alterations in leukocyte function are of no apparent clinical significance.[103]

Musculoskeletal Effects

Rhabdomyolysis after pure salicylate overdoses probably is another result of the dissipation of heat and energy from uncoupling oxidative phosphorylation.[71,80,81] Paratonia, characterized by extreme muscle rigidity, was present in 3 of the 51 cases of salicylate deaths reviewed in Ontario between 1983 and 1984.[79] Rapid rigor mortis and paratonia (which are not unique to salicylate poisoning) probably are related to the extreme depletion of ATP and the inability of the muscle fibers to relax.

Clinical Manifestations of Acute and Chronic Salicylate Poisoning

Acute Toxicity

The earliest signs and symptoms of salicylate toxicity include nausea, vomiting, diaphoresis, and tinnitus, which is a subjective sensation of ringing or hissing, with or without hearing loss.[15,44,110] As CNS salicylate concentrations increase, tinnitus is rapidly followed by diminished auditory acuity that sometimes leads to deafness.[15] Other early CNS effects may include vertigo and hyperventilation manifested as hyperpnea or tachypnea (Chap. 3), hyperactivity, agitation, delirium, hallucinations, convulsions, lethargy, and stupor. Coma is rare and generally occurs only after massive ingestions (serum salicylate concentrations >100 mg/dL) or mixed overdoses (Table 35-1).[44] A marked elevation in temperature resulting from the uncoupling of oxidative phosphorylation caused by salicylate

poisoning[80] is an indication of severe toxicity and typically a preterminal condition.

Unfortunately, many of the signs and symptoms of salicylate toxicity may be mistakenly attributed to the illness for which the salicylates were administered, with disastrous consequences.[24,110] In the review of all salicylate deaths in Ontario, Canada, in 1983 and 1984, the author noted that in 6 of the 23 (26%) patients who arrived alert, no salicylate determination appears to have been made and that probably neither the diagnosis nor severity of the lethal salicylate poisoning was recognized.[79]

TABLE 35-1. Clinical Manifestations and Diagnostic Testing Results of Salicylate Toxicity

Acidâ€“base and electrolyte disturbances
Anion gap increased
Metabolic acidosis
Metabolic alkalosis (vomiting)
Respiratory alkalosis (predominates early)
Respiratory acidosis (late, grave prognosis)
Hyponatremia or hypernatremia
Hypokalemia
CNS
Tinnitus
Diminished auditory acuity
Vertigo
Hallucinations
Agitation
Hyperactivity
Delirium
Stupor
Coma

Lethargy
Convulsions
Cerebral edema
Syndrome of inappropriate antidiuretic hormone
Coagulation abnormalities
Hypoprothrombinemia
Inhibition of factors V, VII, X
Platelet dysfunction
Gastrointestinal
Nausea
Vomiting
Hemorrhagic gastritis
Decreased motility
Pylorospasm
Hepatic
Abnormal liver enzymes
Altered glucose metabolism
Metabolic
Diaphoresis
Hyperthermia
Hypoglycemia
Hyperglycemia
Hypoglycorrhachia
Ketonemia
Ketonuria
Pulmonary
Hyperpnea
Tachypnea
Respiratory alkalosis
Acute lung injury
Renal
Tubular damage
Proteinuria
NaCl and water retention

Hypouricemia

Chronic Toxicity

Chronic salicylate poisoning most typically occurs in the elderly as a result of unintentional overdosing on salicylates used to treat chronic conditions such as rheumatoid arthritis and osteoarthritis.[5,32,64] Although neither age nor gender appears to affect the absorption rate or plasma clearance of acute therapeutic doses of aspirin (900 mg) administered to healthy adults,[82] when used chronically, a small increase in dosage (eg, in response to increasing pain) or a small decrease in metabolism or renal function can result in substantial increases in serum salicylate concentrations and toxicity.[64]

Presenting signs and symptoms of *chronic* salicylate poisoning include hearing loss and tinnitus, nausea, vomiting, dyspnea and hyperventilation, tachycardia, hyperthermia, and neurologic manifestations such as confusion, delirium, agitation, hyperactivity, slurred speech, hallucinations, seizures, and coma.[4,44,70] In one review, the authors went so far as to suggest that the diagnosis of salicylate poisoning should be borne in mind when an older patient presents with recent deterioration in activities of daily living of no known cause.[31] Although there is considerable overlap with some of the presenting signs and symptoms of *acute* salicylate poisoning, the slow onset and less severe appearance of some of these signs of chronic poisoning in the elderly frequently cause delayed recognition of the true etiology of the patient's presentation.[45]

Typically, ill patients who suffer from chronic salicylate poisoning may be misdiagnosed as having delirium, dementia, encephalopathy of undetermined origin, diseases such as sepsis (fever of unknown origin), alcoholic ketoacidosis, respiratory failure, or cardiopulmonary disease, especially congestive heart failure, acute pulmonary edema, or even unstable angina.[4,8,24,34,44]

In a study of 73 consecutive adults hospitalized with salicylate poisoning, 27% were not correctly diagnosed for as long as 72 hours after admission.[4] These patients manifested toxicity with standard or excessive therapeutic regimens and had significant associated diseases without a history of previous overdoses. In this group, 60% previously had a neurologic consultation before the diagnosis of salicylism was established. When diagnosis is delayed in the elderly, the morbidity and mortality associated with salicylate poisoning are high. Mortality was reported to be as high as 25% in the 1970s,[4] and no data suggest that survival after delayed diagnosis is substantially better today (Table 35-2).

Underrecognition or misdiagnosis of chronic salicylate poisoning is not confined to the elderly and may be a problem at the other end of the age spectrum. In one study of all children admitted to a district hospital in Kenya over a 3-month period with the primary diagnosis of severe malaria, 90% had detectable blood salicylate concentrations, and 6 of 143 had plasma concentrations â‰¥20 mg/dL. All 6 of the children with plasma salicylate concentrations of â‰¥20 mg/dL had neurologic impairment and metabolic acidosis, and 4 had hypoglycemia, suggesting that salicylates cause or contribute to those complications of malaria that are associated with high mortality.[34]

TABLE 35-2. Differential Characteristics of Acute and Chronic Salicylate Poisoning

	Acute	Chronic
Age	Younger	Older
Etiology	Overdose usually intentional	Therapeutic misadventures; iatrogenic
Diagnosis	Easily recognized	Frequently unrecognized
Other disease states	None	Underlying disorders (especially chronic pain conditions)
Suicidal ideation	Typical	No
Clinical differences	Rapid progression of signs	Acute lung injury (ALI) CNS abnormalities
Serum concentrations	Marked elevation	Intermediate elevation
Mortality	Uncommon when recognized, unless ingestion massive	Approximately 25%

Diagnostic Testing

Rapid Confirmation of Salicylate Use

Serum salicylate concentrations are relatively easy to obtain in most hospital laboratories and with proper attention to the units reported (mg/dL vs. mg/L) and concomitant arterial blood pH values, clinicians can quickly confirm or exclude toxic salicylate concentrations. Salicylate *use* may be rapidly confirmed qualitatively with a simple point-of-care ferric chloride ($FeCl_3$) test that uses several drops of 10% $FeCl_3$ added to 1 mL of urine. A purple color indicates the *presence* of salicylic acid, acetoacetic acid, or phenylpyruvic acid.[119] However, because this test is extremely sensitive to very small quantities of salicylates, a positive result indicates only salicylate usage and not necessarily poisoning or overdosage. A positive $FeCl_3$ test result must be confirmed by determination of actual serum salicylate concentration, whereas false-negative $FeCl_3$ results either do not occur or are exceedingly rare.[42] A false-positive $FeCl_3$ test may also result from use of a small quantity of urine that has already been subjected to dipstick analysis with N-Multistix or Bili Labstix reagent strips. Presumably in this instance impregnated chemical from the dipstick that has dissolved in the urine subsequently causes a false-positive $FeCl_3$ reaction.

When urine is not available for $FeCl_3$ testing (because of anuria or oliguria, too short a time after ingestion, or chronic use of salicylates), a possible salicylate-containing product itself can be tested with $FeCl_3$. All 15 of the salicylate-containing products tested in one study demonstrated a positive $FeCl_3$ reaction, whereas none of the 15 nonsalicylate containing controls did.[55] $FeCl_3$ reagent is rarely available in hospital emergency departments, and the unsupervised performance of $FeCl_3$ testing outside of a certified laboratory is not consistent with the federal Clinical Laboratory Improvement Amendments (CLIA) in the United States.

Another rapid colorimetric urine test for determination of salicylate usage is the Trinder spot test,[66] which uses a premixed reagent consisting of mercuric chloride, ferric nitrate, deionized water, and concentrated hydrochloric acid. When 1 mL of urine containing salicylates is mixed with 1 mL of Trinder reagent, it instantly turns violet or purple. The sensitivity of the test was 100% when applied to urine collected 2â€“4 hours after oral ingestion of 975 mg of salicylate by volunteers.[66] (Because of the composition of the testing reagents, this test presumably would be available only in a laboratory.)

â€œPoint-of-careâ€• determinations that may help rapidly indicate salicylate *poisoning* are (A) a positive urine ketone determination reflecting ketogenesis from increased fatty acid metabolism[53] and perhaps the ketone forms of salicylates present; (B) a whole-blood glucose and electrolyte determination performed on a handheld analyzer (I-stat and others); this test can quickly demonstrate decreased HCO_3^-[2] (indicating a possible wide anion gap metabolic acidosis) and other glucose and electrolyte abnormalities characteristic of salicylate toxicity; and (C) a whole-blood ABG determination performed on a handheld analyzer indicating acidâ€“base disturbance(s) characteristic of salicylate poisoning.

Serum Salicylate Concentrations and Correlation with Toxicity

Serum salicylate concentrations should be requested when clinically significant salicylate exposures are suspected and not as part of a general toxicologic screen. For some, the confusion in correctly identifying aspirin and acetaminophen products and the consequent possibility that either or both may be used in a suicide attempt, coupled with the initial absence (acetaminophen) or unreliability (salicylates) of clinical findings associated with these poisonings, make toxicologic analysis for both salicylates and acetaminophen reasonable when either one is implicated in an intentional poisoning.

The authors of two studies concluded that universal salicylate screening is not indicated for patients with acute self-poisonings (Hong Kong)[22] or patients with suicidal ingestions or altered mental status (United States).[107] The latter study found that 0.16% of patients with suicidal ingestions had a toxic salicylate exposure *not* suggested by history, compared to 0.3% of patients with potentially toxic acetaminophen exposures not suggested by history. Although these authors recommended universal acetaminophen screening to evaluate patients with suspected ingestions, they concluded that salicylate screening was unnecessary because severe salicylate exposures are less frequent and usually are accompanied by an elevated anion gap and altered mental status.[107]

Except in certain narrowly defined situations, the toxicity of salicylates correlates poorly with serum concentrations. The Done nomogram,[29] first published in 1960, continues to be republished in texts despite severely limited applicability. It was based on data from a predominantly pediatric population and intended to be applied only 6 hours or more after a single acute ingestion of nonenteric-coated, orally ingested aspirin. Moreover, the patient's blood pH must be approximately 7.4 or higher. Such conditions rarely apply to patients with serious acute and chronic salicylate overdoses and poisonings. An example of the shortcomings of the nomogram is a patient who presents with lethargy and/or a coagulation abnormality associated with salicylism. Such a patient can be classified on the Done nomogram as â€œmildâ€• or â€œmoderate,â€• although it is obvious clinically that the patient must be considered severely poisoned. The poor predictive value of the Done nomogram when applied retrospectively to a group of 55 predominantly adults with salicylate poisoning is evident from a 1989 study.[32]

Patients with acute exposures whose initial serum salicylate concentrations are considered acceptable, low, or moderate sometimes

deteriorate rapidly thereafter. For this reason, careful observation of the patient, correlation of the serum salicylate concentrations with blood pH values, and repeat determinations of serum salicylate concentrations every 2â€“4 hours are essential until the patient is clinically improving and has a low salicylate concentration in the presence of a normal or high blood pH. Methyl salicylate exposures have resulted in deaths in <6 hours, emphasizing the need for early determinations of salicylate concentrations in addition to frequent testing after such exposures. In all cases, once a peak serum salicylate concentration has been reached, at least one additional concentration should be obtained after several hours and more frequent concentrations obtained in managing the seriously ill patient to assess efficacy of treatment and possible need for hemodialysis (HD).

A concurrent arterial blood pH should be determined when a blood salicylate concentration is obtained because in the presence of acidemia, more salicylic acid leaves the blood and enters the CSF and other tissues (Fig. 35-2), increasing the toxicity. Therefore, meaningful interpretation of *serum* salicylate concentrations must take into account the effect of blood pH on salicylate distribution, unless the serum salicylate concentration is so high that HD is indicated regardless of the pH. A decreasing serum salicylate concentration may be difficult to interpret because it can reflect either an increased tissue distribution with increased toxicity or an increased clearance with decreased toxicity. A decreasing serum salicylate concentration accompanied by a decreasing or low blood pH should be presumed to reflect a serious or worsening situation, not a benign or improving one.

When the patient's clinical signs and symptoms are given the highest priority and the serum salicylate concentration is interpreted in conjunction with a simultaneously obtained arterial blood pH, the severity of toxicity usually can be predicted and the need for HD accurately determined.

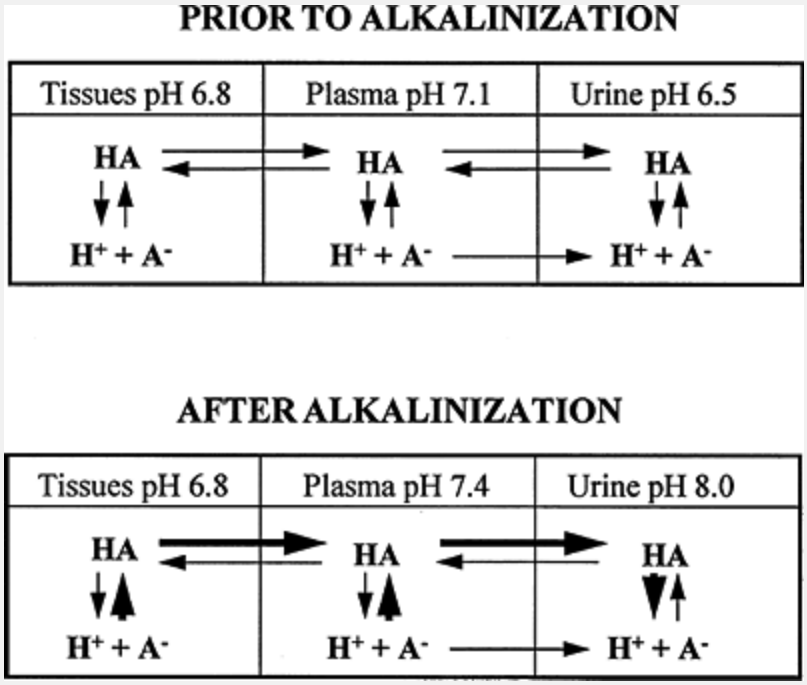

Figure 35-2. Rationale for alkalinization. Alkalinization of the plasma with respect to the tissues and alkalinization of the urine with respect to plasma shifts the equilibrium to the plasma and urine and away from the tissues (including the brain). This equilibrium shift results in â€œion trapping.â€• *(Adapted, with permission, from Temple AR: Acute and chronic effects of aspirin toxicity and their treatment. Arch Intern Med 1981;141:367.)*

Errors in Reporting Serum Salicylate Concentrations

Laboratory errors probably are more common and problematic when reporting serum salicylate concentrations compared to other drug concentrations. Analyzing and reporting salicylate concentrations as mg/L when the clinician is accustomed to receiving results as mg/dL or inadvertently reporting actual mg/L results erroneously as

â€œmg/dLâ€• multiplies the true salicylate concentration by 10 and suggests a toxic salicylate concentration in a patient whose serum salicylate concentration is actually within the therapeutic range (eg, â€œ165â€• instead of â€œ16.5â€•). Most errors can be eliminated prior to initiation of aggressive therapy, such as HD, by determining whether the reported salicylate concentration is consistent with the clinical presentation and ABG results and, when time permits, repeating the salicylate determination with appropriate consideration for methodology and conversion calculations.

Correlation Between CSF and Serum Salicylate Concentrations

Although peak serum salicylate concentrations may provide useful clinical correlations at a normal or high blood pH, serum salicylate determinations not reflecting the peak concentration may be of limited value. Experimentally, there appeared to be a critical CSF salicylate concentration that correlated closely with mortality.[52] In addition, the CSF salicylate concentration correlated best with the peak serum salicylate concentration and reequilibrated more slowly than the serum salicylate concentration. As noted above in â€œSerum Salicylate Concentrations and Correlation with Toxicity,â€• a serum salicylate concentration in the presence of acidemia may have little or no correlation with the CSF salicylate concentration. However, even if CSF salicylate concentrations in humans are more accurate predictors of toxicity, their use in clinical management is currently impractical.

Management

Gastric Decontamination and Use of Activated Charcoal

The use of gastric decontamination (orogastric lavage) and activated

charcoal (AC) are discussed throughout this text, but their effects on the absorption and elimination of salicylates probably have been studied more extensively than with any other xenobiotic. In vitro studies suggest that each gram of AC can adsorb approximately 550 mg of salicylic acid.[75,85] In vitro, aspirin is adsorbed to AC with moderate efficacy. In humans, AC reduces the absorption of therapeutic aspirin doses by 50â€“80%, effectively binding aspirin from enteric-coated and sustained-release preparations in addition to immediate-release tablets.[75] Presumably, the sooner AC is given after salicylate ingestion, the more effective it will be in reducing absorption. A 10:1 ratio of AC to salicylate ingested appears to result in maximal efficiency. Although peak serum concentrations are markedly decreased from predicted concentrations, aspirin desorption from the aspirinâ€“AC complex may diminish the impact on total absorption.[40,77,85] The addition of a cathartic to the initial dose of AC has been questioned and largely abandoned for most xenobiotics, but the benefits of adding sorbitol to AC in preventing salicylate absorption have been demonstrated in one study.[65]

Repetitive or multiple-dose activated charcoal (MDAC) appears to increase the elimination of unabsorbed salicylates over that achieved by single-dose AC,[9,53] although the charcoal used in one of these studies contained â€œsubstantial amounts of sodium bicarbonate.â€•[3,53] MDAC probably prevents desorption, which may reduce the concentration of initially absorbed salicylate to only 15â€“20%.[40] It is not clear, however, that MDAC enhances the excretion of salicylates that have already been systemically absorbed.[3,60]

In one volunteer study of 2800 mg of aspirin followed by 25 g of AC at 4, 6, 8, and 10 hours after ingestion, the total amount of salicylate excreted from the body increased by 9â€“18% but was not considered statistically significant.[67] The authors hypothesized that MDAC was more effective in enhancing salicylate excretion in the *overdose* situation, when more salicylate is available because of

decreased protein binding. However, in another study of the effects of MDAC on the clearance of high-dose intravenous aspirin in a porcine model, MDAC did not enhance the clearance of salicylates under alkaline conditions, that is, when the venous bicarbonate was kept at â‰¥15 mEq/L and urine pH kept at â‰¥7.5.[60] In contrast to the findings of both of these studies, two pediatric patients with salicylate overdoses were successfully treated with MDAC given every 4 hours for 36 hours, and the authors concluded that MDAC is effective in an overdose situation, even after alkalinization.[115]

Theoretical support may be found for use of whole-bowel irrigation (WBI) consisting of polyethylene glycol electrolyte lavage solution (PEG-ELS) in addition to AC to diminish potential desorption, particularly for enteric-coated aspirin preparations.[112] Moreover, WBI alone may be effective in preventing absorption of other xenobiotics. However, the addition of WBI to MDAC did not increase the clearance of *absorbed* salicylate.[77]

The value of MDAC in enhancing salicylate elimination may be considered controversial, and the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists (AACT/EAPCCT) position statement concludes that data are presently insufficient to recommend MDAC for salicylate poisoning.[3] Nevertheless, the use of MDAC probably is warranted in attempting to decrease gastrointestinal absorption of salicylate overdoses (see Antidotes in Depth: Activated Charcoal).

Fluid Replacement

There is a need to differentiate between restoration of fluid and electrolyte balance in salicylate-poisoned patients as opposed to increasing the fluid load presented to the kidneys in an attempt to achieve â€œforced diuresis.â€• Fluid losses from salicylate poisoning are prominent, especially in children, and can be attributed to tachypnea, vomiting, fever, a hypermetabolic state, hyperpnea, and insensible perspiration.[111] The kidneys also respond to salicylate

poisoning by excreting an increased solute load, including large quantities of bicarbonate, sodium, potassium, and organic acids, but renal tubular damage leading to renal failure is rare. Ketoacidosis, hypoglycemia, or hyperglycemia may occur.[5] For all of these reasons, the patient's volume status must be adequately assessed and corrected if necessary, along with any glucose and electrolyte abnormalities. As in other cases, accurate management of volume status in the poisoned patient may require invasive monitoring with a central venous pressure monitor or, preferably, a pulmonary artery catheter, especially in patients with cardiac disease, ALI, or renal compromise.

Increasing fluids *beyond* restoration of fluid balance in order to achieve a forced diuresis is a practice that was inappropriately promoted in the past. Although forced diuresis theoretically increases renal tubular flow and reduces the urine tubular cell diffusion gradient for reabsorption, renal excretion of salicylate depends much more on urine pH than on flow rate, and use of forced diuresis alone is not effective regardless of whether diuretics, osmotic agents, or fluid volumes are used to achieve the diuresis.[90] Although renal salicylate clearance varies in direct proportion to flow rate, its relation to pH is logarithmic.[69] In summary, although fluid imbalance must be corrected, forced saline diuresis does little more than oral fluids to enhance elimination over a 24-hour period[90] and subjects the patient to the hazards of fluid overload.

Salicylate Elimination by Urine Alkalinization

Because salicylic acid is a weak acid (pK_a 3.5), it will be ionized in an alkaline milieu and theoretically can be â€œtrappedâ€• there. Alkalinization of the blood by a substance that does not easily cross the bloodâ€“brain barrier (ie, intravenously administered sodium bicarbonate) can keep salicylates from entering the brain and CSF; alkalinization of the urine (defined as pH â‰¥7.5) will enhance

urinary salicylate excretion. Alkalinization with sodium bicarbonate for salicylate poisoning results in enhanced excretion of the ionized acid form of salicylate in an alkaline urine.

In 2004, an AACT/EAPCCT position paper on urine alkalinization concluded that to increase the urinary elimination of salicylates, â€œurine alkalinization should be considered as first line treatment for patients with moderately severe salicylate poisoning who do not meet the criteria for hemodialysis.â€• [93] The paper only briefly discusses how this is achieved and the specific role of ion trapping. However, in a separate paper, the coauthor of the AACT/EAPCCT position paper points out that salicylic acid is almost completely ionized within *physiologic* pH limits; therefore, alkalinizing the urine could not significantly increase the extent of ionization further, making impossible the conventional explanation for the increased excretion of salicylic acid in alkalinized urine.[91] At least one other investigator maintained many years ago that ion trapping alone does not account for the increased excretion caused by sodium bicarbonate.[78] In any case, renal excretion of salicylic acid *is* very dependent on urinary pH[90,116] (Fig. 35-2; see Antidotes in Depth: Sodium Bicarbonate).

Alkalinization increases free salicylate secretion from the proximal tubule but does not affect renal elimination of salicylate conjugates. The percentage of a single dose of 1.5 g of sodium salicylate administered to volunteers that was excreted unchanged increased from 2.3 Â± 1.5% under acidic conditions to 30.5 Â± 9.1% under alkaline conditions. When urine acidity was maintained using ammonium chloride, salicylic acid had a terminal plasma $t_{1/2}$ value of 3.29 Â± 0.52 hours, which was significantly reduced to 2.50 Â± 0.41 hours when an alkaline urine was maintained with sodium bicarbonate treatment. The total body clearance of salicylic acid was significantly less under acidic urine conditions (1.38 Â± 0.43 L/h) than under alkaline urine conditions (2.27 Â± 0.83 L/h).[116]

Alkalinizing the urine from a pH of 5 to 8 logarithmically increased

renal salicylate clearance from 1.3 to 100 mL/min.[83] Assuming an overdose Vd of 0.5 L/kg, this increased clearance would decrease salicylate half-life from 310 to 4 hours. However, alkalinizing the urine from a pH of 5 to 8 has a more modest

effect on *serum* salicylate clearance.[90] The apparent serum half-life decreased from 48 to 6 hours at a fixed rate of 2 hours per unit pH change. This difference between serum and renal half-lives reflects the fact that renal clearance only applies to free salicylate, whereas serum clearance applies to both free and protein-bound salicylate.

Because acidemia enhances salicylate transfer into tissue, and particularly into the brain, it must be treated aggressively by raising the blood pH compared to the brain pH, thereby shifting the equilibrium from the tissues to the plasma[50,110] (Fig. 35-2). To accomplish this, hyperventilation alone should not be relied upon, and $NaHCO_3$ (but not acetazolamide) should be used for alkalinization. Although the administration of acetazolamide, a noncompetitive carbonic anhydrase inhibitor, results in the formation of a bicarbonate-rich alkaline urine, it also causes a systemic metabolic acidosis and acidemia.[39,50] The effect of acetazolamide usually is self-limited and mild but nevertheless increases the concentration of freely diffusible nonionized molecules of salicylic acid, thereby increasing the volume of distribution and most probably enhancing the penetrance of salicylate into the CNS.[74] Because salicylate also appears to inhibit acetazolamide plasma protein binding and acetazolamide renal tubular secretion, older patients with diminished protein binding and renal function may be at even greater risk for significant metabolic acidosis from acetazolamide use.[50,108]

Alkalemia by Hyperventilation versus Sodium Bicarbonate and the Risks

Associated with Assisted Ventilation

Endotracheal intubation followed by assisted ventilation of a salicylate-poisoned patient poses particular risks and may contribute to mortality in several ways. Death has occurred following sedation during initial airway management.[11] Additionally, although early endotracheal intubation to *maintain* hyperventilation may aid in the management of patients whose respiratory efforts are faltering after many hours, few healthcare providers are trained or skilled at maintaining the appropriate concentration of hypocarbia and hyperventilation necessary for managing a salicylate-poisoned patient who is receiving assisted ventilation on a respirator. Even when achieved, a respiratory alkalosis sustained by hyperventilation (assisted or unassisted) alone should *never* be considered a substitute for use of either sodium bicarbonate (to achieve both alkalemia and alkalinuria) or HD (when indicated). Because sodium bicarbonate does not easily cross the bloodâ€“brain barrier whereas CO_2 does, sodium bicarbonate will create a compartmentalized environment conducive to keeping salicylates in the blood and away from the brain and liver (Fig. 35-2).

Alkalinization with intravenous sodium bicarbonate should be considered for patients whose serum salicylate concentration exceeds 35 mg/dL and for clinically suspected cases of salicylism until a salicylate concentration and simultaneously obtained blood pH are available to guide treatment. Patients on therapeutic regimens of salicylates who feel well with salicylate concentrations of 30â€“40 mg/dL and who do not manifest toxicity do not require intervention. Oral bicarbonate administration should never be substituted for intravenous bicarbonate to achieve alkalinization because the oral route may increase salicylate absorption from the gastrointestinal tract by enhancing dissolution.[101]

Alkalinization in hemodynamically stable adults and children with significant salicylate concentrations may be achieved with a bolus of 1â€“2 mEq/kg, followed by an intravenous infusion of 3 ampules of

sodium bicarbonate (132 mEq) in 1 L of 5% dextrose in water (D_5W), to run at 1.5â€“2 times maintenance fluid range. Urine pH must be maintained at 7.5â€“8.0 and hypokalemia must be corrected (see below) to achieve maximum salicylate excretion. Volume load should remain modest while repleting previous losses. Early HD must be considered when a patient cannot tolerate the increased solute load that results from alkalinization because of congestive heart failure, renal failure, or cerebral edema. However, even when the decision for HD has been made, alkalinization (when possible) helps to achieve a more rapid initial reduction in blood concentrations.[51]

Hypokalemia

Hypokalemia is a common complication of salicylate poisoning and prevents urinary alkalinization unless corrected. Hypokalemia results from the movement of potassium into cells in exchange for hydrogen ions in the presence of alkalemia, potassium loss in the urine, diarrhea as a result of sorbitol use, and vomiting with subsequent metabolic alkalosis and bicarbonaturia.[44] If urinary alkalinization cannot be achieved easily, hypokalemia, excretion of organic acids, and volume depletion should be considered possible reasons. Calcium should be monitored, because decreases in both ionized[30] and total serum calcium[43] are also complications of bicarbonate therapy.

Frequent blood gas monitoring is required for all patients exposed to significant amounts of salicylates. Although maintaining alkalemia clearly is essential for treatment, arterial pH probably should not be allowed to rise above 7.55, as alkalemia shifts the oxyhemoglobin dissociation curve to the left and may be otherwise detrimental. Note, however, that even with blood pH 7.45â€“7.50 in patients with moderately severe salicylism, boluses of bicarbonate have been given without necessarily further increasing the pH. Perhaps this is a result of sodium bicarbonateâ€“induced metabolic alkalosis causing a decrease in the amount of salicylates acting on the brainstem to cause hyperventilation and a resultant respiratory alkalosis. Frequent

reassessment of blood pH (and fluid status) almost always allows administration of more sodium bicarbonate than was initially thought possible.

Indications for Extracorporeal Measures

Extracorporeal measures are indicated if the patient is very ill, has a very high serum salicylate concentration, has severe fluid or electrolyte disturbances, or is unable to eliminate the salicylates (Table 35-3). In most instances of severe salicylate poisoning, HD is the extracorporeal technique of choice, not only to clear the xenobiotic but also to rapidly correct fluid, electrolyte, and acidâ€“base disorders that will not be corrected by hemoperfusion

(HP) alone. HP provides better clearance than HD and may be an advantage if a mixed overdose might be better treated with HP. The combination of HD and HP in series is feasible and theoretically may be useful for treating severe or mixed overdoses[28] but is rarely used. Favorable results in rapidly reducing serum salicylate concentrations in severely poisoned patients have been described with use of continuous venovenous hemodiafiltration. This technique may be especially valuable for patients who are too unstable to undergo HD or in situations where HD is unavailable.[122]

TABLE 35-3. Indications for Hemodialysis in the Salicylate-Poisoned Patient

Renal failure
Congestive heart failure (relative)
Acute lung injury
Persistent CNS disturbances
Progressive deterioration in vital signs
Severe acidâ€“base or electrolyte imbalance, despite appropriate treatment
Hepatic compromise with coagulopathy Salicylate concentration (acute) >100 mg/dL (in the absence of the above)

A combination of therapies that are both useful and practical is to ensure effective alkalinization with sodium bicarbonate while a patient is waiting and then undergoing HD. In one unique case report, a patient who overdosed twice on salicylates within a 2-month period was treated in the first instance with 4 hours of HD but no effective alkalinization and in the second instance with sodium bicarbonate alkalinization but no HD. In both instances, blood concentrations of salicylates were >65 mg/dL. Although similar decreases in salicylate concentrations were achieved with the two techniques, the rate of decline during the first 4 hours was faster with alkalinization.[51] Combining the two therapies makes sense even if part of the reason for the increased early effectiveness of sodium bicarbonate treatment is related to the rapidity with which it can be achieved compared to the 2â€“4 hours required to institute HD after a patient presents under even the most favorable circumstances.[51]

Peritoneal dialysis (PD) was sometimes suggested in the past as a simpler extracorporeal procedure for eliminating salicylates in the

setting of hemodynamic compromise, coagulopathy, or inability to perform HP or HD. However, PD is only 10â€“25% as efficient as HP or HD and not even as efficient as renal excretion itself. The 24-hour clearance of salicylates with PD is less than the 4-hour clearance of salicylates by HP or HD; therefore PD is not recommended (Chap. 10).

Pregnancy

Considered a rare event, salicylate poisoning during pregnancy poses a particular hazard to the fetus because of the acidâ€“base and hematologic characteristics of the fetus and placental circulation: salicylates cross the placenta and are present in higher concentrations in the fetus than in the mother. The respiratory stimulation that occurs in the mother after toxic exposures does not occur in the fetus, which has a decreased capacity to buffer acid. The ability of the fetus to metabolize and excrete salicylates is also less than in the mother. In addition to its toxic effects on the mother, including coagulation abnormalities, acidâ€“base disturbances, tachypnea, and hypoglycemia, repeated exposure to salicylates late in gestation displaces bilirubin from protein-binding sites in the fetus.

A case report describing fetal demise in a woman who claimed to ingest 50 aspirin tablets per day for several weeks during the third trimester of pregnancy supports the conclusion that the fetus is at greater risk from salicylate exposures than is the mother and that emergent delivery of near-term fetuses of salicylate-poisoned mothers should be considered very seriously[86] (Chap. 30).

Summary

Initial assessment of a patient who has ingested excessive amounts of salicylates includes a determination of the vital signs, particularly the depth and frequency of respiration, and temperature. The clinical

presentation of a patient with a salicylate overdose is characterized by early onset of nausea, vomiting, abdominal pain, blood-tinged vomitus or gross hematemesis, tinnitus, and lethargy. The presence of hyperventilation, hyperthermia, confusion, coma, seizures, and any other nonspecific neurologic presentation should heighten suspicion of salicylate poisoning (Tables 35-1 and 35-2). If either salicylism or salicylate poisoning is suspected, a bedside $FeCl_3$ test can confirm salicylate *exposure* (but may be unnecessary). Using a combination of symptoms, signs, bedside laboratory studies, and characteristic ABG findings, the clinician can rapidly confirm a significant salicylate ingestion, institute immediate alkalinization with sodium bicarbonate, achieve gastric decontamination by orogastric lavage (if indicated), AC, or MDAC (if indicated), and consider the need for HD (or perhaps hemodiafiltration) early in the course of management.

For the salicylate-poisoned patient who presents as severely ill, maintenance of the airway requires an extremely careful approach because during initial airway management, death has occurred following sedation.[11] In patients with pulmonary and CNS manifestations of salicylate toxicity, the protective nature of the hyperpnea or hyperventilation in maintaining alkalemia may be compromised by assisted ventilation, unless the clinician is extremely skilled at adjusting the ventilator to ensure hyperventilation, decreased PCO_2, and high pH (7.5) at all times. Moreover, any unnecessary study, such as obtaining a computed tomographic scan that delays definitive treatment aimed at immediately reducing the patient's burden of salicylates quickly by HD can only place the patient at greater risk of death. Urinary alkalinization with sodium bicarbonate to eliminate salicylates is important, even though use of sodium bicarbonate may further complicate electrolyte abnormalities. Maintenance of eukalemia is important to ensure success, and fluid and electrolyte replacement is essential.

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Antidotes in Depth

Sodium Bicarbonate

Paul M. Wax

Sodium bicarbonate ($NaHCO_3$) is one of the most useful agents available for treatment of the poisoned patient. Unlike more specific antidotes in which utility usually is limited to antagonizing a single drug or toxin, sodium bicarbonate is a nonspecific antidote effective in the treatment of a variety of poisonings by means of a number of distinct mechanisms (Table A6-1). The support for its use in these settings is predominantly based on animal evidence, case reports, and opinion.[6] It is most commonly used in the treatment of tricyclic antidepressant (TCA) and salicylate poisonings. Sodium bicarbonate may also have a role in the treatment of phenobarbital, chlorpropamide, and chlorophenoxy herbicide poisonings and wide-complex tachydysrhythmias induced by type IA and IC antidysrhythmics and cocaine. Correcting the life-threatening acidosis generated by methanol and ethylene glycol poisoning and enhancing formate elimination are other important indications for sodium bicarbonate. Use of sodium bicarbonate in the treatment of rhabdomyolysis, lactic acidosis,

cardiac resuscitation, and diabetic ketoacidosis is controversial and is not a focus of this Antidote in Depth.[1,21,32,37,39,84,86]

Altered Drug Ionization Resulting in Altered Drug Distribution

Tricyclic Antidepressants

Sodium bicarbonate's most important role in toxicology appears to be its ability to reverse potentially fatal cardiotoxic effects of the TCA drugs and other type IA and IC antidysrhythmics. Use of sodium bicarbonate for TCA overdose developed as an extension of sodium bicarbonate use in the treatment of other cardiotoxic exposures. Noting similarities in electrocardiographic findings between hyperkalemia and quinidine toxicity (ie, QRS widening), investigators in the 1950s began to use sodium lactate (which is metabolized to sodium bicarbonate) for the treatment of quinidine toxicity.[2,5,89] In a canine model, quinidine-induced electrocardiographic changes and hypotension were consistently reversed by infusion of sodium lactate.[4] Clinical experience confirmed this benefit.[5] Similar efficacy in the treatment of procainamide cardiotoxicity was also reported.[89]

With the introduction of the TCAs during the late 1950s and early 1960s, conduction disturbances, dysrhythmias, and hypotension following overdose were reported. Extending the use of sodium lactate from the type I antidysrhythmics to the TCAs, uncontrolled observations in the early 1970s showed a decrease in mortality from 15% to <3% when sodium lactate was administered to patients with TCA poisoning.[24] In 1976, the first report of successful use of sodium bicarbonate in the treatment of a series of TCA-induced dysrhythmias in children was reported.[12] In this series, 9 of 12 children who had developed multifocal premature ventricular contractions (PVCs), ventricular tachycardia, or heart

block reverted to normal sinus rhythm with sodium bicarbonate therapy alone. An early animal experiment in amitriptyline-poisoned canines demonstrated resolution of dysrhythmias upon alkalinization of the blood to pH >7.40.[12] Other methods of alkalinization, including hyperventilation and administration of the nonsodium buffer tris (hydroxymethyl) aminomethane (THAM), was also effective in reversing the dysrhythmias.[13,36]

A better understanding of the mechanism and utility of sodium bicarbonate has come from a series of animal experiments during the 1980s. In amitriptyline-poisoned canines, sodium bicarbonate reversed conduction slowing and ventricular dysrhythmias and suppressed ventricular ectopy.[56] When comparing sodium bicarbonate, hyperventilation, hypertonic sodium chloride, and lidocaine, sodium bicarbonate and hyperventilation proved most efficacious in reversing ventricular dysrhythmias and narrowing QRS interval prolongation. Although lidocaine transiently antagonized dysrhythmias, this antagonism was demonstrable only at nearly toxic lidocaine concentrations and was associated with hypotension. In these studies, hypertonic sodium chloride failed to reverse dysrhythmias. Furthermore, prophylactic alkalinization protected against the development of dysrhythmias in a pH-dependent manner.

In desipramine-poisoned rats, the isolated use of either sodium chloride or sodium bicarbonate was effective in decreasing QRS duration.[61] Both sodium bicarbonate and sodium chloride also increased mean arterial pressure, but hyperventilation or direct intravascular volume repletion with mannitol did not. In further studies both in vivo and on isolated cardiac tissue, alkalinization and increased sodium concentration improved TCA effects on cardiac conduction.[72,73] Although respiratory alkalosis and sodium chloride each independently improved conduction velocity, this effect was greater when sodium bicarbonate was administered.

Another study on amitriptyline-poisoned rats demonstrated that

treatment with sodium bicarbonate was associated with shorter QRS interval, longer duration of sinus rhythm, and increased survival rates.[38] Sodium bicarbonate seems to work independently of initial blood pH. Animal studies show that cardiac conduction improves after treatment with sodium bicarbonate or sodium chloride in both normal pH and acidemic animals.[61] Clinically, TCA-poisoned patients who already were alkalemic also responded to repeat doses of sodium bicarbonate.[53]

Although several authors suggest that sodium bicarbonate's efficacy is modulated via a pH-dependent change in protein binding that decreases the proportion of free drug,[13,43] further study failed to support this hypothesis.[64] The administration of large doses of a binding protein Î±$_1$-acid glycoprotein (AAG) (to which TCAs show great affinity) to desipramine-poisoned rats only minimally decreased cardiotoxicity. Although the addition of AAG increased the concentrations of total desipramine and protein-bound desipramine in the serum, the concentration of active free desipramine did not decline significantly. A redistribution of TCA from peripheral sites may have prevented lowering of free desipramine concentration. The persistence of other TCA-associated toxicity, such as the anticholinergic effects and seizures, also

argues against changes in protein-binding modulating toxicity. In vitro studies performed in a protein-free bath further support that sodium bicarbonate's efficacy is independent of protein binding.[72]

TABLE A6-1. Sodium Bicarbonate in Toxicology: Mechanisms, Site of Action, and Uses

Mechanism	Site of Action	Uses

Altered interaction between drug and sodium channel	Heart	Amantadine Carbamazepine Cocaine Diphenhydramine Flecainide Mesoridazine Procainamide Propoxyphene Quinidine Quinine Thioridazine Tricyclic antidepressants
Altered drug ionization leads to altered tissue distribution	Brain	Formic acid Phenobarbital Salicylates
Altered drug ionization leads to enhanced drug elimination	Kidneys	Chlorophenoxy herbicides Chlorpropamide Formic acid Methotrexate Phenobarbital Salicylates
Correct life-threatening acidosis	Metabolic	Cyanide Ethylene glycol Methanol
Increase drug solubility	Kidneys	Methotrexate

Neutralization	Lungs	Chlorine gas, HCl
Reduce free radical formation	Kidneys	Contrast media

Sodium bicarbonate has a crucial antidotal role in TCA poisoning by increasing the number of open sodium channels, thereby partially reversing fast sodium channel blockade. This decreases QRS prolongation and reduces life-threatening cardiovascular toxicity such as ventricular dysrhythmias and hypotension.[56,61,72] The animal evidence supports two distinct and additive mechanisms for this effect: a pH-dependent effect and a sodium-dependent effect. The pH-dependent effect increases the fraction of the more freely diffusible nonionized drug. Both the ionized drug and the nonionized forms are able to bind to the sodium channel, but assuming TCAs act like local anesthetics, it is estimated that 90% of the block results from the ionized form. By increasing the nonionized fraction, less drug is available to bind to the sodium channel binding site. The sodium-dependent effect increases the availability of sodium ions to pass through the open channels. Decreased ionization should not significantly decrease the rate of TCA elimination because of the small contribution of renal pathways to overall TCA elimination (<5%).

Although many anecdotal accounts support the efficacy of sodium bicarbonate in treating TCA cardiotoxicity in humans,[30] these reports are all uncontrolled observations; controlled studies are not available. In one of the largest retrospective observational studies involving 91 patients who received sodium bicarbonate after TCA overdose, QRS prolongation corrected in 39 of 49 patients who had QRS duration >0.12 seconds, and hypotension corrected within 1 hour in 20 of 21 patients who had systolic blood pressure <90 mm Hg.[31] Use of sodium bicarbonate was not

associated with any complications in this study.

Prospective validation of treatment criteria for use of sodium bicarbonate after TCA overdose has not been performed. The most common indications are conduction delays manifested by QRS >0.10 seconds, amplitude of terminal R wave in lead aVR (R_{aVR}) = 3 mm, or right bundle-branch block, wide-complex tachydysrhythmias, and hypotension.[44] Because studies show that there is a critical threshold QRS duration at which ventricular dysrhythmias may occur (â‰¥0.16 seconds),[9] it seems reasonable that narrowing the QRS interval through use of sodium bicarbonate or hyperventilation may prophylactically prevent against development of dysrhythmias. Practice patterns vary considerably over use of sodium bicarbonate in situations where the QRS interval is <0.16 seconds.[76] Although sodium bicarbonate has no proven efficacy in either the treatment or prophylaxis of TCA-induced seizures, seizures often cause acidemia, which rapidly increases the risks of conduction disturbances and ventricular dysrhythmias. Administering sodium bicarbonate in situations where the QRS duration is â‰¥0.10 seconds may establish a theoretical margin of safety in the event the patient suddenly deteriorates, without adding significant demonstrable risk. In situations where the QRS duration is <0.10 seconds (given the negligible risk of seizures or dysrhythmias), prophylactic use of sodium bicarbonate is not indicated.

Because cardiotoxicity may worsen during the first few hours after ingestion, we recommend starting sodium bicarbonate immediately if QRS interval widens to >0.10 seconds. Because TCA-induced hypotension also responds to sodium bicarbonate, hypotension is another indication for sodium bicarbonate. However, no evidence supports a role for sodium bicarbonate in TCA-poisoned patients who present with altered mental status or seizures without QRS widening or hypotension.

Because the potential benefits of alkalinization in TCA overdose

usually outweigh the risks, sodium bicarbonate should be administered regardless of whether the patient has an acidemic or normal pH. The most commonly used preparations are an 8.4% solution (1 M), containing 1 mEq each of sodium and bicarbonate ions per milliliter (calculated osmolarity of 2000 mOsm/L) and a 7.5% solution, containing 0.892 mEq each of sodium and bicarbonate ions per milliliter (calculated osmolarity of 1786 mOsm/L). Fifty-milliliter ampules of the 8.4% and 7.5% solutions contain 50 and 44.6 mEq of $NaHCO_3$, respectively. One to two milliequivalents of sodium bicarbonate per kilogram body weight should be administered intravenously as a bolus over a period of 1â€“2 minutes.[62] Greater amounts may be required to treat unstable ventricular dysrhythmias. Sodium bicarbonate can be repeated as needed to achieve a blood pH of 7.50â€“7.55.[63,78] The end point of treatment is narrowing of the QRS interval. Excessive alkalemia (pH >7.55) and hypernatremia should be avoided. Because sodium bicarbonate has a brief duration of effect, a continuous infusion usually is required after the intravenous bolus. Three 50-mL ampules should be placed in 1 L of 5% dextrose in water (D_5W) and run at twice maintenance with frequent checks of QRS and pH depending on the fluid requirements and blood pressure of the patient. Frequent evaluation of fluid status should be performed to avoid precipitating pulmonary edema. Optimal duration of therapy has not been established. The time to resolution of conduction abnormalities during continuous bicarbonate infusion significantly varies, ranging from several hours to several days.[45] Sodium bicarbonate

infusion usually is discontinued once there is improvement in hemodynamics and cardiac conduction and resolution in altered mental status, although controlled data supporting such an approach are lacking.

Other Sodium Channel Blocking Drugs

Sodium bicarbonate is useful in treating cardiotoxicity from other drugs, with sodium channel blocking effects manifested by widened QRS complexes, dysrhythmias, and hypotension. Isolated case reports provide the bulk of the evidence in these situations. The utility of sodium bicarbonate in treating type IA and IC antidysrhythmics, diphenhydramine, propoxyphene, and quinine is demonstrated.[4,8,70,77,81,89]

Use of sodium bicarbonate in the treatment of amantadine overdose manifested by prolongation of the QRS and QTc intervals was associated with narrowing of the QTc but not the QRS interval.[19] Although the usefulness of sodium bicarbonate in reversing QTc prolongation occasionally observed during fluoxetine and citalopram overdose has been reported,[18,25] sodium channel disturbances are uncommon in most cases of selective serotonin receptor inhibitor (SSRI) overdose, and routine use of alkalinization therapy in this setting is unwarranted. Sodium bicarbonate may help in the management of other ingestions associated with type IA-like cardiac conduction abnormalities and dysrhythmias, such as the phenothiazines thioridazine and mesoridazine, and carbamazepine, but documentation of such benefit is lacking.

The role of sodium bicarbonate as an antidote has been studied in experimental models of calcium channel toxicity and Î²-blocker toxicity. In the calcium channel blocker study, hypertonic sodium bicarbonate increased mean arterial pressure and cardiac output in verapamil-poisoned swine.[82] Possible explanations for this beneficial effect include the increase in serum pH, reversal of a sodium channel effect, lowering of serum potassium concentration, and/or volume expansion. In a canine model of propranolol toxicity, sodium bicarbonate failed to increase heart rate or blood pressure.[46]

Cocaine (a local anesthetic with membrane-stabilizing properties resembling other type I antidysrhythmics) may cause similar conduction disturbances. In several canine models of cocaine toxicity, sodium bicarbonate 2 mEq/kg successfully reversed cocaine-induced QRS prolongation[3,60] and improved myocardial function.[91] Of interest, sodium loading by itself (sodium chloride 2 mEq/kg) failed to produce a benefit. Similar findings were demonstrated in cocaine-treated guinea pig hearts.[92] Patients with pH-dependent cocaine-induced cardiotoxicity responded to treatment with sodium bicarbonate.[35,59,88] In many of these cases, simultaneous treatment with sedation, active cooling, and hyperventilation confounds the contribution of the sodium bicarbonate to overall recovery.

Altered Drug Ionization Resulting in Enhanced Elimination

Salicylates

Although there is no known specific antidote for salicylate toxicity, judicious use of sodium bicarbonate is an essential treatment modality of salicylism. Sodium bicarbonate, through its ability to change the concentration gradient of the ionized and nonionized fractions of salicylates, is useful in decreasing tissue (eg, brain) concentrations of salicylates and enhancing urinary elimination of salicylates.[66] This therapy may limit the need for more invasive treatment modalities, such as hemodialysis.

Salicylate is a weak acid with pK_a = 3.0. As pH increases, more of the drug is in the ionized form. Ionized molecules penetrate lipid-soluble membranes less rapidly than do nonionized molecules because of the presence of polar groups on the ionized form. Consequently, weak acids, such as salicylates, may accumulate in an alkaline milieu, such as an alkaline urine, when the ionized

forms predominate.[50,79]

Although alkalinizing the urine to increase salicylate elimination is an important intervention in the treatment of salicylate poisoning, increasing the serum pH in patients with severe salicylism may prove even more consequential by protecting the brain from a lethal central nervous system (CNS) salicylate burden. Using sodium bicarbonate to â€œtrapâ€• salicylate in the blood (keeping it out of the brain) may prevent clinical deterioration of the salicylate-poisoned patient. Salicylate lethality is directly related to primary CNS dysfunction, which, in turn, corresponds to a â€œcritical brain salicylate level.â€•[29] At physiologic pH, where a very small proportion of the salicylate is in the nonionized form, a small change in pH is associated with a significant change in amount of nonionized molecules (eg, at pH = 7.4, 0.004% of the salicylate molecules is in the nonionized form; at pH = 7.2, 0.008% of the salicylate is in the nonionized form). In experimental models, lowering the blood pH produces a shift of salicylate into the tissues.[14] Hence, acidemia that is observed in significant salicylate poisonings can be devastating. In salicylate-poisoned rats, increasing the blood pH with sodium bicarbonate produced a shift in salicylate out of the tissues and into the blood.[28] This change in salicylate distribution did not result from enhanced urinary excretion because occlusion of the renal pedicles failed to alter these results.

Enhancing the urinary elimination of salicylate by trapping ionized salicylate in the urine also provides great benefit. Salicylate elimination at low therapeutic concentrations consists predominantly of first-order hepatic metabolism. At these low concentrations, without alkalinization, only approximately 10â€“20% of salicylate is eliminated unchanged in the urine. With increasing concentrations, enzyme saturation occurs (Michaelis-Menten kinetics); thus, a larger percentage of elimination occurs as unchanged free salicylate. Under these conditions, in an alkaline urine, urinary excretion of free salicylate becomes even

more significant, accounting for 60â€“85% of total elimination.[26,68]

The exact mechanism of pH-dependent salicylate elimination has generated controversy. The pH-dependent increase in urinary elimination initially was ascribed to â€œion trappingâ€•: the filtering of both ionized and nonionized salicylate while reabsorbing only the nonionized salicylate.[75] However, limiting reabsorption of the ionizable fraction of filtered salicylate cannot be the primary mechanism responsible for enhanced elimination produced by sodium bicarbonate.[47] Because the quantitative difference between the percentage of molecules trapped in the ionized form at pH = 5.0 (99% ionized) and pH = 8.0 (99.999% ionized) is small, decreases in tubular reabsorption cannot fully explain the rapid increase in urinary elimination seen at pH >7.0.

â€œDiffusion theoryâ€• offers a reasonable alternative explanation. Fick's law of diffusion states that the rate of flow of a diffusing substance is proportional to its concentration gradient. A large concentration gradient between the nonionized salicylate in the peritubular fluid (and blood) and the tubular luminal fluid is found

in alkaline urine. Because at a higher urinary pH, a greater proportion of secreted nonionized molecules quickly becomes ionized upon entering the alkaline environment, more salicylate (ie, nonionized salicylate) must pass from the peritubular fluid into the urine in an attempt to reach equilibrium with the nonionized fraction. In fact, as long as nonionized molecules are rapidly converted to ionized molecules in the urine, equilibrium in the alkaline milieu will never be achieved. The concentration gradient of peritubular nonionized salicylates to urinary nonionized salicylates continues to increase with rising urinary pH. Hence, increased tubular diffusion, not decreased reabsorption, probably accounts for most of the increase in salicylate elimination observed in the alkaline urine.[47]

Controversies regarding the indications for alkalinization in the treatment of salicylism persist. Although urinary alkalinization undoubtedly works to lower serum salicylate concentrations and enhance urinary elimination, the risks associated with alkalinization in the management of salicylism are of concern. Questions regarding excessive alkalemia, hypernatremia, fluid overload, hypokalemia, and hypocalcemia, as well as the potential delay in achieving alkalinization with sodium bicarbonate (as opposed to more rapid response achieved with hyperventilation), have all been raised.[22,42,62,68,75] Patients with pure respiratory alkalosis often have alkaluria, as well as alkalemia, and do not require urinary alkalinization. In the more common scenario in which patients present with a mixed respiratory alkalosis and metabolic acidosis, sodium bicarbonate must be administered cautiously. The young child, who rapidly develops a metabolic acidosis, often requires alkalinization but should be at less risk for complications of this therapy.[58]

Sodium bicarbonate is indicated in the treatment of salicylate poisoning for most patients with evidence of significant systemic toxicity. Although some authors have suggested alkali therapy for asymptomatic patients with concentrations >30 mg/dL,[90] there are limited data supporting this approach. For patients suffering from chronic poisoning, concentrations are not as helpful and may be misleading; clinical criteria remain the best indicators for therapy. Patients with contraindications to sodium bicarbonate use, such as renal failure and acute lung injury, should be considered for intubation and subsequent hyperventilation, but extracorporeal removal will often be required because of the difficulty and danger of intubation.

Dosing recommendations depend on the acidâ€“base status of the patient. For the patient with acidemia, rapid correction is indicated with intravenous administration of 1â€“2 mEq of sodium bicarbonate per kilogram of body weight.[83] Once the blood is

alkalinized or if the patient has already presented with an alkalemia, continued titration with sodium bicarbonate over 4â€“8 hours is recommended until the urinary pH reaches 7.5â€“8.0.[80,83] Alkalinization can be maintained with a continuous sodium bicarbonate infusion of 100â€“150 mEq in 1 L of D_5W at 150â€–200 mL/h (or about twice the maintenance requirements in a child). Obtaining a urinary pH of 8.0 is difficult but is considered to be the goal. Fastidious attention to the changing acidâ€“base status is required. Systemic pH should be kept below 7.55 to prevent complications of alkalemia.

Hypokalemia can make urinary alkalinization particularly problematic.[42,74] In the hypokalemic patient, regardless of total body potassium stores, the kidney preferentially reabsorbs potassium in exchange for hydrogen ions. Urinary alkalinization will be unsuccessful as long as hydrogen ions are excreted into the urine. Thus, appropriate potassium supplementation to achieve normokalemia may be required in order to alkalinize the urine.[93]

In the past, proper urinary alkalinization was thought to require forced diuresis in order to maximize salicylate elimination.[17,42] Suggestions included administering enough fluid (2 L/h) to produce a urine output of 500 mL/h. Because forced alkaline diuresis appears unnecessary and is potentially harmful as a result of its unnecessarily large fluid load, alkalinization at a rate of approximately twice maintenance requirements to achieve a urine output of 3â€“5 mL/kg/h is the goal.

Phenobarbital

Although cardiopulmonary support is the most critical intervention in the treatment of patients with severe phenobarbital overdose, sodium bicarbonate may be a useful adjunct to general supportive care. The utility of sodium bicarbonate is particularly important considering the long plasma half-life (approximately 100 hours) of phenobarbital. Phenobarbital is a weak acid (pK_a = 7.24) that

undergoes significant renal elimination. As in the case of salicylates, alkalinization of the blood and urine can reduce the severity and duration of toxicity. In a study of mice, the median anesthetic dose for mice receiving phenobarbital increased by 20% with the addition of 1 g/kg of sodium bicarbonate (raising the blood pH from 7.23 to 7.41), demonstrating decreased tissue concentrations associated with increased pH.[87] Extrapolating the animal evidence to humans has suggested that phenobarbital-poisoned patients in deep coma might develop a respiratory acidosis, secondary to hypoventilation, with the acidemia enhancing the entrance of phenobarbital into the brain, thus worsening CNS and respiratory depression. Alternatively, increasing the pH with bicarbonate and/or ventilatory support would enhance the passage of phenobarbital out of the brain, thus lessening toxicity. Given the relatively high pK_a of phenobarbital, significant phenobarbital accumulation in the urine is evident only when urinary pH is raised above 7.5.[7] As the pH approaches 8.0, a 3-fold increase in urinary elimination occurs. The urine-to-serum ratio of phenobarbital, although much higher in alkaline urine than in acidic urine, remains less than unity, thereby suggesting less of a role for tubular secretion than in salicylate poisoning.

Clinical studies examining the role of alkalinization in phenobarbital poisoning have been inadequately designed. Many are poorly controlled and fail to examine the effects of alkalinization, independent of coadministered diuretic therapy. In one uncontrolled study, a 59â€“67% decrease in duration of unconsciousness in patients with phenobarbital overdoses occurred in patients administered alkali compared to nonrandomized controls.[52] In other older studies, treatment with sodium lactate and urea reduced mortality and frequency of tracheotomy to 50% of controls, enhanced elimination, and shortened coma.[41,55] In a later human volunteer study, urinary alkalinization with sodium bicarbonate was associated with a decrease in phenobarbital elimination half-life from 148 to 47 hours.[23] However, this

beneficial effect was less than the effect achieved by multiple-dose activated charcoal (MDAC), which reduced the half-life to 19 hours.[23] In a nonrandomized study of phenobarbital-poisoned patients comparing urinary alkalinization alone, MDAC alone, and both methods together, both the phenobarbital half-life decreased most rapidly and the clinical course improved most rapidly in the group of patients who received MDAC alone.[51] Interesting, the combination approach proved inferior to MDAC alone but was better than alkalinization alone. The authors speculated that when both treatments were used together, the increased ionization of phenobarbital resulting from

sodium bicarbonate infusion may have decreased the efficacy of MDAC. These studies suggest that MDAC is more efficacious than urinary alkalinization in the treatment of phenobarbital poisoning, although both approaches are beneficial and indicated.

Sodium bicarbonate therapy does not appear warranted in the treatment of ingestions of other barbiturates, such as pentobarbital and secobarbital, each of which has pK_a >8.0 and is predominantly eliminated by the liver.

Chlorpropamide

Chlorpropamide is a weak acid (pK_a = 4.80) and has a long half-life (30â€“50 hours). In a human study using therapeutic doses of chlorpropamide, urinary alkalinization with sodium bicarbonate significantly increased renal clearance of the drug.[57] This study showed that nonrenal clearance was the more significant route of elimination at a urinary pH of 5.0â€“6.0 (only slightly above pK_a), whereas at pH = 8.0, renal clearance was 10 times that of nonrenal clearance. Alkalinization reduced the area under the curve almost 4-fold and shortened elimination half-life from 50 to 13 hours. Acidification increased the area under the curve by 41% and increased the half-life to 69 hours. Although not a study in

overdose patients, this report suggests that sodium bicarbonate may be useful in the management of patients with chlorpropamide overdose. The effect of urinary alkalinization on elimination of other sulfonylureas is unnecessary because the benefit presumably is limited as these agents are largely metabolized in the liver.

Chlorophenoxy Herbicides

Alkalinization is indicated in the treatment of poisonings from weed killers that contain chlorophenoxy compounds, such as 2,4-dichlorophenoxyacetic acid (2,4-D), or 2-(4-chloro-2-methylphenoxy) propionic acid (MCPP).[65] Poisoning results in muscle weakness, peripheral neuropathy, coma, hyperthermia, and acidemia. These compounds are weak acids (pK_a = 2.6 and 3.8 for 2,4-D and MCPP, respectively) that are excreted largely unchanged in the urine. In an uncontrolled case series of 41 patients poisoned with a variety of chlorophenoxy herbicides, 19 of whom received sodium bicarbonate, alkaline diuresis significantly reduced the half-life of each compound by enhancing renal elimination.[20] In one patient, resolution of hyperthermia and metabolic acidosis and improvement in mental status were associated with a transient elevation of serum concentrations of these compounds, perhaps reflecting chlorophenoxy compound redistribution from the tissues into the more alkalemic blood. The limited data suggest that the increased ionized fractions of the weak-acid chlorophenoxy compounds produced by alkalinization is trapped in both the blood and the urine (as demonstrated with salicylates and phenobarbital); thus its use ameliorates toxicity and shortens duration of effect.

Correcting Metabolic Acidosis

Toxic Alcohols

Sodium bicarbonate has two important roles in treating toxic

alcohol ingestions. As an immediate temporizing measure, administration of sodium bicarbonate may reverse the life-threatening acidemia associated with methanol and ethylene glycol ingestions. In rats poisoned with ethylene glycol, the administration of sodium bicarbonate alone resulted in a 4-fold increase in median lethal dose.[10] Clinically, titrating the endogenous acid with bicarbonate greatly assists in reversing the consequences of severe acidemia, such as hemodynamic instability and multiorgan dysfunction.

The second role of bicarbonate in the treatment of toxic alcohol poisoning involves its ability to favorably alter the distribution and elimination of certain toxic metabolites.[69] In cases of methanol poisoning, the proportion of ionized formic acid can be increased by administering bicarbonate, thereby trapping formate in the blood compartment.[34,48] Consequently, decreased visual toxicity results from removal of the toxic metabolite from the eye. In cases of formic acid (pK_a = 3.7) ingestion, sodium bicarbonate decreases tissue penetration of the formic acid and enhances urinary elimination.[54] Further investigation is required to delineate the beneficial effects of sodium bicarbonate in the treatment of toxic alcohol ingestions.

Early treatment of acidemia with sodium bicarbonate is strongly recommended in cases of methanol and ethylene glycol poisoning.[27] Sodium bicarbonate should be administered to toxic alcohol-poisoned patients with an arterial pH <7.30.[40] More than 400â€“600 mEq of sodium bicarbonate may be required in the first few hours.[33] In cases of ethylene glycol toxicity, sodium bicarbonate administration may worsen hypocalcemia, so serum calcium concentration should be monitored. Combating the acidemia, however, is not the mainstay of therapy, and concurrent administration of intravenous ethanol or fomepizole and preparation for possible hemodialysis are almost always indicated.

Increasing Drug Solubility

Methotrexate

Urinary alkalinization with sodium bicarbonate is routinely used during high-dose methotrexate cancer chemotherapy therapy. Methotrexate is predominantly eliminated unchanged in the urine. Unfortunately, it is poorly water soluble in acidic urine. Under these conditions, tubular precipitation of the methotrexate may occur, leading to nephrotoxicity and decreased elimination, increasing the likelihood of methotrexate toxicity. Administration of sodium bicarbonate (as well as intensive hydration) during high-dose methotrexate infusions increases methotrexate solubility and the elimination of methotrexate.[16,71]

Neutralization

Chlorine Gas

Nebulized sodium bicarbonate serves as a useful adjunct in the treatment of pulmonary injuries resulting from chlorine gas inhalation.[15,85] Inhaled sodium bicarbonate neutralizes the hydrochloric acid that is formed when the chlorine gas reacts with the water in the respiratory tree. Although oral sodium bicarbonate is not recommended for neutralizing acid ingestions because of the problems associated with the exothermic reaction and production of carbon dioxide in the relatively closed gastrointestinal tract, the rapid exchange in the lungs of air with the environment will facilitate heat dissipation. In a chlorine-inhalation sheep model, animals treated with 4% nebulized sodium bicarbonate solution demonstrated higher PO_2 and lower PCO_2 than did the normal, saline-treated animals.[15] There was no difference, however, in 24-hour

mortality or pulmonary histopathology. Anecdotal experience suggests that nebulized bicarbonate therapy may lead to improvement of symptoms.[85] In a retrospective review, 86 cases of chlorine gas inhalation were treated with nebulized sodium bicarbonate.[11] Sixty-nine patients were sent home from the emergency department, 53 of whom had clearly improved. Such uncontrolled observations do not provide convincing evidence for the efficacy of such an approach, but the nebulized sodium bicarbonate was well tolerated. Further clinical studies are required to further assess the efficacy and safety of this treatment.

Reduction in Free Radical Formation

Contrast Media

A study has suggested that sodium bicarbonate may be beneficial in preventing contrast-induced nephropathy.[49] A randomized trial on 119 patients compared an infusion of 154 mEq/L of either sodium bicarbonate or sodium chloride before (3 mL/kg for 1 hour) and after (1 mL/kg/h for 6 hours) iopamidol administration. Contrast-induced nephropathy, defined as a â‰¥25% increase in serum creatinine concentration within 2 days of contrast, occurred in 8 patients in the sodium chloride group and 1 patient in the sodium bicarbonate group. It is suggested that increasing medullary pH with sodium bicarbonate infusion might protect the kidney from oxidant injury by slowing free radical production. Further study of this treatment is warranted.

Summary

Despite the increasing tendency to avoid sodium bicarbonate administration in the critically ill acidemic patient, sodium bicarbonate remains an important agent in the treatment of a wide variety of xenobiotic exposures. In fact, its utility in the poisoned

patient continues to expand. Sodium bicarbonate is effective in the treatment of poisonings by TCAs and other sodium channel blockers through its effects on drug ionization and subsequent diffusion from the sodium channel binding site. Sodium bicarbonate is effective for salicylates, phenobarbital, and other weak acids because of its ability to ion trap in the blood or brain and keep toxin away from the target organ.[67] Sodium bicarbonate is effective as a neutralizing agent for inhaled acids such as chlorine gas. In the more common causes of metabolic acidosis (eg, lactic acidosis), specific therapy such as antibiotics, volume resuscitation, and inotropic support usually takes precedence over bicarbonate administration.

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Chapter 36

Nonsteroidal Antiinflammatory Drugs

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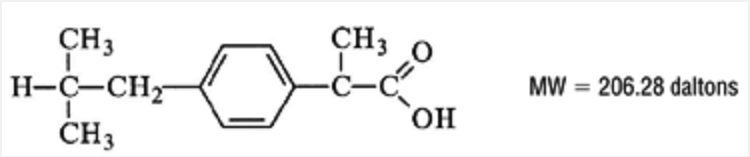

Ibuprofen

A 40-year-old man presented to the emergency department approximately 4 hours after ingesting approximately 100 ibuprofen tablets (400 mg each). He complained of diffuse abdominal pain and several episodes of vomiting. The patient had no other significant past medical history. His initial vital signs were: blood pressure, 125/75 mm Hg; pulse, 130 beats/min; respiratory rate, 24 breaths/min; temperature, 98.6Â°F (37Â°C). Shortly after arriving, the patient's mental status deteriorated, and he became lethargic but remained responsive to moderately painful stimuli. Physical examination revealed 4-mm normally reactive pupils, a supple neck, and no overt toxicologic syndrome. Neurologic examination revealed a depressed mental status, normal muscle tone in his extremities, and normal, symmetric reflexes.

A nasogastric tube was inserted, and stomach aspiration did not return pill fragments or blood. The patient was given 50 g of oral activated charcoal. Arterial blood gas analysis performed on 100% oxygen revealed pH, 7.30; PCO_2, 32 mm Hg; PO_2, 520 mm Hg, with a lactic acid concentration of 2.5 mmol/L. Serum chemistry analysis noted the following: sodium, 138 mEq/L; potassium, 3.5 mEq/L; chloride, 102 mEq/L; bicarbonate, 18 mEq/L, with an anion gap of 18 mEq/L. Blood urea nitrogen (BUN), creatinine, and serum glucose concentrations were normal (BUN, 12 mg/dL; creatinine, 1.4 mg/dL; serum glucose, 103 mg/dL). Complete blood count and calcium concentration were normal. Salicylate and acetaminophen concentrations were undetectable. The urine was negative for ketones and blood. An electrocardiogram noted sinus tachycardia but was otherwise normal.

The patient received 1 L of intravenous 0.9% sodium chloride followed by an infusion at 300 mL/h. On the second hospital day, the BUN concentration rose to 40 mg/dL and the creatinine concentration to 2.0 mg/dL. Without any specific treatment, both concentrations returned to baseline by the fourth hospital day. Hepatic aminotransferase concentrations and prothrombin time remained normal. Stool specimens remained negative for occult

blood.

An ibuprofen concentration of 900 Âµg/mL was reported 1 week later by a specialty laboratory (therapeutic reference range 20â€“30 Âµg/mL).

Nonsteroidal antiinflammatory drugs (NSAIDs) are a heterogeneous group of chemicals that share similar therapeutic properties. NSAIDs have analgesic, antipyretic, and antiinflammatory effects. The first NSAIDs commercially available inhibited cyclooxygenase (COX) in a nonselective fashion. With the realization that COX inhibition could be divided into COX-1 and COX-2 forms, and that most of the adverse gastrointestinal (GI) effects were mediated by COX-1, selective COX-2 inhibitors were introduced and marketed as having less GI toxicity than the older, less selective NSAIDs. Rofecoxib (Vioxx) and celecoxib (Celebrex) were launched in the United States in 1999 and valdecoxib (Bextra) shortly thereafter. The 2003 worldwide sales of Vioxx were $2.5 billion[42] and that of Celebrex were also several billion dollars. In the fall of 2004, the manufacturer of Vioxx voluntarily withdrew the drug from sale because of an increased cardiovascular (CV) mortality associated with Vioxx use. In April 2005, the FDA findings led the manufacturer of Bextra to withdraw that COX-2 inhibitor from the market, leaving Celebrex as the only COX-2 inhibitor available in the United States. Moreover, many nonselective NSAIDs have been implicated in increasing the risk of CV disease. Because many structurally different NSAIDs have been implicated but not every NSAID has been subjected to large epidemiologic studies, the problem appears to be with the class of drugs, rather than with an individual formulation. It appears that some NSAIDs are more prone to increasing cardiovascular risk than others.

History and Epidemiology

At the turn of the 20th century, aspirin (acetylsalicylic acid)

became the first available nonsteroidal antiinflammatory, antipyretic analgesic. Ibuprofen was first introduced in the United States in 1974 and was approved for nonprescription use in 1984.[41] With the ability to track exposure patterns provided by the Toxic Exposure Surveillance

System (TESS) since 1983, it has become apparent that nonsteroidal exposures are increasingly common, accounting for >3% of all reported cases in 2003 and ranking first among all pharmaceutical product exposures reported.[75] In 2003, >91,000 NSAID exposures (excluding aspirin) were reported to TESS, of which 77% involved ibuprofen, 15% naproxen, and 7% COX-2 inhibitors. Remarkably, only 48 deaths were reported, with all but one, presumably the result of a consequential coingestant[75] (Chap. 130).

Three NSAIDs (ibuprofen, naproxen, and ketoprofen) currently are available as both prescription and nonprescription products, and individually, as well as in combination with analgesics or analgesic cough and cold products. NSAIDs are available as veterinary products, and additional human exposures are occasionally secondary to inclusion of NSAID adulterants in patent herbal preparations.[48]

Pharmacology

The NSAID class includes at least 20 drugs that share the mechanism of COX inhibition (Table 36-1). Competitive inhibition of COX produces both the therapeutic and some of the toxic effects of this group of drugs.

Arachidonic acid is the precursor for the COX enzyme system. The process begins when arachidonic acid is cleaved from the phospholipid membrane of the cell by the action of phospholipase A (Figure 36-1). COX inhibition prevents the formation of prostaglandins, prostacyclins, and thromboxane A_2, but not

leukotrienes and other eicosanoids.[28,74] The two isoforms of COX are labeled COX-1 and COX-2.[64]

COX-1 is present in the kidney and GI tract and is responsible for vascular hemostasis, GI wall integrity, and renal homeostasis.[19] Inhibition of COX-1 decreases synthesis of thromboxane A_2 in platelets and interferes with their aggregation.

COX-2 is induced by inflammatory mediators and produces prostaglandins at the site of inflammation. The prostaglandins are responsible for mediating vasodilatation, increasing vascular permeability, and sensitizing pain fibers.[47] The discovery that inhibition of COX-2 is associated with both the analgesic and antiinflammatory actions of the NSAIDs led to the introduction of COX-2â€“specific inhibitors. COX-2 inhibitors demonstrate this property only at therapeutic doses; at very high concentrations the COX-2 specificity is lost.

An unanticipated finding of use of COX-2 selective NSAIDs was the finding that COX-2 NSAIDs increased the risk of CV disease. It now appears that this result probably is true of the entire class, although some drugs such as rofecoxib and valdecoxib appear to increase the risk more than others. Salicylates differ from the other NSAIDs in that they irreversibly bind to COX and produce an effect that lasts for the life of the platelet unless it can produce more enzyme. NSAIDs, such as diclofenac and indomethacin, also inhibit various lipoxygenase enzymes and decrease the production of leukotrienes in animals.[22,28] Acetaminophen inhibits COX in the central nervous system but does not have clinical antiinflammatory effects and therefore is not an NSAID. Acetaminophen and salicylates are described in Chaps. 34 and 35, respectively.

Pharmacokinetics and Toxicokinetics

NSAIDs are rapidly absorbed from the GI tract, with peak levels occurring within 2 hours of oral administration for most drugs.

Sustained-release indomethacin, enteric-coated diclofenac, mefenamic acid, piroxicam, and the prodrugs sulindac and nabumetone require 2â€“5 hours to reach peak levels.[7,68] All of these drugs are weakly acidic and highly protein bound (>90%), with volumes of distribution of approximately 0.1â€“0.2 L/kg. The NSAIDs cross the bloodâ€“brain barrier and are found in cerebrospinal fluid (CSF) and brain tissue. Peak CSF concentrations lag behind serum concentrations by at least 2 hours, and the relative ability of different NSAIDs to cross the bloodâ€“brain barrier is determined by lipophilicity.[2,40]

TABLE 36-1. Classes of Nonsteroidal Antiinflammatory Drugs

COX-1 and COX-2 inhibitors
- Salicylates
  - Acetyl salicylic acid (aspirin)
  - Nonacetylated derivatives (metabolized to salicylic acid)
    - Salsalate (Disalcid)
    - Sodium salicylate
    - Choline salicylate
    - Magnesium salicylate
    - Magnesium choline salicylate (Trilisate)
  - Diflunisal (Dolobid; not metabolized to salicylic acid)
- Pyrazolones
  - Phenylbutazone
- Fenamates (anthranilic acids)
  - Meclofenamate (Meclomen)
  - Mefenamic acid (Ponstel)
- Acetic acids
  - Diclofenac (Voltaren)
  - Etodolac (Lodine)

Indomethacin (Indocin)
Ketorolac (Toradol)
Nabumetone (Relafen)
Sulindac (Clinoril)
Tolmetin (Tolectin)
Propionic acids
Fenoprofen (Nalfon)
Flurbiprofen (Ansaid)
Ibuprofen (Motrin, Advil, Medipren)[b]
Ketoprofen (Orudis)[b]
Naproxen (Naprosyn, Anaprox)[b]
Oxaprozin (Daypro)
Oxicams
Piroxicam (Feldene)
COX-2 selective inhibitors
Celecoxib (Celebrex)
Meloxicam[a] (Mobic)
Rofecoxib (Vioxx)
Valdecoxib (Bextra)

[a] COX-2 preferential
[b]Nonprescription

Hepatic metabolism is the primary route for NSAID elimination, with renal elimination of unchanged drug accounting for <10% of clearance (except indomethacin with 10â€“20%).[28] The elimination half-life for the majority of NSAIDs is less than 8 hours; however, the half-lives of diflunisal, nabumetone, naproxen, and sulindac are between 8 and 30 hours, and the half-life of phenylbutazone and piroxicam is 30 hours.

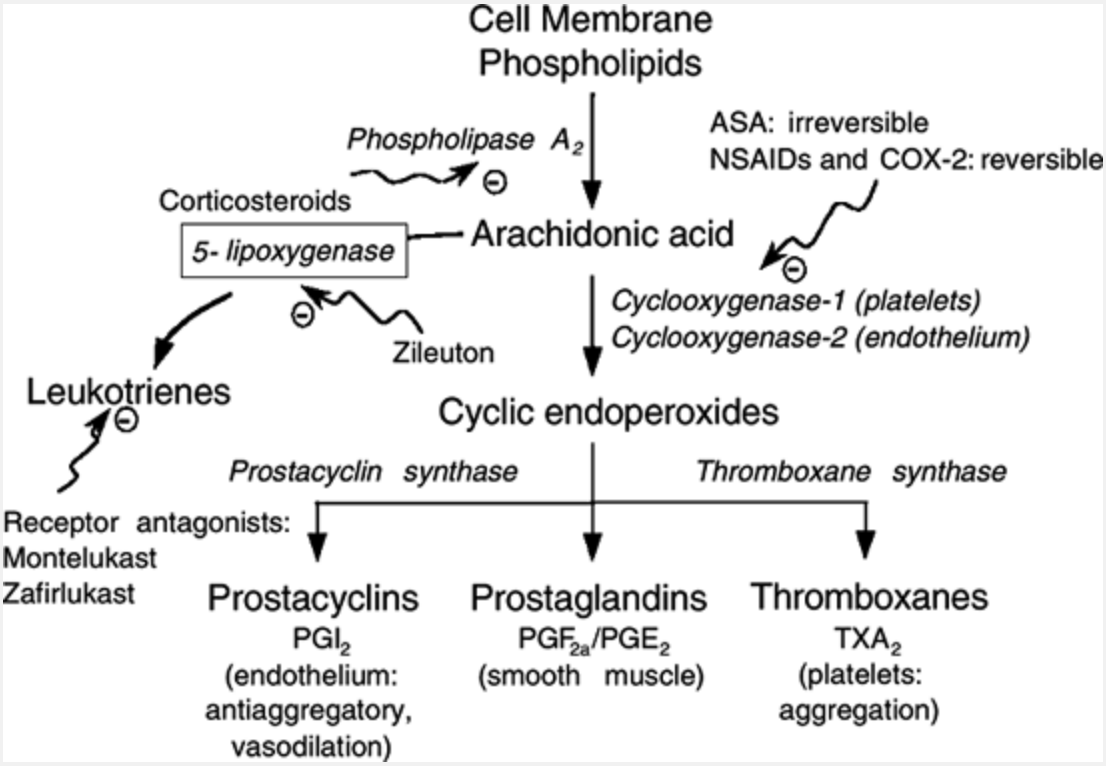

Figure 36-1. Mechanism of action of NSAIDs. Cyclooxygenase-1 (COX-1) is present in the kidney and GI tract. Cyclooxygenase-2 (COX-2) is induced by inflammatory mediators, such as cytokines and endotoxin, and produces prostaglandins at the site of inflammation. Most NSAIDs block these enzymes nonselectively, with the exception of the newer COX-2 inhibitors. Leukotrienes and other products of lipoxygenase are blocked by corticosteroids but not by salicylates or the newer COX-2 inhibitors. Leukotrienes may be involved in the sensitivity or asthmatic reactions produced by NSAIDs. Leukotriene receptor antagonists are designed to alleviate the effects of leukotrienes.

Some NSAIDs undergo extensive biliary-fecal elimination

(carprofen, indomethacin, piroxicam, sulindac), so theoretically, they should be susceptible to enhanced excretion with multiple-dose activated charcoal. However, toxicity rarely is severe enough to warrant this therapy.

The ingestion of a large dose alters the kinetics of some NSAIDs. The absorption rate of naproxen is slower with larger doses, delaying peak concentrations to 3â€“4 hours after the ingestion of 12 (250-mg) naproxen tablets.[61] Similar delays are found with ibuprofen, as determinations of serum concentrations in poisoning and overdose patients demonstrate continued absorption over at least the first 2 hours in some patients.[24,41]

Because NSAIDs are mostly bound to plasma proteins, the percentage of unbound drug likely will increase with increasingly larger doses, resulting in a larger volume of distribution.[51] Theoretically, this could result in a greater proportion of the dose available for distribution into tissue and the central nervous system and in a nonlinear doseâ€“toxicity curve. Renal elimination may be increased with naproxen overdose. In one study of 16 healthy volunteers, the rate of excretion tended to increase as naproxen levels rose.[61]

Ketorolac (Toradol) is available as the tromethamine salt in 10-mg tablets for oral administration and in solutions of 15â€“30 mg/mL for intramuscular and intravenous use. Similar to most other NSAIDs, ketorolac is well absorbed, is extensively metabolized by the liver to largely inactive metabolites, and has a short half-life (3.5â€“9.2 hours).[3]

Pathophysiology

Numerous reviews of adverse effects associated with NSAIDs are available[14,54,72,77] (Table 36-2). Many of the adverse effects, and probably all or most of the acute toxicities of the NSAIDs, are associated primarily with inhibition of COX-1. NSAIDs are directly

cytotoxic to the GI mucosa, and they inhibit formation of the cytoprotective prostaglandins PGI_2 and PGE_2 mediated by the COX-1 enzyme. Decreased concentration of these two prostaglandins in gastric tissue decreases mucus and bicarbonate production, promotes HCl secretion, and decreases gastric blood flow, resulting in loss of gastric cytoprotection. In addition to NSAID use, a risk factor for GI toxicity may be concomitant infection with *Helicobacter pylori*.[23] Statistically, the nonselective NSAIDs increase the relative risk of a serious GI hemorrhage by approximately 3-fold compared to control populations.[18,79] However, GI toxicity is not solely confined to COX-1 NSAIDs. GI bleeding is also associated with use of the selective COX-2 inhibitors rofecoxib and celecoxib.[4,17]

Chronic NSAID use frequently causes transient asymptomatic increases in hepatic aminotransferase activity, most commonly associated with phenylbutazone, diclofenac, and sulindac. Serious adverse drug events from chronic use are rare but occur more frequently with diclofenac.[59,60]

The acidosis associated with NSAID overdose occurs infrequently and usually is a high-anion-gap metabolic acidosis. It appears to result from mechanisms including the formation of NSAID metabolites that are weak acids, hypotension, and relative hypoxia.[27] No information indicates that inhibition of COX itself is responsible for production of the metabolic acidosis.

In the presence of renal vasoconstrictor substances such as angiotensin, prostaglandins produce vasodilation of renal arterioles.[45] In patients with normal mechanisms for maintaining renal blood flow, NSAIDs have little effect on renal blood flow and renal function because the concentrations of angiotensin are low in these situations. However, in patients with congestive heart failure, cirrhosis, intrinsic renal disease, or hypovolemia, which are characterized by high angiotensin and low intravascular volume, an NSAID-induced decrease in prostaglandins results in

vasoconstriction. This in turn causes a decrease in both renal blood flow and glomerular filtration rate, which may lead to renal failure, particularly in the elderly. This vasoconstrictive effect may also be caused by selective COX inhibitors of all classes and usually is reversible upon discontinuation of therapy.[57]

Acute and chronic forms of interstitial nephritis and nephrotic syndrome occur in NSAID users.[11,46] The term *analgesic nephropathy* has been used to describe the form of chronic renal disease

characterized by papillary necrosis and interstitial nephritis in patients with prolonged excessive consumption of combination antipyretic analgesics who have no other discernible cause of their disease.[63]

TABLE 36-2. Selected Adverse Effects of Nonsteroidal Antiinflammatory Drugs

Gastrointestinal
Dyspepsia
Ulceration
Perforation
Hemorrhage
Elevated hepatic aminotransferase concentrations (transient)
Hepatocellular injury (rare)
Renal
Acute renal failure
Fluid and electrolyte retention
Interstitial nephritis
Nephrotic syndrome
Papillary necrosis

Hypersensitivity/pulmonary
Asthma exacerbation
Anaphylactoid reaction
Pneumonitis
Hematologic
Increased bleeding time
Agranulocytosis
Aplastic anemia
Thrombocytopenia
Neutropenia
Hemolytic anemia
Central nervous system
Headache
Aseptic meningitis
Delirium
Cognitive dysfunction, especially in the elderly
Hallucinations
Drug interactions
Anticoagulants: NSAIDs increase risk of GI bleeding
Antihypertensives (especially diuretics, Î²-adrenergic antagonists, and ACE inhibitors): NSAIDs reduce antihypertensive effects
Sulfonylureas: NSAIDs increase hypoglycemic effect
Lithium: NSAIDs increase risk of lithium toxicity
Digoxin: NSAIDs increase risk of digoxin toxicity
Aminoglycosides: NSAIDs increase risk of aminoglycoside toxicity

NSAID use causes many hematologic effects. Inhibition of COX-1 results in decreased formation of thromboxane A_2 which is responsible for platelet aggregation. Therefore, bleeding problems and interactions with concomitant anticoagulant usage may occur. NSAIDs are associated with other hematologic abnormalities including aplastic anemia (indomethacin and etodolac),

agranulocytosis (naproxen), hemolytic anemia (mefenamic acid), methemoglobinemia (celecoxib), neutropenia (indomethacin), and thrombocytopenia (indomethacin, ibuprofen, and naproxen).[13,62,33,73] All of these are considered idiosyncratic reactions.

The most common central nervous system (CNS) signs and symptoms associated with the chronic use of NSAIDs are drowsiness, confusion, and headache.[24,35] Abnormal electroencephalogram waves have been described in one case of naproxen toxicity, similar to changes seen with CNS depressant overdoses.[8] Aseptic meningitis in patients with and without autoimmune disorders have been reported with the use of ibuprofen, sulindac, and tolmetin.[10,50] Some drugs can cause tinnitus (ibuprofen, naproxen, fenoprofen, sulindac, tolmetin) or transient hearing loss (ibuprofen and indomethacin).[28,53]

Visual disturbances associated with use of nonselective NSAIDs include toxic amblyopia, scotoma, and blurred vision. The causality and mechanism by which these effects are produced are unclear, although visual disturbances also occur with COX-2â€“selective drugs.[39]

Because uterine production of prostaglandins increases dramatically in the hours before parturition, NSAIDs are often used as tocolytics.[43] However, NSAID use may be associated with premature intrauterine closure of the fetal ductus arteriosus, renal failure, and oligohydramnios in neonates.[31]

Life-threatening anaphylactoid reactions can occur after NSAID administration. Up to 25% of adult asthmatics with nasal polyps or chronic urticaria develop acute bronchospasm minutes to hours after NSAID exposure.[71] These reactions are often accompanied by flushing of the head and neck, rhinorrhea, conjunctivitis, and/or angioedema. All NSAIDs regardless of COX selectivity pattern may function as haptens that are capable of inducing allergic sensitization.[5,34]

There are many potential clinically significant drug interactions with NSAIDs (Table 36-2).

COX-2 Selective Inhibitors and Cardiotoxicity

Atherosclerosis is a process with inflammatory features, and selective COX-2 inhibitors theoretically could have antiatherogenic effects by inhibiting inflammation. However, by decreasing vasodilatory and antiaggregatory prostacyclin production, COX-2 antagonists may lead to increased prothrombotic activity. The potential for COX-2 inhibitors to increase the risk for myocardial infarction (MI) has now been studied directly and indirectly in several large studies. The safety profile of the COX-2 inhibitors with regard to the risk of CV events first came into question in 2001.[44] Data from a major randomized trial in 2000, the Vioxx Gastrointestinal Outcomes Research (VIGOR) study (8076 patients), confirmed that the incidence of MI was significantly lower among patients with rheumatoid arthritis taking naproxen than among those taking rofecoxib.[6] Some researchers concluded that naproxen has a cardioprotective benefit rather than rofecoxib having a cardiotoxic effect.[30,37,76] This conclusion was also based on results from the company's rofecoxib development program in which 5435 osteoarthritis trial participants reportedly had similar rates of CV thrombotic events with rofecoxib, placebo, and nonselective NSAIDs (ibuprofen, diclofenac, and nabumetone).[76] A subsequent pooled analysis from 23 studies (including VIGOR) encompassing multiple disease states and including >14,000 patient-years at risk also demonstrated that rofecoxib was not associated with excess CV thrombotic events compared with either placebo or nonnaproxen NSAIDs.[76]

Since 2003, various studies have demonstrated (1) no detectable risk reduction for occurrence of MI with NSAID use,[20] (2) no increased CV risk with use of COX-2 inhibitors over nonnaproxen

NSAIDS,[66] or (3) increased risk of CV events with rofecoxib (Vioxx) use.[9,21,69] Dosages of rofecoxib >25 mg in the first 90 days of use have been associated with a higher risk for MI than dosages â‰¤25 mg.[69]

On September 30, 2004, Merck Pharmaceuticals announced the withdrawal of Vioxx based on 3-year data from a prospective,

randomized, double-blind, placebo-controlled clinical trial, the APPROVE (Adenomatous Polyp Prevention on Vioxx) trial.[42] In this trial, use of Vioxx in patients with colorectal adenomas was associated with an increased risk of thrombotic events beginning after 18 months of treatment, compared to those taking placebo (relative risk 1.92; p = 0.008).[9]

Clinical Manifestations

Although the severity and frequency of some clinical manifestations may differ, the toxic effects of the different nonselective NSAIDs are generally similar in acute overdose. Clinical effects typically occur within 4 hours of ingestion.[27,38,68] COX-2 receptor selectivity is lost at high concentrations, so overdoses of these drugs are expected to cause toxicity similar to the nonselective NSAIDs.

The most common toxic effects in acute overdose are GI distress (nausea, vomiting, epigastric pain, GI hemorrhage) and CNS depression.[24] Other CNS effects may include changes in cognition, hallucinations, muscle twitching, or seizures and are most frequent after mefenamic acid overdose.[1,12] Muscle twitching may be focal or generalized and in one series, lasted 3â€“10 minutes, with 20% of 54 patients progressing to grand mal seizures 2â€“7 hours postingestion. Reported doses as low as 2 g of mefenamic acid in a child and 6 g (over 24 hours) in an adult were implicated in the production of seizures.[1]

Coma, apnea, or metabolic acidosis developed in 9% of adults and 5% of children who overdosed on ibuprofen.[25] Patients who ingested >400 mg/kg of ibuprofen by history (especially in the pediatric population) were more likely to have seizures, apnea, hypotension, bradycardia, metabolic acidosis, and renal and hepatic dysfunction. The cause of the metabolic acidosis is undefined, but the serum lactic acid concentration generally is only mildly elevated. Because all of the NSAIDs are derivatives of organic acids (eg, ibuprofen is a propionic acid derivative), the NSAID itself or a metabolite, such as propionic acid, may be responsible. Fulminant hepatic failure is rarely seen in acute overdose.[59,60]

Before its removal from the US market in the 1970s, phenylbutazone was associated with the majority of severe toxicity attributed to NSAIDs. In a review of 99 cases, phenylbutazone overdoses were characterized by early GI symptoms, acidâ€“base and electrolyte disturbances, acute lung injury, dizziness, seizures, coma, hypotension, and respiratory and cardiac arrest.[12,56] Acute signs were followed by renal, hepatic, and hematologic dysfunction 2â€“7 days after overdose. At least 50 phenylbutazone-related fatalities have occurred in children.[55] The fatal dose in a 1-year-old was reported to be 2 g, with serious symptoms occurring in adults after ingestions of >4 g.[12,58,70] Although phenylbutazone has long been gone from the US market, it is still available from veterinary sources and for humans in other countries.[49]

Diagnostic Testing

Measurement of serum NSAID concentrations is unnecessary for the clinical assessment and management of patients with NSAID exposures. Although a nomogram describing ibuprofen serum concentrations and their relationship to toxicity is available,[26,29] serum ibuprofen assays correlate poorly with outcome.[65]

For the patient with intentional overdose, a complete blood count, prothrombin time, and serum electrolyte, creatinine, and BUN concentrations should be considered baseline parameters. A serum pregnancy test should be obtained for women of child-bearing age. If significant respiratory or CNS toxicity is present, acidâ€“base status should be assessed. A serum acetaminophen concentration should be obtained to determine whether there is concurrent acetaminophen ingestion, especially in patients with a history of recent painful or febrile conditions.[52] Baseline studies should be considered in children who unintentionally ingested >400 mg/kg.

Management

Most NSAID toxicity resolves with supportive care. Otherwise healthy patients with a history of NSAID poisoning generally require only GI decontamination with activated charcoal, fluid and electrolyte replacement, and supportive management of airway, breathing, and circulation as necessary. Patients who may have ingested a large dose of an NSAID, and who present with CNS or CV toxicity, or who have known risk factors for organ system toxicity associated with NSAIDs, should be considered at higher risk for complications.

Because of the rapid absorption of NSAIDs, symptoms should be evident by 4â€“6 hours after ingestion. Because of this rapid absorption, gastric decontamination by orogastric lavage probably is not indicated. In a human volunteer, comparative trial on the efficacy of activated charcoal alone versus activated charcoal and orogastric lavage after administration of 400 mg of ibuprofen, no difference in ibuprofen plasma concentrations were found 10 hours after ingestion between the two groups.[36] Administration of single-dose activated charcoal within approximately 1â€“2 hours of ingestion is most likely to be the safest and most efficacious means of decontamination after an overdose of NSAIDs.

The high degree of protein binding characteristic of all NSAIDs

makes hemodialysis ineffective in overdose, and experience with hemoperfusion is insufficient to determine its utility.

There is no antidote for NSAID poisoning. Several therapeutic interventions have been tried to prevent the adverse GI effects resulting from loss of cytoprotection from prostaglandins. Use of proton pump inhibitors has shown some success,[15,78] whereas H_2-receptor blockade was unsuccessful in 1920 patients.[67]

Concurrent administration of misoprostol, a PGE analog, may be effective in preventing GI side effects of NSAIDs. Other experimental efforts have involved the coadministration of nitric oxide[16] or substance P inhibitors.[32] These approaches to minimizing adverse effects have not been used for treatment of NSAID overdoses.

Summary

The NSAIDs are a large class of drugs that share similar clinical toxicity based on their ability to inhibit COX. The toxicity that results from overdose usually consists of epigastric pain, nausea or vomiting, and mild CNS depression. Uncommonly, severe overdoses result in metabolic acidosis and CNS toxicity, including seizures, apnea, and coma.

Necessary clinical management usually is limited to general supportive care and assessment for the presence of additional substances (especially acetaminophen) and risk factors for organ system toxicity. Activated charcoal is indicated as GI decontamination

if it can be administered within 1â€“2 hours after ingestion of large doses of NSAIDs. The presence of significant CNS effects or risk factors mandates a more comprehensive evaluation of acidâ€–base, fluid, renal, and electrolyte status.

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Chapter 37
Colchicine and Podophyllin

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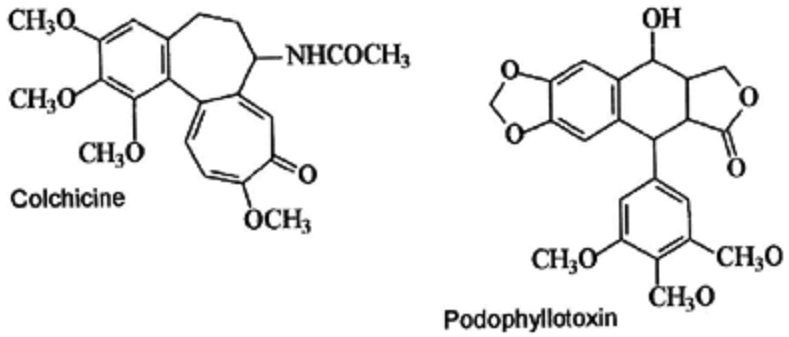

Figure. No Caption Available.

A 48-year-old man presented to the emergency department with chief complaints of uncontrollable nausea, vomiting, and diarrhea. The patient stated that approximately 30 hours earlier, while he was intoxicated with ethanol, he had taken 20 colchicine tablets (0.6 mg) for a gout exacerbation. He developed mild nausea and vomiting several hours after ingestion, followed by diarrhea 14 hours later. The patient

decided to seek medical attention 16 hours after the onset of diarrhea when his symptoms did not improve and he was unable to urinate. He had a medical history significant for gout and ethanol abuse and reported taking only colchicine, naproxen, and indomethacin.

On presentation, the patient was a well-nourished, anxious-appearing man in no acute distress. Vital signs were as follows: blood pressure, 117/53 mm Hg; pulse, 88 beats/min; respiratory rate, 22 breaths/min; temperature, 101.2Â°F (38.4Â°C). His physical examination was significant only for dry mucous membranes. Initial laboratory results revealed the following: sodium, 148 mEq/L; potassium, 4.5 mEq/L; chloride, 105 mEq/L; bicarbonate, 13 mEq/L; blood urea nitrogen, 20 mg/dL; creatinine 4.5 mg/dL. A complete blood count showed the following: white blood cell count, 15,500/mm^3 ; hematocrit, 62.3%; platelets, 394,000/mm^3 . Other laboratory results included prothrombin time, 18.7 seconds; activated partial thromboplastin time, 43.9 seconds; creatine kinase 883 IU/L; creatine kinase (MB fraction), 4.11 IU/L; aspartate aminotransferase, 336 U/L; alanine aminotransferase, 53 U/L; total bilirubin, 0.7 mg/dL; direct bilirubin, <0.1 mg/dL. Urinalysis revealed specific gravity of 1.029 and many red blood cells (11â€“25) per high-power field.

The patient was admitted to the hospital, and aggressive fluid resuscitation was begun. The nephrology and hematology services were consulted for renal failure and anticipated development of colchicine-induced pancytopenia. During the next 12 hours, the patient received approximately 5 L of intravenous 0.9% sodium chloride solution, and urinary flow improved minimally. However, the next morning the patient's electrolytes and renal function tests were essentially unchanged. His white blood cell count peaked at 30,400/mm^3 . The patient developed acral cyanosis and a fever 103.3Â°F (39.6Â°C) of unclear etiology. He was started on broad-spectrum antibiotics (vancomycin and cefepime), and continuous venovenous hemodialysis was instituted for renal failure. During the following several days, the patient's condition deteriorated. He became encephalopathic and developed respiratory failure, which required endotracheal intubation.

He also developed disseminated intravascular coagulation and was started on heparin and fresh-frozen plasma. Granulocyte colony-stimulating factor was started for colchicine-induced pancytopenia: white blood cell count, 3500/mm^3 ; hematocrit, 34%; platelets, 80,000/mm^3 . His white blood cell count eventually fell to 700/mm^3 .

The patient's clinical course continued to worsen, and he developed localized sloughing of his skin, consistent with a toxic epidermal necrolysis reaction. (See ILCOLCHICINE in the Image Library at http://www.goldfrankstoxicology.com) A skin biopsy revealed multiple keratinocytes in metaphase arrest. Despite aggressive respiratory, cardiovascular, and nephrologic support, the patient died on day 9 of his hospitalization.

Colchicine

History and Epidemiology

The origins of colchicine and its history in poisoning can be traced back to Greek mythology. Medea was the evil daughter (and a known poisoner) of the King of Colchis, a country that lay east of the Black Sea in Asia Minor. After she was betrayed by her husband Jason (Jason and the Argonauts), she killed their children and her husband's lover. Medea often used plants of the Liliaceae family, of which *Colchicum autumnale* is a member, to poison her victims.[15 , 99 , 132] Use of colchicum for medicinal purposes also is reported in *Pedanius Dioscorides De Materia Medica* , an ancient medical text, written in the 1st century A.D.[15 , 99 , 132] More extensive use of colchicum might have started as early as the 6th century A.D. by Alexander of Trallis, who recommended it for arthritic conditions.[15 , 22 , 85 , 132] However, colchicum fell out of favor, perhaps because of its pronounced gastrointestinal effects, until it was introduced for dropsy and various other nonrheumatic conditions by Baron von Storck of Vienna in 1763.[15 , 132] In the late 18th century, a colchicum-containing product known as

Eau Medicinale appeared, which reportedly had strong antigout effects.[132] Colchicine, the active alkaloidal component in colchicum, was isolated in 1820 by Pellstier and Caventou and rapidly became popular as an antigout medication.[99, 132] Benjamin Franklin reportedly suffered from gout and is credited with introducing colchicine in the United States for that reason.[99] Colchicine still is used in the treatment of gout as well as a multitude of other disorders, including amyloidosis, BehÃ§et syndrome, familial Mediterranean fever, pericarditis, arthritis, pulmonary fibrosis, vasculitis, biliary cirrhosis, pseudogout, certain spondyloarthropathies, calcinosis, and systemic scleroderma.[6, 15, 91, 95] Systematic data supporting the efficacy of colchicine therapy in many of these other diseases are lacking. Colchicine also has been touted as a â€œgrowth changerâ€• to increase the tetrahydrocannabinol (THC) component of adult marijuana plants by a popular Web site for illicit drugs.[102]

Colchicine is derived from two plants of the Liliaceae family: *Colchicum autumnale* (autumn crocus, meadow saffron, wild saffron, naked lady, son-before-the-father) and *Gloriosa superba* (glory lily).[132] Autumn crocus can contain different amounts of colchicine by weight, depending upon the plant part (bulb, 0.8%; flowers, 0.1%; seeds, 0.8%; and the corm or underground stem, 0.6%).[85, 99, 120] Colchicine concentrations within the plant peak during the summer months.[99] The leaves of *Colchicum autumnale* closely resemble those of the *Allium ursinum* or wild garlic and have been mistaken for them.[25, 26, 76] The tubers of *Gloriosa superba* can be confused with *Ipomoea batatas* (sweet potatoes).[132]

Good epidemiologic data on colchicine poisoning are lacking. The Toxic Exposure Surveillance System records several hundred exposures annually. The majority of these exposures are in adults older than 19 years of age and categorized as unintentional. Of these cases with a recorded outcome, approximately 10% were noted to be major or have resulted in death (Chap. 130)

Pharmacology

Colchicine is a potent inhibitor of microtubule formation and function, which interferes with cellular mitosis, intracellular transport mechanisms, and maintenance of cell structure and shape.[95,132] The ubiquitous presence of microtubules in cells composing various tissues and organs throughout the body presents a wide variety of targets for colchicine poisoning.[95,132] Colchicine accumulates in leukocytes and has inhibitory effects on leukocyte adhesiveness, ameboid motility, mobilization, lysosome degranulation, and chemotaxis.[15,31,39,57,64,95,100,101,129,130 and 131,133] At concentrations used clinically, colchicine can inhibit neutrophil and synovial cell release of chemotactic glycoproteins.[135,154] Colchicine also reduces symptoms by inhibiting microtubule polymerization, which disrupts inflammatory cell-mediated chemotaxis and phagocytosis.[139] It reduces expression of adhesion molecules on endothelial and white blood cells and affects polymorphonuclear cell cytokine production.[4,16,114] Colchicine also can act as a competitive antagonist at Î³-aminobutyric acid type A ($GABA_A$) receptors.[172]

Pharmacokinetics/Toxicokinetics

Colchicine is rapidly absorbed in the jejunum and ileum, undergoes extensive first-pass hepatic metabolism, and has a bioavailability generally between 25% and 50%.[15,92,132,143] It is highly lipid soluble.[11,15,132] The volume of distribution has been reported to range from 2.2â€“12 L/kg and, in overdose, may increase to 21 L/kg.[119,132,136,137,163,169] Initial studies reported plasma elimination half-lives ranging from 9â€“108 minutes.[9,74,132,143,169] On closer examination, however, these times probably more accurately reflect a rapid initial distribution phase. The drug undergoes a more delayed terminal elimination phase, which ranges from 1.7â€“30 hours, depending upon the individual, compartment model used to estimate elimination, and amount of colchicine absorbed.[1,62,132,137,141,143,163] Colchicine can remain in measurable tissue

quantities for a long time as evidenced by its detection in white blood cells after 10 days and in urine 7â€“10 days after exposure.[57 , 132] Colchicine can cross the placenta and is secreted in breast milk, but it is not dialyzable.[95] Postmortem examination of colchicine-poisoned patients reveals high concentrations within the bone marrow, testicle, spleen, kidney, lung, brain, and heart.[136]

Colchicine binding to plasma proteins approaches 50%.[15 , 95 , 115 , 132] Colchicine binds principally to albumin, although some binding to $\hat{I}\pm_1$ -glycoprotein acid and other lipoproteins is reported.[143] Colchicine is taken up by white and red blood cells in concentrations 5â€“10 times higher than serum during the first several hours after acute overdose.[143] Peak plasma concentrations following ingestion occur between 1â€“3 hours.[95] Toxic effects usually do not occur with concentrations <3 ng/mL.[58 , 115 , 168]

Colchicine is primarily metabolized through the liver, with up to 20% of the ingested dose excreted unchanged through the urinary system.[84 , 132 , 163] Colchicine undergoes demethylation by the cytochrome P450 3A4 (CYP3A4).[84 , 95 , 162] Detoxification mainly occurs through deacetylation, demethylation, biliary secretion, and excretion in the stool.[84 , 95 , 112 , 141 , 143 , 162] The reliance on biliary excretion strongly suggests that some amount of enterohepatic recirculation must exist, although this elimination pathway is incompletely studied.[1 , 132] Individuals with severe renal failure and liver cirrhosis may have an elimination half-life that is prolonged up to 10-fold.[95]

Xenobiotic and Substrate Interactions

Colchicine metabolism is susceptible to drug interactions. The reliance of colchicine on detoxification through CYP3A4 makes colchicine susceptible to xenobiotics that alter the function of this enzyme, such as erythromycin, clarithromycin, and grapefruit juice.[33 , 52 , 69 , 95] The multidrug

resistant (MDR) gene codes for a cellular efflux pump protein known as

P-glycoprotein.[95] This protein is able to expel certain chemotherapeutic agents, and certain drugs such as cyclosporine can affect its function. Cyclosporine and other agents that can affect MDR expression and function can interfere with colchicine metabolism and ultimate biliary excretion, thereby increasing colchicine toxicity.[95 , 152 , 153] P-glycoprotein inhibition also might play a role in the macrolide interactions.[138]

Pathophysiology

Microtubules play a vital role in cellular mitosis and possess a high amount of dynamic instability.[13 , 56 , 86 , 148] Microtubules are made up of tubulin protein subunits; the three known to exist are Î±, Î², and Î³.[86 , 108 , 148] These structures are highly dynamic with Î±,Î²-tubulin heterodimers, constantly being added at one end and removed at the other.[86 , 87] This equilibrium is needed for multiple cell functions, including cell support, transport, and mitotic spindle formation for cell replication.[86] Xenobiotics that bind to specific regions on tubulin can interfere with microtubule structure and function, thereby causing mitotic dysfunction and arrest.[108 , 148] This leads to cellular dysfunction and death.[148] Colchicine binds to tubulin (specifically on the Î²-subunit) in a specific region known as the *colchicine-binding domain* .[77 , 86 , 125 , 148 , 164] This binding is relatively slow, temperature dependent, and irreversible, resulting in an alteration of the protein's secondary structure.[77 , 86 , 125 , 144] Colchicine also can bind at a second, reversible, but lower-affinity site on tubulin.[86 , 98] Conformational changes in both tubulin and colchicine result, which might weaken the lateral bonds at the microtubule end.[108 , 148] This can prevent adequate binding of the next tubulin subunit and result in cessation of microtubule growth.[108 , 148]

These conformational changes ultimately result in disassembly of the microtubule spindle in metaphase of cellular mitosis, cellular dysfunction, and death.[60 , 77 , 86 , 125 , 144 , 148] Colchicine's effects are dose dependent, with high concentrations inhibiting further

microtubule polymerization and inducing depolymerization of already-formed microtubules.[97] Low concentrations can simply affect new microtubule formation and have no effect on preestablished polymer mass.[97] Colchicine also inhibits microtubule-mediated intracellular granule transport.[15 , 95] Some in vitro animal studies also have shown that colchicine might inhibit DNA synthesis by changing cell regulatory events at a critical time during the mitotic cycle.[55 , 61 , 79 , 97]

Toxic Dose

The toxic dose for colchicine is not well established. An early case series suggested that patients with colchicine ingestions >0.8 mg/kg uniformly died, and those with ingestions >0.5 mg/kg but <0.8 mg/kg survived if they were given supportive care.[19] This information was based on a limited series of patients and likely is not generalizeable.[117] Later literature suggests that severe toxicity and even death can occur with smaller doses, and patients may survive ingestions in excess of 0.8 mg/kg.[48 , 70 , 73 , 81 , 117 , 155] This inability to accurately quantify the toxic dose in humans likely results in great part from difficulty with dose estimation based on the patient's history.

Clinical Presentation

The clinical findings in colchicine poisoned patients is commonly described as triphasic (Table 37-1).[81 , 104 , 119 , 155] Gastrointestinal irritant effects, such as nausea, vomiting, abdominal distress, and diarrhea, initially occur within several hours following an overdose.[2 , 24 , 26 , 46 , 51 , 65 , 88 , 104 , 109 , 166] This can lead to severe volume depletion.[69 , 83 , 101 , 117 , 119 , 121 , 155 , 171] This first stage usually persists for the first 12â€“24 hours following ingestion.[83 , 104] The second stage is characterized by widespread organ system dysfunction, particularly of the bone marrow, and lasts for several days.[26 , 48 , 117 , 119 , 155] The final phase is characterized by recovery or death, and the progression usually can be defined within 1 week.[81 , 83 , 104 , 155]

I
0â€“24 h
Nausea, vomiting, diarrhea
Antiemetics
Consider GI decontamination
Dehydration
Intravenous fluids
Leukocytosis
Close observation for leukopenia
II
1â€“7 d
Possible risk of sudden cardiac death (24â€“36 h)
ICU admission and appropriate resuscitation
Pancytopenia
G-CSF
Renal failure
Hemodialysis
Sepsis
Antibiotics
Acute respiratory distress syndrome
Oxygen, mechanical ventilation
Electrolyte imbalances
Repletion as needed
Rhabdomyolysis
Intravenous fluids, hemodialysis
III
>7 d
Alopecia
Follow-up
Myopathy, neuropathy, or myoneuropathy
EMG testing, biopsy and neurologic follow-up as needed
Interval time course is not absolute, and overlap of symptom presentation may occur.

Phase Time Signs/Symptoms Therapy

TABLE 37-1. Colchicine Poisoning: Common Clinical Findings, Timing of Onset, and Treatment

Colchicine's hematopoietic effects after overdose are characterized by an initial peripheral leukocytosis, which is followed by a profound leukopenia, commonly accompanied by pancytopenia, usually beginning 48â€“72 hours after overdose.[15 , 24 , 62 , 69 , 80 , 104 , 122] The hematopoietic manifestations occur as a result of colchicine's effects on bone marrow division, presumably from arrest of cell division.[22 , 83 , 136 , 107 , 171] A rebound leukocytosis and recovery of other cell lines occur if the patient survives.

Colchicine poisoning is associated with the development of dysrhythmias and cardiac arrest.[22 , 81 , 83 , 104 , 119] Sudden cardiovascular collapse from colchicine typically occurs between 24â€“36 hours after ingestion.[22 , 32 , 104 , 107 , 117] Profound hypovolemia and shock can contribute to this collapse;[15 , 69 , 117 , 119 , 155] however, colchicine has direct toxic effects on skeletal and cardiac muscle, causing rhabdomyolysis.[21 , 40 , 103 , 110 , 118 , 171]

Myopathy,[27 , 28 , 147] neuropathy,[7 , 97] and a combined myoneuropathy[5 , 41 , 47 , 54 , 93 , 94 , 134 , 151 , 176] result from both long-term therapy and acute poisoning with colchicine.[97] A combined myoneuropathy is reported considerably more often, with myopathy dominating the clinical picture.[5 , 41 , 47 , 54 , 93 , 94 , 134 , 151 , 176] The myoneuropathy often is initially misdiagnosed as polymyositis or uremic neuropathy (because of coexistent renal insufficiency).[5 , 94] Myoneuropathy usually develops in the context of chronic, therapeutic dosing in patients with some baseline renal impairment.[5 , 41 , 47 , 54 , 93 , 94 , 134 , 151 , 176] Patients can present with proximal limb weakness, distal sensory abnormalities, distal areflexia, and nerve conduction problems consistent with an axonal neuropathy.[94 , 127]

A small amount of myelin degeneration is reported on autopsy, which

suggests a myelinopathic component.[23] The myopathy is characterized by vacuolar changes on biopsy, accompanied by lysosome accumulation.[5 , 54 , 94 , 176] Elevated serum creatine kinase activity is present concurrently with symptoms.[94 , 119] Weakness usually resolves within several weeks of drug discontinuation.[94]

Other neurologic effects, including delirium, stupor, coma, and seizures, might be at least partly attributable to the multisystem disease caused by poisoning and not necessarily a direct effect of colchicine.[27 , 122 , 132 , 149] The etiology of seizures is unclear, but they might partly result from antagonism of $GABA_A$ receptors.[172]

Acute respiratory distress syndrome occurs with colchicine toxicity.[10 , 46 , 80 , 112 , 145 , 149] The etiology is not well understood, but the syndrome may result from several factors, including respiratory muscle weakness, multisystem organ failure, and possibly a direct toxic effect.[46 , 104 , 112 , 145 , 161] Other indirect effects of colchicine are renal failure and various electrolyte abnormalities resulting from fluid loss and impaired kidney function.[15 , 48 , 69 , 97 , 119]

Alopecia, which usually is reversible, is a well-described complication that occurs 2â€“3 weeks after poisoning in survivors.[15 , 62 , 69 , 70 , 83 , 98 , 160] Dermatologic complications range in severity from epithelial cell atypia to toxic epidermal necrolysis reactions.[3 , 8 , 60 , 68 , 140]

Other reported complications of colchicine poisoning include bilateral adrenal hemorrhage,[43 , 158] disseminated intravascular coagulation,[83 , 132 , 149] pancreatitis,[122] and liver dysfunction.[27 , 119 , 132]

Diagnostic Testing

Colchicine concentrations in body fluids are not readily available in a clinically relevant fashion and have no well-established correlation to severity of illness. However, effective steady-state plasma concentrations for treatment of various illnesses are reported as 0.5â€“3 ng/mL.[115] Concentrations >3 ng/mL are associated with development of toxicity.[58 , 115 , 168] Initial laboratory monitoring

should include a complete blood count; serum electrolyte concentrations; renal and liver function tests; creatine kinase, phosphate, calcium, and magnesium concentrations; prothrombin time; activated partial thromboplastin time; and urinalysis. The need for other laboratory studies, such as arterial blood gases, serum troponin, serum lactate, and fibrinogen concentrations, and fibrin split products, should be considered, depending upon the situation. An electrocardiogram and chest radiograph should be ordered. Frequent complete blood counts should be ordered (at least every 12 hours) to watch for the development of depression in cell lines.

Management

Treatment for patients with colchicine poisoning is mainly supportive and includes intravenous fluid replacement, vasopressor use, hemodialysis (for renal failure), antibiotics for suspected secondary infection, and adjunctive respiratory therapy (endotracheal intubation, positive end-expiratory pressure), as indicated. Consultation with nephrology and hematology specialists should be obtained in cases of impaired renal function and/or evidence of hematotoxicity.

Gastrointestinal Decontamination

Because most patients with an acute oral colchicine overdose present several hours after ingestion, vomiting has already begun, and the usefulness of gastrointestinal decontamination at this time is inadequately defined. However, given the extensive morbidity and mortality associated with colchicine overdose, orogastric lavage probably should be performed in patients who present within 1â€“2 hours of ingestion and are not vomiting.[20 , 165] A dose of activated charcoal should be administered following lavage, or, in its place, multiple-dose activated charcoal (MDAC) should be considered because enterohepatic recirculation might occur.[1 , 132] The delay in presentation to a healthcare facility, coupled with the presence of gastrointestinal symptoms of poisoning (such as vomiting), significantly complicates use

of MDAC as an effective tool. However, antiemetic medications can be given to control emesis and facilitate activated charcoal administration.

Antidotal Therapy

Experimental colchicine-specific antibodies can restore colchicine-affected tubulin activity in vitro also these same colchicine-specific Fab fragments were successfully used in a single case of severe colchicine poisoning.[12] Administration of Fab fragments was temporally associated with a dramatic improvement in clinical and hemodynamic status. This improvement was associated with a significant increase in plasma colchicine concentrations, which suggests a redistribution of peripheral drug to the intravascular space.[12] Unfortunately, this therapy is not commercially available.

Granulocyte colony-stimulating factor (G-CSF) has been of some success in the treatment of colchicine-induced leukopenia and thrombocytopenia.[45, 75, 90, 175] The dose of G-CSF, the dosing frequency, and the route of administration were variable in the reported cases.[45, 75, 90, 175] G-CSF should be started if the patient begins to manifest evidence of leukopenia. Dosing should be determined by specialists in hematology and in conjunction with the manufacturer's instructions.

Extracorporeal Elimination

Hemodialysis and hemoperfusion are not useful options for colchicine poisoning, based on its large volume of distribution and large degree of protein binding.[14, 17, 18, 136, 137, 163, 169]

Disposition

Because of the severe morbidity and mortality associated with colchicine toxicity, all symptomatic patients with suspected or known significant overdose should be admitted to the hospital for observation. There may be an elevated risk of sudden cardiovascular collapse within

the first 24â€“48 hours,[117] and monitoring in the intensive care unit is recommended for all symptomatic patients for at least this initial time period. Poisoned patients will manifest gastrointestinal signs and symptoms within several hours of ingestion and should be observed for at least 8â€“12 hours. Patients who do not manifest gastrointestinal signs and symptoms within that time period after ingestion likely were not significantly poisoned.

Podophyllum Resin or Podophyllin

History and Epidemiology

Podophyllin is the name often used to refer to a resin extract from the rhizomes and roots of certain plants of the genus *Podophyllum* .[49 , 72] Examples include the North American perennial *Podophyllum peltatum* (mayapple or mandrake), the related Indian species *Podophyllum emodi* , and the Taiwanese *Podophyllum pleianthum* .[49] It is more descriptive to refer to it as *podophyllum resin* .[49 , 72] Podophyllum resin, or podophyllin, contains at least 16 physiologically active

compounds.[35 , 49 , 72] These include a variety of lignins and flavonols, including podophyllotoxin, picropodophyllin, Î±- and Î²-pellatins, desoxypodophyllotoxin, and quercetin.[34 , 35 , 49 , 72] Podophyllotoxin is a potent microtubular poison, similar to colchicine, and causes analogous effects in overdose.[49]

The first reported medicinal use of podophyllin preparations was as a laxative in the 19th century.[34 , 35 , 131] Its cathartic properties, as well as its potential toxicity, were noted as early as 1890, when the first fatality from podophyllin was recorded.[53 , 150] Podophyllin has been used historically to treat a variety of other health conditions, including liver disease, scrofula, syphilis, warts, and cancer.[49] Etoposide and teniposide are semisynthetic derivatives of podophyllotoxin[49] and have been investigated for efficacy in the treatment of certain cancers.[49]

Poisoning usually results from systemic absorption following topical application, ingestion of the resin or plant, and consumption of a commercial preparation of the extract. Systemic toxicity is described after unintentional dispensing of the incorrect herb and after ingestion of herbal preparations containing podophyllin.[36, 38, 50]

Pharmacology

Podophyllin is used in modern pharmacopeia primarily as a topical treatment for verruca vulgaris and condyloma acuminatum.[34, 59, 96] The active ingredient is believed to be podophyllotoxin.[11, 49, 89, 150, 159, 167, 174] Numerous synthetic and semisynthetic derivatives of podophyllotoxin exist; however, the most important probably are the chemotherapeutic agents etoposide and teniposide.[49] The antitumor effect of etoposide and teniposide results from interaction with topoisomerase II and free radical production, resulting in DNA strand breakage, an effect not shared by podophyllin and colchicine.[30, 49] Etoposide and teniposide also can induce cessation of cell growth in the late S or early G2 phase of the cell cycle.[30, 49, 67] These agents are discussed further in Chap. 52.

Pharmacokinetics/Toxicokinetics

Limited information exists regarding the pharmacokinetics of podophyllin as a preparation and its major active ingredient podophyllotoxin. Podophyllotoxin is a highly lipid-soluble compound that can easily cross cell membranes.[59, 71, 123, 150] Podophyllotoxin exists in the plant as a Î²-D-glucoside[59, 89, 150] and is reported to be eliminated through the bile with a half-life of 48 hours.[34, 42] However, the referenced articles cited failed to adequately support this statement and may have been based solely on clinical course.[42]

Systemic absorption of podophyllotoxin was measured in 7 men after application of various amounts of a 0.5% ethanol podophyllotoxin preparation for condylomata acuminata.[167] Peak serum concentrations

of 1â€“17 ng/mL were achieved within 1â€“2 hours after administration of doses ranging from 100â€“1500 ÂµL (0.5â€“7.5 mg).[167] Patients treated with â‰¤ 50 ÂµL had no detectable podophyllotoxin in their serum. Administration of 100 ÂµL yielded peak serum concentrations up to 5 ng/mL within 1â€“2 hours and up to 3 ng/mL at 4 hours. Administration of 1500 ÂµL yielded peak serum concentrations ranging from 5â€“9 ng/mL within 1â€“2 hours, concentrations of 5â€“7 ng/mL at 4 hours, 3â€“4.5 ng/mL at 8 hours, and 3.5 ng/mL at 12 hours.[167]

Pathophysiology

The components of podophyllin have numerous actions within the cell, including inhibition of purine synthesis, inhibition of purine incorporation into RNA, reduction of cytochrome oxidase and succinoxidase activity, and inhibition of microtubule structure and function.[34, 67, 170] Podophyllotoxin causes toxicity similar to colchicine[49, 174] because it is able to bind to tubulin subunits and interfere with subsequent microtubule structure and function.[49, 174] Interestingly, radiolabeled podophyllotoxin can inhibit colchicine binding to tubulin, suggesting that the binding sites for the two agents at least overlap.[49] Podophyllotoxin binds more rapidly than colchicine, and binding is reversible in contrast to colchicine.[49] Podophyllotoxin also inhibits fast axoplasmic transport similar to colchicine by interfering with microtubule structure and function.[128] Many other compounds, such as the vinca alkaloids (see Chap. 52) cryptophycins, and halichondrins, also inhibit microtubule polymerization in a similar manner.[87]

Clinical Presentation

Toxicity is described following ingestion[29, 38, 50, 63, 82, 105, 142, 173] and after systemic absorption from topical application of podophyllin.[66, 106, 113, 116, 126, 156, 157] Toxicity also is reported after intravenous administration of podophyllotoxin[146] and ingestion of mandrake root or herbal remedies containing podophyllin.[50, 53, 63]

Nausea, vomiting, abdominal pain, and diarrhea usually begin within several hours after ingestion.[42 , 53 , 66 , 71 , 82 , 106 , 111 , 113 , 142 , 146 , 150 , 156 , 173] Symptoms of poisoning might be delayed for 12 hours or more after topical exposure to podophyllin and often are the result of improper usage (excessive topical exposure, interruption in skin integrity, or failure to remove the preparation after a short period).[106 , 111 , 116 , 150] Initial clinical findings are not necessarily dictated by the route of exposure.[106]

Alterations in central and peripheral nervous system function tend to predominate in podophyllin toxicity. Patients might present with, or rapidly progress to, confusion, obtundation, and coma.[29 , 42 , 50 , 66 , 105 , 111 , 113 , 116 , 142 , 156 , 157 , 159 , 173]

Delirium and both auditory and visual hallucinations are also reported during the initial presentation.[44 , 59 , 157] Patients develop paresthesias, lose deep tendon reflexes, and might develop a Babinski sign.[29 , 35 , 38 , 42 , 50 , 66 , 105 , 113 , 116 , 124 , 150 , 157] Cranial nerve involvement, including diplopia,[35] nystagmus,[42] dysmetria,[38] dysconjugate gaze,[157] and facial nerve paralysis,[44] are all reported. Patients who recover from the initial event are at risk for developing a peripheral sensorimotor axonopathy.[38 , 42 , 50 , 59 , 66 , 105 , 113 , 123 , 124 , 150 , 157] The reported duration for recovery from podophyllin-induced axonopathy is variable but can take several months.[42 , 50 , 66 , 113 , 123] Dorsal radiculopathy[71] and autonomic neuropathy are reported.[96] The neuropathy may have a mild myelopathic component.[37]

Hematologic toxicity from podophyllin most likely results from its antimitotic effects. A review of the limited available literature suggests podophyllin is similar to colchicine but not nearly as consistent in its pattern, severity, and frequency. An initial leukocytosis[66 , 113 , 116 , 150] after poisoning can occur, which can be followed by leukopenia, thrombocytopenia, and/or generalized pancytopenia.[82 , 96 , 111 , 113 , 150 , 156] In patients who recover, cell lines tend to reach their nadir within 4â€“7 days after exposure.[59 , 66 , 82 , 113 , 156]

Other complications of poisoning include fever,[111] ileus,[59 , 111 , 157]

elevated liver enzymes,[50 , 82 , 113 , 156 , 173] hyperbilirubinemia,[82] coagulopathy,[82] seizures,[44 , 142] and renal insufficiency/failure.[111 , 173] Teratogenic effects resulting from exposure during pregnancy can occur.[35 , 89]

Diagnostic Testing

Podophyllin or podophyllotoxin concentrations are not readily available. Routine testing for suspected or known podophyllin

poisoning should include routine laboratory tests and other targeted testing, as needed. Serial cell blood counts should be obtained in cases of poisoning to watch for pancytopenia.

Typical Routes of exposure
Oral
Oral and topical
Intravenous
Intravenous
Initial symptoms
GI[a]
GI[a] and/or neurologic (obtundation delirium)
GI[a] ; fever; neurologic
GI[a] ; fever; myalgias; neurologic
Initial symptom onset
Several hours after ingestion; delayed presentation beyond 12 h very unlikely
Several hours after ingestion; delayed presentation (past 12 h) possible, especially with cutaneous route of exposure
Usually within 24â€“48 h
Usually within 24â€“48 h
Hematotoxic effects
Leukocytosis (24â€“48 h postingestion); pancytopenia (beginning 48â€“72 h postingestion)
Similar to colchicine, but not well characterized and reported less

frequently
May occur; *less* severe compared to vinblastine
May occur; *more* severe compared to vincristine
CNS effects
Late (after 48â€“72 h after ingestion); obtundation, confusion, and lethargy secondary to progression of MSD
Can be early (<12 h after ingestion); obtundation, confusion, delirium; may occur later, secondary to progression of MSD
Variable; cranial neuropathies; seizures; obtundation, and confusion can occur due to progression of MSD
Variable; cranial neuropathies; obtundation, and confusion can occur due to progression of MSD
Delayed PNS effects
Myoneuropathy most common; reported most often in chronic colchicine users with renal insufficiency
Peripheral sensorimotor axonopathy
Autonomic and ascending peripheral neuropathy; *increased* severity compared to vinblastine
Can see autonomic and peripheral neuropathy; *decreased* severity compared to vincristine
Clinical course
Recovery or multisystem organ dysfunction and death
Recovery or multisystem organ dysfunction and death
Recovery or MSOF and death; may develop SIADH
Recovery or MSOF and death; may develop SIADH
Management
Supportive; consider GI decontamination; G-CSF for neutropenia
Supportive; consider GI decontamination
Supportive; unintentional intrathecal administration requires CSF drainage
Supportive; unintentional intrathecal administration requires CSF drainage

[a] Gastrointestinal (nausea, vomiting, diarrhea, abdominal discomfort).
[b] See Chaps. 19 and 52 .

CNS = central nervous system; G-CSF = granulocyte colony-stimulating factor; MSOF = multisystem organ failure;
PNS = peripheral nervous system.

Colchicine	Podophyllum Resin	Vincristine[b]	Vinblastine[b]

TABLE 37-2. Comparison of Antimitotic Xenobiotics in Overdose

Management

Management primarily consists of supportive and symptomatic care. Orogastric lavage should be considered if presentation occurs within 1 hour of ingestion. If the patient presents within 1â€“2 hours of ingestion, a dose of activated charcoal should be given. Any topically applied podophyllin should be removed and the area thoroughly cleansed. Supportive and symptomatic care should be instituted, as needed. Patients either progress to multisystem organ dysfunction and death, or they recover with supportive care.

A few case reports of treatment with extracorporeal elimination techniques exist. These treatments include resin hemoperfusion[78] and charcoal hemoperfusion.[113 , 150] The role these procedures played in the patient's clinical course is unclear. No recommendation regarding the use of these techniques can be made at this time.

Disposition

Significant ingestions of podophyllin can result in gastrointestinal symptoms within a few hours,[38 , 53 , 63 , 82 , 124 , 173] but patients also can present with primarily neurologic symptoms, such as confusion and obtundation.[29 , 34 , 59 , 106] An isolated number of cases suggest the onset of toxicity can be delayed for as long as 12 hours.[29 , 34 , 42 , 50] Dermal exposure might result in even further delayed toxicity, as systemic absorption is delayed and symptom onset is more insidious.[59]

, 66 , 96 , 116 , 150 , 156 , 157 Patients probably should be observed for toxicity for at least 12 hours after ingestion and perhaps even longer after significant dermal exposure.

Summary

Colchicine and podophyllotoxin exert their primary toxicity by binding to tubulin and interfering with microtubule structure and function. The ubiquitous nature of microtubules within human cells and the heavy reliance on them for maintenance of normal cell functions present numerous opportunities for these xenobiotics to cause dysfunction at the cellular, organ, and organ system levels in a dose-dependent fashion. Colchicine toxicity may be evident several hours after ingestion and consists of severe nausea, vomiting, diarrhea, and abdominal pain, followed several days later by pancytopenia. Colchicine-poisoned patients may have a higher risk for sudden cardiac death, especially during the period between 24â€“36 hours after ingestion. Patients poisoned with podophyllin, or more accurately podophyllotoxin, may initially present with gastrointestinal and/or neurologic signs and symptoms, depending on dose and route of exposure (see Table 37-2).

Management and treatment for toxicity resulting from both agents is generally similar. Early gastrointestinal decontamination and supportive treatment are the hallmarks of therapy for both agents since no antidote is commercially available. Serial cell blood

counts should be obtained to watch for the development of cytopenias. G-CSF may be beneficial for colchicine-induced neutropenia.

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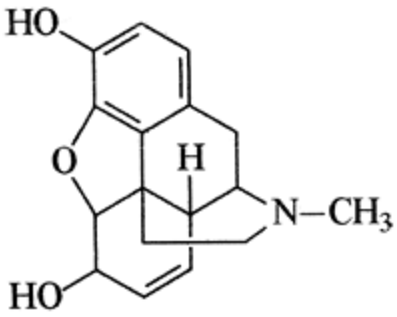
Chapter 38
Opioids

Lewis S. Nelson



Morphine

Emergency Medical Services (EMS) was called to provide assistance to a comatose 23-year-old man. EMS found that the patient was hypoventilating (2 breaths/min) and cyanotic, and he had miotic pupils. Earlier the same day, the patient had been evaluated at another hospital for a similar condition. The patient had been discharged after he supposedly responded to naloxone.

In the current emergency department (ED), the patient was ventilated by bag-valve-mask while preparations were made to perform

endotracheal intubation. Naloxone 0.4 mg was administered intravenously, and the patient became alert with a respiratory rate of 24 breaths/min. At that point, the patient looked uncomfortable, he developed diaphoresis, and his pupils dilated. Physical examination revealed piloerection, hyperactive bowel sounds, and bilateral pulmonary rales. Cardiac examination was normal. An electrocardiogram demonstrated sinus tachycardia., Arterial blood gas analysis revealed pH, 7.38; PCO_2 , 28 mm Hg; PO_2 (on 40% Ventimask), 140 mm Hg. A portable chest radiograph showed diffuse patchy infiltrates.

The patient received continuous low-flow oxygen therapy for 24 hours in the intensive care unit, and his oxygen saturation was maintained in the normal range at all times. His lungs cleared over the observation period. The patient was discharged after an additional day of observation and given a referral back to his methadone maintenance treatment program.

History and Epidemiology

The medicinal value of opium, the dried extract of the poppy plant *Papaver somniferum* , was first recorded around 1500 B.C. in the Ebers papyrus.[150] Raw opium typically is composed of at least 10% morphine, but extensive variability exists according to growing region.[111] Although reformulated as laudanum (deodorized tincture of opium; 10 mg morphine/mL) by Paracelsus, paregoric (camphorated tincture of opium; 0.4 mg morphine/mL),[139] Dover's powder (pulvis Doveri), and Godfrey's cordial in later centuries,[150] the contents remained largely the same: phenanthrene poppy derivatives, such as morphine and codeine. Over the centuries since the Ebers papyrus, opium and its components have been exploited in two distinct manners: medically to produce profound analgesia and nonmedically to take advantage of their psychoactive effects.

Currently the widest clinical application of opioids is for acute or chronic pain relief. Opioids are available in various formulations that

allow administration by virtually any route: epidural, inhalational, intranasal, intrathecal, oral, parenteral (ie, subcutaneously [SC]/IV/IM), rectal, transdermal, and transmucosal. Patients also may benefit from several of the nonanalgesic effects engendered by certain opioids. For example, codeine is widely used as an antitussive agent and diphenoxylate as an anti-diarrheal drug.

Unfortunately, the history of opium and its derivatives is marred by mankind's endless quest for drugs that produce pleasurable effects. Opium smoking was so problematic in China by the 1830s that the Chinese government attempted to prohibit the importation of opium by the British East India Company. This act led to the Opium Wars between China and Britain. China eventually accepted the importation and sale of the drug and was forced to turn over Hong Kong to British rule. The euphoric and addictive

potential of the opioids is immortalized in the works of several famous writers, such as Thomas de Quincey (*Confessions of an English Opium Eater* , 1821), Samuel Coleridge (*The Rime of the Ancient Mariner* , 1798), and Elizabeth Barrett Browning (*Aurora Leigh* , 1856).

Because of mounting concerns of addiction and toxicity in the United States, the Harrison Narcotic Act, enacted in 1914, made nonmedicinal use of opioids illegal. Since that time, recreational and habitual use of heroin and other opioids have remained at epidemic levels in the United States and worldwide despite extensive and diverse attempts to curb their availability.

Morphine was isolated from opium by Armand SÃ©quin in 1804.[150] Charles Alder Wright synthesized heroin from morphine in 1874.[226] Ironically, the development and marketing of heroin as an antitussive agent by Bayer, the German pharmaceutical company, in 1898 legitimized heroin's medicinal role.[226] Subsequently, various agents with opioidlike effects were marketed, each promoted for its presumed advantages over morphine. This assertion proved true for fentanyl because of its pharmacokinetic profile. However, in general

the advantages of such agents have fallen short of expectations, particularly with regard to abuse potential.

The terminology used in this chapter recognizes the broad range of agents commonly considered to be opiumlike. The term *opiate* specifically refers to the relevant alkaloids derived directly from the opium poppy: morphine, codeine, and, to some extent, thebaine and noscapine. *Opioids* are a much broader class of agents that are capable of either producing opiumlike effects or binding to opioid receptors. A *semisynthetic opioid*, such as heroin or oxycodone, is created by chemical modification of an opiate. A *synthetic opioid* is a chemical compound, not derived from an opiate, that is capable of binding to an opioid receptor and producing opioid effects clinically. Synthetic opioids, such as methadone and meperidine, bear little overt structural similarity to the opiates. Opioids include the naturally occurring animal-derived opioid peptides such as endorphin and nociceptin/orphanin FQ. The term *narcotic* refers to a sleep-inducing agent and initially was used to connote the opioids. However, law enforcement and the public currently use the term to indicate any illicit psychoactive substance. The term *opioid* as used hereafter encompasses the opioids and the opiates.

Pharmacology

Opioid-Receptor Subtypes

Despite nearly a century of opioid studies, the existence of specific opioid receptors was not proposed until the mid-20th century.[13] Beckett and Casy[13] noted a pronounced stereospecificity of existing opioids (only the L-isomer is active) and postulated that the drug needed to â€œfitâ€• into a receptor. In 1963, after studies on the clinical interactions of nalorphine and morphine, the theory of receptor dualism[155] postulated the existence of two classes of opioid receptors. Such opioid binding sites were not demonstrated experimentally until 1973.[185] Intensive experimental scrutiny using

selective agonists and antagonists continues to permit refinement of receptor classification. The current, widely accepted schema postulates the coexistence of three major classes of opioid receptors, each with multiple subtypes, and several poorly defined minor classes.

Initially, the reason such an elaborate system of receptors existed was unclear, because no endogenous ligand could be identified. However, evidence for the existence of such endogenous ligands was uncovered in 1975 with the discovery of metenkephalin and leuenkephalin[102] and the subsequent identification of Î²-endorphin and dynorphin. As a group, these endogenous ligands for the opioid receptors are called *endorphins* (*endo* genous mo*rphine*). Each is a 5-amino-acid peptide, cleaved from a larger precursor peptide: proenkephalin, proopiomelanocortin, and prodynorphin, respectively. More recently, a minor related endogenous opioid (nociceptin/orphanin FQ) and its receptor ORL have been described.

All three major opioid receptors have been cloned and sequenced. Each consists of 7 transmembrane segments, an amino terminus, and a carboxy terminus. Significant sequence homology exists between the transmembrane regions of opioid receptors and those of other members of the guanosine triphosphate (GTP)-binding protein (G-protein)-binding receptor superfamily. However, the extracellular and intracellular segments differ from one another. These nonhomologous segments probably represent the ligand-binding and signal transduction regions, respectively, which would be expected to differ among the three classes of receptors. The individual receptors have distinct distribution patterns within the central nervous system and peripherally, mediating unique but not entirely understood clinical effects. Until recently, researchers used varying combinations of agonists and antagonists to pharmacologically distinguish the different receptor subtypes. However, knockout mice (mutant mice lacking the genes for an individual opioid receptor) promise new insights into this complex subject.[72]

Because multiple opioid receptors exist and each elicits a different effect, determining the receptor to which an opioid agent preferentially binds should allow prediction of the drug's clinical effects. However, drug binding typically is not limited to one receptor type, and it is the relative affinity of a drug for differing receptors that accounts for the drug's clinical effects (Table 38-1). Even the endogenous opioid peptides exhibit substantial crossover among the receptors.

Although the familiar pharmacologic nomenclature derived from the Greek alphabet is used throughout this textbook, the International Union of Pharmacology (IUPHAR) Committee on Receptor Nomenclature has twice recommended a nomenclature change from the original Greek symbol system to make opioid receptor names more consistent with those of other neurotransmitter systems.[247] In the first new schema, the receptors were denoted by their endogenous ligand (*o* pioid *p* eptide [OP]), with a subscript identifying their chronologic order of discovery.[48] The Îº receptor was renamed OP_1 , the Îº receptor was renamed OP_2 , and the Âµ receptor was renamed OP_3 . However, adoption of this nomenclature met with significant resistance, presumably because of problems that would arise when merging previously published work that had used the Greek symbol nomenclature. The currently proposed nomenclature suggests the addition of a single letter in front of the OP designation and the elimination of the number. In this schema, the Âµ receptor is identified as MOP. In addition, the latest iteration formally recognizes the nociceptin/orphanin FQ or NOP receptor as a fourth receptor family.

Mu Receptor (Âµ, MOP, OP_3)

The early identification of the Âµ receptor as the *m* orphine binding site gave this receptor its designation.[156] Although many exogenous agents produce supraspinal analgesia via Âµ receptors, the endogenous ligand is elusive. Nearly all of the recognized endogenous

opioids have some affinity for the Âμ receptor, although none is selective for the receptor. Endomorphin-1

and endomorphin-2 are nonpeptide ligands present in brain that may represent the endogenous ligand.[269]

Âμ1
OP3a
MOP
Supraspinal analgesia
Peripheral analgesia
Sedation
Euphoria
Prolactin release
Âμ2
OP3b

Spinal analgesia
Respiratory depression
Physical dependence
Gastrointestinal dysmotility
Pruritus
Bradycardia
Growth hormone release
Î º1
OP2a
KOP
Spinal analgesia
Miosis
Diuresis
Î º2
OP2b

Psychotomimesis
Dysphoria

Î º$_3$
OP$_{2\,b}$

Supraspinal analgesia
Î ´
OP$_1$
DOP
Spinal and supraspinal analgesia
Modulation of Âµ-receptor function
Inhibit release of dopamine
Nociceptin/orphanin FQ
OP$_4$
NOP
Anxiolysis
Analgesia
[a] International Union of Pharmacology Committee on Receptor Nomenclature.

1996 Conventional Name	Proposed IUPHAR Name[a]	IUPHAR Name[a]	Important Clinical Effects of Receptor Agonists

TABLE 38-1. Clinical Effects Related to Opioid Receptors

Experimentally, two subtypes (Âµ$_1$ and Âµ$_2$) are well defined, although currently no agents have sufficient selectivity to make this dichotomy clinically relevant. Experiments with knockout mice suggest that both subtypes derive from the same gene and that either posttranslational changes or local cellular effects subsequently differentiate them.[122] The Âµ$_1$ subtype appears to be responsible for supraspinal (brain) analgesia and for the euphoria sometimes engendered by these agents. Although stimulation of the Âµ$_2$ subtype produces spinal-level analgesia, it also produces respiratory depression. All currently available Âµ agonists have some activity at

the Âμ$_2$ receptor and therefore produce some degree of respiratory compromise. Localization of Âμ receptors to regions of the brain involved in analgesia (periaqueductal gray, nucleus raphe magnus, medial thalamus[81]), euphoria and reward (mesolimbic system), and respiratory function (medulla) is not unexpected.[169] Predictably, Âμ receptors are found in the medullary cough center, peripherally in the gastrointestinal tract, and on various sensory nerve endings, including the articular surfaces (see discussion of analgesia under Clinical Manifestations below).

Kappa Receptor (Îº, KOP, OP$_2$)

Although dynorphins now are known to be the endogenous ligands for Îº receptors, these receptors originally were identified by their ability to bind ketocyclaz-ocine and thus were labeled Îº.[156] Kappa receptors exist predominantly in the spinal cord of higher animals, although they also are found in the antinociceptive regions of the brain and the substantia nigra.[256] Stimulation is responsible for spinal analgesia, miosis, and diuresis (via inhibition of antidiuretic hormone release). Unlike Âμ-receptor stimulation, Îº-receptor stimulation is not associated with significant respiratory depression or constipation. The Îº receptor currently is subclassified into three subtypes. The Îº$_1$ receptor subtype is responsible for spinal analgesia. This analgesia is not reversed by Âμ-selective antagonists,[166] supporting the role of Îº receptors as independent mediators of analgesia. Although the function of the Îº$_2$ receptor subtype is largely unknown, stimulation of cerebral Îº$_2$ receptors by agents such as pentazocine and salvinorin A produces psychotomimesis in distinction to the euphoria evoked by Âμ agonists.[187, 214] The Îº$_3$ receptor subtype is found throughout the brain and participates in supraspinal analgesia. This receptor is primarily responsible for the action of nalorphine, an agonistâ€“antagonist opioid.[184] Nalbuphine, another agonistâ€“antagonist, exerts its analgesic effect via both Îº$_1$ and Îº$_3$ agonism, although both nalorphine and nalbuphine are antagonists to morphine at the Âμ receptor.[189]

Delta Receptor (Î´, DOP, OP_1)

Little is known about Îº receptors, although the enkephalins are known to be their endogenous ligands. Opioid peptides identified in the skin and brain of *Phyllomedusa* frogs, termed *dermorphin* and *deltorphin*, respectively, are potent agonists at the Îº receptor. Delta receptors may be important in spinal and supraspinal analgesia (probably via a noncompetitive interaction with the Âµ receptor[80]) and in cough suppression.[113] Delta receptors may mediate dopamine release from the nigrostriatal pathway, where they modulate the motor activity associated with amphetamine.[173] Delta receptors do not modulate dopamine in the mesolimbic tracts and have only a slight behavioral reinforcing role. Subpopulations, specifically $Î´_1$ and $Î´_2$, are postulated based on in vitro studies but presently are not confirmed in vivo.[247]

Nociceptin/Orphanin FQ Receptor (ORL_1, OP_4)

The ORL_1 receptor was identified in 1994, based on sequence homology during screening for opioid-receptor genes with DNA libraries.[24] It has a similar distribution pattern in the brain and uses similar transduction mechanisms as the other opioid-receptor subtypes. It binds many different opioid agonists and antagonists. Its insensitivity to antagonism by naloxone, often considered the sine qua non of opioid character, delayed its acceptance as a valid opioid-receptor subtype. Simultaneous identification of an endogenous ligand, called *nociceptin* by the French discoverers and *orphanin* FQ by the Swiss investigators, allowed the designation OP_4. A clinical role has not yet been defined, but anxiolytic and analgesic properties have been described.[37, 163]

Sigma Receptor (Ï*f*)

Although originally conceived as an opioid subtype, the Ïƒ receptor is no longer considered opioid in character, and it has not been given an IUPHAR OP designation. Investigation of this receptor revealed that it is insensitive to antagonism by naloxone, prefers ligands with a dextrorotatory stereochemistry, and has no endogenous ligand, all features in contradistinction to the other opioid receptors. Nonetheless, the effects of the Ïƒ receptor are relevant to opioid pharmacology because certain opioids, such as dextromethorphan and pentazocine, are Ïƒ-receptor agonists. Stimulation of the Ïƒ receptor is implicated in psychotomimesis and movement disorders, effects that are reported with both dextromethorphan and pentazocine independently.[91]

Hallucinogens, such as ibogaine,[19] and antipsychotic agents, such as haloperidol, are known Ïƒ-receptor antagonists.

Other Receptors (Epsilon [Îµ], Zeta [Î¶])

Two other opioid-receptor subtypes are largely uncharacterized in humans but ultimately may prove to be important. The Îµ receptor is postulated based on in vivo binding assays and has no known clinical role.[244] The Î¶ receptor has been proposed and may serve as an opioid growth factor receptor.[270]

Opioid-Receptor Signal Transduction Mechanisms

Figure 38-1 illustrates opioid-receptor signal transduction mechanisms. Continuing research on the mechanisms by which an opioid receptor induces an effect has produced confusing and often contradictory results. Despite the initial theory that each receptor subtype is linked to a specific transduction mechanism, individual receptor subtypes may use one or more mechanisms, depending on several factors, including receptor localization (eg, presynaptic vs

postsynaptic). As noted, all opioid-receptor subtypes are members of a superfamily of membrane-bound receptors that are coupled to G proteins.[247] The G proteins are responsible for signaling the cell that the receptor has been activated and for initiating the desired cellular effects. The G proteins are generally of the pertussis toxin-sensitive, inhibitory subtype known as G_i or G_o , although coupling to a cholera toxin-sensitive, excitatory G_S subtype has been described.[39] Regardless of subsequent effect, the G proteins consist of three conjoined subunits, Î±, Î², and Î³. The Î²Î³ subunit is liberated upon GTP binding to the Î± subunit. When the Î± subunit dissociates from the Î²Î³ subunit, it modifies specific effector systems,

such as phospholipase C or adenylate cyclase, or it may directly affect a channel or transport protein. GTP subsequently is hydrolyzed by a GTPase intrinsic to the Î± subunit, which prompts its reassociation with the Î²Î³ subunit and termination of the receptor-mediated effect.

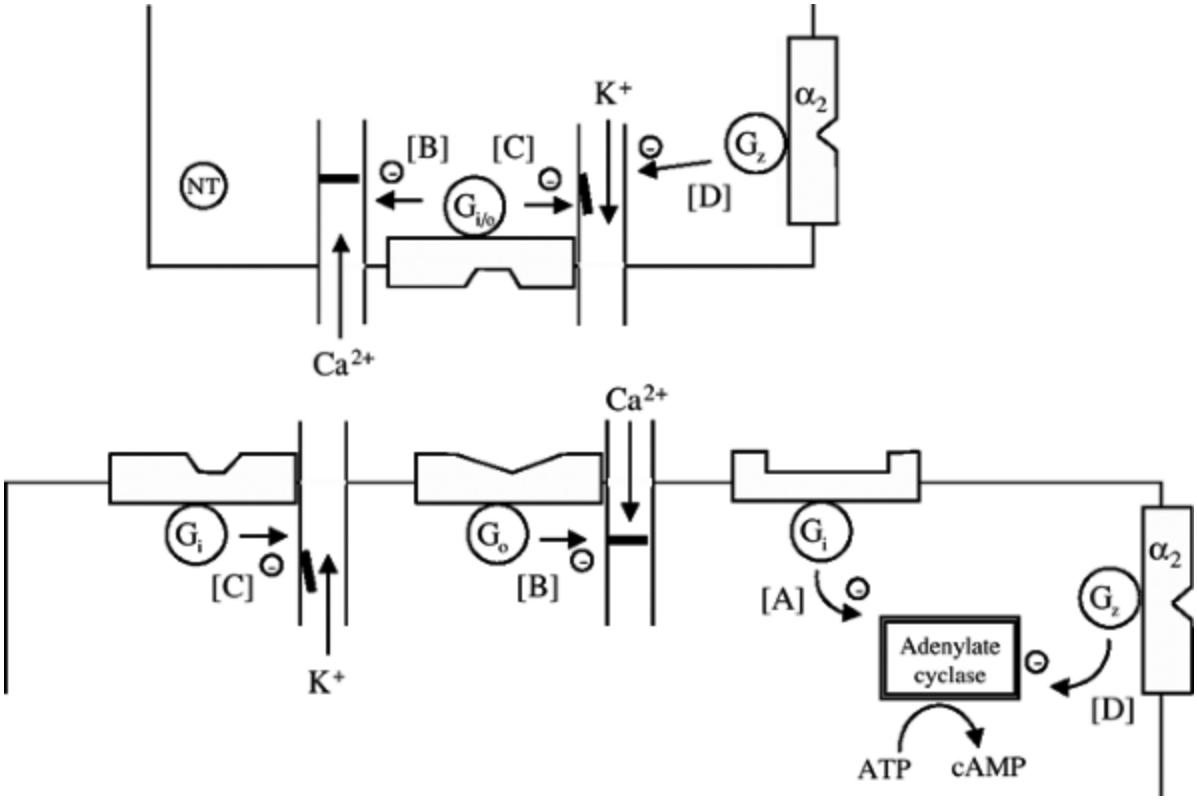


Figure 38-1. Opioid-receptor signal transduction mechanisms. Upon

binding of an opioid agonist to an opioid receptor, the respective G protein is activated. G proteins may (A) reduce the capacity of adenylate cyclase to produce cAMP; (B) close calcium channels that reduce the signal to release neurotransmitters; (C) open potassium channels and hyperpolarize the cell, which indirectly reduces cell activity. Each mechanism has been found coupled to each receptor subtype, depending on location of the receptor (pre/postsynaptic), and the neuron within the brain (see text). Note that $\hat{I}\pm_2$ receptors (D) mediate similar effects, using a different G protein (G_z). NT = neurotransmitter.

Adenylate cyclase/cAMP (A)

Inhibition of adenylate cyclase activity by G_i or G_o is the classic mechanism for postsynaptic signal transduction invoked by the inhibitory Âμ receptors. However, this same mechanism also has been identified in cells bearing either Î´ or Îº receptors. Activation of cAMP production by adenylate cyclase, with subsequent activation of protein kinase A, occurs following exposure to very-low-dose opioid agonists and produces excitatory, antianalgesic effects.[39]

Calcium (Ca^{2+}) channels (B)

Presynaptic Âμ receptors inhibit norepinephrine release from the nerve terminals of cells of the rat cerebral cortex. Adenylate cyclase does not appear to be the modulator for these receptors because inhibition of norepinephrine release is not enhanced by raising intracellular cAMP levels by various methods.[208] Opioid-induced blockade is, however, prevented by increased intracellular calcium levels that are induced either by calcium ionophores, which increase membrane permeability to calcium, or by raising the extracellular calcium concentration.[208] This implies a role for opioid-induced closure of N-type calcium channels, presumably via a G_o protein. Reduced intraterminal concentrations of calcium prevent the neurotransmitter-laden vesicles from binding to the terminal membrane and releasing their contents. Nerve terminals containing dopamine appear to have an analogous relationship with inhibitory Îº

receptors, as do acetylcholine-bearing neurons with Î´ opioid receptors.[208]

Potassium (K^+) channels (C)

Increased conductance through a potassium channel, generally mediated by G_i or G_o, results in membrane hyperpolarization with reduced neuronal excitability. Alternatively, protein kinase Aâ€“mediated reduction in membrane potassium conductance enhances neuronal excitability.

Clinical Manifestations

Table 38-2 outlines the clinical effects of opioids.

Therapeutic Effects

Analgesia

Although classic teaching attributes opioid analgesia solely to the brain, opioids actually appear to modulate cerebral cortical pain perception at supraspinal, spinal, and peripheral levels. The regional distribution of the opioid receptors confirms that Âµ receptors are responsible for most of the analgesic effects of morphine within the brain. They are found in highest concentration within areas of the brain classically associated with analgesiaâ€”the periaqueductal gray, nucleus raphe magnus, locus caeruleus, and medial thalamus.[183] Microelectrode-induced electrical stimulation of these areas[198] or iontophoretic application of agonists into these regions results in profound analgesia.[15] Specifically, enhancement of inhibitory outflow from these supraspinal areas to the sensory nuclei of the spinal cord (dorsal roots) dampens nociceptive neurotransmission. Additionally, inactivation of the Âµ-opioidâ€“receptor gene in embryonic mouse cells results in offspring that are insensitive to morphine analgesia.[157]

Interestingly, blockade of the *N* -methyl-D-aspartate (NMDA) receptor, a mediator of excitatory neurotransmission, enhances the analgesic effects of Âμ-opioid agonists and may reduce the development of tolerance (see Dextromethorphan below).[1 , 194] Even more intriguing is the finding that low-dose naloxone (0.25 Âμg/kg/h) actually improves the efficacy of morphine analgesia.[68] Administration of higher-dose, but still low-dose, naloxone (1 Âμg/kg/h) obliterated its opioid-sparing effect. Although undefined, the mechanism may be related to selective inhibition of G_S -coupled excitatory opioid receptors by extremely low concentrations of opioid-receptor antagonist.[39 , 40]

Cardiovascular
Peripheral vasodilation
Orthostatic hypotension
Bradycardia
Dermatologic
Flushing (histamine)
Pruritus
Endocrinologic
Reduced ADH release
Reduced gonadotrophin release
Gastrointestinal
Reduced motility
Reduced gastric acid secretion
Increased biliary tract pressure
Increased anal sphincter tone
Neurologic
Sedation, coma
Analgesia
Euphoria
Seizures (meperidine, propoxyphene)
Antitussive
Ophthalmic
Miosis

Pulmonary
Respiratory depression
Bronchospasm (histamine)
Acute lung injury

TABLE 38-2. Clinical Effects of Opioids Drugs

Delta and Îº receptors also are responsible for mediation of analgesia, but they exert their analgesic effect predominantly in the spinal cord. Conceptually, these receptors modulate nociceptive impulses in transit to the thalamus via the spinothalamic tract, reducing the brain's perception of the pain. Agents with strong binding affinity for Îº receptors in humans produce significantly more analgesia than morphine administered intrathecally.[171] Indeed, the use of spinal and epidural opioid analgesia is predicated on the direct administration of opioid near the Îº and Î´ receptors in the spinal cord. Agonistâ€“antagonist agents, with agonist affinity for the Îº receptor, and antagonist effects at the Âµ receptor, maintain analgesic efficacy.

Interestingly, communication between the immune system and the peripheral sensory nerves occurs in areas of tissue inflammation. In response to inflammatory mediators (eg, interleukin-1), immune cells locally release opioid peptides, which bind and activate peripheral opioid receptors on sensory nerve terminals.[248] Agonism at these receptors reduces afferent pain neurotransmission and may inhibit the release of other proinflammatory compounds, such as substance P.[232] Of note, intraarticular morphine (1 mg) administered to patients after arthroscopic knee surgery produces significant, long-lasting analgesia that can be prevented with intraarticular naloxone.[231] The clinical analgesic effect of 5 mg of intraarticular morphine is equivalent to 5 mg of morphine given intramuscularly.[32 , 112] Intraarticular analgesia is locally mediated by Âµ receptors.[57]

Despite their well-defined analgesic properties and their recommendation by many clinical practice guidelines, opioids continue

to be underprescribed for patients with acute and chronic pain. Reluctance often stems from the fear that patients may develop addiction or abuse. However, despite extensive investigation, this concern is unfounded.[108 , 130] Furthermore, opioid analgesics often are better tolerated, safer, and less expensive than the alternatives, such as the nonsteroidal antiinflammatory drugs.

Euphoria

The pleasurable effects of many drugs used by humans are mediated by the release of dopamine in the mesolimbic system.[16] This final common pathway is shared by all opioids that activate the Âµâ€“Î´ receptor complex in the ventral tegmental area, which, in turn, indirectly promotes dopamine release in the mesolimbic region. Opioids also may have a direct reinforcing effect on their self-administration through Âµ receptors within the mesolimbic system.[94]

The sense of well-being and euphoria associated with strenuous exercise appears to be mediated by endogenous opioid peptides and Âµ receptors. This so-called â€œrunner's highâ€• is reversible with naloxone.[213] Naloxone may also reverse euphoria or even produce dysphoria in nonexercising, highly trained athletes. Even in normal individuals, high-dose naloxone (up to 4 mg/kg) may produce dysphoria.[34]

Exogenous opioids do not induce uniform psychological effects. Some of the exogenous opioids, particularly the highly lipophilic agents such as heroin, are euphorigenic, whereas morphine is largely devoid of such pleasurable effects.[223] However, morphine administration results in analgesia, anxiolysis, and sedation. Because heroin has little affinity for opioid receptors and must be deacetylated to morphine for effect, these seemingly incompatible properties likely are related to pharmacokinetic differences in bloodâ€“brain barrier penetration.[179] Chronic users note that fentanyl produces effects that are subjectively similar to those of heroin.[135] This effect may explain the higher prevalence of fentanyl, as opposed to other accessible opioids, as an

anesthesiologists who were studied in the 1970s.[251] In distinction, certain opioids (eg, pentazocine) produce dysphoria, an effect that is related to their affinity for Îº or Ïƒ receptors.[187]

Antitussive

Codeine and dextromethorphan are two opioid agents with cough-suppressant activity. Cough suppression likely is not mediated via the Âμ$_1$ opioid receptor because the ability of other opioids to suppress the medullary cough centers is not correlated with their analgesic effect. Various models suggest that cough suppression occurs via agonism of the Âμ$_2$ or Îº opioid receptors, or antagonism of the Î´ opioid receptor,[113] and that the Ïƒ or NMDA receptors also are involved.[114 , 197]

Toxic Effects

When used correctly for medical purposes, opioids are remarkably safe and effective agents.[12 , 142] However, excessive dosing for any reason may result in serious toxicity. Most adverse or toxic effects are predictable, based on â€œopioidâ€• pharmacodynamics (eg, respiratory depression), although several agents produce unexpected â€œnonopioidâ€• or agent-specific responses. Determining that a patient is suffering from opioid toxicity is generally more important than identifying the specific agent involved. Notwithstanding some minor variations, patients poisoned by all available opioids predictably develop a constellation of signs, known as the *opioid syndrome* (Chap. 3). Mental status depression, hypoventilation, miosis, and reduced bowel motility are the classic elements.

Respiratory Depression

Experimental use of various opioid agonists and antagonists

consistently implicates Âμ$_2$ receptors in the respiratory depressant effects of morphine.[144] Through these receptors, opioid agonists reduce ventilation by diminishing the sensitivity of the medullary chemoreceptors to hypercapnea.[254] In addition to loss of hypercarbic stimulation, opioids depress the ventilatory response to hypoxia.[254] The combined loss of hypercarbic and hypoxic drive leaves virtually no stimulus to breathe, and apnea follows. Among the available opioid agonists, equianalgesic doses of all agents produce approximately the same degree of respiratory depression.[54 , 216] This reasoning is supported by experiments in MOR-deficient knockout mice.[202] Patients chronically exposed to opioid agonists, such as those on methadone maintenance, experience chronic hypoventilation, although tolerance to loss of hypercarbic drive may develop over several months.[152] However, such patients never develop complete tolerance to loss of hypoxic stimulation.[205] Although some opioids (notably the agonistâ€“antagonists and partial agonists) demonstrate a ceiling effect on respiratory depression, such sparing generally occurs at the expense of analgesic potency.[67] The different activity profiles likely are a result of differential activities at the opioid-receptor subtypes; that is, agonistâ€“antagonists are predominantly Îº-receptor agonists and either partial agonists or antagonists at Âμ sites.

It is important to recognize that ventilatory depression may be secondary to a reduction in either respiratory rate or tidal volume. Thus, although respiratory rate is more accessible for clinical measurement, it is not an ideal index of ventilatory depression. In fact, morphine-induced respiratory depression in humans initially is related more closely to changes in tidal volume.[216] Large doses of opioids also result in a reduction of respiratory rate.

Acute Lung Injury

Reports linking opioids with the development of acute pulmonary abnormalities became common in the 1960s, although the first report was made by William Osler in 1880.[181] Almost all opioids are

implicated, and opioid-related acute lung injury is reported in diverse clinical situations. Typically, the patient regains normal ventilation following a period of profound respiratory depression, either spontaneously or following the administration of an opioid antagonist, and over the subsequent several minutes to hours develops hypoxemia and pulmonary rales. Occasionally, classic frothy, pink sputum is present in the patient's airway or in the endotracheal tube of an intubated patient. Acute lung injury was described in 71 (48%) of 149 hospitalized heroin overdose patients in New York City.[53] The outcome generally is dependent on comorbid conditions and the delay to adequate care. Acute lung injury may be an isolated finding or may occur in the setting of multisystem organ damage.

No single mechanism can be consistently invoked in the genesis of opioid-associated acute lung injury. Several prominent theories are each well supported by experimental data. Although several authors ascribe acute lung injury to naloxone, the majority of affected patients had already suffered respiratory arrest and had been given naloxone to reestablish spontaneous breathing. In these patients, naloxone likely â€œuncoveredâ€• the clinical findings of acute lung injury that were not evident because an adequate examination could not be performed. Other evidentiary cases involve surgical patients given naloxone postoperatively who subsequently awoke with clinical signs of pulmonary edema. In addition to presumably receiving the naloxone for ventilatory compromise or hypoxia, these patients received multiple intraoperative medications, further obscuring the etiology.[195] Although naloxone ordinarily is safe when administered to nonopioid-tolerant individuals, the production of acute opioid withdrawal may be responsible for â€œnaloxone-inducedâ€• acute lung injury. In this situation, as in patients with â€œneurogenicâ€• pulmonary edema, massive sympathetic discharge from the central nervous system occurs and produces â€œcardiogenicâ€• pulmonary edema from the acute effects of catecholamines on the myocardium. In an interesting series of experiments, precipitated opioid withdrawal in nontolerant dogs was associated with dramatic cardiovascular

changes and abrupt elevation of serum catecholamine concentrations.[167, 168] The effects were more dramatic in dogs with an elevated PCO_2 than in those with a normal or low PCO_2, suggesting the potential benefit of adequately ventilating patients prior to opioid reversal with naloxone. Similar effects occur in humans undergoing ultrarapid opioid detoxification (UROD ; see below).[56]

Even though abrupt precipitation of withdrawal by naloxone may contribute to the development of acute lung injury, it cannot be the sole etiology. Alveolar filling was noted in 50â€“90% of the postmortem examinations performed on heroin overdose patients,[93, 97] many of whom were declared dead before arrival to medical care and thus never received naloxone. In addition, neither naloxone nor any other opioid antagonist was available when Osler and others described their initial cases of pulmonary edema. Alternatively, the negative intrathoracic pressure generated by attempted inspiration against a closed glottis creates a large pressure gradient across the alveolar membrane and draws fluid into the alveolar space.[129] This mechanical effect, also known as the *MÃ¼ller maneuver*, was invoked as the etiology of ventilator-associated acute lung injury prior to the advent of demand ventilators and neuromuscular blockers. In the setting of opioid poisoning, glottic

laxity may prevent adequate air entry during inspiration. This effect may be especially prominent at the time of naloxone administration, in which case breathing may be reinstituted before the return of adequate upper airway function.

Cardiovascular

Arteriolar and venous dilation secondary to opioid use may result in mild reduction in blood pressure.[252] This effect is clinically useful for treatment of acute cardiogenic pulmonary edema. However, although patients typically do not develop significant supine hypotension, orthostatic changes in blood pressure and pulse routinely occur.[272]

Bradycardia is unusual, although a reduction in heart rate is common as a result of the associated reduction in central nervous system stimulation. Opioid-induced hypotension appears to be mediated by histamine release,[58] although induction of histamine release does not appear to occur through interaction with an opioid receptor. It may be related to the nonspecific ability of certain compounds to activate mast cell G proteins,[10] which induce degranulation of histamine-containing vesicles. Many agents share this ability, which seems to be conferred by the presence of a positive charge on a hydrophobic molecule. Accordingly, not all opioids are equivalent in their ability to release histamine.[10] After administration of 1 of 4 different opioids to 60 healthy patients, meperidine produced the most hypotension and elevation of plasma histamine concentrations, whereas fentanyl produced the least.[62] The combination of H_1 and H_2 antagonists is effective in ameliorating the hemodynamic effects of opioids in humans.[188]

Prominent cardiovascular toxicity may occur with use of propoxyphene, which causes wide-complex dysrhythmias and negative contractility through sodium channel antagonism similar to that of type IA antidysrhythmic agents (see Propoxyphene below). Adulterants or coingestants also may produce significant cardiovascular toxicity. For example, quinine-adulterated heroin is associated with dysrhythmias.[149, 203, 215] Cocaine, surreptitiously added to heroin, may cause significant myocardial ischemia or infarction.[99] Similarly, concern that naloxone administration may â€œunmaskâ€• cocaine toxicity in patients simultaneously using cocaine and heroin (â€œspeedballâ€•) probably is warranted but rarely is reliably reported.[165]

Certain opioids at therapeutic concentrations, particularly methadone, can interfere with normal cardiac repolarization and produce QTc interval prolongation, an effect that predisposes to the development of torsade de pointes.[133, 175] Many patients who receive methadone experience minor increases in QTc interval, although a small percentage of patients experience a substantial increase to >500

msec.[151] Methadone and levo-Î±-acetylmethadol (LAAM) both prolong the QTc interval via interactions with cardiac K^+ channels.[116, 119] LAAM was given a black box warning because of its association with torsade de pointes; this action essentially removed LAAM from use in the United States. Additionally, certain opioids, primarily propoxyphene, can alter the function of myocardial Na^+ channels in a manner similar to that of the antidysrhythmics (Chap. 61).

Miosis

The mechanisms by which opioids induce miosis remain controversial. Support for each of several mechanisms can be found in the literature. Stimulation of parasympathetic pupilloconstrictor neurons in the Edinger-Westphal nucleus of the oculomotor nerve by morphine produces miosis. Additionally, morphine increases firing of pupilloconstrictor neurons to light,[138] which increases the sensitivity of the light reflex (central reinforcement of light reflex).[255] Although sectioning of the optic nerve may blunt morphine-induced miosis, the consensual reflex in the denervated eye is enhanced by morphine. Because opioids classically mediate inhibitory neurotransmission, hyperpolarization of sympathetic nerves or of inhibitory neurons to the parasympathetic neurons (removal of inhibition) ultimately may be found to mediate the classic â€œpinpoint pupilâ€• associated with opioid use.

Not all patients using opioids present with miosis. Meperidine has a lesser miotic effect than other conventional opioids, and propoxyphene use does not result in miosis.[75] Use of agents with predominantly Îº-agonist effects, such as pentazocine, may not result in miosis. Mydriasis may occur in severely poisoned patients secondary to hypoxic brain insult. Additionally, concomitant drug use or the presence of adulterants may alter pupillary findings. For example, the combination of heroin and cocaine (â€œspeedballâ€•) may produce virtually any size pupil, depending on the relative contribution by each drug. Similarly, patients ingesting diphenoxylate

and atropine (Lomotil) or those using scopolamine-adulterated heroin[86] routinely develop mydriasis.

Seizures

Seizures are a rare complication of therapeutic use of most opioids. In patients with acute opioid overdose, seizures most likely are caused by hypoxia. However, experimental models demonstrate a proconvulsant effect of morphine[101] in that it potentiates the convulsant effect of other xenobiotics.[263] These effects are variably inhibited by naloxone, suggesting the involvement of a mechanism other than opioid receptor binding. In humans, morphine-induced seizures are reported in neonates and are reversible by naloxone, although opioid withdrawal seizures in neonates are more common.[41]

Seizures should be anticipated in patients with meperidine, propoxyphene, or tramadol toxicity. Naloxone antagonizes the convulsant effects of propoxyphene in mice, although it is only moderately effective in preventing seizures resulting from meperidine or its metabolite normeperidine.[76] Interestingly, naloxone potentiates the anticonvulsant effects of benzodiazepines and barbiturates, although in a single study, it antagonized the effects of phenytoin.[106] The ability of fentanyl and its analogs to induce seizures is controversial. They are used to activate epileptiform activity for localization in patients with temporal lobe epilepsy who are undergoing surgical exploration.[162] Electroencephalograms (EEGs) performed on patients undergoing fentanyl anesthesia did not identify seizure activity even though the clinical assessment suggested that approximately one third had seizures.[225] It appears likely that the rigidity and myoclonus associated with fentanyl are readily misinterpreted as a seizure.

Movement Disorders

Patients may experience acute muscular rigidity with rapid intravenous injection of certain high-potency opioids, especially

fentanyl and its derivatives.[238] This condition is particularly prominent during induction of anesthesia[7] and in neonates.[59] This rigidity primarily involves the trunk and may impair chest wall movement sufficiently to exacerbate hypoventilation. Chest wall rigidity may have contributed to the lethality associated with epidemics of fentanyl-adulterated heroin. Although the mechanism of muscle rigidity is unclear, it may be related to blockade of dopamine receptors in the basal ganglia. Other postulated mechanisms include Î³-aminobutyric acid (GABA) antagonism and NMDA agonism.[64] Opioid antagonists generally are

therapeutic[59 , 174] but may produce adverse hemodynamic effects, withdrawal phenomena, or uncontrollable pain, depending on the situation.

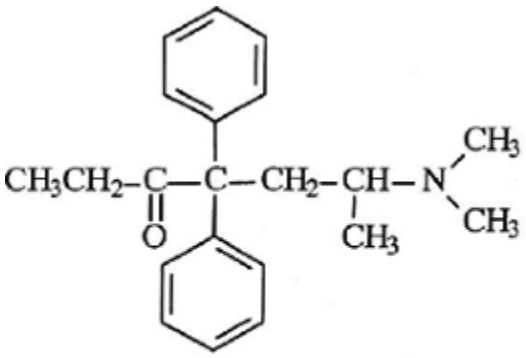
Although not a problem for patients taking stable doses of methadone,[70] rapid escalation of methadone doses may produce choreoathetoid movements.[17] The movement disorder may be related to the opposing effects on GABAergic interneurons produced by Âμ and Îº receptors. Methadone, a Âμ agonist, inhibits the release of GABA, an inhibitory neurotransmitter, within the striatum and mesolimbic system. The ultimate effect is enhancement of striatal dopamine release. This possibility is intriguing, given the developing concept that many forms of addiction result from the final common pathway of enhanced mesolimbic dopamine neurotransmission.

Gastrointestinal Effects

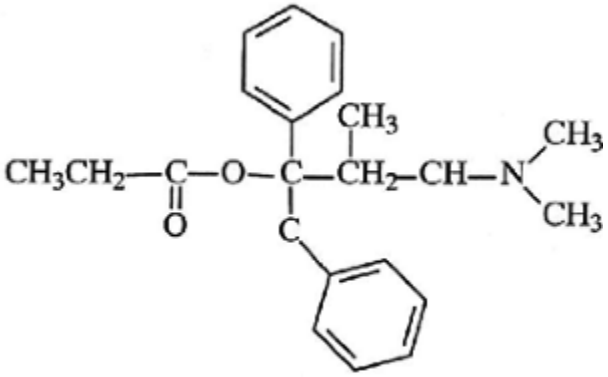
Historically, the morphine analog apomorphine was used as a rapidly acting emetic whose clinical use was limited by its tendency to depress the patient's level of consciousness. Emesis induced by apomorphine is mediated through agonism at D_2 receptor subtypes within the chemoreceptor trigger zone of the medulla. Many opioids, particularly morphine, produce significant nausea and vomiting when used therapeutically.[27] Whether these effects are inhibited by

naloxone is not clearly established, but they likely are not.

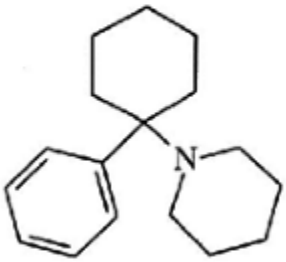
Although diphenoxylate and loperamide are widely used therapeutically to manage diarrhea, opioid-induced constipation is most frequently a bothersome side effect of both medical and nonmedical use of opioids. Constipation, mediated by $\hat{A}\mu_2$ receptors within the smooth muscle of the intestinal wall,[100] is ameliorated by oral naloxone. Provided the hepatic glucuronidative capacity is not exceeded (at doses of approximately 6 mg), enteral naloxone is poorly bioavailable and thus induces few, if any, opioid withdrawal symptoms.[164] Methylnaltrexone and alvimopan are bioavailable, peripherally acting opioids that antagonize the peripheral effects of other opioids on the gastrointestinal tract.[261, 266] Opioid withdrawal does not occur because methylnaltrexone and alvimopan cannot cross the bloodâ€“brain barrier.



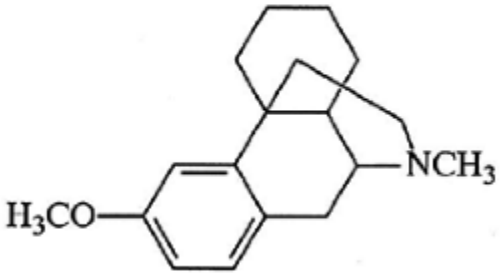
Methadone



Propoxyphene



Phencyclidine



Dextromethorphan

Figure 38-2. Structural similarity between methadone and propoxyphene and between phencyclidine and dextromethorphan.

Diagnostic Testing

Laboratory Considerations

Although it is always tempting to seek laboratory confirmation of an ingested substance in acutely poisoned patients, current laboratory methodology suffers from several important limitations and the potential for many confounding variables. The most apparent impediment to use of laboratory testing in the acute care setting is the lack of timely reporting of results. Patients may suffer grave consequences if therapy is withheld pending test results. Opioid-poisoned patients are particularly amenable to rapid clinical diagnosis because of the uniqueness of the opioid syndrome. Additionally, even in situations where the assay results are available rapidly, the fact that several distinct classes of agents can produce similar opioid effects limits the use of laboratory tests, such as immunoassays, that rely on structural features to identify drugs. Furthermore, because opioids may be chemically detectable long after their clinical effects have dissipated, assay results cannot be considered in isolation but rather viewed in the clinical context. Several well-described problems with laboratory testing of opioids are described below and in Chap. 7 .

Cross-Reactivity

Many opioids share remarkable structural similarities. Interestingly, structurally similar agents, such as methadone and propoxyphene, do not necessarily share the same clinical characteristics (Figure 38-2). Because most clinical assays depend on structural features to identify a drug, structurally similar agents may be detected in lieu of the desired drug. Whether a similar drug is noted by the assay depends on the sensitivity and specificity of the assay used and the serum

concentration of the agent. Some cross-reactivities are predictable, such as that of codeine with morphine, on a variety of screening tests. Other cross-reactivities are less predictable, as with the cross-reaction of dextromethorphan and the phencyclidine (PCP) component of the fluorescence polarization immunoassay (Abbott TDx),[206] a widely used drug-abuse screening test (Chap. 7).

Congeners and Adulterants

Commercial opioid assays, which are specific for morphine, likely will not detect most of the semisynthetic and synthetic opioids. In some cases, epidemic fatalities involving fentanyl derivatives remained unexplained despite obvious opioid toxicity until the ultrapotent fentanyl derivative, Î±-methylfentanyl (although initially misidentified as 3-methylfentanyl), was identified by more sophisticated testing.[132 , 154] Oxycodone, hydrocodone, and other common morphine derivatives have variable detectability by different opioid screens.[224]

Drug Metabolism

A fascinating dilemma may arise in patients who ingest moderate to large amounts of poppy seeds.[124] These seeds, which are widely used for culinary purposes, are derived from poppy plants and contain both morphine and codeine. Following ingestion of a single poppy seed bagel, patients may develop elevated serum morphine and codeine concentrations[170] and test positive for morphine.[201] Because the presence of morphine on a drug-abuse screen may suggest illicit heroin use, the implications are substantial. Federal workplace testing regulations thus require corroboration of a positive morphine assay with assessment of another heroin metabolite, 6-monoacetylmorphine, prior to reporting a positive result.[172 , 246] Humans cannot acetylate morphine and therefore cannot synthesize 6-monoacetylmorphine, but humans can readily deacetylate heroin, which is diacetylmorphine.

A similar problem may occur in patients taking therapeutic doses of codeine. Because codeine is demethylated to morphine by CYP2D6, a morphine screen may be positive as a result of metabolism and not structural cross-reactivity.[69] Thus, determination of the serum codeine or 6-monoacetylmorphine concentration is necessary in these patients. Determination of the serum codeine concentration is not foolproof, however, because codeine is present in the opium preparation used to synthesize heroin.

Forensic Testing

Decision making regarding the cause of death in the presence of systemic opioids often is complex.[42] Variables that often are incompletely defined contribute substantially to the difficulty in attributing or not attributing the cause of death to the opioid. These variables include the specifics regarding the timing of exposure, the preexisting degree of sensitivity and/or tolerance, the role of cointoxicants including parent opioid metabolites, and postmortem redistribution and metabolism.[51, 118] Interesting techniques to help further elucidate the likely cause of death that have been studied include the application of postmortem pharmacogenetic principles[107] and the use of alternative specimens (Chap. 33).

Management

The consequential effects of acute opioid poisoning are central nervous system and respiratory depression. Although early support of ventilation and oxygenation is generally sufficient to prevent death, prolonged use of bag-valve-mask ventilation and endotracheal intubation may be avoided by cautious administration of an opioid antagonist. Opioid antagonists, such as naloxone, competitively inhibit binding of opioid agonists to opioid receptors, allowing the patient to resume spontaneous respiration. Naloxone competes at all receptor subtypes, although not equally, and is effective at reversing almost all adverse effects mediated through opioid receptors.

(Antidotes in Depth: Opioid Antagonists contains a complete discussion of naloxone and other opioid antagonists.)

Because many clinical findings associated with opioid poisoning are nonspecific, the diagnosis requires clinical acumen. Differentiating acute opioid poisoning from other etiologies with similar clinical presentations may be challenging. Patients manifesting opioid toxicity, those found in an appropriate environment, or those with characteristic physical clues such as fresh needle marks require little corroborating evidence. However, subtle presentations of opioid poisoning may be encountered, and other entities superficially resembling opioid poisoning may occur. Hypoglycemia, hypoxia, and hypothermia are common clinical presentations that share features with opioid poisoning and may exist concomitantly. Each can be rapidly diagnosed with routinely available, real-time testing, but the proof of their existence does not exclude opioid toxicity. Other drugs responsible for similar clinical presentations include clonidine, PCP, pheno-thiazines, and sedative-hypnotic agents, primarily benzodiazepines. In such patients, clinical evidence usually is available to assist in diagnosis. For example, nystagmus nearly always is noted in PCP-intoxicated patients, hypotension or electrocardiographic abnormalities in phenothiazine-poisoned patients, and coma with virtually normal vital signs in patients poisoned by benzodiazepines. Most difficult to differentiate on clinical grounds may be toxicity produced by the centrally acting antihypertensive agents such as clonidine (see Clonidine below and Chap. 60). Additionally, a myriad of traumatic, metabolic, and infectious etiologies may occur simultaneously and must always be considered and evaluated appropriately.

Antidote Administration

The goal of naloxone therapy is not necessarily complete arousal; rather, the goal is reinstitution of adequate spontaneous ventilation. Because precipitation of withdrawal is potentially detrimental and

often unpredictable, the lowest practical naloxone dose should be administered initially, with rapid escalation as warranted by the clinical situation. Most patients respond to 0.05 mg of naloxone administered intravenously, although the requirement for ventilatory assistance may be slightly prolonged because the onset may be slower than with larger doses. Administration in this fashion effectively avoids endotracheal intubation and allows timely identification of patients with nonopioid causes of their clinical condition yet diminishes the risk of precipitation of acute opioid withdrawal. Subcutaneous administration may allow for smoother arousal than the high-dose intravenous route[250] but is unpredictable in onset and likely prolonged in offset. Prolonged effectiveness of naloxone by the subcutaneous route can be a considerable disadvantage if the therapeutic goal is exceeded and the withdrawal syndrome develops.

In the absence of a confirmatory history or diagnostic clinical findings, the cautious empiric administration of naloxone may be both diagnostic and therapeutic. Naloxone, even at extremely high doses, has an excellent safety profile in patients with nonopioid-related indications, such as those with spinal cord injury[20] or acute ischemic stroke. Thus, administration in an empiric fashion to most nonopioid-poisoned patients likely will not be harmful. However, administration of naloxone to opioid-dependent patients may result in adverse effects; obviously, precipitation of an acute withdrawal syndrome should be anticipated. The resultant agitation, hypertension, and tachycardia may produce significant distress to both the patient and the clinical staff and occasionally may be life threatening. Additionally, emesis, a common feature

of acute opioid withdrawal, may be particularly hazardous in patients who do not rapidly regain consciousness after naloxone administration. For example, patients with concomitant ethanol or sedative-hypnotic exposure, or those with head trauma, are at substantial risk for pulmonary aspiration of vomitus if their airway is

unprotected.

Identification of patients likely to respond to naloxone conceivably would reduce the unnecessary and potentially dangerous precipitation of withdrawal in opioid-dependent patients. Routine prehospital administration of naloxone to all patients with subjectively assessed altered mental status or respiratory depression was not beneficial in 92% of patients.[264] Alternatively, although not perfectly sensitive, a respiratory rate â‰¤12 breaths/min in an unconscious patient presenting via EMS best predicted a response to naloxone.[98] Interestingly, neither respiratory rate <8/min nor coma was able to predict a response to naloxone in hospitalized patients.[257] Whether the discrepancy between the latter two studies is a result of the demographics of the patient groups, or whether patients with prehospital opioid overdose present differently than patients with iatrogenic poisoning, is unclear. Regardless, relying on the respiratory rate to assess the need for ventilatory support or naloxone administration is not ideal because hypoventilation secondary to hypopnea may precede that caused by bradypnea.[199 , 220] The decision to discharge a patient who awakens appropriately following naloxone administration is based on practical considerations. Patients presenting with profound hypoventilation or hypoxia are at risk for development of acute lung injury or posthypoxic encephalopathy. Thus, it seems prudent to observe these patients for at least 24 hours in a medical setting. Patients manifesting only moderate signs of poisoning, who remain normal for at least several hours following parenteral naloxone, likely are safe to discharge. However, the need for psychosocial intervention in patients with uncontrolled drug use, or following a suicide attempt, may prevent discharge from an ED.

Patients with recurrent or profound poisoning by long-acting opioids, such as methadone, or patients with large gastrointestinal burdens (eg, â€œbody packersâ€• or those taking sustained-release preparations), may require continuous infusion of naloxone to ensure continued adequate ventilation (Table 38-3). An hourly infusion rate of two thirds of the initial reversal dose of naloxone is sufficient to

prevent recurrence.[79] Titration of the dose may be necessary as indicated by the clinical situation. Although repetitive bolus dosing of naloxone may be effective, it is labor intensive and subject to error.

Despite the availability of long-acting opioid antagonists (eg, naltrexone and nalmefene[117]) that theoretically permit single-dose reversal of methadone poisoning, the attendant risk of precipitating an unrelenting withdrawal syndrome hinders their use as agents for initial opioid reversal. However, these agents may have a clinical role in the maintenance of consciousness and ventilation in opioid-poisoned patients already awakened by naloxone. Prolonged observation and perhaps antidote readministration may be required in order to match the pharmacokinetic parameters of the two agents. Otherwise well children who ingest short-acting opioids may be given a long-acting opioid antagonist initially because they are not expected to develop a prolonged, potentially hazardous withdrawal. However, the same caveats remain regarding the need for extended hospital observation periods if ingestion of methadone or other long-acting opioids is suspected.

1. If a naloxone bolus (start with 0.05 mg IV and titrate) is successful, administer two thirds of the effective bolus dose per hour by IV infusion; frequently reassess the patient's respiratory status.
2. If respiratory depression is not reversed following the bolus dose:
   Intubate the patient, as clinically indicated.
   Administer up to 10 mg of naloxone as an intravenous bolus. If the patient does not respond, do not initiate an infusion.
3. If the patient develops withdrawal following the bolus dose:
   Allow the effects of the bolus to abate.
   If respiratory depression recurs, administer half of the initial bolus dose and begin an intravenous infusion at two thirds of the initial bolus dose per hour. Frequently reassess the patient's respiratory status.
4. If the patient develops withdrawal signs or symptoms during the

infusion:

Stop the infusion until the withdrawal symptoms abate.

Restart the infusion at half the initial rate; frequently reassess the patient's respiratory status.

Exclude withdrawal from other xenobiotics.

5. If the patient develops respiratory depression during the infusion:

Readminister half of the initial bolus and repeat until reversal occurs.

Increase the infusion by half of the initial rate; frequently reassess the patient's respiratory status.

Exclude continued absorption, readministration of opioid, and other etiologies as the cause of the respiratory depression.

TABLE 38-3. How to Use a Naloxone Infusion

Rapid and Ultrarapid Opioid Detoxification

The concept of antagonist-precipitated opioid withdrawal is promoted extensively as a â€œcureâ€• for opioid (particularly heroin and oxycodone) dependency. Rather than slow, deliberate withdrawal, or detoxification, from opioids over several weeks, antagonist-precipitated withdrawal occurs over several hours or days.[218] The purported advantage of this technique is a reduced risk of relapse to opioid use because the duration of discomfort is reduced and a more rapid transition to naltrexone maintenance can be achieved. Although most studies find excellent short-term results, relapse to drug use is very common.[161] This finding may suggest a need for improved aftercare or may reflect a fundamental flaw in the mechanistic rationalization of the therapy. In addition, selection bias; the lack of randomization, control groups, or blinding; and variations in treatment protocols and end points hinder the external applicability of

much of the available research on antagonist-precipitated opioid withdrawal.[178]

Rapid opioid detoxification techniques are usually offered by outpatient clinics and typically consist of naloxone- or naltrexone-precipitated opioid withdrawal, tempered with varying amounts of clonidine, benzodiazepines, antiemetics, or other drugs. UROD uses a similar concept but involves the use of deep sedation or general anesthesia for greater patient control and comfort. Unique to this setting, and perhaps to unintentional precipitated opioid withdrawal following therapeutic naloxone, is the development of delirium, a clinical effect that is absent when opioid withdrawal develops more slowly.[78] Mechanistic explanations for the rapid detoxification strategies include withdrawal-induced catecholamine depletion, rapid normalization of receptor regulation, and enhanced endogenous opioid release,[237] but each is based largely on unsubstantiated evidence. Both techniques are costly; UROD under anesthesia commonly costs thousands of dollars.

The risks of these techniques are not fully defined but are of substantial concern. Massive catecholamine release, acute lung injury, renal insufficiency, and thyroid hormone suppression are

reported following UROD, and many patients still manifest opioid withdrawal 48 hours after the procedure.[56, 85, 160, 186] As with other forms of opioid detoxification, the loss of tolerance following successful completion of the program paradoxically increases the likelihood of death from heroin overdose of these individuals compared to those who do not complete a detoxification program.[236]

The Opioids

The vast majority of opioid-poisoned patients follow predictable clinical courses that can be anticipated based on our understanding of opioid receptor pharmacology. However, certain opioids taken in overdose may produce atypical manifestations. Therefore, careful

clinical assessment and institution of empiric therapy usually are necessary to ensure proper management (Table 38-4).

Buprenorphine (Buprenex)
P/AA
Semisynthetic
0.4 IM
Opioid substitution therapy requires 6â€“16 mg/d
Butorphanol (Stadol)
AA
Semisynthetic
2 IM

Codeine
Ag
Natural
120 PO
Often combined with acetaminophen; requires demethylation to morphine by CYP2D6
Dextromethorphan (Robitussin DM)
NEC
Semisynthetic
Nonanalgesic (10â€“30 PO)
Antitussive; psychotomimetic via Ïƒ or NMDA receptor
Diphenoxylate (Lomotil)
Ag
Synthetic
Nonanalgesic (2.5 PO)
Antidiarrheal agent, combined with atropine; difenoxin is potent metabolite
Fentanyl (Sublimaze)
Ag
Synthetic
0.125 IM
Very short-acting (<1 h)

Heroin (Diamorph)
Ag
Semisynthetic
5 SC
Diacetylmorphine, used therapeutically in some countries, schedule I in the United States
Hydrocodone (Vicodin, Hycodan)
Ag
Semisynthetic
10 PO

Hydromorphone (Dilaudid)
Ag
Semisynthetic
1.3 SC

LAAM (Orlaam)
Ag
Synthetic
(Flexible oral dosing[d])
L-Î±-Acetylmethadol or levomethadyl acetate; 3 times per week dosing for substitution therapy; long acting, potent metabolites; no longer distributed in US because of QTc interval prolongation
Levorphanol (Levodromoran)
Ag
Semisynthetic
2 SC/IM

Loperamide (Imodium)
Ag
Synthetic
Nonanalgesic (2 PO)
Antidiarrheal agent
Meperidine, pethidine (Demerol)

Ag
Synthetic
75 SC/IM
Seizures due to metabolite accumulation
Methadone (Dolophine)
Ag
Synthetic
10 IM
Very long-acting (24 h)
Morphine
Ag
Natural
10 SC/IM

Nalbuphine (Nubain)
AA
Semisynthetic
10 IM

Nalmefene (Revex)
Ant
Semisynthetic
Nonanalgesic (0.1 IM)
Long-acting antagonist (4â€“6 h)
Nalorphine
AA
Semisynthetic
15 IM
Historically used as an opioid antagonist[a]
Naloxone (Narcan)
Ant
Semisynthetic
Nonanalgesic (0.1â€“0.4 IV/IM)
Short-acting antagonist (0.5 h)

Naltrexone (Trexan)
Ant
Semisynthetic
Nonanalgesic (50 PO)
Very long-acting antagonist (24 h)
Oxycodone (Percocet, OxyContin)
Ag
Semisynthetic
10 PO
Often combined with acetaminophen; OxyContin is sustained release
Oxymorphone (Numorphan)
Ag
Semisynthetic
1 SC

Paregoric (Parapectolin)
Ag
Natural
25 mL PO
Tincture of opium (0.4 mg/mL)
Pentazocine (Talwin)
AA
Semisynthetic
50 SC
Psychotomimetic via Ïƒ receptor
Propoxyphene (Darvon)
Ag
Synthetic
65 PO
Seizures, dysrhythmias; combined with acetaminophen
Tramadol (Ultram)
Ag
Synthetic
50â€“100 PO

Seizures possible with therapeutic dosing

[a] Agonistâ€“antagonists, partial agonists, and antagonists may cause withdrawal in tolerant individuals.

[b] Typical dose (mg) for agents without analgesic effects is given in parentheses.

[c] Duration of therapeutic clinical effect 3â€“6 hours unless noted; likely to be exaggerated in overdose.

[d] Although approximately equipotent with methadone, LAAM is not used as an analgesic.

Ag=full agonist (Âμ$_1$, Âμ$_2$, Îº); AA=agonist antagonist (Îº agonist, Âμ antagonist); Ant=full antagonist (Âμ$_1$, Âμ$_2$, Îº antagonist); P=partial agonist (Âμ$_1$, Âμ$_2$ agonist, Îº antagonist); NEC=not easily classified.

Opioid (Representative Trade Name)	Type[a]	Derivation	Analgesic Dose (mg) (via route, equivalent to 10 mg morphine SC[b])	Comments[a],[c]

TABLE 38-4. Classification, Potency, and Characteristics of Opioids

Morphine/Codeine

Morphine is poorly bioavailable by the oral route because of extensive first-pass elimination. Morphine is hepatically metabolized primarily to morphine-3-glucuronide (M3G) and, to a lesser extent, to morphine-6-glucuronide (M6G), both of which are cleared renally. Unlike M3G, which is essentially devoid of activity, M6G has Âμ-agonist effects in the central nervous system.[3] However, M6G administered peripherally

is significantly less potent as an analgesic than is morphine.[219] The polar glucuronide has a limited ability to cross the bloodâ€“brain barrier and P-glycoprotein is capable of expelling M6G from the cerebrospinal fluid. The relative potency of morphine and M6G in the brain is incompletely defined, but the metabolite is generally considered to be several-fold more potent.[3] Interestingly, glucuronidation occurring in the brain

may account in part for the increased clinical effect of heroin over morphine.[204]

Codeine itself is an inactive opioid agonist, and it requires metabolic activation by *O* -demethylation to morphine by CYP2D6 (Figure 38-3). This typically represents a minor metabolic pathway for codeine metabolism. *N* -demethylation into norcodeine by CYP3A4 and glucuronidation are more prevalent but produce inactive metabolites. The need for conversion to morphine explains why approximately 5â€“7% of white patients, who are devoid of CYP2D6 function,[105] cannot derive an analgesic response from codeine.[147] Rarely, ultrarapid CYP2D6 metabolizers produce unexpectedly large amounts of morphine, with resulting life-threatening opioid toxicity.[69]

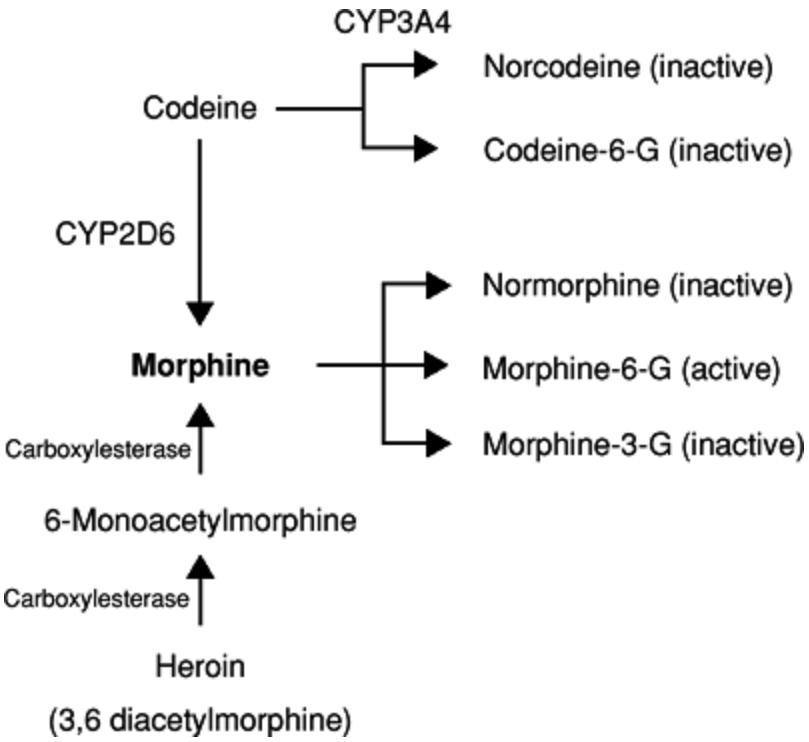


Figure 38-3. Opiate/opioid metabolism. Codeine can be *O* -methylated to morphine, *N* -demethylated to norcodeine, or glucuronidated to codeine-6-glucuronide. Morphine can be *N* -demethylated to normorphine or glucuronidated to either morphine-3-glucuronide or morphine-6-glucuronide. Heroin is converted to morphine by a two-step process involving pseudocholinesterase and two human liver carboxylesterases known as human carboxylesterase-1 and human carboxylesterase-2.

Heroin

Heroin is 3,6-diacetylmorphine, and its exogenous synthesis is performed relatively easily from morphine and acetic anhydride. Heroin has a lower affinity for the Âμ receptor than does morphine, but it is rapidly metabolized by pseudocholinesterase and liver human carboxylesterase (hCE)-2 to 6-monoacetylmorphine, a more potent Âμ agonist than morphine[212] (Figure 38-3). Users claim that heroin has an enhanced euphorigenic effect, often described as a â€œrush.â€•

This effect likely is related to the enhanced bloodâ€“brain barrier penetration occasioned by the additional organic functional groups of heroin[179] and its subsequent metabolic activation within the central nervous system. Interestingly, cocaine and heroin compete for metabolism by pseudocholinesterase and the two human liver carboxylesterases hCE-1 and hCE-2. This interaction may have pharmacokinetic and clinical consequences in patients who â€œspeedball.â€•[14,115]

Heroin can be obtained in two distinct chemical forms: base or salt. The hydrochloride salt form typically is a white or beige powder and was the common form of heroin available prior to the 1980s.[109] Its high water solubility allows simple intravenous administration. Heroin base, on the other hand, now is the more prevalent form of heroin in most regions of the world. It often is brown or black. â€œBlack tar heroinâ€• is one appellation referring to an impure South American import available in the United States. Because heroin base is virtually insoluble in water, intravenous administration requires either heating the heroin until it liquefies or mixing it with acid. Alternatively, because the alkaloidal form is heat stable, smoking or â€œchasing the dragonâ€• is gaining popularity as an alternative route. Street-level heroin base frequently contains caffeine or barbiturates,[109] which improves the sublimation of heroin and enhances the yield.[103]

Widespread intravenous use has led to many significant direct and indirect medical complications, particularly endocarditis and AIDS, in addition to fatal and nonfatal overdose. Nearly two thirds of all long-term (>10 years) heroin users in Australia had self-overdosed on heroin,[44] whereas among recent-onset heroin users, 23% had overdosed on heroin and 48% had been present when someone else overdosed.[82] Risk factors for fatality following heroin use include the concomitant use of other drugs, particularly ethanol,[140] recent abstinence, as occurs during incarceration,[210] and perhaps unanticipated fluctuations in the purity of available heroin.[43,200] Because most overdoses occur in seasoned heroin users, and as many as 85% occur in the company of other users,[44] a trial distribution of

naloxone to heroin users was initiated. Although earlier administration of antidote could be beneficial, certain issues make this approach controversial. For example, despite the acknowledged injection skills of the other users in the â€œshooting gallery,â€• their judgment likely is impaired. In one survey, summoning an ambulance was the initial response to overdose of a companion in only 14% of cases.[45] A survey of heroin users suggested they lacked an understanding of the pharmacology of naloxone, which might lead to inappropriate behaviors regarding both heroin and naloxone administration.[209]

Recognition of the efficacy of intranasal administration, or snorting, has fostered a resurgence of heroin use, particularly in suburban communities.[65 , 230] The reasons for this trend are unclear, although it is widely suggested that the rising purity of the available heroin has rendered it more suitable for intranasal use.[50] However, because intranasal administration of a mixture of 3% heroin in lactose produces clinical and pharmacokinetic effects similar to an equivalent dose administered intramuscularly,[36] the relationship between heroin purity and price and intranasal use is uncertain.[200] Needle avoidance certainly is important, reducing the risk of transmission of various infectious diseases, including HIV.[120] Heroin smoking also has increased in popularity in the United States, albeit not to the extent in other countries (see â€œChasing the Dragon â€• below).

Celebrities and musicians have popularized intranasal heroin use as a â€œsafeâ€• alternative to intravenous use. This usage is occurring despite a concomitantly reported rise in heroin deaths in regions of the country where its use is prevalent. Although intranasal use may be less dangerous than intravenous use from an infectious disease perspective, it is clear that both fatal overdose and drug dependency remain common.[241]

Adulterants, Contaminants, and â€œHeroinâ€• Substitutes

The history of heroin adulteration and contamination has been

extensively described. Street-level heroin almost always contains

adulterants or contaminants. What differentiates the two is the intent of their admixture. Adulterants typically are benign because inflicting harm on the consumer with their addition would be economically and socially unwise, although adulterants occasionally are responsible for epidemic death. Interestingly, most heroin overdose fatalities do not have serum morphine concentrations that substantially different from those of living users, raising the possibility that the individual death is related to an adulterant or contaminant.[46]

Historically, alkaloids, such as quinine and strychnine, were used to adulterate heroin in order to mimic the bitter taste of heroin and to mislead clients. Quinine may have first been added in a poorly reasoned attempt to quell an epidemic of malaria among intravenous heroin users in New York City in the 1930s.[93] That quinine adulteration was common is demonstrated by the common practice of urine screening for quinine as a surrogate marker for heroin use.[260] However, quinine was implicated as a causative factor in an epidemic of heroin-related deaths in the District of Columbia between 1979 and 1982.[203] Toxicity attributed to quinine in heroin users includes cardiac dysrhythmias (Chap. 23), amblyopia, and thrombocytopenia. Quinine adulteration currently is much less important than it was in the past. Trend analysis of illicit wholesale and retail (street-level) heroin adulteration over a 12-year period in Denmark revealed that although caffeine, acet-aminophen, methaqualone, and phenobarbital all were prevalent adulterants, quinine was not found.[109] Recent data on adulteration in the United States are unavailable. Many other adulterants or contaminants, including thallium,[196] lead,[182] cocaine,[99] and amphetamines,[31] have been reported.

Poisoning by scopolamine-tainted heroin reached epidemic levels in the northeastern United States in 1995.[86] Exposed patients presented with acute psychosis and unmistakable anticholinergic signs. Several patients were treated with physostigmine, with excellent therapeutic results.

â€œChasing the Dragon.â€•

Intravenous injection and insufflation are the preferred means of heroin self-administration in the United States. In other countries, including the Netherlands, the United Kingdom, and Spain, the prevalent method is â€œchasing the dragon.â€• When chasing the dragon, users inhale a thick, white pyrolysate that is generated by heating heroin base on aluminum foil using a hand-held flame. Although some of the heroin effluvium is dissipated into the surroundings, this means of administration produces heroin pharmacokinetics similar to those observed following intravenous administration.[95] Chasing the dragon is not a new phenomenon, but it has gained acceptance recently among both intravenous heroin users and drug-naive individuals.[235] The reasons for this shift are diverse but probably are related to the avoidance of injection drug use with its concomitant infectious risks. The increasing availability of the smokable base form of heroin is clearly associated, but whether it is a cause or an effect of this trend is unknown.

In the early 1980s, an unexplainable cluster of spongiform leukoencephalopathy occurring solely in individuals who smoked heroin was identified in the Netherlands.[262] Other causes of this unique clinicopathologic entity include various viral infections (eg, bovine spongiform leukoencephalopathy), hexachlorophene, pentachlorophenol, and metal poisoning, although none appeared responsible for this phenomenon. Since the initial report, similar cases have been reported in other parts of Europe and in the United States.[134 , 146] Initial findings may occur after as few as 2 weeks of use and include bradykinesia, ataxia, abulia, and speech abnormalities. Of those whose symptoms do not progress, half may recover. However, in others progression to spastic paraparesis, pseudobulbar palsy, or hypotonia may occur over several weeks. Approximately half of individuals in this group do not develop further deficits or improve, whereas death occurs in approximately 25% of

reported cases. The prominent symmetric cerebellar and cerebral white matter destruction noted on brain imaging with CT and MRI[121] corresponds to that noted at necropsy. The syndrome has the characteristics of a point-source toxic exposure, but no culpable contaminants have been identified.[22] Although initially postulated to be related to excessive exposure to aluminum fumes, neither the dose inhaled nor the serum concentrations support this hypothesis. Furthermore, the widespread administration of heroin by this route without notable adverse effect and the clustering of cases argue against the involvement of aluminum. A component or pyrolysis product unique to certain batches of â€œheroinâ€• is likely.[22] Treatment is largely supportive. Based on the finding of regional mitochondrial dysfunction on functional brain imaging and an elevated brain lactate concentration, supplementation with coenzyme Q 300 mg qid has purported benefit[134] but has not undergone controlled study.

Other Opioids

Fentanyl and Its Analogs

Fentanyl is a short-acting, highly potent opioid agonist that is widely used in clinical medicine. Fentanyl has approximately 50â€“100 times the potency of morphine. It is well absorbed by the transmucosal route, accounting for its use in the form of a â€œlollipop.â€• Fentanyl is widely abused as a heroin substitute and is the controlled substance most often abused by anesthesiologists.[18]

Transdermal fentanyl in the form of a patch (Duragesic) was approved in 1991. It is widely used by patients with chronic pain syndromes, including those with cancer-related pain. It has adequate solubility in both lipid and water for transdermal delivery. The transdermal pharmacokinetics differ markedly from those of the more conventional routes.[131] A single patch contains an amount of drug to provide a transdermal gradient sufficient to maintain a steady-state plasma

concentration for approximately 3 days (eg, a 50 Âµg/h patch contains 5 mg). However, even after the patch is considered exhausted, approximately 50% of the total initial fentanyl dose remains.[153] Interindividual variation in dermal drug penetration[137] and errors in proper use (excessive patches, warming of the skin[63]) may lead to iatrogenic fentanyl overdose. Not unexpectedly, fentanyl patch abuse occurs either by direct application of one or more patches to the skin or indirectly by withdrawal or extraction of the fentanyl from the patch for subsequent administration.[11 , 240]

Sufentanil and alfentanil are anesthetic opioids with increased potency compared to fentanyl. In some regions of the country, fentanyl and both licit and illicit fentanyl analogs (eg, 3-methylfentanyl and para-fluorofentanyl) are common drugs of abuse. Experienced heroin users could not easily differentiate fentanyl from heroin, although in one study, the heroin was noted to provide a more intense â€œrush.â€• [135] Although unconfirmed, the agent used by Russian authorities to overcome terrorists and subdue a hostage situation in Moscow in October 2002 may have been carfentanil, a potent Âµ-receptor agonist that is commonly used as a positron emission tomography (PET) scan radioligand.[253]

Regional epidemics of heroin substitutes with â€œsuperpotentâ€• activity occasionally produce a dramatic rise in â€œheroin-relatedâ€•

fatalities. Epidemic deaths among heroin users first appeared in Orange County, California, in 1979 and were traced to Î±-methylfentanyl sold under the brand name China White.[132] Similar epidemics of China White poisoning occurred in Pittsburgh in 1988 and in Philadelphia in 1992, although the adulterant in these cases was 3-methylfentanyl, another potent analog. A later epidemic in New York City marked the reappearance of 3-methylfentanyl under the brand name Tango and Cash. Typically, patients present comatose and apneic, with no opioids detected on routine blood and urine analysis. In such cases, unsuspecting users had administered their usual â€œdose of heroin,â€• measured in 25-mg â€œbagsâ€• that

contained variable amounts of the fentanyl analog. Because of the exceptional potency of this fentanyl analog (as much as 6000 times greater than that of morphine), higher than usual doses of naloxone may be needed to successfully compete for the opioid receptor.

Oxycodone and Hydrocodone

Although media reports highlight the abuse of these and other prescription pharmaceutical opioids by sports figures and other personalities, this trend has reached epidemic levels in regions of the country where heroin is difficult to obtain (thus the term â€œHillbilly heroinâ€•).[92] Although many users initially receive oxycodone or hydrocodone for legitimate pain management, the majority obtain the drugs illicitly.[21 , 192] Regulatory agencies, law enforcement, and the drug manufacturer have made tremendous efforts to control drug diversion to illicit use.[73] Physicians have been charged criminally with complicity for inappropriately writing prescriptions for patients with the intent to sell or abuse these drugs.[73] Many of these agents are sold in fixed combination with acetaminophen (eg, Percocet [oxycodone 5 mg], Vicodin [hydrocodone]), raising concerns about the complications of acetaminophen hepatotoxicity. Unlike most immediate-release prescription opioids, oxycodone can be obtained in a controlled-release form (OxyContin) that contains as much as 80 mg (a 160-mg tablet was removed from the market). Abusers typically crush the tablet, which destroys the sustained-release matrix and liberates large amounts of insufflatable or injectable oxycodone. The psychoactive effects of these agents are similar to other Âμ-receptor agonists[267] and often are used as a substitute for heroin.[21] Opioid dependence, overdose, and death are common sequelae of oxycodone abuse.[35 , 228]

Clostridial Infections

Heroin-related clostridial infections, although uncommon, present in a manner similar to those of conventional botulism or tetanus but may

be atypical (Chap. 46). Interestingly, during the 1950s and early 1960s, users of quinine-adulterated heroin in New York City[30] and Chicago[141] were substantially more likely to develop tetanus than were users of nonquinine-adulterated heroin. This likely is a result of the extensive tissue destruction caused by subcutaneous quinine administration, which also occurs in patients receiving therapeutic intramuscular quinine.[265] â€œBlack tar heroin,â€• an impure form of heroin, is implicated in multiple epidemics of wound botulism.[26] Whether the minimally processed heroin was contaminated with *Clostridium botulinum* or whether it led to improved anaerobic growing conditions for the spores is not known. Early antitoxin therapy is associated with improved outcome.[29] Other *Clostridia* (eg, *C. novyi* and *C. sordellii*) are responsible for epidemics of necrotizing fasciitis that are common among users of black tar heroin. Nearly half of the victims of necrotizing fasciitis die of the disease.[123]

Body Packers

In an attempt to transport illicit drugs from one country to another, â€œmules,â€• or body packers, ingest large numbers of multiple-wrapped packages of concentrated cocaine or heroin. After they arrive at their destination, they administer cathartics so that the packets can be passed and delivered. When the authorities discover such individuals or when individuals in custody become ill, they may be brought to a nearby hospital for evaluation and management. Although these patients generally are asymptomatic on arrival, they are at risk for delayed, prolonged, or lethal poisoning as a consequence of packet rupture.[243] An abdominal radiograph usually is sufficient to confirm gastrointestinal smuggling,[96] but occasional false-negative radiographic results occur, even in patients with enormous packet counts.[159] Patients who are suspected body packers should be observed, even in the absence of packets on plain abdominal radiograph. Computed tomography can identify packets but should be considered only in suspicious cases with negative radiographs or potentially to document packet clearance from the

gastrointestinal tract. Computed tomography may provide information about the contents of the packets. However, although heroin, cocaine, and hashish can be differentiated by their Hounsfield unit values in vitro, there is no evidence that such measurements are accurate in the clinical setting. Magnetic resonance imaging also can identify packets but cannot differentiate their contents. Ultrasonography does not offer any advantage over radiography and is both user dependent and more difficult to perform.[96] Rapid urine testing for drugs of abuse may assist in determining the packet content,[74] but the same information usually is obtained more rapidly by simply asking the patient or by identifying clinical syndromes (almost invariably opioid vs sympa-thomimetic). In the past, determining the country of origin of the current journey was nearly diagnostic of packet content. However, because most of the heroin imported into the United States now originates from South America, which is also the major source of imported cocaine, the discernment from cocaine on this basis is impossible. Given the current greater revenue potential of heroin, the vast majority of body packers carry heroin.[77] Still, given the common source of the two drugs, body packers may be â€œdouble breasting,â€• that is, carrying both heroin and cocaine packets simultaneously.

Regardless of the content, appropriate treatment for asymp-tomatic patients should include whole-bowel irrigation with polyethylene glycol solution (Chap. 4).[60] Subsequent management differs based on the presumed packet content. Patients body-packing cocaine who develop symptoms require immediate surgical packet removal (Chap. 74), whereas those with heroin packets often can be managed nonoperatively with continuous infusion of naloxone, oral activated charcoal, and whole-bowel irrigation.[243] Intestinal perforation or obstruction by the packets requires surgical intervention. Packets that do not progress beyond the stomach probably should be removed surgically, although endoscopic removal of a single or small number of packets may be carefully performed. The need to remove multiple packets requires repeated insertions of the endoscope, possibly

increasing the likelihood of packet rupture by the endoscope. However, most modern packets are constructed solidly and unlikely to tear or rupture.

Agonistâ€“Antagonists

The opioid agonists in common clinical use tend to have specific binding affinity toward the Âµ-opioidâ€“receptor subtype. The

agonistâ€“antagonist agents differ in that they interact with multiple receptor types and may have different effects at each receptor. Thus, although most opioids typically produce either agonist or antagonist effects, the agonistâ€“antagonists generally have agonist effects at the Îº-receptor subtype and antagonistic effects at the Âµ-receptor subtype. Therefore, agents such as pentazocine (Talwin) may elicit a withdrawal syndrome in a Âµ-opioidâ€“tolerant individual because of antagonist effects at the Âµ receptor. This effect forms the basis of the claim offered by many methadone-dependent patients that they are â€œallergic to Talwin.â€• However, this same drug can act as an analgesic in nonopioid-using patients through its agonist effects at the $Îº_1$ -receptor subtype. Although the clinical effects following overdose resemble those of the other opioid agents, the agonistâ€“antagonists are significantly less likely than the full agonists to produce severe morbidity or mortality because of their ceiling effect on respiratory depression (see Respiratory Depression above).

Pentazocine

Historically, patients abusing pentazocine (Talwin) administered it with tripelennamine, a blue capsule, accounting for the appellation â€œT's and Blues.â€• Although this mixture has largely fallen out of favor, pentazocine abuse occurs occasionally, and newer combinations, such as pentazocine with methylphenidate, are reported.[25, 28] The psychotomimetic effects noted with high doses of pentazocine likely are mediated by $Îº_2$ or perhaps Ï*f* receptors.

Because pentazocine can be readily dissolved, intravenous injection was a preferred route for its abuse until the commercial formulation was altered to include 0.5 mg naloxone (Talwin NX).[191] When ingested, the naloxone is eliminated by first-pass hepatic metabolism; if injected, naloxone prevents the euphoria sought by users.

Agents Used in Opioid Substitution Therapy: Methadone, LAAM, Buprenorphine

Two contrasting approaches to the management of patients with chronic opioid use exist: detoxification and maintenance therapy. Detoxification probably is most appropriate for patients motivated or compelled to discontinue opioid use. It can be performed either by tapered withdrawal of an opioid agonist or with the assistance of opioid antagonists. Maintenance therapy may include use of a long-acting opioid antagonist, such as naltrexone, to pharmacologically proscribe opioid use. Alternatively, and more commonly, maintenance therapy involves opioid substitution therapy.

Methadone is a synthetic Âµ-opioidâ€“receptor agonist used both for treatment of chronic pain and as a maintenance substitute for opioid dependence. Methadone has been available for the latter use for more than 40 years through methadone maintenance treatment programs (MMTPs).[49] In MMTPs, methadone replaces the opioid with a legal, oral, and long-acting agent. This agent allows patients to abstain from activities associated with procurement and administration of the abused opioid and eliminates much of the morbidity and mortality associated with illicit drug use. Although often successful, some methadone users continue to use heroin or other illicit substances.[2, 118]

Although therapeutic methadone is generally safe, rapid dose escalation during induction in the treatment program may unintentionally produce toxicity and, rarely, fatal respiratory

depression. This adverse effect is generally the result of the long duration of effect of methadone and the time lag for development of tolerance.[52] Similarly, acute overdose results in clinical findings typical of opioid poisoning of a duration substantially longer than expected following overdose of prototypical therapeutic opioids. Following an appropriate response to the administration of naloxone, recurrence should be expected because naloxone's duration of effect is only approximately 1 hour. In many cases, continuous infusion of naloxone or possibly administration of a long-acting opioid antagonist is indicated to maintain adequate ventilation.

Intentional, nonsuicidal methadone overdosage ironically may be related to the manner in which MMTPs dispense the drug. Most patients attending MMTPs are given supratherapeutic doses to prevent surreptitious heroin or other opioid use.[5 , 234] Additionally, many MMTPs supply their established patients with sufficient methadone to last through a weekend or holiday without the need to revisit the program. Taken together, such dosing regimens may allow diversion of portions of the dose without the attendant risk of opioid withdrawal because the entire daily dose of methadone is not needed to suppress opioid withdrawal. Furthermore, home storage of this surplus drug in inappropriate containers, such as juice containers or baby bottles,[88] is a cause of unintentional methadone ingestion by children. Such events can be anticipated because methadone is frequently formulated as a palatable liquid and may not be distributed in child-resistant containers. The primary reason for distribution as a liquid, as opposed to the pill form given to patients with chronic pain syndromes, is to ensure dosing compliance at the MMTP. Unfortunately, death is frequent in children who overdose.[143]

LAAM (Orlaam), also known as levomethadyl acetate, is used in heroin substitution programs in a manner analogous to methadone.[55] LAAM is a long-acting synthetic opioid agonist, an effect partly attributable to its metabolism to two separate active metabolites, nor-LAAM and dinor-LAAM. LAAM rapidly produces characteristic opioid effects that are due to the parent compound. The peak effect, due to the

metabolites, is achieved in several hours.[249] The opioid effects of LAAM may be more resis-tant to reversal by naloxone than are those caused by methadone,[249] but they probably will respond to escalating antagonist dosing. Its duration of effect approaches 4 days, allowing thrice weekly dosing. Predictably, reemergence of opioid intoxication following naloxone therapy is common. Although LAAM still is available in certain countries, it was removed from the US market by its distributor, Roxane Laboratories, because of the drug's consequential effect of QTc interval prolongation. This effect occurs even with therapeutic LAAM use and is associated with ventricular dysrhythmias, particularly torsades de pointes.

Because prescription of methadone is in great part restricted to certain federally licensed programs, it is inaccessible and inconvenient for many patients. Buprenorphine was approved in 2000 as a schedule III agent for office-based prescription, providing an attractive alternative for patients with substantially broader potential for obtaining outpatient therapy. However, because of the novelty of the delivery (private office and not clinic based), limitations on patient volume, requirement for physician certification, and possibly the hesitation on the part of community physicians to welcome patients with substance use problems into their practices, many of the purported benefits of buprenorphine therapy over methadone have not been realized.[61]

Buprenorphine (Subutex), a partial Âμ-opioid agonist, in doses of 8â€“16 mg is effective at suppressing both opioid withdrawal symptoms and the covert use of illicit drugs.[83 , 110] Because buprenorphine competes with the extant opioid for the Âμ receptor

and may produce acute opioid withdrawal, the initial dose typically is administered in the presence of a physician. Following the initial doses of buprenorphine, tablets containing both buprenorphine and naloxone (Suboxone) are prescribed to prevent their intravenous use. The withdrawal syndrome from buprenorphine itself may be milder than that occurring following naloxone. Buprenorphine has been

suggested as a gentler agent for use in rapid opioid detoxification.[4]

Buprenorphine at therapeutic doses produces nearly complete occupancy of the Âμ opioid receptors, where it prevents other opioids from binding.[84] Interestingly, naloxone may prevent the clinical effects of buprenorphine but is relatively ineffective at reversing the effects once they are manifest.[66] This finding likely is related to the very slow dissociation of buprenorphine from the Âμ receptor. Furthermore, it is consistent with buprenorphine's long duration of clinical effect (allowing thrice-weekly dosing) despite its elimination half-life of 3 hours and mild withdrawal syndrome. Buprenorphine is administered by the sublingual route because of its poor oral bioavailability.

As a partial agonist, buprenorphine has a ceiling effect on respiratory depression, particularly at lower doses, although respiratory depression may occur at higher doses.[242 , 245] Although most fatal poisonings with buprenorphine are linked to polysubstance use,[190] some cases of isolated buprenorphine overdose are reported.[125 , 242] Death appears to be more common after intravenous injection of crushed pills than after oral overdose.[125]

Clonidine, a presynaptic $Î±_2$ -adrenergic agonist of the imidazoline class, is widely used by both clinicians and patients to reduce the disturbing autonomic effects of opioid withdrawal. Although clonidine is not structurally related to any opioid, in overdose clonidine produces a clinical syndrome identical to that produced by the Âμ-active opioids.[127 , 259] Mechanistically, there is functional overlap between $Î±_2$ and Âμ receptors within the brain (Figure 38-1). For these reasons, clonidine is commonly used to ameliorate the autonomic effects of opioid withdrawal. However, although the autonomic abnormalities can be normalized with this approach, the psychological aspects of withdrawal, including drug craving and poor judgment, may not be alleviated.

Specific or Unique Agents

Meperidine

Meperidine, also called pethidine outside of the United States, is widely used for treatment of chronic and acute pain syndromes. Meperidine produces clinical manifestations typical of the other opioids and may lead to greater euphoria.[268] Pupillary constriction is less pronounced and, if it occurs, is less persistent than that associated with morphine.[75] However, normeperidine, a toxic, renally eliminated hepatic metabolite, accumulates in patients receiving chronic high-dose meperidine therapy, such as those with sickle cell disease or cancer. A similar accumulation occurs in patients with renal insufficiency, in whom the elimination half-life increases from a normal of 14â€“21 hours to 35 hours.[239] Normeperidine causes excitatory neurotoxicity, which manifests as delirium, tremor, myoclonus, or seizures. Based on animal studies, the seizures should not be expected to respond to naloxone.[76] In fact, experimental evidence suggests that naloxone may potentiate normeperidine-induced seizures, presumably by inhibiting an anticonvulsant effect of meperidine.[38] Hemodialysis using a high-efficiency membrane may be of limited clinical benefit but rarely, if ever, is indicated because the toxicity generally is self-limited.[89]

Although primarily an opioid, meperidine is capable of exerting effects at other types of receptors. The most consequential nonopioid-receptor effects occur through the serotonin receptor. Blockade of the presynaptic reuptake of released serotonin may produce the serotonin syndrome, characterized by muscle rigidity, hyperthermia, and altered mental status, particularly in patients using monoamine oxidase inhibitors (MAOIs) (Chap. 69). However, dextromethorphan (see Dextromethorphan below) also may produce this syndrome. Conversely, the simultaneous use of MAOIs and morphine, fentanyl, or methadone is not expected to produce the serotonin syndrome based on the currently appreciated pharmacology of these drugs. Despite its purported (and likely overstated) beneficial effects on biliary tract physiology, meperidine offers little to support its clinical

use and has significant disadvantages. Meperidine use has been dramatically reduced or is closely monitored in many institutions[217] and has been eliminated in other centers because of its pharmacologic and toxicologic disadvantages. Paradoxically, and with significant liability, it has been used in some institutions for patient-controlled analgesia.[211]

MPTP

In 1982, several cases of acute, severe parkinsonian symptoms were identified in intravenous drug users.[136] The patients were labeled â€œfrozen addictsâ€• because of the severe bradykinesia, and extensive investigations into the etiology of the problem ensued. This ultimately led to the discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), an inadvertent product of presumed errors in the attempted synthesis of the illicit meperidine analog MPPP (1-methyl-4-phenyl-4-propionoxy-piperidine). MPTP is metabolized to the ultimate toxicant MPP^+ by monoamine oxidase-B in glial cells. Toxicity is inhibited by pretreatment with deprenyl, a monoamine oxidase-B inhibitor. MPP^+ is a paraquatlike agent capable of selectively destroying the dopamine-containing cells of the substantia nigra by inhibiting mitochondrial oxidative phosphorylation.[207] The index cases initially responded to standard antiparkinsonian therapy, but none improved substantially and the effects of the medications waned.[9] Although calamitous for exposed patients, MPTP has proved to be invaluable in the development of experimental models for the study of Parkinson disease.[258] Several of the original â€œfrozenâ€• patients subsequently underwent stereotactic implantation of fetal adrenal tissue grafts into their basal ganglia, with significant clinical improvement.

Dextromethorphan

Dextromethorphan is devoid of analgesic properties altogether, even though it is the optical isomer of levorphanol, a potent opioid

analgesic. Based on this structural relationship, dextromethorphan is commonly considered an opioid, although its receptor pharmacology actually is extremely complex. At high doses, dextromethorphan does bind to opioid receptors to produce miosis, respiratory depression, and central nervous system depression. Reversal of these opioid effects by naloxone is reported. Binding to the PCP site on the NMDA receptor, and subsequent inhibition of calcium influx through this receptor-linked ion channel, causes sedation. This same activity may account for its antiepileptic properties and for its neuroprotectant effects in ischemic brain injury. Because NMDA receptor blockade also enhances the analgesic effects of Âμ-opioid agonists, combination therapy with morphine and dextromethorphan (MorphiDex) has been introduced.

Blockade of presynaptic serotonin reuptake by dextromethorphan may elicit the serotonin syndrome in patients receiving

MAOIs.[227] Movement disorders, described as choreoathetoid or dystonialike, occasionally occur and presumably result from alteration of dopaminergic neurotransmission. Dextrorphan, the active *O* -demethylation metabolite of dextromethorphan, is produced by CYP2D6, an enzyme with a well-described genetic polymorphism.[6] Patients with the extensive metabolizer polymorphism appear to experience more drug-related psychoactive effects, whereas poor metabolizers suffer more adverse effects related to the parent compound.[271]

Dextromethorphan is available without prescription in cold preparations, primarily because of its presumed lack of significant addictive potential. However, abuse of dextromethorphan is increasing, particularly among high school students.[8] This increase in use likely is related to the drug's easy availability and its limited toxicity. Abundant promotional information is available on the Internet. Pure, powdered dextromethorphan is available without substantial regulatory oversight. Common street names include â€œDXM,â€• â€œdex,â€• and â€œroboshots.â€• Users often have

expectations of euphoria and hallucinations, not the PCP-like dysphoria that commonly occurs.[177] Reports of substantial cold medicine consumption raise several considerations, including acetaminophen poisoning,[126] opioid dependency, and bromide toxicity.[104] This last concern relates to the common formulation of dextromethorphan as the hydrobromide salt and is most easily recognized as a dramatically elevated serum chloride concentration when measured on certain autoanalyzers[176] (Chap. 7).

Tramadol

Tramadol (Ultram) is a novel synthetic analgesic agent with both opioid and nonopioid mechanisms responsible for its clinical effects. Although it binds only weakly to Âμ opioid receptors, tramadol exhibits cross-tolerance with morphine in rats, suggesting an opioid-mediated mechanism of analgesia.[128] The demethylated tramadol metabolite M1 exhibits higher-affinity binding to Âμ receptors in vitro and may be important in patients chronically using the drug. However, the role of M1 as an acute analgesic is not well defined. Naloxone only partially reverses tramadol-induced analgesia in mice and in humans, suggesting that an independent, nonopioid mechanism is also involved in mediating the clinical effects of tramadol.[180] This effect appears to be inhibition of reuptake of biogenic amines, specifically serotonin and norepinephrine. This mechanism is supported by the nearly complete reversal of analgesic efficacy by yohimbine, an Î±$_2$ -adrenergic antagonist that inhibits release of these neurotransmitters.[47] Patients using MAOIs may be at risk for development of the serotonin syndrome.

A large number of spontaneous reports to the FDA suggest that therapeutic use of tramadol may cause seizures, particularly on the first day after initiating therapy. However, epidemiologic studies have not confirmed this association.[71] Tramadol-related seizures are not responsive to naloxone but are suppressed with benzodiazepines. In fact, the package insert cautions against using naloxone in tramadol

overdose because, in animals treated with naloxone, the risk of seizure is increased. Correspondingly, one patient in the prospective series had a seizure that was temporally related to naloxone administration.[229] Acute overdose of tramadol is generally considered nonâ€“life threatening, and most fatalities were associated with polysubstance overdose.[33]

Tramadol abuse is reported but its extent is undefined.[23 , 221] In a review of physician drug abuse in several states, tramadol was the second most frequent opioid reported.[221] Opioid users recognized tramadol as an opioid only when given in an amount that was 6 times the therapeutic dose, but at this dose the users did not develop opioidlike clinical effects such as miosis.[193] Patients may develop typical opioid manifestations after a large overdose. Significant respiratory depression is uncommon and should respond to naloxone.[229] Urinary drug screening generally is negative for opioids in tramadol-exposed patients.

Propoxyphene

Like its structural analog methadone, propoxyphene binds Âμ-opioid receptors and produces the expected opioid clinical findings. However, unanticipated properties of propoxyphene manifest after overdose. Propoxyphene and its hepatic metabolite, norpropoxyphene, produce myocardial sodium channel blockade identical to the type IA antidysrhythmic agents.[148] This process results in QRS complex widening and negative inotropy. QRS prolongation was identified in 42 (19%) of 222 propoxyphene-overdosed patients.[222] These symptoms can be corrected with parenteral administration of hypertonic sodium bicarbonate[233] or with lidocaine. As in patients with tricyclic antidepressant overdose, the sodium ion component of the sodium bicarbonate enhances sodium influx through a partially occluded sodium channel by augmenting the extracellular to intracellular sodium concentration gradient. The paradoxical effect of lidocaine, another sodium channel blocker, can be explained by the very

different dissociation constants of these two agents with the sodium channel. Lidocaine, a class IB agent, may competitively displace propoxyphene and norpropoxyphene, both more highly toxic sodium channel blockers (Chap. 61). Naloxone has never been shown to be effective therapy for the cardiotoxic effects of propoxyphene, although hemodynamic improvement in one reported case probably was related to naloxone-induced propoxyphene withdrawal.[87]

Propoxyphene overdose may produce acute central nervous system toxicity that usually manifests as seizures. In one study of propoxyphene-overdosed patients, 10% of the subjects developed seizures.[222] Although the exact mechanism is unclear, experimental models demonstrate that only propoxyphene, and not norpropoxyphene, is capable of inducing seizures.[148] Therapy for seizures should follow standard management strategies, including benzodiazepines or barbiturates. High-dose naloxone (60 mg/kg intraperitoneally) prevents experimental propoxyphene-induced seizures,[76] but its role in seizure termination is undefined.

Propoxyphene use and overdose in the United States is relatively uncommon compared with the other opioids. However, in the United Kingdom, propoxyphene overdose may account for up to 5% of all suicides.[90] Propoxyphene often is formulated with acetaminophen (Darvocet-N, Coproxamol) or salicylates (Darvon compound) to enhance the analgesic effects. Patients who overdose on the combinations may suffer toxicity from either of these two nonopioid analgesics. Because patients consequently may be acetaminophen poisoned, yet be asymptomatic or manifest only opioid toxicity, empiric quantitative serum analysis for acetaminophen is indicated. Delayed peak serum acetaminophen concentrations after ingestion of combination opioid products may occur. The precise clinical implication of this delay is unclear (Chap. 34). Furthermore, propoxyphene's respiratory depressant effects may hinder the ability to detect salicylate poisoning by clinical examination, suggesting a situation where empiric laboratory testing for salicylates may be indicated.

Diphenoxylate and Loperamide

Although diphenoxylate is structurally similar to meperidine, its extreme insolubility limits

absorption from the gastrointestinal tract. This factor may enhance its use as an antidiarrheal agent, which presumably occurs via a local opioid effect at the gastrointestinal Âμ receptor. However, the standard adult formulation may result in significant systemic absorption and toxicity in children, and all such ingestions should be deemed consequential. Diphenoxylate is formulated with a small dose (0.025 mg) of atropine (as Lomotil), both to enhance its antidiarrheal effect and to discourage illicit use.

Because both components of Lomotil may be absorbed and because their pharmacokinetic profiles differ somewhat, a biphasic clinical syndrome is occasionally noted.[158] Patients may manifest atropine poisoning (anticholinergic syndrome), either independently or concomitantly with the opioid effects of diphenoxylate. Delayed, prolonged, or recurrent toxicity is common and is classically related to the delayed gastric emptying effects inherent to both opioids and anticholinergic agents. However, these effects are more likely explained by the accumulation of the hepatic metabolite difenoxin, which is a significantly more potent opioid than diphenoxylate and possesses a longer serum half-life. Still, the relevance of gastroparesis is highlighted by the retrieval of Lomotil pills by gastric lavage as late as 27 hours postingestion.

A review of 36 pediatric reports of Lomotil overdoses found that although naloxone was effective in reversing the opioid toxicity, recurrence of central nervous system and respiratory depression was common.[158] This series included a patient with an asymptomatic presentation 8 hours postingestion who was observed for several hours and then discharged. This patient returned to the ED 18 hours postingestion with marked signs of atropinism. In this same series,

children with delayed onset of respiratory depression and other opioid effects were reported, and others describe cardiopulmonary arrest 12 hours postingestion. Naloxone infusion may be appropriate for patients with recurrent signs of opioid toxicity. Because of the delayed and possibly severe consequences, all children, and adult patients with potentially significant ingestions, should be admitted for monitored observation in the hospital.

Loperamide (Imodium) is another insoluble meperidine analog that is used to treat diarrhea. This agent is available without a prescription, and the paucity of adverse patient outcomes reported in the medical literature suggests the safety profile of this agent is extremely high.[145]

Summary

Opioid use is widespread. Overdose and toxicity, both intentional and unintentional, remain major causes of drug-related morbidity and mortality. Lethality related to opioids is primarily caused by respiratory depression. Thus mechanical ventilation, or administration of a short-acting opioid antagonist such as naloxone, should be adequate initial therapy. An appreciation of the pharmacologic differences between the various opioids allows for the identification and appropriate management of patients poisoned or otherwise adversely affected by these agents.

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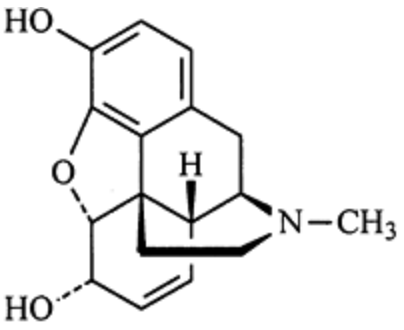
Antidotes in Depth

Opioid Antagonists

Mary Ann Howland



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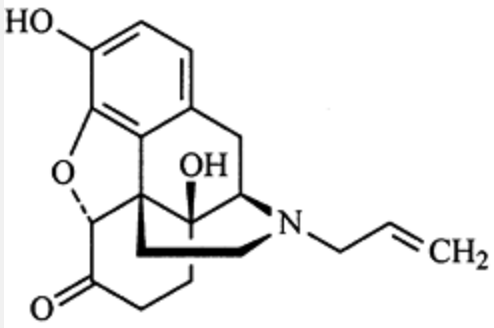
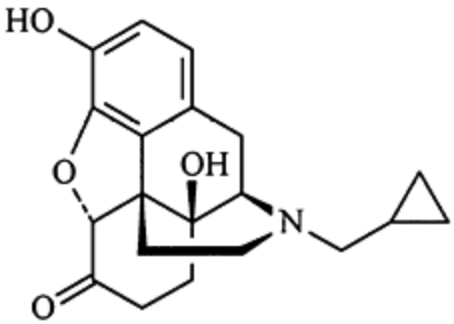
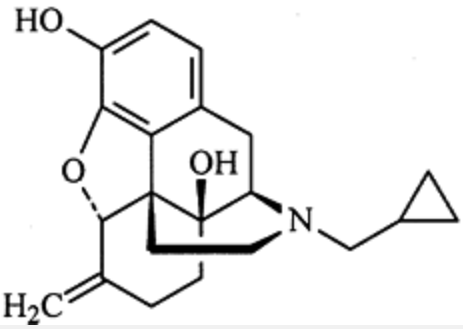


Naloxone



Naltrexone



Nalmefene

Figure. No Caption Available.

Naloxone, nalmefene, and naltrexone are pure competitive opioid antagonists at the mu (Âμ), kappa (Îº), and delta (Î´) receptors. Naloxone is used to reverse respiratory depression in patients manifesting opioid toxicity. The parenteral dose should be titrated to maintain adequate airway reflexes and ventilation.[22] Dose titration, beginning with 0.05 mg and increasing as indicated to 0.4 mg, 2 mg, and finally 10 mg, prevents abrupt opioid withdrawal. This method of administration limits withdrawal-induced adverse effects, such as vomiting and the potential for aspiration pneumonia, and a surge in catecholamines with the potential for cardiac dysrhythmias and acute lung injury. Naltrexone is used orally for patients following opioid detoxification to maintain opioid abstinence and as an adjunct to achieve ethanol abstinence. Nalmefene is a parenteral agent whose duration of action falls between that of naloxone and naltrexone.

History

The effects of opium were recognized as early as the 3rd century B.C.[39] By the 19th century, morphine (named for Morpheus, the god of dreams) was isolated from opium. In the 20th century, the presence of endogenous opioid peptides and families of opioid receptors, including Âμ, Î´, and Îº, were elucidated. The 20th century also witnessed an ever-evolving series of complications of opioid addiction and abuse. Awareness of these social problems resulting from opioid abuse and the ability to understand structureâ€“activity relationships led to the synthesis of many new drugs in the hope of producing potent opioid agonists free of abuse potential. Although this goal has not been achieved, opioid antagonists and partial agonists were developed. *N*-Allylnorcodeine

was the first opioid antagonist synthesized by J. Pohl in 1915. The pharmacology of *N*-allylnormorphine (nalorphine) was characterized in the 1940s.[43,86] Nalorphine was recognized as having both agonist and antagonist effects in 1954.[39] This recognition eventually led to the development of levallorphan, naloxone, naltrexone, and nalmefene. Naloxone was synthesized in 1960, and naltrexone was synthesized in 1963.[8]

Chemistry

Minor alterations can convert an agonist into an antagonist.[42] The substitution of the *N*-methyl group on morphine by a larger group led to nalorphine and converted the agonist levorphanol to the antagonist levallorphan.[39] Naloxone, naltrexone, and nalmefene are derivatives of oxymorphone.

Pharmacology

Naloxone, naltrexone, and nalmefene are pure competitive opioid antagonists at the Âμ receptors, which are responsible for analgesia,

sedation, miosis, feeding, euphoria, respiratory depression, and decreased GI motility. Îº Receptors are responsible for weaker analgesia, sedation, miosis, feeding, decreased GI motility, dysphoria, anxiety, nightmares, and hallucinations. Î´ Receptors are responsible for analgesia and hunger.[39] These antagonists are most potent at the Âμ receptor, often necessitating higher doses for effects at the Îº and Î´ receptors. They all bind to the opioid receptor in a competitive fashion, preventing the binding of agonists, partial agonists, or mixed agonistâ€“antagonists without producing any independent action. Naloxone, naltrexone, and nalmefene are similar in their antagonistic ability but differ primarily in their pharmacokinetics. Both nalmefene and naltrexone have longer durations of action than naloxone.

Naltrexone can be administered orally. Selective antagonists for Âµ, Îº, and Î´ are available experimentally and are undergoing investigation.[49,71]

Both nalorphine and levallorphan are weak competitive antagonists at the Âµ receptor and are agonists at the Îº receptor. Nalorphine and levallorphan are no longer marketed because of undesirable Îº agonist properties.

In the proper doses, pure opioid antagonists reverse all of the effects of endogenous and exogenous opioid agonists at the Âµ, Îº, and Î´ receptors, except for those of buprenorphine, which has a very high affinity for, and slow rate of dissociation from, the Âµ receptor.[26,39,70,71] Effects on other receptors and receptor subtypes are under investigation.[49] Actions of opioid agonists that are not mediated by interaction with opioid receptors, such as direct mast-cell liberation of histamine or the sodium channel-blocking effects of propoxyphene, are not reversed.[4] Opioid-induced seizures in animals tend to be antagonized by opioid antagonists, with the exception of seizures caused by meperidine and tramadol.[9,33,39,85] A report of two newborns who developed seizures associated with fentanyl and morphine infusion demonstrated abrupt resolution following administration of naloxone.[16] Both patients underwent electroencephalographic monitoring during the seizures, and the documented burst-suppression pattern apparently was terminated after naloxone administration.

Opioids operate bimodally on opioid receptors.[14] At low concentrations, stimulation is excitatory and actually antianalgesic. This antianalgesic effect is modulated through a G_s protein and usually is less important clinically than the well-known inhibitory actions that result from coupling to a G_o protein at usual analgesic doses. Extremely low doses of opioid antagonists (ie, 0.25 Âµg/kg/h of naloxone) enhance the analgesic potency of the opioid and attenuate or prevent the development of tolerance and

dependence.[14,32] Coadministration of these very low doses of antagonists or derivatives (ie, methylnaltrexone) with the opioid also limit opioid-induced adverse effects such as nausea, vomiting, constipation, and pruritus.[14,28,32,97] These beneficial effects are hypothesized to result from modulation of the opposing excitatory effects of opioids.

Research investigating the ability of Î´ and Îº opioid agonists to produce cardioprotective effects through their action at the sarcolemmal and mitochondrial K^+(ATP) channels is ongoing.[72,75,77] Nonselective opioid antagonists may negate these protective effects.

Pharmacokinetics and Pharmacodynamics

Oral naloxone is poorly bioavailable because of extensive first-pass effect.[23] The bioavailability of sublingual naloxone is 10%.[41] Naloxone is well absorbed by all other parenteral routes of administration, including intramuscular, subcutaneous, endotracheal, intranasal, intralingual, and nebulized. The onset of action after IV administration is extremely fast and occurs within 1â€“2 minutes. The distribution half-life of approximately 5 minutes is rapid because of its high lipid solubility, and the volume of distribution is 0.8â€“2.64 L/kg.[34,36,67] The elimination half-life is 60â€“90 minutes in adults and approximately 2â€“3 times longer in neonates.[13,66] A dose of 13 Âµg/kg in an adult occupied approximately 50% of the available opioid receptors, as demonstrated by positron detection system.[57] Naloxone is metabolized by the liver to several compounds, including a glucuronide.[13] The duration of action of naloxone is approximately 20â€“90 minutes[7,24] and depends on the dose of the agonist, the dose and route of administration of the naloxone, and the rates of elimination of the agonist and naloxone. The onset of action with the various routes of administration are subcutaneous,

approximately 5.5 minutes; intralingual, 30 seconds; intranasal, 3.4 minutes; nebulization, 5 minutes (when 2 mg is mixed with 3 mL of 0.9% sodium chloride solution); endotracheal, 60 seconds; and intramuscular, no precise data available.[54,64,82,94]

Naltrexone is rapidly absorbed, with peak plasma concentrations occurring at 1 hour and oral bioavailability of 5â€“60%.[37,59,91,93] Distribution is rapid, with a volume of distribution of approximately 15 L/kg and low plasma-protein binding.[48,52] Naltrexone is metabolized in the liver to Î²-naltrexol (with 2â€“8% activity) and 2-hydroxy,3-methoxy-Î²-naltrexol.[90] Naltrexone has an enterohepatic cycle.[31,93] The plasma elimination half-life is 10 hours for naltrexone and 13 hours for Î²-naltrexol.[59,91,93] The terminal phase of elimination is 96 hours for naltrexone and 18 hours for Î²-naltrexol.[2]

Nalmefene is a derivative of naltrexone, with an oral bioavailability of 40%. After oral administration, peak plasma concentrations usually are reached within 1â€“2 hours.[18] Protein binding is approximately 45%.[18] Following oral administration, the half-life is 8â€“9 hours and demonstrates first-order kinetics up to 300-mg doses.[18] Although one study showed the half-life was 108Â±38 minutes after IV dosing, the study design may have been inadequate to determine the half-life.[34] Another study demonstrated a terminal half-life of 10.8 Â± 5 hours after a 1-mg IV dose.[65] The apparent volume of distribution (Vd) is 3.9 L/kg for the central compartment and 8.6 L/kg at steady state. Nalmefene is metabolized in the liver to an inactive glucuronide conjugate that probably undergoes enterohepatic recycling, accounting for approximately 17% of the amount of drug in the feces. Less than 5% is excreted unchanged in the urine.

Adverse Drug Effects

Opioid antagonists prevent the actions of opioid agonists if administered as pretreatment, reverse the effects of endogenous

and exogenous opioids, and cause the manifestations of opioid withdrawal in opioid-dependent patients. Pure opioid antagonists produce no clinical effects in the nonopioid-dependent, nonstressed patient, even when administered in high doses.[18,19,55,90] Antagonists stimulate the release of hormones from the pituitary, resulting in increased levels of leuteinizing hormone, follicle-stimulating hormone, and adrenocorticotropic hormone and stimulate the release of prolactin in women.[39] Adverse effects, excluding withdrawal and resedation, are rare. Patients tolerant of opioid agonists, such as morphine, exhibit opioid withdrawal reactions (yawning, lacrimation, diaphoresis, rhinorrhea, piloerection, mydriasis, vomiting,

diarrhea, myalgias, mild elevations in heart rate and blood pressure, insomnia) when exposed to opioid antagonists or agonistâ€“antagonists such as pentazocine. An â€œovershootâ€• phenomenon is described in which reversal leads to a transient increase in catecholamines, resulting in hyperventilation, tachycardia, and hypertension to higher levels than prior to baseline, with the potential for myocardial ischemia.[39] Ultrarapid heroin detoxification is associated with fatalities occurring in the postoperative period. This rapid form of enforced detoxification discussed in Chap. 38 differs significantly from the usual transient opioid withdrawal associated with volitional personal opioid abstinence.

If vomiting occurs because of withdrawal while the patient's airway is unprotected, aspiration pneumonia may complicate the patient's recovery. Resedation is a function of the relative duration of action of the opioid antagonist and the opioid agonist. Most opioid agonists have a duration of action longer than that of naloxone and shorter than that of naltrexone, whereas the relationship is variable with nalmefene. A long duration of action is advantageous when the antagonist is used to promote abstinence (naltrexone) but is unwanted when an inappropriately large dose is

administered to an opioid-dependent patient (nalmefene).

Rare case reports describe acute lung injury (previously termed *noncardiogenic pulmonary edema*), hypertension, and cardiac dysrhythmias in association with naloxone administration.[3,15,29,59,60,73,76,81] Acute lung injury occurs following heroin overdose in the absence of naloxone and can be exacerbated by naloxone in certain patients. The exact contribution of naloxone to the problem is unclear because naloxone may be unmasking the acute lung injury previously induced by the opioid but which was unrecognized because of the patient's respiratory depression.[21]

Hypertension and cardiac dysrhythmias are most frequently reported following anesthesia and opioid reversal in patients with underlying cardiac or pulmonary disorders. The clinical complexities of the setting and case reports make it difficult to analyze and attribute these adverse effects solely to naloxone.[13] Unmasking an underlying clinical condition may reveal a logical cause of cardiac dysrhythmias developing after naloxone-induced heroin reversal in a patient simultaneously abusing cocaine.[58]

Delirium, although rarely reported, may occur when naloxone is used to reverse effects in patients tolerant of high doses of opioids or during rapid opioid detoxification.[11,35]

Considering the large number of naloxone doses administered, naloxone has a remarkably safe profile, especially when used in low doses and titrated to effect.[12]

Use for Opioid and Ethanol Abstinence

Opioid dependence is managed by detoxification and prolonged opioid abstinence or by substitution with either methadone or naltrexone.[56] Any pure opioid antagonist could be substituted, but naltrexone is chosen because of its oral absorption and long duration of action compared to that of naloxone or

nalmefene.[47,55,74] Naloxone 1 mg administered intravenously blocks 25 mg of IV heroin for 1 hour, whereas 50 mg of oral naltrexone blocks this dose of heroin for 24 hours; 100 mg has a blocking effect for 48 hours, and 150 mg is effective for 72 hours. Nalmefene blocks the actions of 2 Âµg/kg of IV fentanyl with a duration of action that is also dose dependent: 0.5 mg IV, 2 mg IV, and 50 mg orally last 4, 8, and 50 hours, respectively.[30,31] Before naltrexone can be administered, the patient must be detoxified from the opioid dependence. Then naloxone usually is administered intravenously to confirm that the patient is no longer physically dependent. Opioid withdrawal, if it occurs, will be short lived following naloxone, whereas it will be prolonged following naltrexone or nalmefene. Naltrexone does not produce tolerance, although prolonged treatment with naltrexone produces upregulation of opioid receptors.[96]

Naltrexone is used as adjunctive therapy in ethanol dependence, based on the theory that the endogenous opioid system modulates ethanol intake.[52,69] Naltrexone reduces ethanol craving, the number of drinking days, and relapse rates.[62,92] Naltrexone induces moderate to severe nausea in 15% of these patients, possibly as a result of alterations in endogenous opioid tone induced by prolonged ethanol ingestion.[69]

Miscellaneous Uses

Endogenous opioids, including endorphins, dynorphins, and enkephalins, are involved in the regulation of many bodily functions.[87] Opioid receptors are found not only in the central nervous system but also throughout the body. Often these receptors and endogenous opioids work in concert with other neurotransmitter systems to modulate many effects.[23,25,88,90] For instance, during shock, the release of circulating endorphins produces an inhibition of central sympathetic tone by stimulating Îº receptors within the locus caeruleus, resulting in vasodilation.

Also, by stimulating the nucleus ambiguus, vagal tone is enhanced. However, the benefits of naloxone treatment in patients with septic shock are variable; treatment may result in adverse effects, especially in patients who are opioid tolerant.[17,66,84] Naloxone may have a temporizing effect via elevation of mean arterial pressure.[40]

Although promising in animal models of spinal cord injury, an investigation of naloxone at doses approximately 100 times that used in the management of overdoses failed to demonstrate improvement in neurologic recovery in humans.[10]

Opioid antagonists are used infrequently in the management of overdoses with nonopioids such as ethanol,[5,20,63,79] clonidine,[78,95] captopril,[89] and valproic acid.[1,61] In none of these instances was improvement as dramatic or consistent as in the reversal of the toxic effects of an opioid.

Opioid antagonists are used infrequently for treatment of morphine-induced pruritus resulting from systemic or epidural opioids and for treatment of the pruritus associated with cholestasis.[45,46,53]

Low doses of oral naloxone and peripherally acting opioid antagonists such as methylnaltrexone are used to prevent or treat the constipation that occurs as a side effect of opioid pain management.[38,97]

Dosing

The initial dose of antagonist is dependent on the dose of agonist and the relative binding affinity of the agonist and antagonist at the opioid receptors. The presently available antagonists have a greater affinity for the Âμ receptor than for the Îº or Î´ receptors. Therefore, the presence of an opioid with a greater affinity for the Îº or Î´ receptor, such as pentazocine or butorphanol, requires a larger than ordinary dose of antagonist to cause reversal.[62] The

dose of antagonist necessary for a child may equal the dose for an adult because antagonists are competitive and dependent on the size of the ingested dose of agonist. The duration of action of the antagonist

depends on many drug and patient variables, such as the dose and clearance of both antagonist and agonist.

A dose of naloxone 0.4 mg IV will reverse the respiratory depressant effects of most opioids and is an appropriate starting dose in the nonopioid-dependent patient. Naloxone can also be administered intranasally.[6] However, this dose in an opioid-tolerant patient usually produces withdrawal. The goal is to reverse respiratory depression without inducing withdrawal. Therefore, 0.05 mg is a practical starting dose in most patients, increasing to 0.4 mg, 2 mg, and finally 10 mg. If the patient has no response to 10 mg, then an opioid likely is not responsible for the respiratory depression. A practical way to administer 0.05 mg if using 0.4 mg/mL naloxone is to draw up 3 mL of 0.9% sodium chloride solution in a 5-mL syringe and then draw up 1 mL of the 0.4 mg/ mL naloxone, creating 0.4 mg naloxone in 4 mL, which is equivalent to 0.05 mg in 0.5 mL. If using the 1 mg/ mL concentration, first draw up 4.5 mL of 0.9% sodium chloride solution in a 5-mL syringe, then draw up 0.5 mL (0.5 mg) of naloxone, creating 0.5 mg in 5 mL, which is equivalent to 0.05 mg in 0.5 mL.

Evaluation of the return of respiratory depression should be monitored continuously. Resedation should be treated with either repeated doses of the antagonist or, if necessary, with another bolus followed by a continuous infusion. What constitutes an observation period depends on many factors. Following IV naloxone, observation for 2 hours should be adequate to determine whether sedation and respiratory depression will return. Following an oral opioid overdose, return of sedation and respiratory depression may be less predictable and the observation

period should therefore be extended.

Return of respiratory depression requires repeated bolus doses or a continuous infusion.[50] Two thirds of the bolus dose of naloxone that resulted in reversal, when given hourly, usually maintains the desired effect.[79] Naloxone is stable in 0.9% sodium chloride solution at a variety of concentrations for up to 24 hours.[27,80]

This dose can be prepared for an adult by multiplying the effective bolus dose by 6.6, adding that quantity to 1000 mL, and administering the solution intravenously at an infusion rate of 100 mL/h. Titration upward or downward is easily accomplished as necessary to maintain adequate ventilation and avoid withdrawal. A continuous infusion of naloxone is not a substitute for continued vigilance. An arbitrary period of 12â€“24 hours often is chosen for observation based on the presumed opioid, the route of administration, and the dosage form. The patient must be observed for 2 hours after naloxone is discontinued to ensure that respiratory depression does not recur. Body packers are a unique subset of patients who must have special individualized management strategies (Chap. 38).

Naloxone is a pregnancy category C drug.[66] A risk-to-benefit analysis must be considered in pregnant women, particularly those who are opioid tolerant, and their newborns. Inducing opioid withdrawal in the mother probably will induce withdrawal in the fetus and should be avoided. Likewise, administering naloxone to newborns of opioid-tolerant mothers will induce withdrawal[44] (Chaps. 30, 31, and 38).

Use of longer-acting opioid antagonists, such as naltrexone and nalmefene, has substantial risks for protracted withdrawal syndromes and should be reserved for special indications associated with extended periods of observation.

An oral dose of naltrexone 150 mg generally lasts 72 hours and should be adequate as an antidote for the majority of ingestions

except for opioids, such as levo-Î±-acetylmethadol (LAAM), which have extremely long durations of action. Naltrexone should never be administered to a patient who is opioid tolerant.[83] Naltrexone is administered orally in a variety of dosage schedules for treatment of opioid dependence. A common dosing regimen is 50 g daily Monday through Friday and 100 mg on Saturdays. Alternatively, 100 mg every other day or 150 mg every third day can be administered.

The initial IV dose of nalmefene is 0.1 mg in a 70-kg person in whom opioid dependency is suspected. If withdrawal does not ensue, 0.5 mg can be given, followed by 1 mg in 2â€“5 minutes as necessary. If IV access is unavailable, the intramuscular or subcutaneous route can be used, but the onset of action is delayed by 5â€“15 minutes after a 1-mg dose. For reversal of postoperative opioid depression, a starting dose of 0.25 Âµg/kg is used, followed by incremental doses of 0.25 Âµg/kg every 2â€“5 minutes to the desired effect or to a total of 1 Âµg/kg.

The experience with nalmefene is too limited to estimate an adequate observation time, although 24 hours seems prudent.

Availability

Naloxone (Narcan) for IV, intramuscular, or subcutaneous administration is available in concentrations of 0.02, 0.4, and 1 mg/mL, with and without parabens in 1-mL and 2-mL ampules; and in 10-mL multidose vials with parabens. Naloxone can be diluted in 0.9% sodium chloride solution or 5% dextrose to facilitate continuous IV infusion. Any prepared solution should be used within 24 hours.

Nalmefene (Revex) is available in a 1-mL ampule containing 100 Âµg/mL and in a 2-mL ampule containing 1 mg/mL.

Naltrexone is available as a 50-mg capsule-shaped tablet.

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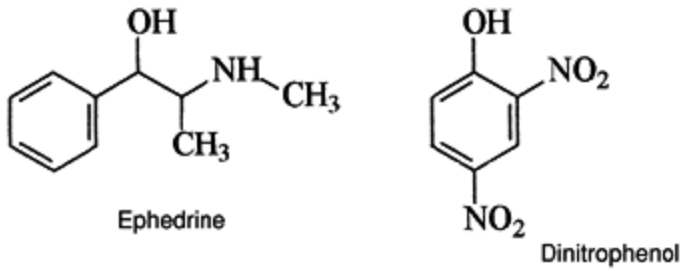
Chapter 39
Dieting Agents and Regimens

Christine Haller



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A 46-year-old woman who was found unconscious on the floor of her bedroom after she failed to show up for work was brought to the emerge department. The patient previously was healthy and had no medical conditions other than obesity. She was a nonsmoker and took no illicit substances. She was taking no prescription medications, although she dic use Metabolife 356 (which contains Ma-huang, guarana, vitamin E, chromium picolinate, bee pollen, ginseng, ginger, lecithin, bovine comple damiana [*Turnera* spp.], and sarsaparilla) twice per day for the past mon

for weight loss. Although her dosing history was not clear, she recently m have doubled her usual dose; if so she was consuming approximately 96 of ephedrine per day.

Her examination was notable for lethargy, aphasia, left hemiparesis, and visual loss. Her vital signs were: blood pressure, 117/61 mm Hg; pulse, 6 beats/min; respiratory rate, 20 breaths/min; oral temperature, 96.9Â°F (36Â°C). Neurologic examination revealed flaccid paralysis of the left upp and lower extremities, and the patient had difficulty swallowing. A head C showed infarction of the brain in the distribution of the anterior portion o the right middle cerebral artery but no intracerebral hemorrhage. Urine toxicology screening was negative. Laboratory values were within normal limits, except for creatine kinase concentration of 242 U/L (reference ran 40â€“150 U/L).

She was admitted for evaluation and treatment of a massive right-sided stroke. Because no other etiology was identified, the stroke was presume to be related to ephedrine use. She improved gradually over the course o weeks and was transferred to a rehabilitation facility. Three months after the stroke, she continued to have left arm weakness and left visual impairment, and she required assistance with walking. She had profound psychomotor impairment, including short-term memory loss, impulsivity, emotional lability, and poor judgment. She was unable to resume work or live independently.

Americans are the most overweight people in the world. One third of adu are overweight (defined as having a body mass index [BMI] between 25 a 29.9 kg/m^2), and another 27% of adults are obese (BMI >30 kg/m^2).[67] The proportion of Americans who are obese has grown almost 10% since 1980,[50] representing 58 million Americans and contributing to 325,000 deaths annually.[4] Americans are not alone; obesity is also an increasing problem throughout the world. A particularly disturbing trend is the grow obesity problem in children. Because obesity is linked to a number

of health risks, including type II diabetes, atherosclerotic cardiovascular disease, hypertension, and certain cancers, it can be considered a leading

preventable health risk, second only to cigarette smoking. Americans spe $33 billion per year on weight loss therapies and modalities. Dieting and weight loss are attempted by many more people than just those who are overweight and obese by medically defined criteria.

Sympathomimetics
Diethylpropion (Tenuate)
Mazindol (Mazanor, Sanorex)
Phentermine (Fastin, Adipex)
Increased release of norepinephrine and dopamine
Schedule IV prescription drug
Dry mouth, tremor, insomnia, headache, agitation, palpitations, hypertension, stroke, dysrhythmias
Contraindications: MAOI use within 14 days, glaucoma, hyperthyroidism
Bitter orange extract (*Citrus aurantium*)
Contains synephrine increased thermogenesis and lipolysis (unproven)
Dietary supplement
Hypertension, cerebral ischemia, myocardial ischemia, prolonged QTc interval
Guarana
Contains caffeine, which may increase thermogenesis
Dietary supplement
Nausea, vomiting, insomnia, diuresis, anxiety, palpitations
Serotonergics
Sibutramine (Meridia)
Inhibits reuptake of serotonin and norepinephrine
Schedule IV prescription drug
Anxiety, dry mouth, insomnia, headache, hypertension, palpitations, dysmenorrhea Contraindications: Same as sympathomimetics
GI Agents
Orlistat (Xenical)
Inhibits gastric and pancreatic lipases
Prescription drug
Abdominal pain, oily stool, fecal urgency or incontinence; fat-soluble vitamin loss

			Contraindications: Cholestasis, chronic malabsorptive states
Chitosan	Insoluble marine fiber that binds dietary fat	Dietary supplement	Decreased absorption of fat-soluble vitamins Contraindications: Shellfish allergy
Fibers/Other Supplements			
Glucomannan	Expands in stomach to increase satiety	Dietary supplement	GI obstruction with tablet form Contraindications: Abnormal GI anatomy
Garcinia cambogia	Increases fat oxidation (unproven)	Dietary supplement	None reported
Chromium picolinate	Improves blood glucose and lipids; produces fat loss (unproven)	Dietary supplement	Dermatitis, hepatitis, possibly mutagenic in high doses

[a] Trade names or Latin binomials are given in parentheses.

[b] All agents are contraindicated during pregnancy and lactation.

Drug or Supplement[a]	Mechanism of Action	Regulatory Status	Adverse Effects/Contraindications

TABLE 39-1. Approved Weight Loss Drugs and Dietary Supplements

Obesity and attempts at weight loss probably have existed since antiquity One of the earliest accounts of weight loss therapy dates back to 10th-century Spain. King Sancho I, who was obese, underwent successful treatment with a â€œtheriacaâ€• thought to contain plants and possibly opioids, administered with wine and oil. In addition, he was closely

supervised and treated by a physician.[41]

Currently, medicinal weight loss therapies (Table 39-1) are available as prescription medications (sibutramine, phentermine) and nonprescription dietary supplements (*Citrus aurantium* , chitosan, *Garcinia cambogia*). U of natural weight loss remedies has undergone a resurgence since passag of the Dietary Supplement Health and Education Act (DSHEA) of 1994. Th DSHEA created a new category separate from food and drugs. The new category includes vitamins, minerals, herbs, and amino acids, which are minimally regulated by the Food and Drug Administration (FDA). As a res of the DSHEA, numerous botanicals and other substances are offered to consumers as weight loss aids, some with no proven efficacy and some w potentially serious toxicity.

Although dieting aids can be divided into disparate classes, they generally act through one or more of the following mechanisms: (1) appetite suppression, known as *anorectics;* (2) alteration of food absorption or elimination; or (3) increased energy expenditure. Dieting aids that are anorectic agents are designed to decrease appetite and calorie intake. Anorectic agents may be serotonergic drugs (sibutramine), or sympathomimetics (amphetamines and derivatives). They have the potential to cause adverse stimulant effects and dependence. Certain agents, such as â€œstarch blockersâ€• and â€œfat blockersâ€• (orlista chitosan), inhibit absorption of ingested nutrients. Dietary fiber pills act l absorbing large amounts of water and expanding in the stomach and intestinal tract. They produce the satiety sensation of a large meal and a causally linked to intestinal obstruction. Very-low-calorie diets, high-prot liquid supplements, and â€œdieter's teasâ€• containing laxatives are associated with dehydration, severe electrolyte disturbances, and sudden cardiac death. Dinitrophenol and thyroid hormone have been used to increase basal energy expenditure and are associated with severe toxicity

A number of weight loss therapies were withdrawn or banned by the FDA because of serious adverse health effects (Table 39-2). The unapproved use of fenfluramine-phentermine (Fen-Phen) was linked to cardiac valvulopathy and primary pulmonary hypertension. Î³-Hydroxybutyrate

(GHB) and its congeners initially were sold as a dietary supplement (Chap 78) and promoted to body builders as a means to â€œconvert fat into muscle.â€• Because of overdose toxicity and its association with drug-facilitated sexual assault,

GHB is strictly controlled as a schedule I agent, with limited availability a a schedule III drug for narcolepsy (Xyrem). Clenbuterol is an unapproved long-acting $Î²_2$ -adrenergic agonist with stimulant properties that is abus by body builders as an energy source and anorectic agent[40 , 74] (Chap. 4).

Amphetamine
Increased release of NE and dopamine
Sympathomimetic effects, psychosis, dependence
Schedule II
Benzphetamine (Didrex)
Increased release of NE and dopamine
Sympathomimetic effects, psychosis, dependence
Schedule III
Clenbuterol
$Î²_2$ -Adrenergic agonist activity
Tachycardia, headache, nausea, vomiting; may be prolonged
Not approved
Dexfenfluramine (Redux)
Promotes central serotonin release and inhibits its reuptake
Valvular heart disease, primary pulmonary hypertension
Withdrawn September 1997
Dieter's teas (senna, cascara, aloe, buckthorn)
Stimulant laxative herbs that promote colonic evacuation
Diarrhea, vomiting, nausea, abdominal cramps, electrolyte disorders, dependence
FDA required label warningâ€”June 1995
Dinitrophenol
Alters metabolism by uncoupling oxidative phosphorylation
Hyperthermia, cataracts, hepatotoxicity, fatalities

Drug or Supplement[a]	Mechanism of Action	Adverse Effects	Regulation Status DE Schedule or Withdrawal Date
Not approved			
Ma-huang (*Ephedra sinica*)	Increased release of NE and dopamine	Sympathomimetic effects, psychosis	Banned by FDAâ€”April 2004
Fenfluramine (Pondimin)	Increased release and decreased reuptake of serotonin	Valvular heart disease, primary pulmonary hypertension	Withdrawn September 1997
Guar gum (Cal-Ban 3000)	Hygroscopic polysaccharide swells in stomach, producing early satiety	Esophageal and small bowel obstruction, fatalities	Banned by FDAâ€”July 1990
Lipokinetix (sodium usniate, norephedrine, 3,5-diiodothyronine, yohimbir caffeine)	Unknown	Acute hepatitis	FDA warningâ€”November 2001
Phendimetrazine (Adipost, Bontril)	Increased release of NE and dopamine	Sympathomimetic effects, psychosis	Schedule III
Phenylpropanolamine (Dexatrim, Acutrim)	Î ±$_1$ -Adrenergic agonist	Headache, hypertension, myocardial infarction, intracranial hemorrhage	Withdrawn November 2000

[a] Trade names are given in parentheses.

NE = norepinephrine.

TABLE 39-2. Unapproved Weight Loss Drugs and Supplements

Sympathomimetics

Although controversial, certain sympathomimetic amines still carry officia indications for short-term weight reduction according to physician prescribing information (Table 39-1).[73] Sympathomimetic amines share Î²-phenylethylamine parent structure and include phentermine, diethylpropion, and mazindol, which are restricted as schedule IV agents and carry warnings that advise prescribers to limit use to only a few wee Regardless of their source and legal status, sympathomimetics generally share a spectrum of toxicity and produce adverse effects similar to amphetamine (Chap. 73).

Sympathomimetic amines that act at Î±- and Î²-adrenergic receptors are clinically effective in promoting weight loss but have numerous side effec that limit their clinical use. Soon after its introduction as a pharmaceutica for nasal congestion in the 1930s, the prototype sympathomimetic drug amphetamine (Figure 39-1) was noted to cause weight loss (Chap. 73). The weight loss effect of amphetamine also was well demonstrated in ear animal studies, although tolerance to the anorectic effects was noted.[88] T primary mechanism of action of the weight loss effects of sympathomime drugs is central nervous system stimulation, resulting from increased release of norepinephrine and dopamine.[86] The effects include direct suppression of the appetite center in the hypothalamus and reduced taste and olfactory acuity leading to decreased interest in food. Increased ener and euphoriant effects of the stimulant drugs also contribute to weight lo However, the rate of weight loss diminishes within a few weeks of initiati therapy. Significant side effects and abuse potential severely limit the therapeutic use of this class of drugs.

Absence of polar hydroxyl groups from a sympathomimetic amine increas its lipophilicity; therefore, unsubstituted or predominantly alkyl group-substituted compounds (eg, amphetamine, ephedrine, phenylpropanolam [PPA]) have greater central nervous system activity. Mild cardiovascular and central nervous system (CNS) stimulant effects include headache, tremor, sweating,

palpitations, and insomnia. More severe effects that may occur after overdose of sympathomimetic amines include anxiety, agitation, psychos seizures, palpitations, and chest pain (Chap. 73).[49 , 64 , 72 , 76] Cardiac ischemia, dysrhythmias, and stroke are reported.[28 , 56 , 64 , 91] Life-threatening drug interactions with monoamine oxidase inhibitors[22] may occur.

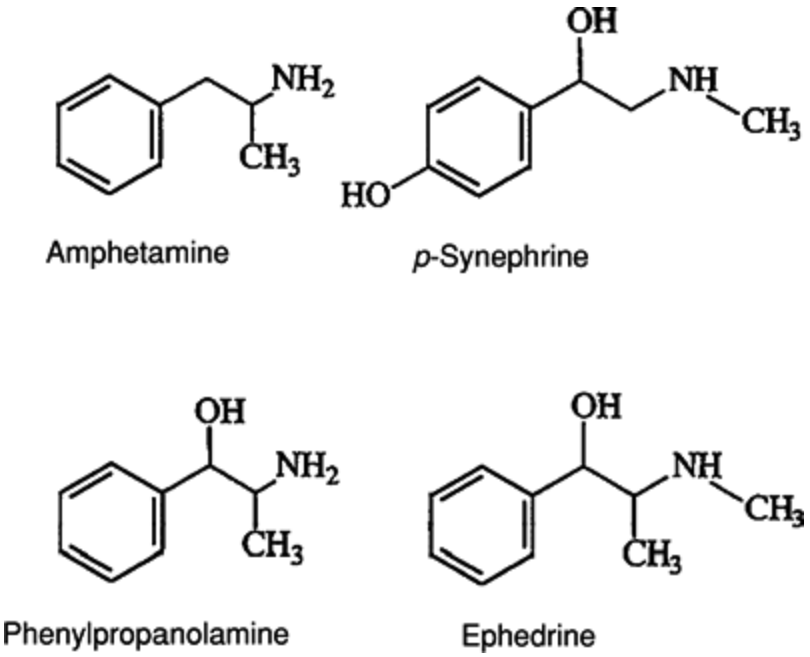

Figure 39-1. Sympathomimetic amines formerly and currently used for weight loss.

Hypertension is common following overdose and occasionally following therapeutic use. Patients may present with confusion and altered mental status as a result of hypertensive encephalopathy. Reflex bradycardia aft exposure to agents with predominantly Î±-adrenergic agonist effects may accompany the hypertension and provides a clue to the diagnosis. Childre with unintentional ingestions may be at especially high risk for hypertens episodes because of the relatively significant dose per kilogram of body weight. Other manifestations include chest pain, palpitations, tachycardia syncope, hypertension, mania, psychoses, convulsions, and coronary

vasospasm.[12 , 16 , 25 , 69 , 98]

Clinically significant hypertension should be treated aggressively with eit phentolamine, a rapidly acting Î±-adrenergic antagonist, or nitroprusside Analogous to the management of cocaine toxicity, Î²-adrenergic antagoni should be avoided because the resultant unopposed Î±-adrenergic agonis effects may lead to greater vasoconstriction and increased hypertension.[3] Agitation, tachycardia, and seizures should be treated with benzodiazepines.

Phenylpropanolamine

Phenylpropanolamine, a sympathomimetic amine (Figure 39-1), was available until 2000 as a nonprescription diet aid (eg, Dexatrim, Acutrim) It is both a direct-acting agent, via stimulation of Î±-adrenergic receptor and an indirect-acting agent, through release of norepinephrine. Both of these actions tend to cause a net increase in blood pressure when given i high doses. PPA-induced anorexia is mediated via Î±-adrenergic receptors in the hypothalamus.[96] PPA was formally available in various doses from 25â€“75 mg for appetite suppression and nasal decongestion. PPA was voluntarily withdrawn after its use was linked to increased risk of hemorrhagic stroke in women.[47]

Reported toxicity associated with PPA generally results from severe hypertension.[27 , 28 and 29 , 35 , 42 , 46 , 64] A comprehensive review of more than 100 case reports of adverse drug effects involving PPA reveale 24 intracranial hemorrhages, 8 seizures, and 8 fatalities between 1965 a 1990.[34 , 52] Some adverse events occurred following ingestion of diet preparations that contained both PPA and caffeine, which have pharmacokinetic and pharmacodynamic interactions.[48 , 53] Cardiac toxicit although less common, was reported in 2 young patients who suffered myocardial injury following therapeutic daily dosing in 1 and acute overd in the other.[56] Hypertensive emergencies resulting from adverse drug interactions between PPA and drugs such as monoamine oxidase inhibitor have been reported.[84]

Ephedrine

Ephedra *(Ephedra sinica)* , or Ma-huang in Chinese herbal nomenclature, a plant that contains 6 sympathomimetic amines, known collectively as *ephedra alkaloids.* The two primary alkaloids are ephedrine and pseudoephedrine (Figure 39-1). Ephedra was popular as a weight loss dietary supplement (eg, Metabolife 356, Xenadrine RFA, Ripped Fuel) unt the FDA banned ephedra-containing products in April 2004 because of a large number of reported cases of serious cardiovascular toxicity[12 , 16 , 1 , 20 , 25 , 36 , 91 , 98] as well as acute hepatitis[65] associated with use of these products. In a review of 140 adverse events reported to MedWatch following use of ephedra, 31% of the cases were considered to be definit or probably related to the use of ephedra supplements, including 4 stroke 5 cardiac arrests, 2 myocardial infarctions, and 3 fatalities.[36] The ban wa partially overturned by the courts in 2005, and the final fate of ephedra l yet to be determined. Ephedra still can be obtained from practitioners of complementary medicine as a traditional Chinese herbal medicine for sho term treatment of wheezing and nasal congestion associated with asthma allergies, and colds. Synthetic ephedrine is available as a nonprescription medication (eg, Primatene) for asthma. Although it is approved in the United States for treatment of obesity, ephedrine in combination with aspirin and caffeine was formerly available as a weight loss product in ot countries. Because ephedrine is abused for its amphetaminelike stimulant properties and is used in the illicit manufacture of methamphetamine (Chap. 73), its nonprescription sale is restricted in many states.

Since ephedra was banned, herbal weight loss supplements have been reformulated. Many now contain an extract of bitter orange (*C. aurantiun*), a natural source of the sympathomimetic amine synephrine, often in combination with caffeine, willow bark (containing salicylates), diuretics, and other constituents. The dried fruit peel of bitter orange, known in Chinese herbal medicine as Zhi shi, is a traditional remedy for gastrointestinal ailments. The predominant constituent, *p*- synephrine (Figure 39-1), is structurally similar to norepinephrine. Its isomer *m* - synephrine (phenylephrine or Neo-Synephrine) is used extensively as a

vasopressor and nasal decongestant. Although synephrine's physiologic actions are not fully characterized, synephrine appears to interact with trace amine receptors in the brain and acts at peripheral Î±1 -adrenergic receptors, resulting in vasoconstriction and increased blood pressure.[30] Some evidence indicates that synephrine may also have Î²3 -adrenergic agonist activity, which could increase lipolysis, although this activity has not demonstrated in humans.[30] Adverse effects associated with use of *C. aurantium* -containing weight loss products have been reported, including case of cerebral ischemia in a 38-year-old man,[10] 1 case of exercise-induced syncope and QTc interval prolongation in a 22-year-old woman,[66] and a possible case of myocardial infarction in a 55-year-old woman.[68]

Serotonergic Agents

Drugs that affect central release and reuptake of serotonin are approved a number of indications, including depression, anxiety, nicotine addiction and premenstrual dysphoric syndrome. Although these drugs all reduce fo intake to varying degrees, sibutramine (Meridia) is the only FDA-approve serotonergic agent specifically indicated for treatment of obesity.

Sibutramine acts by blocking the reuptake of both serotonin and norepinephrine, but it does not promote neuronal release of serotonin. It clinical effects include reduced appetite and increased satiety. This prescription drug is recommended in doses of 10â€“15 mg per day for obese patients with BMI >30 kg/m^2 without comorbid conditions, and for patients with BMI >27 kg/m^2 with comorbid diseases of diabetes mellitus dyslipidemia, or hypertension. Its effectiveness in producing weight loss demonstrated in several randomized, double-blind studies.[55 , 60] Patients receiving intermittent sibutramine therapy have significantly fewer adver effects than patients who take sibutramine continuously.[97] Clinical use of sibutramine for more than 1 year is unstudied.

The pharmacologic activity of sibutramine results from hepatic first-pass metabolism by cytochrome P450 (CYP3A4) transforming sibutramine into the 2 active metabolites, mono-desmethylsibutramine and di-

desmethylsibutramine, which have half-lives of 14 and 16 hours, respectively. These metabolites are further metabolized and renally excreted. Medications that inhibit CYP3A4, such as cimetidine, erythromycin, and ketoconazole, may slow sibutramine metabolism. Moderate hepatic or renal impairment does not significantly alter the pharmacokinetics of sibutramine or its active metabolites.

Sibutramine use is associated with psychosis,[87] hypertension, cardiac ischemia, and death.[37] Since Meridia was approved in 1998, 397 serious adverse reactions have been reported to the FDA, including 29 deaths. Nineteen of the deaths were due to cardiovascular causes, including 3 deaths in women younger than 30 years.[37] Sibutramine was banned in It in March 2002 after 2 cardiovascular deaths, and its use as a weight loss drug is being scrutinized in other European countries and in the United States. Because sibutramine raises heart rate and blood pressure, it shou not be used in patients with poorly controlled hypertension, coronary art disease, glaucoma, or previous stroke. Use of sibutramine is contraindicated in patients with anorexia nervosa, severe hepatic or rena dysfunction, or seizure disorders. Sibutramine taken in combination with monoamine oxidase inhibitors or selective serotonin reuptake inhibitors, any drug that affects serotonin release or reuptake, could induce seroton syndrome, which is characterized by agitation, hyperthermia, autonomic instability, and myoclonus.

Serotonergic drugs used in the past to treat obesity include dexfenfluramine (Redux) and fenfluramine (Pondimin), but these agents have been withdrawn because of postmarketing reports of serious cardiac effects associated with their therapeutic use.[11, 14, 20, 24, 31, 95] The diet drug combination known as â€œFen-Phenâ€• for its two-drug prescription regimen of fenfluramine and phentermine (an amphetamine derivative) was popular in the 1990s because of the presumed improved side effect profile and efficacy achieved with lower doses of each drug. Th drug combination was never approved by the FDA for treatment of obesit and fenfluramine was withdrawn in 1997 when an unusual cardiac valvulopathy was described in 24 women taking Fen-Phen.[20] All of the women presented with new heart murmurs and either right- or left-sided

valvular abnormalities. Eight of the 24 women also developed newly documented pulmonary hypertension. Several of these patients required cardiac surgery and were found to have plaquelike encasement of the leaflets and chordae, with preservation of valvular structure. These pathologic findings are identical to those described in patients with ergotamine-induced valvular disease and in those with carcinoid syndrom Although subsequent studies confirmed this association, the reported magnitude of risk associated with these drugs has varied.[44, 45, 95] Case of regression of these valvular lesions with cessation of the drugs are reported,[15] and limited evidence indicates that the valvular effects are milder than initially described.[31]

Primary pulmonary hypertension has been described in association with fenfluramine and dexfenfluramine since 1981.[6, 14, 24, 63, 75] Primary pulmonary hypertension in association with another anorectic drug aminorex fumarate, was reported earlier in Europe.[35] In one multicenter case control study of patients with primary pulmonary hypertension, use anorectic drugs such as dexfenfluramine and fenfluramine for more than months was associated with a 30-fold increased risk of primary pulmonar hypertension in these patients compared with nonusers.[1] Several theorie are proposed to explain the mechanism of pulmonary toxicity of these agents,[14] namely, serotonin-mediated constriction of pulmonary arteries, [62] serotonin-mediated platelet aggregation, and vasoconstriction in the lungs leading to microembolization, elevated pulmonary vascular resistance, and pulmonary hypertension.[62]

Agents that Alter Food Absorption, Metabolism, and Elimination

Fat Absorption Blockers

Orlistat (Xenical) was approved by the FDA in 1999 for treatment of obesity. At the time of this writing, orlistat is the only FDA-approved drug that alters the absorption, distribution, and metabolism of food. Orlistat is

potent inhibitor of gastric and pancreatic lipase, thus reducing lipolysis a increasing fecal fat excretion.[17] The drug is not systemically absorbed bu exerts its effects locally in the gastrointestinal tract. It inhibits hydrolysis of dietary triglycerides and reduces absorption of the products of lipolysis monoglycerides, and free fatty acids. Several clinical trials demonstrate that orlistat reduces gastrointestinal fat absorption by as much as 30%.[9] When taken in association with a slightly calorie-restricted diet, weight lo of approximately 10% body weight can be achieved in 1 year.[82]

Orlistat should be taken only in conjunction with meals that have a high- content; it should not be consumed in the absence of food intake. Advers effects correlate with the amount of dietary fat consumption and include abdominal pain, oily stool, fecal incontinence, fecal urgency, flatus, and increased defecation. Concomitant use of natural fibers (6 g of psyllium mucilloid dissolved in water) may reduce the gastrointestinal side effects orlistat.[18] Because orlistat reduces absorption of fat-soluble food constituents, daily ingestion of a multivitamin supplement containing vitamins A, D, and K, and Î²-carotene is advised to prevent resultant deficiency.

Chitosan is a weight loss dietary supplement derived from exoskeletons o marine crustaceans. It is thought to act similarly to orlistat by binding to dietary lipids in the gastrointestinal tract and reducing breakdown and absorption of fat. Some evidence indicates that chitosan may decrease to serum cholesterol concentration in overweight people, but the majority o clinical studies indicate chitosan is ineffective for weight loss in the abse of dietary and lifestyle modifications.[80] Chitosan is contraindicated in people with shellfish allergy.

Dietary Fibers

Guar gum is derived from the bean of the *Cyamopsis psorabides* plant. It was marketed in pill or tablet form as Cal-Ban 3000 until it was banned b the FDA in 1992 because of its potential to cause gastrointestinal obstruction. The guar gum in Cal-Ban 3000 is a hygroscopic polysacchari that expands 10â€“20-fold in the stomach, forming a gelatinous mass. Th

purpose of ingesting guar was to cause gastric distension and create the sensation of satiety in the dieter, thus decreasing appetite and food intak Guar gum resulted in numerous cases of esophageal and small-bowel obstruction both in patients with preexisting anatomical lesions such as strictures and in individuals with normal gastrointestinal anatomy.[32 , 57 77 , 79]

Glucomannan is a dietary fiber consisting of glucose and mannose, which derived from konjac root, a traditional Japanese

food. Edible forms of glucomannan include konjac jelly and konjac flour, which is mixed with liquid prior to ingestion. Purified glucomannan is available in capsule form and is found in various proprietary products marketed for weight loss. On contact with water, glucomannan swells to approximately 200 times its original dry volume, turning into a viscous liquid. It lowers blood cholesterol and glucose concentrations and decrea systolic blood pressure,[5 , 93] but significant weight loss benefits have not been demonstrated. Following several reports of esophageal obstruction, oral glucomannan tablets were banned in Australia in 1985.[38] Serious adverse effects are not described with encapsulated glucomannan, presumably because slower dissolution allows for gastrointestinal transit prior to expansion. Glucomannan capsules are available as a nutritional supplement in the United States, although adequate safety and efficacy studies are not published.

Dinitrophenol

One of the earliest attempts at a pharmaceutical treatment for obesity wa 2,4-dinitrophenol (DNP), which was popularized as a weight loss adjuvant the 1930s.[90] This chemical, which is used in dyes, wood preservatives, herbicides, and explosives, was never approved as a drug product but wa legally available as a diet remedy prior to enactment of the US Federal Food, Drug, and Cosmetic Act of 1938. By increasing metabolic energy expenditure in doses of 100 mg three times per day, it reportedly produc weight loss of 1â€“2 pounds per week.[21] DNP increases metabolic work b

uncoupling oxidative phosphorylation in the mitochondria via its action as an ionophore. Through this mechanism, the hydrogen ion gradient that allows ATP synthesis is dissipated, preventing the proton motive force fro creating high-energy phosphate bonds (Chap. 13). Because the energy l resulting from inefficient substrate utilization is dissipated as heat, eleva temperature and, occasionally, life-threatening hyperthermia can occur.[89] DNP reportedly was administered to Russian soldiers during World War II keep them warm during winter battles.[51] Symptoms related to DNP toxici include malaise, skin rash, headache, diaphoresis, thirst, and dyspnea. Severe toxic effects include hyperpyrexia, hepatotoxicity, agranulocytosis respiratory failure, coma, and death.[8 , 33 , 51 , 89] Delayed-onset cataract was a frequent and serious complication of DNP use.[8]

Use of DNP as a dieting aid reemerged in the 1980s when a physician in Texas processed industrial DNP into tablets and distributed them at his weight loss center under the trade name Mitcal. An intentional overdose fatality with Mitcal in 1984 led a Texas court to stop the use of this chemical for weight loss.[51] DNP continues to reappear sporadically as a weight loss treatment, and cases of serious toxicity still are reported. Tw recent cases include a 22-year-old man who developed fever, agitation, a delirium 16 hours after taking DNP, and a 17-year-old girl who developed fever, hypotension, and seizures.[61 , 70] Both young victims died despite maximal resuscitative efforts. Intensive care management and emergent cooling are required in patients who present with hyperthermia after use a weight loss product containing DNP.

Hypocaloric Diets and Cathartic/Emetic Abuse

Medication abuse among individuals with various eating disorders is common.[13] Starvation, as well as abuse of laxatives, syrup of ipecac, diuretics, and anorectic agents, has led to many fatalities, often in young patients.[29 , 43] Fad diets and laxative abuse should be strongly considere in young people with unexplained dehydration, syncope, hypokalemia, an metabolic alkalosis. A variety of extreme calorie-restricted diets resulting

profound weight loss were very popular in the late 1970s, but reports of possible association between these diets and sudden death followed.[81] Myocardial atrophy was a consistent finding on autopsy. Torsades de pointes and other ventricular tachycardias as a result of hypokalemia[81], and protein-calorie malnutrition of the heart are proposed causes of deat in these cases.[26, 81, 85]

Following the negative reports and FDA warnings, the enthusiasm for liqu protein diets waned. Several current diets (Atkin's plan, South Beach diet advocate intake of high protein, high fat, and low carbohydrates while allowing unlimited amounts of meat, fish, eggs, and cheese. Lack of carbohydrates induces ketosis, which results in diuresis and dehydration, giving the user the appearance of rapid weight loss. With rehydration and resumption of a normal diet, weight gain generally occurs. In addition, dehydration may cause orthostatic hypotension and ureterolithiasis.[2] Atherosclerosis and hypercholesterolemia may occur as a result of substitution of high-calorie, high-fat foods for carbohydrates.

Dieter's teas that contain combinations of herbal laxatives, including senn and *Cascara sagrada*, can produce profound diarrhea, volume depletion, and hypokalemia. They are associated with cases of sudden death, presumably as a result of cardiac dysrhythmias. Despite FDA warnings of the dangers of these weight loss regimens, dieter's teas remain available retail stores that sell nutritional supplements and are easily accessible to adolescents.

Chronic laxative use can result in an atonic colon (â€œcathartic bowelâ€ and development of tolerance, with the subsequent need to increase dosi to achieve catharsis. Because cathartics do not decrease food absorption, these agents have limited effects on weight control.[7] Various test metho can be used to detect laxative abuse.[23] Phenolphthalein can be detected a pink or red coloration to stool or urine following alkalinization. Colonoscopy reveals the benign, pathognomonic â€œmelanosis coli,â€• dark staining of the colonic mucosa secondary to anthraquinone laxative abuse.

Chronic use of syrup of ipecac to induce emesis by patients with eating

disorders, such as bulimia nervosa, leads to the development of cardiomyopathy, subsequent dysrhythmias, and death.[29, 71] Emetine, a component of syrup of ipecac, is the alkaloid responsible for the severe myopathy experienced by these patients. In addition, chronic administrat of syrup of ipecac results in tolerance to the emetic effects and increased systemic absorption of emetine.[71] Emetine can be detected in serum by high-pressure liquid chromatography or thin-layer chromatography. It persists for weeks to months after ingestion. In 2003, an FDA advisory committee recommended that the nonprescription drug status of syrup of ipecac be rescinded because of its use by patients with bulimic disorders.

Novel Therapeutic Approaches to Weight Loss

Leptin and the leptin gene have been explored as a basis for obesity and a therapeutic strategy. Genetically leptin-deficient mice are obese, and leptin replacement produces weight loss. Subcutaneous leptin supplementation appears to induce weight loss in lean and obese adults.[3] Leptin replacement therapy in three humans with genetically based obesi resulted in profound weight loss and normalization of endocrine function.[5] Because Î²3 -adrenergic

receptors mediate lipolysis in adipose tissue, Î²3 -selective agonists also are under investigation as weight loss agents.[78] Neuropeptide Y, a peptid found in the arcuate and paraventricular nucleus of the hypothalamus, is potent central appetite stimulant. Future drug therapy may target these genes, receptors, and proteins to modify metabolism. As obesity research proceeds and the biologic basis for obesity is defined, new approaches ar mechanisms for drug therapy may be identified.

Other Herbal Remedies

Several herbal remedies for weight loss have resulted in serious toxicity. France, germander (*Teucrium chamaedrys*) supplements taken for weigh

loss resulted in 7 cases of hepatotoxicity.[54] A â€œslimming regimenâ€• first prescribed in a weight loss clinic in Belgium produced an epidemic of progressive renal disease, known as Chinese herb nephropathy, when botanical misidentification led to the substitution of *Stephania tetrandra* with the nephrotoxic plant *Aristolochia fangji* .[92] The toxic constituent, identified as aristolochic acid, is implicated in numerous cases of renal failure and urothelial carcinoma.[59] A case of profound digitalis toxicity occurred with a laxative regimen contaminated with *Digitalis lanata* .[83] U regulation of herbal products is improved and manufacturing practices worldwide are standardized, sporadic reports of herb-related toxicity like will continue (Chap. 43).

Summary

Although obesity is a major health challenge and a major cause of preventable morbidity and mortality, unproven weight loss treatments ar fraught with failure and potential toxicity. There probably is no appropria substitute for a balanced weight loss plan that encompasses decreased caloric intake with increased energy expenditure through exercise. Clinicians should be aware of the lack of regulation of most available diet remedies and should report adverse events involving these products to poison control centers and to the FDA MedWatch system so that appropri regulatory actions can be taken to prevent further instances of toxicity. A historical review of compounds used as weight loss agents readily uncov numerous examples of poorly conceived drug regimens, popular misunderstanding of the benefits and risk of the drugs involved, and relatively poor postmarketing surveillance leading to unnecessary morbid and mortality.

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Chapter 40

Iron

Jeanmarie Perrone

Iron

MW = 55.85 daltons

Serum normal = 80â€“180 Âµg/dL

= 14â€“32 Âµmol/L

A 17-month-old boy was found by his mother playing with a bottle of iron supplements. The mother noted greenish discoloration around the child's lips and pill fragments in his mouth. She brought him to the emergency department (ED). En route to the hospital, spontaneous vomiting of pill fragments and hematemesis occurred. In the ED, the boy was noted to be lethargic with the following vital signs: blood pressure, 95/55 mm Hg; heart rate, 130 beats/min; respiratory rate, 35 breaths/min; temperature, 96.9Â°F (36Â°C). High-flow supplemental oxygen was given, IV access obtained, and fluid resuscitation (20 mL/kg) initiated. An abdominal radiograph revealed a large number of radiopaque fragments in the stomach.

Orotracheal intubation, orogastric lavage (with removal of more green pill fragments), and whole-bowel irrigation were performed. An arterial blood gas following intubation revealed significant metabolic acidosis: pH, 7.15; PCO_2, 34 mm Hg; PO_2, 441 mm Hg.

Chelation with deferoxamine 135 mg/h (15 mg/kg/h) was started intravenously. Small amounts of dark brownish red urine from a Foley catheter were noted. Transfer of the patient to a tertiary care pediatric intensive care unit (ICU) was arranged. Other significant laboratory values were: white blood cell count (WBC), 22,000/mm^3; hemoglobin, 11.6 g/dL; serum bicarbonate concentration, 10 mEq/L; glucose, 384 mg/dL; international normalized ratio (INR), 4.5; iron, 18,570 Âµg/dL; alanine aminotransfersase (ALT), 700 IU/mL. Upon arrival in the tertiary care pediatric ICU 3.5 hours after initial presentation, the patient was tachycardic with a pulse of 188 beats/min (normal 80â€“150 beats/min). He was hypotensive with a systolic blood pressure of 70 mm Hg (normal for age 80â€“110 mm Hg). Additional fluid boluses, transfusions of fresh-frozen plasma, and 2 units of packed red blood cells were administered. A repeat abdominal radiograph revealed persistent radiopaque pill fragments in the gut lumen (Figure 40-1). Lavage was performed again with upper gastrointestinal (GI) endoscopy, but pill fragments were adherent to the gastric mucosa. The patient was taken to the operating room, and a gastrotomy was performed to remove the remaining pill fragments (Figure 40-2). Sixteen hours postingestion, his oxygenation and hemodynamic status deteriorated. Acute lung injury was noted on chest radiograph. Oxygenation worsened despite maximal ventilatory support on 100% FIO_2: pH, 7.18; PCO_2, 41 mm Hg; PO_2, 37 mm Hg. Hypotension refractory to vasopressors and further transfusions of red blood cells and fresh-frozen plasma developed. A fatal cardiac arrest ensued approximately 20 hours postingestion. The patient's terminal serum iron concentration was 4000 Âµg/dL.

History and Epidemiology

Iron has been used therapeutically for thousands of years and continues to be available, both with and without prescription, for the prevention and treatment of iron-deficiency anemia in patients of all ages. Despite this long history of use, the first reports of iron toxicity only occurred in the mid-20th century. Since then, numerous cases of iron poisoning and fatalities have been reported, most of them in children.[56,57] In 1950, the manufacturer of â€œfersolateâ€• included a package warning: â€œExcessive doses of iron can be dangerous. Do not leave these tablets within reach of young children, who may eat them as sweets with harmful results.â€•[84]

The incidence of iron exposures continued to increase in the 1980s, and in the 1990s iron exposure became the leading cause of poisoning deaths in children younger than 6 years. This finding was publicized by a case series of tragic fatalities involving 5 toddlers in Los Angeles during a 6-month period in 1992. All cases involved prenatal vitamins containing iron.[91] This association highlights the availability of these potentially lethal medications in the homes of families with young children, paradoxically as a result of more attentive prescribing of prenatal iron. A case control

study in Canada identified a 4-fold increase in the risk of iron poisoning to the older sibling of a newborn during the first postpartum month.[41] The authors concluded that almost half of all hospital admissions of young children for iron poisoning could be prevented by safer storage of iron supplements in the year before and the year after the birth of a sibling.

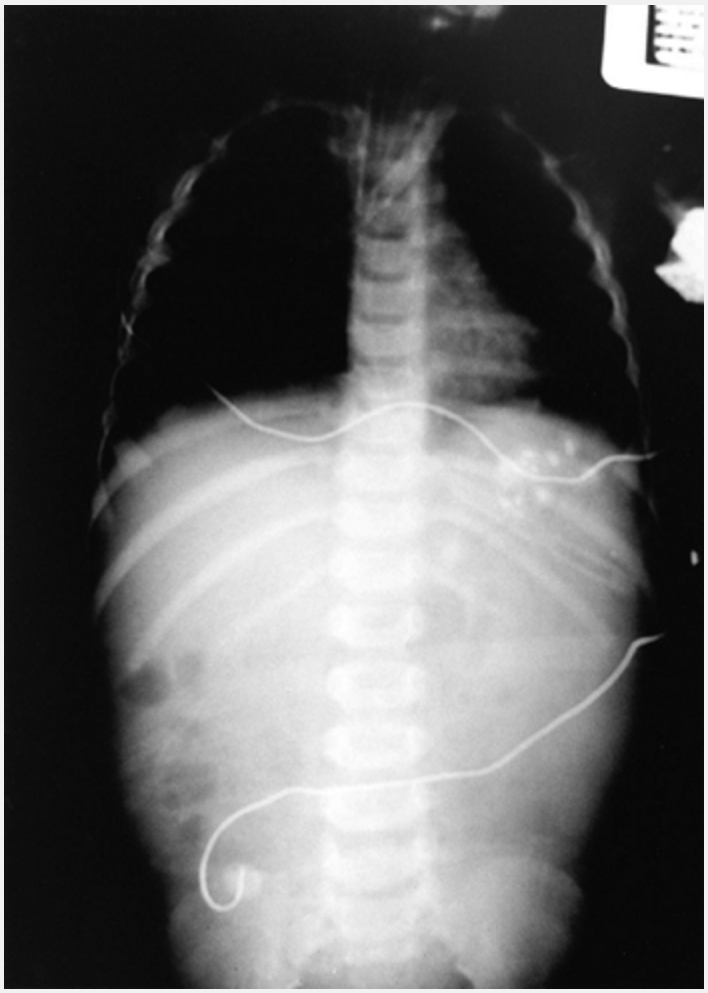

Figure 40-1. A 17-month-old boy presented to the hospital with lethargy and hematemesis following a large ingestion of iron supplement pills. Despite orogastric lavage and whole-bowel irrigation, iron pills and fragments can be visualized in the stomach 4 hours postingestion.

In 1997, the Food and Drug Administration (FDA) mandated that all iron salt-containing preparations have warning labels regarding the dangers of pediatric iron poisoning.[23] In addition to the warning labels, the FDA launched an educational campaign to alert caregivers

and prescribers of the potential toxicity of iron supplements.[22] Other preventive initiatives instituted by the FDA in 1997 included unit dosing (blister packs) of prescriptions containing more than 30 mg of elemental iron and limitations on the number of pills dispensed (ie, maximum 30-day supply).[23] These efforts to prevent unintentional exposure dramatically decreased the incidence of poisoning and are pivotal in decreasing morbidity and mortality associated with iron poisoning (Chap. 130 and associated references). Unfortunately, in 2003 the FDA rescinded the blister packaging requirement in response to a lawsuit charging that the FDA did not have jurisdiction over the packaging of dietary supplements.[21] Although isolated fatalities continue to occur,[55] the trend in American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System (TESS) data suggests they are becoming less common (Chap. 130 and associated references).

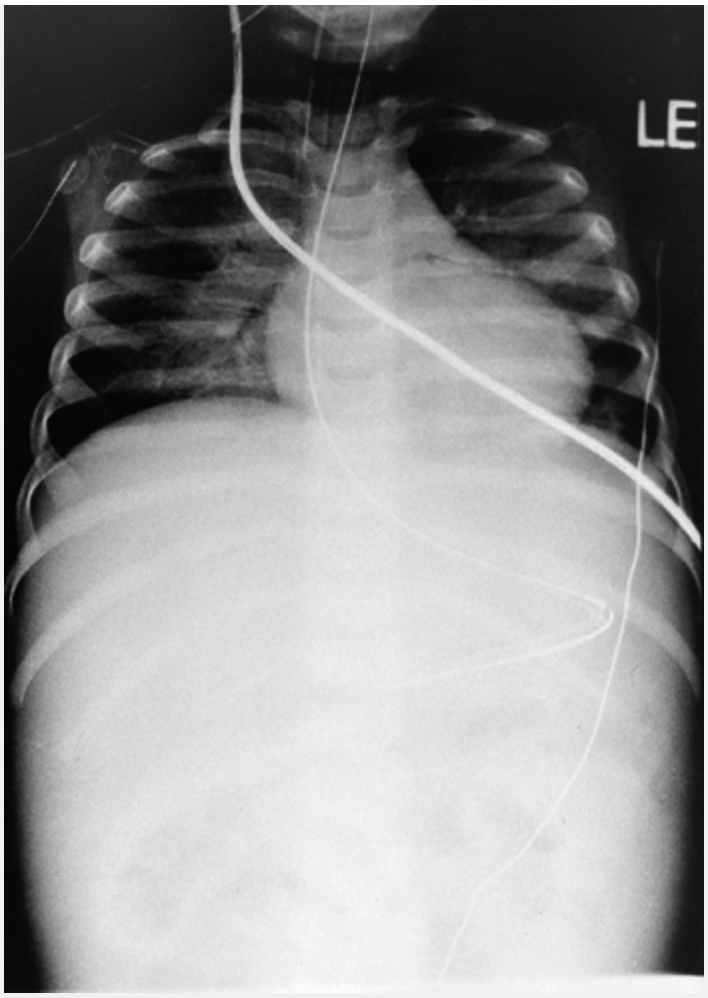

Figure 40-2. Ten hours postingestion. Persistent iron pills were removed from the stomach by gastrotomy. No further radiopaque fragments can be visualized; however, acute lung injury is now visible.

Iron poisoning can occur after ingestion of other iron salts, such as ferric chloride, used in industry.[99] Parenteral iron, such as iron dextran, administered intravenously to patients with renal failure and chronic anemia, also can result in toxicity, especially anaphylactoid reactions. Newer parenteral formulations, including iron sucrose and sodium ferrous gluconate, appear to be safer.[20] Iron supplements

are available in two nonionic forms, carbonyl iron and iron polysaccharide, both of which appear to be less toxic following overdose than are iron salts.[74]

Pharmacology and Toxicokinetics

Iron is an element critical to organ function. As a transition metal, iron can easily accept and donate electrons, thereby shifting from a ferric (Fe^{3+}) to a ferrous (Fe^{2+}) state (Chap. 12). This redox interchange allows iron to fulfill its role in multiple protein and enzyme complexes, including cytochromes and myoglobin, although it is principally found incorporated into hemoglobin in erythrocytes. Insufficient iron availability results in anemia, whereas excess total body iron results in hemochromatosis.

The body cannot directly excrete iron, so body iron stores are regulated by controlling iron absorption from the gastrointestinal tract. Iron absorption, which occurs predominantly in the duodenum, is determined by the body's iron requirements. In iron deficiency, iron uptake into intestinal mucosal cells may increase from a normal of 10â€“35% to as much as 80â€“95%. Following uptake into the intestinal mucosal cells, iron is either stored as ferritin and lost when the cell is sloughed, or released to transferrin, a serum iron-binding protein. In therapeutic doses, some of these processes become saturated, and absorption into the intestinal cell may be limited. However, in overdose the oxidative effects of iron on gastrointestinal mucosal cells lead to dysfunction of this regulatory balance, and increased passive absorption of iron occurs down its concentration gradient[78] (see Pathophysiology below).

Iron supplements are available as the iron salts ferrous gluconate, ferrous sulfate, and ferrous fumarate, and as the nonionic preparations carbonyl iron and polysaccharide iron. Additional sources of significant quantities of iron are vitamin preparations, especially prenatal vitamins (Table 40-1). Toxic effects of iron

poisoning occur at doses of 10â€“20 mg/kg elemental iron (elemental iron is a measure of the amount of iron present in an iron salt; Table 40-1). Significant gastrointestinal symptoms occurred in human adult volunteers who ingested 10â€“20 mg of elemental iron/kg.[9,49] In one volunteer study, 6 subjects who ingested 20 mg/kg elemental iron developed nausea and voluminous diarrhea within 2 hours, and 5 of the 6 subjects had serum iron concentrations above 300 Âµg/dL.[9]

Chewable vitamins continue to entice children with their sweet taste and recognizable character shapes, increasing the risk of significant exposure. Children's chewable multivitamins contain less iron per tablet (10â€“18 mg elemental iron) than typical prenatal vitamins (65 mg elemental iron). Toxicity still results when large quantities are ingested, but fatalities are not reported.[2] One animal study paradoxically demonstrates higher iron concentrations following ingestion of equivalent doses of chewable versus solid iron tablets.[59] This finding was attributed, in part, to the limited gastric irritation associated with the chewable iron preparations, resulting in less vomiting and higher iron concentrations.

Iron polysaccharide and carbonyl iron appear to be safer formulations than iron salts despite their high elemental iron content.[45] Carbonyl iron is a form of elemental iron that is highly bioavailable in therapeutic doses because of its high elemental iron content and its very fine, spherical particle size (5 Âµm). However, toxicity is limited in overdose because carbonyl iron has poor solubility and a slow rate of conversion to the toxic ionic form that occurs in the acid milieu of the stomach. This delayed oxidation is the rate-limiting step that prevents excess absorption.[33] In a rat model of iron toxicity, carbonyl iron had an LD_{50} (median lethal dose for 50% of test subjects) of 50 g/kg compared with an LD_{50} of 1.1 g/kg for ferrous sulfate.[94] No significant toxicity in humans exposed to carbonyl iron has been reported.[74]

TABLE 40-1. Common Iron Formulations and Their Elemental Iron Contents

Iron Formulation	Elemental Iron
Ionic	
Ferrous chloride	28%
Ferrous fumarate	33%
Ferrous gluconate	12%
Ferrous lactate	19%
Ferrous sulfate	20%
Nonionic	
Carbonyl iron	98%[a]
Iron polysaccharide	46%[a]

[a]Although these nonionic iron formulations contain higher elemental iron content than ionic formulations, carbonyl iron and iron polysaccharide have better therapeutic-to-toxic ratios.

Iron polysaccharide contains approximately 46% elemental iron by

weight. It is synthesized by neutralization of a ferric chloride carbohydrate solution. This form of iron also appears to have much lower toxicity than iron salts. The estimated LD_{50} in rats is more than 5 g/kg body weight. Retrospective poison center data have shown little toxicity from either of these products.[45]

Pathophysiology

As a transition metal, iron can assume one of several different oxidation, or valence, states. It is an active participant in reduction-oxidation (redox) reactions. In particular, iron's participation in the Fenton reaction and Haber-Weiss cycle explains its toxicologic effects as a generator of oxidative stress and inhibitor of several key metabolic enzymes (Chaps. 12 and 90). Reactive oxygen species oxidize membrane-bound lipids and cause loss of cellular integrity and tissue injury (Chap. 12).[68,70]

The initial oxidative damage to the gastrointestinal epithelium produced by iron-induced reactive oxygen species permits iron ions to enter the systemic circulation. Iron ions are rapidly bound to circulating binding proteins, particularly transferrin. Once transferrin is saturated with iron, â€œfreeâ€• iron (iron not bound to a transport protein) is widely distributed to the various organ systems, where it promotes damaging oxidative processes. A postmortem series of 11 patients following iron ingestion substantiated these findings with measurements of elevated iron concentrations in most major organs examined: stomach, liver, brain, heart, lung, small bowel, and kidney.[63] Consistent with oxidative damage, congestion, edema, necrosis, and iron deposition in the gastric and intestinal mucosa, as well as hemorrhage and congestion in the lungs, are noted on postmortem examination.[30,31,51]

Iron ions disrupt critical cellular processes such as mitochondrial oxidative phosphorylation. Subsequent buildup of unused hydrogen ions normally incorporated into the synthesis of ATP, leads to liberation of H^+ and development of metabolic acidosis (Chap. 13).

In addition, absorption of iron from the gastrointestinal tract leads to conversion of ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}). Ferric iron ions exceed the binding capacity of plasma, leading to formation of ferric hydroxide and production of three protons ($Fe^{3+} + 3H_2O$ â†' $Fe(OH)_3 + 3H^+$).[68,78]

Decreased cardiac output contributes to hemodynamic shock in animals.[88,97] Although this finding has been attributed to decreased venous filling pressures, decreased preload, and relative bradycardia,[88] a direct negative inotropic effect of iron on the myocardium also is demonstrated in animal models.[3] Reports of early coagulopathy unrelated to hepatotoxicity[80] led to the identification of free iron inhibition of thrombin formation and the effect of thrombin on fibrinogen.[71]

Clinical Manifestations

Classic teaching posits five clinical stages of iron toxicity based on the pathophysiology of iron poisoning.[6,40,66] Although these stages

are conceptually important, they are of limited benefit to the clinician managing a poisoned patient. A clinical stage should never be assigned based on the number of hours postingestion because patients do not necessarily follow the same temporal course through these stages.

The first stage of iron toxicity is characterized by nausea, vomiting, abdominal pain, and diarrhea. The â€œlocalâ€• toxic effects of iron predominate, and subsequent salt and water depletion contribute to the ill appearance of the iron-poisoned patient. Intestinal ulceration, edema, transmural inflammation, and, in some extreme cases, small-bowel infarction and necrosis may occur.[24,69,82] Hematemesis, melena, or hematochezia may cause hemodynamic instability. Gastrointestinal symptoms always follow significant overdose. Conversely, the absence of symptoms, specifically vomiting, in the first 6 hours postingestion, essentially excludes serious iron toxicity.

The second or â€œlatentâ€• stage of iron poisoning commonly refers to the period 6â€“24 hours following resolution of gastrointestinal symptoms and before development of overt systemic toxicity. Delineation of this stage may have evolved from early case reports of patients whose gastrointestinal symptoms had resolved prior to subsequent deterioration.[84] This second stage is not a true quiescent phase, as ongoing cellular organ toxicity occurs during this phase.[6] Although clinicians should be wary of patients who no longer have active gastrointestinal complaints following iron overdose, most such patients have recovered and are not in the latent phase. Patients in the latent phase generally have lethargy, tachycardia, or a metabolic acidosis. They should be readily identifiable as clinically ill, despite resolution of their gastrointestinal symptoms. In summary, patients who have remained well since ingestion and who have stable vital signs, a normal mental status, and a normal acidâ€“base balance will have a benign clinical course.

Patients who progress to the third or â€œshockâ€• stage of iron poisoning have profound toxicity. This stage may occur in the first few hours after a massive ingestion or 12â€“24 hours after a more moderate ingestion. The etiology of shock may be multifactorial, resulting from hypovolemia, vasodilation, and poor cardiac output,[88,97] with decreased tissue perfusion and an ongoing metabolic acidosis. An iron-induced coagulopathy may worsen bleeding and hypovolemia.[80] Systemic toxicity produces CNS effects with lethargy, hyperventilation, seizures, or coma.

The fourth stage of iron poisoning is characterized by hepatic failure, which may occur 2â€“3 days following ingestion.[30] The hepatotoxicity is directly attributed to iron uptake by the reticuloendothelial system in the liver, where it causes oxidative damage.[26,98]

The fifth stage of iron toxicity rarely occurs. Gastric outlet obstruction, secondary to strictures and scarring from the initial gastrointestinal injury, can develop 2â€“8 weeks following ingestion.[29,35,82]

Patients with chronic iron overload are at increased risk for *Yersinia enterocolitica* infection. Iron is a required growth factor for *Y. enterocolitica;* however, the bacterium lacks the siderophore to solubilize and transport iron intracellularly. Because deferoxamine is a siderophore, it fosters the growth of *Y. enterocolitica*. Patients with chronic iron overload or acute poisoning develop *Yersinia* infection or sepsis as a complication of iron poisoning or deferoxamine therapy.[10,53,55,76] *Yersinia* infection should be suspected in patients who experience abdominal pain, fever, and diarrhea following resolution of iron toxicity. In this setting, cultures should be obtained and appropriate antibiotic therapy initiated.

Diagnostic Testing

Radiography

Iron is available in many forms, and the different preparations vary with respect to radiopacity on abdominal radiography.[75] Factors such as time since ingestion and amount of elemental iron also play a role.[58,75] Liquid iron formulations and chewable iron tablets typically are not radiopaque.[18] A retrospective review of iron ingestions in children revealed that abdominal radiographs were positive in only 1 of 30 patients who ingested chewable vitamins.[18] Because adult preparations have a higher elemental iron content and do not readily disperse, they tend to be more consistently radiopaque.[58] Finding radiopaque pills on an abdominal radiograph is helpful in guiding and evaluating the success of gastrointestinal decontamination.[36] However, the absence of radiographic evidence of pills is not a reliable indicator to exclude potential toxicity[58,62] (Chap. 6).

Laboratory Studies

Many different laboratory studies are used as surrogate markers to assess the severity of iron poisoning. An anion-gap metabolic acidosis resulting primarily from lactate is a common finding in

patients with serious iron ingestions. Serial electrolyte concentrations can be used to assess progression and response to volume replacement. Anemia can result from gastrointestinal blood loss but may not be evident initially because of hemoconcentration secondary to plasma volume loss.

Although one small retrospective study of iron-poisoned children found that WBC >15,000/mm^3 or blood glucose concentration >150 mg/dL was 100% predictive of iron concentration >300 Âµg/dL,[48] three subsequent studies that similarly examined this issue were unable to validate this association.[11,47,62] In practice, an elevated WBC or glucose concentration should raise concern about an elevated serum iron concentration; however, assessment of the signs and symptoms of the patient probably is more reliable.

Although iron poisoning remains a clinical diagnosis, serum iron concentrations can be used effectively to gauge toxicity and the success of treatment.[6] In the previously mentioned human volunteer study of 6 adults who ingested 20 mg/kg elemental iron, all 6 adults demonstrated significant gastrointestinal toxicity, and the 4 who required intravenous fluid resuscitation had peak serum iron concentrations in the range of 300 Âµg/dL between 2 and 4 hours after ingestion.[9] In another study of human volunteers who ingested 5â€“10 mg/kg elemental iron in the form of chewable vitamins, peak serum iron concentrations occurred between 4.2 and 4.5 hours in all subjects.[49] In overdose, peak concentrations of iron are thought to occur 2â€“6 hours after ingestion, depending on the iron preparation.[9,49] Serum iron concentrations between 300 and 500 Âµg/dL usually correlate with significant gastrointestinal toxicity and modest systemic toxicity. Concentrations between 500 and 1000 Âµg/dL are associated with pronounced systemic toxicity and shock.[92] Concentrations >1000 Âµg/dL are associated with significant morbidity and mortality.[92] Although elevated serum iron concentrations may be an additional indicator of potentially serious toxicity, lower concentrations cannot be used to exclude the possibility of serious toxicity. A single serum iron concentration may

not represent a peak concentration or may be falsely lowered by the presence of deferoxamine, unless an atomic absorption technique is used for measurement.[28,34]

Total iron-binding capacity (TIBC) is a measurement of the total amount of iron that can be bound by transferrin in a given volume of serum.[19] Previously, clinical iron toxicity was thought not to occur if the serum iron concentration was less than the TIBC because insufficient circulating â€œfreeâ€• iron was present to cause tissue damage. Although this may be conceptually true, further research has clarified the limitations of TIBC values. Most importantly, the in vitro value of TIBC factitiously increases as a result of iron poisoning and thus has a tendency to apparently falsely rise above a concurrently measured serum iron concentration.[9,83] Because of many confounding issues, the TIBC as currently analyzed has no value in the assessment of the iron-poisoned patient.

Management

Initial Approach

As with any serious ingestion, initial stabilization must include supplemental oxygen, airway assessment, and establishment of intravenous access. Evidence of hematemesis or lethargy following an iron exposure may be a manifestation of significant toxicity. Intravenous volume repletion should begin while orogastric lavage and whole-bowel irrigation (WBI) are considered. In any lethargic patient who likely will deteriorate progressively, early orotracheal intubation may facilitate safe gastrointestinal decontamination measures. An abdominal radiograph can be used to estimate the iron burden in the gastrointestinal tract given the caveats discussed earlier. Laboratory values including chemistries, hemoglobin, iron concentration, coagulation, and hepatic profiles are necessary in the sickest patients. An arterial blood gas, venous blood gas, or stat

electrolytes rapidly detects a metabolic acidosis. Patients who appear well or had only 1â€“2 brief episodes of vomiting can be observed pending discharge. Alternatively, a serum iron concentration can be measured.

Limiting Absorption

Gastrointestinal decontamination procedures should be initiated following stabilization. Adequate gastric emptying is critical following ingestion of substances, such as iron, that are not well adsorbed to activated charcoal. Because vomiting is a prominent early symptom in patients with significant toxicity, little benefit is expected from induced emesis, and this technique is no longer recommended. Orogastric lavage is more effective but can be limited because of the large size and poor solubility of most iron tablets, their ability to form adherent masses,[24,87] and their movement into the bowel several hours after ingestion.[42] The presence and location of radiopaque pills on abdominal radiograph can help guide lavage. Lavage likely will not be successful once iron tablets move past the pylorus, so WBI may be more effective (Figures 40-1 and 40-2).

Many strategies used in the past attempted to improve the efficacy of orogastric lavage. At the present time, no data support the use of oral deferoxamine,[32,39,95,96,101] bicarbonate,[14,15] phosphosoda,[4,27] or magnesium.[12,73,90] Although some of these techniques demonstrate efficacy, the associated risks mandate use of only 0.9% sodium chloride solution or tap water for orogastric lavage.

Use of WBI in patients with iron poisoning is supported primarily by case reports and one uncontrolled case series.[17,42,79,80] However, the rationale for WBI use is logical, especially considering the limitations of other gastric decontamination modalities. The usual dose of WBI with polyethylene glycol electrolyte lavage solution is 500 mL/h in children and 2 L/h in adults. This rate is best achieved by starting slowly and increasing as tolerated, often using a nasogastric tube and an infusion pump to administer large volumes.

Antiemetics such as metoclopramide or serotonin antagonists can be used to treat nausea and vomiting. A large volume (44 L) of WBI was administered safely over a 5-day period to a child who had persistent iron tablets on serial abdominal radiographs[42] (Antidotes in Depth: Whole-Bowel Irrigation).

For patients who demonstrate persistent iron in the gastrointestinal tract despite orogastric lavage and WBI, upper endoscopy or gastrotomy and surgical removal of iron tablets adherent to the gastric mucosa may be necessary and lifesaving.[24,64,87]

Deferoxamine

Deferoxamine has been available since the 1960s as a specific chelator for patients with acute iron overdose or chronic iron overload (eg, multiple transfusions). Deferoxamine, which is derived from culture of *Streptomyces pilosus*, has high affinity and specificity for iron. In the presence of ferric iron (Fe^{3+}), deferoxamine forms the complex ferrioxamine, which is excreted by the kidneys,[43] imparting a reddish-brown color to the urine. (See ILD fourine in the Image Library at http://www.goldfrankstoxicology.com)
Deferoxamine chelates free iron and the iron transported between transferrin and ferritin,[50,65] but not the iron present in transferrin, hemoglobin, hemosiderin, or ferritin.[5,43] Deferoxamine may work by other mechanisms in addition to binding excess systemic iron.
Because 100 mg deferoxamine mesylate chelates approximately 8.5 mg ferric iron, recommended or typical therapeutic dosing of deferoxamine does not produce significant excretion of chelated iron in the urine, yet it does often result in dramatic clinical benefits (Antidotes in Depth: Deferoxamine). Sufficient evidence suggests that deferoxamine can reach intracytoplasmic and mitochondrial free iron, thereby limiting intracellular iron toxicity.[50]

Intravenous administration of deferoxamine should be considered in iron-poisoned patients with any of the following findings: metabolic acidosis, repetitive vomiting, toxic appearance, lethargy,

hypotension, or signs of shock. Deferoxamine administration also should be considered for any patient with an iron concentration >500 Âµg/dL. In patients manifesting serious signs and symptoms of iron poisoning, deferoxamine should be initiated as an intravenous infusion, starting slowly and gradually increasing to a dose of 15 mg/kg/h. Hypotension is the rate-limiting factor as more rapid infusions are used.[37,93,95] Intramuscular administration of deferoxamine once was a popular method of therapy and part of the â€œdeferoxamine challengeâ€• test but is no longer recommended. The â€œchallengeâ€• test consisted of administration of an IM dose of deferoxamine 1â€“2 g (90 mg/kg), followed by collection of urine samples to assess for a color change indicating the availability of free iron.[25] Patients who appear toxic and/or have serum iron concentrations >500 Âµg/dL should be treated with deferoxamine intravenously. Patients who have concentrations <500 Âµg/dL or who do not appear toxic should be treated supportively without administration of parenteral deferoxamine (Figure 40-3).

Clinicians have attempted to define the earliest clear end points for deferoxamine therapy because of possible deferoxamine toxicity. In one report, a urine iron-to-creatinine ratio (U_I/Cr) was used to determine if free iron excretion into the urine continued during deferoxamine therapy.[100] This ratio is a more objective measure of the presence of ferrioxamine in the urine than the less reliable and more subjective use of urinary color change.[16,46,89] This method

must be further studied clinically before its use can be advocated. Most authors agree that deferoxamine therapy should be discontinued when the patient appears clinically well, the anion-gap acidosis has resolved, and urine color undergoes no further change.[54] In patients with persistent signs and symptoms of serious toxicity after 24 hours of intravenous deferoxamine, continuing therapy should be undertaken cautiously and perhaps at a lower dose (Antidotes in Depth: Deferoxamine).

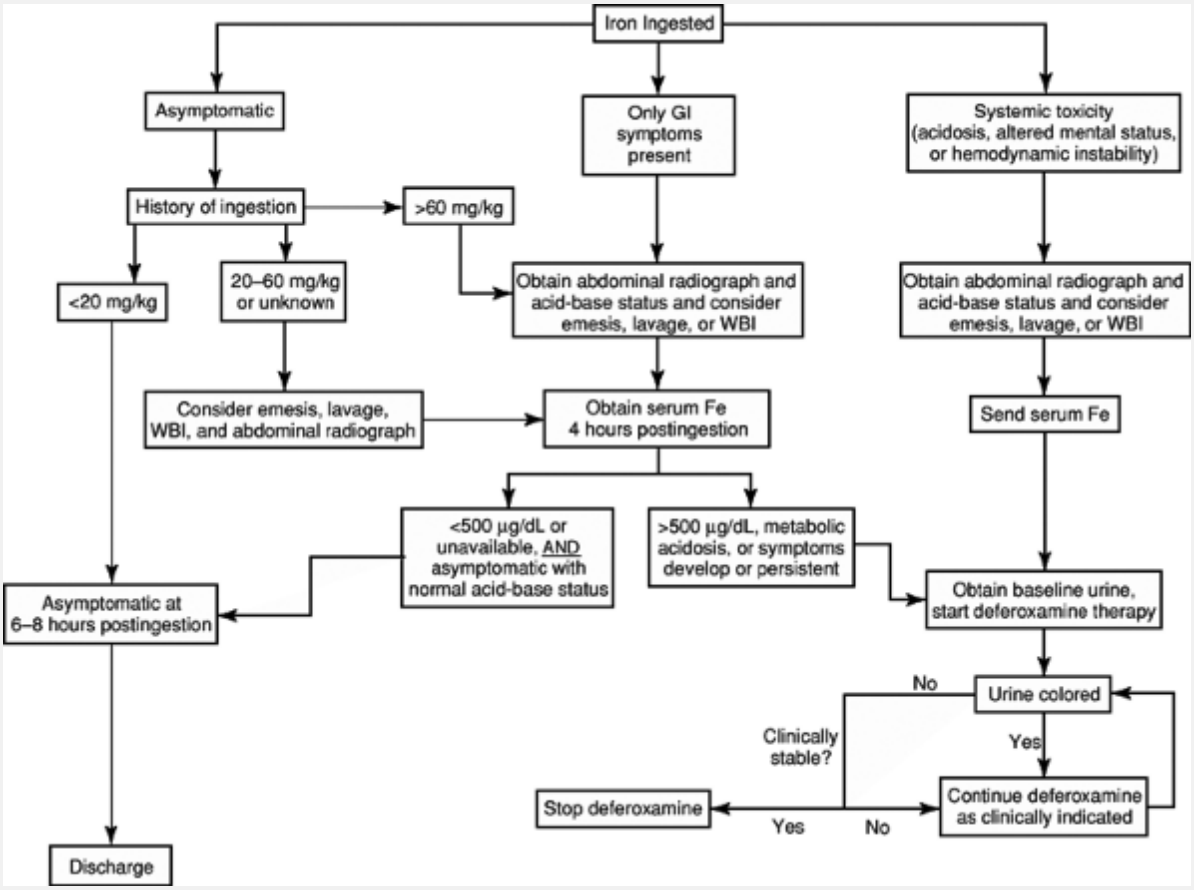

Figure 40-3. Algorithm for decision analysis following iron ingestion.

Patient Disposition

Many patients who ingest iron do not develop significant toxic effects. Recommendations for hospital referral of toddlers who ingest iron range from potential exposures of 20 mg/kg[6] up to 60 mg/kg.[46] These wide ranges probably result from the interpretation of retrospective studies in possibly â€œexposedâ€• toddlers for whom the actual doses were estimated. Many authors suggest that dose was overestimated in patients who subsequently did not develop

toxicity (Chap. 130). If a toddler remains asymptomatic or develops minimal or no gastrointestinal manifestations after a 6-hour observation period in the ED, discharge to an appropriate home situation can be considered. Patients who develop gastrointestinal symptoms and signs of mild poisoning (vomiting, diarrhea) should be observed as inpatients on regular hospital services. Patients who manifest signs and symptoms of significant iron poisoning, such as metabolic acidosis, hemodynamic instability, or lethargy, should be monitored and treated in an intensive care unit. Except in the case of carbonyl iron, hospital evaluation is recommended for any child with an estimated unintentional ingestion of >40 mg/kg elemental iron. Children who appear well with unintentional ingestions between 10 and 20 mg/kg elemental iron and <2 episodes of vomiting should be closely followed at home in consultation with the poison control center.

Pregnant Patients

The frequent diagnosis of iron-deficiency anemia during pregnancy has led to serious and even fatal iron ingestions in pregnant women.[8,44,60,67,85] In all cases of toxic exposures during pregnancy, maternal resuscitation should always be the primary objective, even if an antidote poses a real or theoretical risk to the fetus. Completely unfounded concerns regarding possible deferoxamine toxicity to the fetus have inappropriately, and at times, disastrously delayed therapy.[60,77] These fears about fetal deferoxamine toxicity are not supported in either human or animal studies,[13,52,86] demonstrating that neither iron nor deferoxamine is transferred to the

fetus in appreciable quantities. An animal study demonstrated that fetal serum iron concentrations were not elevated and fetal deferoxamine concentrations could not be detected in pregnant near-term ewes poisoned with iron and treated with deferoxamine. Fetal demise under these circumstances presumably results from maternal iron toxicity and not from direct iron toxicity to the fetus. Thus,

deferoxamine should be used to treat serious maternal iron poisoning and should never be withheld because of unfounded concern for fetal exposure to deferoxamine.

Adverse Effects of Deferoxamine

Most adverse effects of deferoxamine are reported in the setting of chronic administration for treatment of hemochromatosis.[38,61,72] The same effects, such as acute lung injury and acute respiratory distress syndrome (ARDS), also are described after treatment for acute iron overdose.[81] Four patients with serum iron concentrations ranging from 430â€“620 Âµg/dL developed ARDS after intravenous administration of deferoxamine for 32â€“72 hours. An animal study revealed significantly increased pulmonary toxicity when high-dose deferoxamine therapy was administered in the presence of high concentrations of oxygen (75â€“80% FiO_2).[1] The authors suggested that this effect was mediated via an oxygen free radical mechanism (Antidotes in Depth: Deferoxamine).

Alternative Therapies

Another modality used experimentally for treatment of iron intoxication is continuous arteriovenous hemofiltration (CAVH). In a study of five iron-poisoned dogs, increased elimination of ferrioxamine in the ultrafiltrate was demonstrated when increasing doses of deferoxamine were infused into the arterial side of the system.[7] This technique is not described in iron-poisoned humans. Theoretically, ferrioxamine in the blood could be dialyzable with new high-molecular-weight (large-pore) dialysis filters, but this technique has not been studied.

In toddlers with severe poisoning, exchange transfusion may help to physically remove free iron from the blood while replacing it with normal blood. Exchange transfusion in children is effective for poisonings (eg, with theophylline) where the volume of drug

distribution is small and removal from the blood compartment can be expected. However, removal of blood volume may not be well tolerated by iron-poisoned patients, who tend to have hemodynamic instability.

Summary

Despite FDA-mandated warnings on iron preparations, morbidity and mortality secondary to iron exposures continue. A toddler presenting to the ED after presumed iron exposure who has evidence of gastrointestinal toxicity and lethargy is at high risk for significant iron toxicity and possibly death. Although iron is available in multiple formulations (prenatal vitamins, ferrous gluconate supplements), toxicity is determined by the amount of elemental iron present; signs and symptoms occur after ingestions of 20 mg/kg elemental iron. After the patient's condition is stabilized, gastrointestinal decontamination, including orogastric lavage and WBI (polyethylene glycol electrolyte lavage solution), should be initiated when indicated because activated charcoal is ineffective in binding iron. An abdominal radiograph may be helpful in determining the iron burden in the GI tract with preparations that are radiopaque. After iron is absorbed, gastrointestinal symptoms of nausea, vomiting, diarrhea, hematemesis, and abdominal pain are prominent. Systemic iron toxicity leads to metabolic acidosis, hypotension, coagulopathy, and multiorgan system failure. Diagnosis and treatment of shock and acidosis, as well as chelation with deferoxamine, may be lifesaving. Education of parents, caregivers, and prescribers may decrease the incidence of serious iron ingestions in the future.

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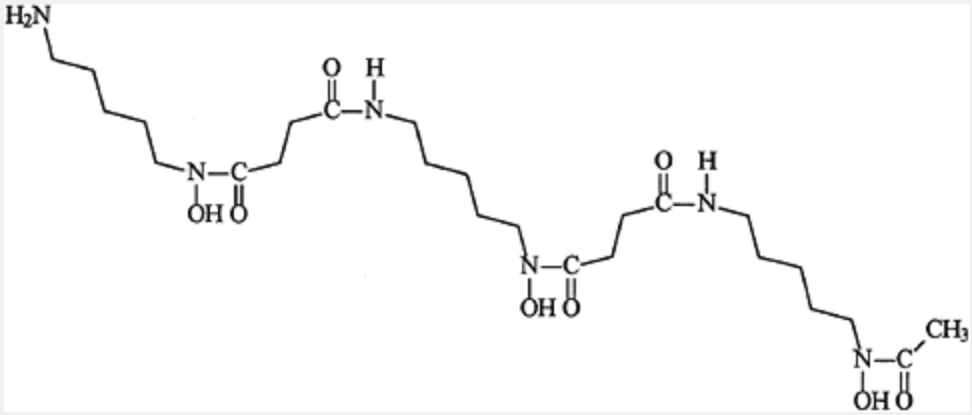
Antidotes in Depth

Deferoxamine

Mary Ann Howland



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History and Chemistry

The development of deferoxamine (DFO or desferrioxamine B)

resulted from analysis of the metabolites of actinomycetes. DFO is the colorless compound that results when the trivalent iron is chemically removed from ferrioxamine B (Figure A8-1).[33] Ferrioxamine is a brownish-red compound containing trivalent iron (ie, ferric, Fe^{3+}) and 3 molecules of trihydroxamic acid isolated from the organism *Streptomyces pilosus*.[33]

DFO is a water-soluble hexadentate chelator with a molecular weight of 561 daltons. The commercial formulation is the mesylate salt with a molecular weight of 657 daltons. One mole of DFO binds 1 mole of Fe^{3+}; therefore, 100 mg DFO as the mesylate salt theoretically can bind 8.5 mg Fe^{3+}.

DFO has a far greater affinity constant for iron (10^{31}) than for zinc, copper, nickel, magnesium, or calcium (10^{2}â€“10^{14}).[33] Thus, at physiologic pH values, DFO complexes almost exclusively with ferric iron.[24,68]

Mechanism of Action

DFO binds Fe^{3+} at the 3 Nâ€“OH sites, forming an octahedral iron complex (Figure A8-1). Once bound, the resultant ferrioxamine is very stable. DFO appears to benefit iron-poisoned patients by chelating free iron (nontransferrin plasma iron) and iron in transit between transferrin and ferritin (chelatable labile iron pool),[27,39,54] while not directly affecting the iron of hemoglobin, hemosiderin, or ferritin.[33] In vitro studies suggest that DFO removes iron from ferritin and transferrin but only very little from hemosiderin.[44] However, in vivo experiments demonstrate that DFO cannot remove iron once the iron is bound to transferrin.[4] DFO does bind â€œfree ironâ€• found in the plasma as nontransferrin plasma iron after transferrin is saturated. This situation occurs in the overdose setting or in chronic iron overload syndromes.[27] In vitro studies demonstrate that DFO chelates and inactivates cytoplasmic and mitochondrial iron, preventing disruption of mitochondrial function and injury.[39] In chronic iron

overload, DFO chelates iron deposited in the reticuloendothelial cells found in the spleen, liver, and bone marrow and excretes it in the urine as ferrioxamine.[27] Whether DFO actually chelates the iron within the reticuloendothelial cells or after liberation into the plasma is unclear. In vitro studies demonstrate that the liver can donate iron to DFO, and chelation subsequently may lead to biliary excretion and fecal elimination.[27,43]

Pharmacokinetics

The volume of distribution of DFO ranges from 0.6â€“1.33 L/kg.[33,36,51] The initial distribution half-life of DFO is 5â€“10 minutes.[35,58] The terminal elimination half-life of DFO is approximately 6 hours in healthy patients[2] but approximately 3 hours in patients with thalassemia. DFO is metabolized in the plasma to several metabolites (Aâ€“F), of which metabolite B is believed to be toxic.[33,36,51,52] Unchanged DFO undergoes glomerular filtration and tubular secretion.[43]

In comparison, ferrioxamine has a smaller volume of distribution than DFO. In nephrectomized dogs, the volume of distribution of ferrioxamine was calculated to be 19% of body weight compared to 50% of body weight for DFO.[33] This finding implies that DFO has a more extensive tissue distribution. The different pharmacokinetic patterns may be related to the potential for penetrance of the straight-chain molecule DFO compared to that of the octahedral ferrioxamine.[52] Experiments in dogs demonstrate that intravenous (IV) ferrioxamine is entirely eliminated by the kidney within 5 hours[33] via glomerular filtration and partial reabsorption.[43]

The pharmacokinetics of DFO and ferrioxamine differ in healthy versus iron-overloaded patients. Plasma DFO concentrations in healthy patients are approximately twice the concentrations noted in patients with thalassemia major, whereas ferrioxamine concentrations are 5 times greater in patients with thalassemia

major compared to healthy patients.[33,59]

Some investigators suggest that DFO can be administered during hemodialysis to remove ferrioxamine.[69] Although hemodialysis[14,58] and hemoperfusion[14] both are effective in ferrioxamine removal, whether these interventions are indicated is unclear.

Animal Studies

Studies in guinea pigs given LD_{50} and LD_{100} oral doses of ferrous sulfate show dramatically improved survival rates after administration of oral DFO in a dose calculated to bind most of the iron, which is substantially less than the DFO dose that is given clinically.[44] Mortality rates in this study and in a similar study in swine[18] directly correlate with the delay in DFO administration.[44]

In 2 subsequent canine studies by the same authors, dogs that received the ironâ€“DFO complex orally had 40â€“100% mortality.[68,69] When both oral and IV DFO were administered, the mortality rate was 67%.[67] A similar followup study demonstrated a 50% mortality rate in dogs given a lethal dose (225 mg/kg) of iron, followed by oral DFO (2.6 g) and IV DFO (0.75â€“1.5 mg/kg/min for 8â€“12 hours).[69] Study results have discouraged substantial interest in the use of oral DFO despite the more favorable results in noncanine species.[5,29,44,63]

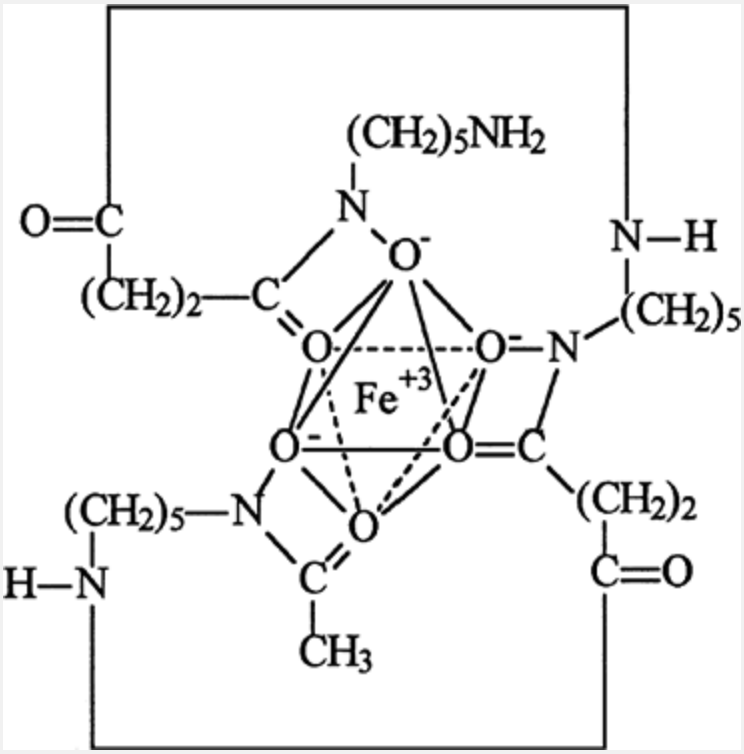

Figure 8-1. Ferrioxamine.

Early Human use and History of Dosing Recommendations

In one of the earliest case series, 172 children who were not severely poisoned and who were hemodynamically stable were treated with 5â€“10 g oral DFO and either 1 or 2 g intramuscular (IM) DFO every 3â€“12 hours.[67] One gram DFO administered intravenously at a maximum of 15 mg/kg/h every 4â€“12 hours, was continued for 2â€“3 days as necessary for patients who were in shock or severely ill. Of the 28 patients who developed coma, shock, or both, only 3 died. One of the 3 patients who died had

received late treatment with DFO.

This case series was expanded to 472 patients, and guidelines for DFO dosing were formulated based on this clinical experience.[66] The recommended IM dose of DFO was suggested as 1 g initially, followed by 0.5 g 4 and 8 hours later and then every 4â€“12 hours as necessary, not to exceed 6 g in 24 hours. For patients in shock, IV DFO was recommended at an initial dose not to exceed 1 g and a rate not to exceed 15 mg/kg/h, followed by two 0.5-g doses separated by 4 hours, and a total dosage not to exceed 6 g in 24 hours. These recommendations for total dosages were not scientifically developed and appear to be based on arbitrary assumptions. However, the manufacturer continues to recommend these doses.[19]

Urinary Color Change

To further define the role of DFO, investigators studied urinary samples. A vin rosÃ© color to the urine following DFO was found to be indicative of 10â€“30 mg urinary iron excretion per 24 hours.[44] In a review of 107 patients with acute iron poisoning who had received 5 g DFO orally and 90 mg/kg DFO IV, at a rate not greater than 15 mg/kg/h,[41] the appearance of a vin rosÃ© color in urine or a serum iron concentration >500 Âµg/dL prompted chelation for at least 24 hours. Further studies investigated the correlation between urinary iron concentrations and systemic toxicity.[71] Most data suggest that the absence of a urine color change following DFO administration, indicates very little renal excretion of ferrioxamine.[23] Unless a baseline urine is obtained prior to DFO administration, post-DFO administration comparisons of urine color are unreliable. No relationship between urinary iron excretion, clinical iron toxicity, and the effectiveness of DFO has been established.

IM Versus IV Administration

Prior to 1976, IM DFO was the preferred route of administration and IV DFO was reserved for patients in shock. However, when transfusion-induced iron overload was studied and IM and IV DFO administration were compared, IV DFO significantly enhanced urinary iron elimination.[55] This study provided compelling arguments against IM dosing, as did data showing higher peak concentrations and more stable levels with IV infusions. A single patient was given 425 mg/kg IV over 24 hours without incident, although the increase in urinary iron excretion seen when the DFO dose increased from 4 to 16 g/d appeared to be of limited consequence.

Duration of Dosing

Optimum duration of DFO administration is unknown. In canine models, serum iron concentrations peak within 3â€“5 hours and then fall quickly as iron is transported out of the blood into the tissues.[64,70] In one human study, initial iron concentrations of approximately 500 Âµg/dL fell to approximately 100 Âµg/dL within 12 hours.[37] Other case reports also suggest that most of the easily accessible iron is distributed out of the blood compartment by 24 hours.[20] Although severely poisoned patients have received DFO for more than 24 hours, pulmonary toxicity has been associated with prolonged DFO infusions.[26,49,61] Intuitively, in patients with acute iron overdose DFO should be administered early and for a shorter duration while the iron is easily accessible in the blood. In patients with chronic iron overdose, prolonged infusions of smaller DFO doses are necessary to act as a sink and to slowly remove iron from the labile pool and tissue stores.[30]

Adverse Effects

DFO administration to patients with acute iron overdose is associated with rate-related hypotension, pulmonary toxicity, and infection. DFO administration to patients with chronic iron overload

is associated with auditory, ocular, and pulmonary toxicity and infection.[9,30]

Significant hypotension was first noted in 1965 in 2 children who were administered approximately 80â€“150 mg/kg DFO intravenously over 15 minutes.[68] The mechanism for rate-related hypotension is not fully understood, although histamine release is implicated. Elevated histamine concentrations were documented in a canine experiment, but pretreatment with diphenhydramine was not protective.[69] Intravascular volume depletion due to iron toxicity also contributes to the hypotension. No experiment has determined the maximum safe rate of DFO administration. Adverse effects of DFO were reported when DFO was infused rapidly, including tachycardia, hypotension, shock, erythema, and urticaria,[67] resulted in the current recommendations for less rapid IV infusions of DFO not exceeding 15 mg/kg/h.[67,68 and 69] Currently suggested IV infusion rates are somewhat empirical because of the lack of robust evidence. Higher rates were administered successfully in critically ill patients when time was of the essence.[11,15,20]

Acute lung injury (ALI) has been described in the setting of acute iron overdoses following IV administration of DFO (15 mg/kg/h) therapy for >24 hours.[3,32,61] Usually iron concentrations returned to therapeutic levels in these patients within 24 hours, and the rationale for continued administration of DFO was not reported. Examination of the nontoxicologic literature reveals other instances of ALI occurring in patients receiving continuous IV DFO for hemosiderosis and malignancies.[13,22,65] Administration of continuous IV doses of DFO for prolonged (>24 hours) periods was common to all of these patients. The mechanism for development of pulmonary toxicity after DFO is unknown. Pulmonary toxicity may result from excessive DFO chelation of intracellular iron and depletion of catalase, resulting in oxidant damage[25] or generation of free radicals.[1]

DFO therapy may lead to infection with a number of unusual organisms, including *Yersinia enterocolitica*, *Zygomycetes*, and *Aeromonas hydrophilia.* The virulence of these organisms is facilitated when the DFOâ€“iron complex acts as a siderophore for their growth.[38,42,45] Most cases of septicemia occurred when DFO was used for treatment of aluminum toxicity in patients receiving chronic hemodialysis.[43] Several cases of *Yersinia* sepsis were reported following acute iron overdose and treatment with DFO.[42,45]

Ocular toxicity characterized by decreased visual acuity, night blindness, color blindness, and retinal pigmentary abnormalities has occurred in patients who received continuous IV DFO for thalassemia and other nonacute iron- and aluminum-excess conditions.[8,12,17,48,50] Ototoxicity documented by abnormal audiograms indicating partial or total deafness has been reported.[52,53] However, neither ocular toxicity nor ototoxicity has been reported in the acute toxicologic literature.

Use in Pregnancy

A review of the literature identified 61 cases of intentional iron overdose in pregnant women.[62] Serious iron toxicity with organ involvement is associated with spontaneous abortion, preterm delivery, and maternal death. No evidence indicates that DFO is teratogenic.[62] Neither iron nor DFO appears to cross the ovine placenta.[16] A case report of a pregnant woman with thalassemia and a review of 40 other pregnant patients with thalassemia treated extensively with DFO found no evidence of teratogenicity.[57] DFO should be administered to pregnant women with acute iron overdose for the same indications as for nonpregnant women.

Use in Aluminum Toxicity

Patients with renal insufficiency are at high risk for aluminum toxicity.[72] Acute aluminum toxicity resulting from bladder irrigations with alum for hemorrhagic cystitis is also reported. Chronic aluminum toxicity is reported from administration of aluminum salts as phosphate binders or from hemodialysis with a water source containing aluminum. DFO binds aluminum to form aluminoxamine, analogous to Fe and ferrioxamine. The chelate is a 1:1 octahedral complex with aluminum.[72] Aluminoxamine is excreted renally. In patients with renal insufficiency, hemodialysis (especially with a high-flux membrane) is effective in removing the aluminoxamine and should be used to prevent aluminum redistribution to the CNS and other tissues.[46] The dosing of DFO should be tailored to the patient's serum aluminum concentrations, symptomatology, and response.[46] DFO doses of 15 mg/kg/d, infused over 1 hour and 6â€“8 hours before hemodialysis, have been successful and maximize aluminoxamine removal.[46]

Indications and Dosing

The indications and dosage schedules for DFO administration are largely empirical.[6,56] Systemic toxicity associated with acute iron poisoning manifested by coma, shock, or metabolic acidosis warrants IV infusion of DFO. The duration of therapy probably should be limited to 24 hours to maximize effectiveness while minimizing the risk of pulmonary toxicity. Some investigators have suggested that more than the recommended dose of 15 mg/kg/h be infused during the first 24 hours for life-threatening iron toxicity, but this recommendation remains to be validated experimentally.[30] Although patients with mild toxicity can be treated with IM injections of DFO 90 mg/kg (maximum 1 g in children or 2 g in adults), this volume of antidote cannot be given intramuscularly with ease or painlessly in children. Therefore, few clinicians administer DFO IM and most choose the preferable IV route (Chap. 40). The total daily parenteral dose is limited by the infusion rate in children (if manufacturer's recommendations are

followed). Conservative recommendations in adults limit the dose to 6â€“8 g/d, although doses as high as 16 g/d with diverse dosing regimens have been administered without incident.[15,20,40,49,55,60]

Availability

Deferoxamine mesylate (Desferal) is available in vials containing 500 mg or 2 g sterile, lyophilized powder. Adding 5 or 20 mL of sterile water for injection to either the 500-mg or the 2-g vial, respectively, results in a 100 mg/mL solution. This solution is isotonic, clear, and colorless to slightly yellowish.[19] The resulting solution can be diluted further with 0.9% NaCl solution, glucose in water, or Ringer lactate solution for IV administration. For IM administration, a smaller volume of solution is preferred. Adding 2 or 8 mL of sterile water for injection to the 500-mg or 2-g vial, respectively, results in a stronger yellow-colored solution containing 250 mg/mL.

Additional Iron Chelators

New iron chelators are being investigated. Pyridoxal isonicotinylhydrase and pyridoxal benzoylhydrazone are potent lipophilic chelators. Lipophilicity increases iron mobilization but may also increase toxicity. Deferiprone is a bidentate oral iron chelator. Three moles of deferiprone are required to bind 1 mole of ferric ion to form a stable complex.[27] Inappropriate ratios of drug to iron may be ineffective or even harmful because of the formation of potentially toxic intermediates.[27] Preliminary animal studies of acute toxicity are contradictory.[10,21,31,34] The effectiveness and long-term safety of deferiprone for chronic iron overload associated with thalassemia major have been questioned.[7,35,47] Other hexadentate drugs and prodrugs are under investigation.[27]

Summary

DFO is the parenteral chelator of choice for treatment of iron poisoning. Although DFO has been used to treat acute iron overdose

for many years,[28] no controlled studies have evaluated efficacy or dosing. Much of our knowledge derives from animal studies and case series in the 1960s and early 1970s and from limited case reports throughout the ensuing years. DFO is used for chelation of aluminum in patients with chronic renal failure.

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Chapter 41
Vitamins

Beth Y. Ginsburg

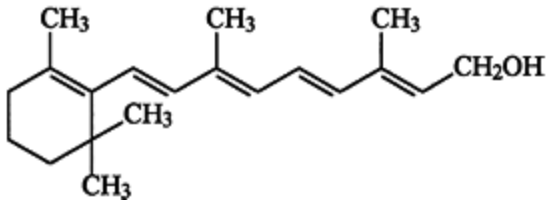
Vitamins are essential for normal human growth and development.[36] By definition, a vitamin is a substance that is present in small amounts in natural foods, is necessary for normal metabolism, and whose lack in the diet causes a deficiency disease.[30] According to the American Medical Association, healthy men and nonpregnant women who eat a varied diet do not need supplemental vitamins.[8] However, millions of people in the United States regularly ingest quantities of vitamins in great excess of the recommended dietary allowances (RDAs) (Table 41-1). Many of these individuals share the mistaken beliefs that vitamin preparations provide extra energy or promote muscle growth. Fortunately, for the most part, even large doses of vitamins do not lead to significant toxicity. However, some vitamins are associated with significant adverse effects when ingested in very large doses.

Vitamins can be divided into two general classes. Most of the vitamins in the *water-soluble* class have minimal toxicity because they are stored to only a limited extent in the body. Thiamine, riboflavin,

cyanocobalamin (vitamin B_{12}), pantothenic acid, folic acid, and biotin are not reported to cause any toxicity following oral ingestion.[36] Ascorbic acid (vitamin C), nicotinic acid, and pyridoxine (vitamin B_6) are associated with toxicity syndromes. The *fat-soluble* vitamins can bioaccumulate to massive degrees. As a result, the potential for toxicity greatly exceeds that of the water-soluble group. Vitamins A, D, and E but not K are associated with toxicity in the setting of very large overdoses. Adverse effects secondary to vitamin K are limited to severe, and sometimes fatal, anaphylactoid reactions with administration of the intravenous (IV) preparation.[58]

Vitamin A

MW	= 272.43 daltons
Therapeutic serum level	= 65–275 IU/dL 16.6–83.3 μg/dL



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History and Epidemiology

The term *vitamin A*, classically used to refer to the compound retinol, now is also used to describe other naturally occurring derivatives of retinol. Vitamin A activity is expressed in retinol equivalents (RE). One RE corresponds to 1 Âµg of retinol or 3.3 international units (IU) of vitamin A activity as retinol. As a group, these compounds are called *retinoids.* They have specific sites of action and varying degrees of biologic potency. Vitamin A, in the form of 11-*cis*-retinal, plays a critical role in retinal function.[187] Deficiency results in

nyctalopia, which is decreased vision in dim lighting, more commonly known as *night blindness.* Retinoic acid is primarily responsible for maintaining normal growth and differentiation of epithelial cells in mucus-secreting or keratinizing tissue.[122] Vitamin A deficiency results in the disappearance of goblet mucous cells and replacement of the normal epithelium with a stratified, keratinized epithelium. Dermal manifestations are the earliest to develop and include dry skin and hair and broken fingernails. In the cornea, hyperkeratization is called *xerophthalmia* and can lead to permanent blindness. Alterations in the epithelial lining of other organ systems may lead to increased susceptibility to respiratory infections, diarrhea, and urinary calculi.

Two independent groups discovered vitamin A in 1913.[126 , 144] They reported that animals fed an artificial diet with lard as the sole source of fat developed a nutritional deficiency characterized by xerophthalmia. They found that this deficiency could be corrected by adding to the diet a factor contained in butter, egg yolks, and cod liver oil. They named this substance â€œfat soluble vitamin A.â€• The chemical structure of vitamin A was determined later in 1930.[99] Preformed vitamin A is also found in liver, fish, cheese, and whole milk. In the United States, many breakfast cereals, margarine, and most fat-free milk and dried nonfat milk solids are fortified with vitamin A.[193] In some developing countries, sugar, oil, margarine, milk, wheat and corn flours, noodles, and rice are fortified with vitamin A.[6] In addition, infant formulas and cereals usually are fortified with vitamin A. Vitamin A content varies widely among different food types. A 3-oz serving of cooked beef liver contains 30,325 IU of vitamin A, whereas 1 cup of whole milk contains 305 IU of vitamin A. Fish-liver oils, such as swordfish and Black Sea bass, have extremely large amounts of vitamin A and may contain more than 180,000 IU of vitamin A per gram of oil. Carotenoids, vitamin A precursors, are present in yellow and green fruits and vegetables. A raw carrot has a high Î²-carotene content of approximately 20,250 IU. One half-cup serving of spinach contains approximately 7395 IU of Î²-carotene, whereas an apricot or peach

contains 500â€“600 IU. The average American diet provides about half of its daily vitamin A intake as carotenoids and about half as preformed vitamin A.[34] The RDA of vitamin A is 900 Âµg RE/d (3000 IU/d) for adult men and 700 Âµg RE/d (2300 IU/d) for women (Table 41-1).[62] The tolerable upper intake level for adults is 3000 Âµg/d (9900 IU/d).[62]

Infants
0.0â€“0.5
400/1300*
5/200*
4/4*
40*
0.1*
2*
0.5â€“1.0
500/1700*
5/200*
5/5*
50*
0.3*
4*
Children
1â€“3
300/990
5/200*
6/6
15
0.5
6
4â€“8
400/1300
5/200*
7/7

25
0.6
8
Males
9â€“13
600/2000
5/200*
11/11
45
1.0
12
14â€“18
900/3000
5/200*
15/15
75
1.3
16
19â€“49
900/3000
5/200*
15/15
90
1.3
16
50â€“70â€“
900/3000
10/400*
15/15
90
1.7
16
>70
900/3000

15/600*
15/15
90
1.7
16
Females
9â€“13
600/2000
5/200*
11/11
45
1.0
12
14â€“18
700/2300
5/200*
15/15
65
1.2
14
19â€“49
700/2300
5/200*
15/15
75
1.3
14
50â€“70
700/2300
10/400*
15/15
75
1.5
14

>70
700/2300
15/600*
15/15
75
1.5
14
Pregnant
â ‰ ¤18
750/2500
5/200*
15/15
80
1.9
18
19â€“50
770/2500
5/200*
15/15
85
1.9
18
Lactating
â ‰ ¤18
1200/4000
5/200*
19/19
115
2.0
17
19â€“50
1300/4300
5/200*
19/19

120
2.0
17
Adapted from Food and Nutrition Information Center homepage. http://www.nal.usda.gov/fnic/etext/000105.html . Accessed April 27, 2005.

Age (yr)	Vitamin A (Âµg RE/IU)	Vitamin D (Âµg/IU)	Vitamin E (mg Î±-TE/IU)	Vitamin C (mg)	Vitamin B_6 (mg)	Niacin (mg NE)

TABLE 41-1. Recommended Dietary Daily Allowances/Adequate Daily Intakes

Hypervitaminosis A can occur in people who ingest large doses of vitamin A in their daily diets. Vitamin A toxicity is believed to occur in the Inuit population whose diet includes polar bear liver. Polar Eskimos in the 16th century recognized that ingestion of large amounts of polar bear liver caused a severe illness characterized by headaches and prostration.[59] Arctic explorers in the 1800s knew of the poisonous qualities of polar bear liver and described an acute illness following its ingestion.[66] However, the toxic substance in polar bear liver was not identified as vitamin A until 1942.[158] The vitamin A content of polar bear liver is as high as 34,600 IU/g, supporting the view that vitamin A is the toxic factor in liver.[159] Hypervitaminosis A also is implicated in the etiology of pibloktoq, or â€œarctic hysteria,â€• as some somatic and behavioral effects of vitamin A toxicity closely parallel many of the symptoms reported in Inuit patients diagnosed with pibloktoq.[108]

Vitamin A toxicity was reported in an adult who chronically ingested large amounts of beef liver.[93] Symptomatology consistent with vitamin A toxicity was reported following ingestion of the liver of the grouper fish *Cephalopholis boenak* , which has an average vitamin A

content high enough to cause acute toxicity.[31] Ingestion of sea whale and seal liver, as well as the livers of large fish, such as shark, tuna, and sea bass, also is associated with development of hypervitaminosis A.

The majority of cases of vitamin A toxicity result from use of vitamin supplements.[14, 16] In the United States, approximately 5% of adults take vitamin A supplements.[76] Vitamin A is prescribed for some people for dermatologic and ophthalmic conditions. Hypervitaminosis A often occurs in adults who continue to use the vitamin without medical supervision.[67]

Isotretinoin (Accutane), 13-*cis* -retinoic acid, is prescribed for treatment of severe cystic acne. Of great concern is the teratogenicity associated with its use. According to the National Disease and Therapeutic Index, 38% of isotretinoin users are females aged 13â€“19 years. The high likelihood of pregnancy in this group underscores the need to inform all users of the contraindication of this drug's use during pregnancy and the need to demonstrate the absence of pregnancy prior to initiating treatment. In addition, patients must consider the consequences of unintentional pregnancy while they are taking isotretinoin.

Pharmacology and Toxicokinetics

Absorption of vitamin A in the small intestine is nearly complete. However, some vitamin A may be eliminated in the feces when large doses are taken. The majority of vitamin A is ingested as retinyl esters, the storage form of retinol.[122] Retinyl esters undergo enzymatic hydrolysis to retinol by digestive enzymes in the intestinal lumen and brush border of the intestinal epithelial wall. A small portion of retinol is absorbed directly into the circulation, where it is bound to retinol-binding protein (RBP) and transported to the liver. Most of the retinol is taken into intestinal epithelial cells by the carrier protein cellular RBP.[141] Subsequently, retinol is reesterified and incorporated into chylomicrons, which are taken up by the liver.

doses, significant amounts of retinyl esters circulate in association with low-density lipoproteins (LDLs) and are delivered to the liver. Approximately 90% of the body's total vitamin A content is stored in the liver as retinyl esters. Vitamin A is released into the plasma for delivery to other tissues as needed.

Carotenoid absorption requires the presence of bile and absorbable fat in the intestinal tract. Only a portion of these vitamin A precursors is cleaved into retinaldehyde, which subsequently is reduced to retinol. This process occurs in the intestinal wall. Retinol then is absorbed and transported by RBP or converted to retinyl esters and transported by lipoproteins via lymphatics to the liver and other tissues. Massive doses of carotenoids are not converted rapidly enough to produce vitamin A toxicity. However, high blood concentrations of carotenoids are achieved. Hypercarotenemia produces a yellow-orange skin discoloration that can be differentiated from jaundice by the absence of scleral icterus.

The normal plasma retinol concentration is approximately 30â€“70 Âµg/dL.[169] Blood concentrations are maintained at the expense of hepatic reserves when insufficient amounts of vitamin A are ingested. A normal adult liver contains enough vitamin A to fulfill the body's requirements for approximately 2 years.[132] Thus symptoms of vitamin A deficiency can be prevented for many months. Excessive intake of vitamin A is not initially reflected as elevated blood concentrations because vitamin A is soluble in fat but not in water. Instead, hepatic accumulation is increased. This storage system allows for cumulative toxic effects. Although no relationship exists between the magnitude of liver stores and blood concentrations of vitamin A, in chronic hypervitaminosis A, serum concentrations are generally > 3.49 Âµmol/L (95 Âµg/dL).[16] Vitamin A has a half-life of 286 days in the blood.[171 , 191]

Clinical toxicity correlates well with total body vitamin A content,

which is a function of both dosage and duration of administration. Hypervitaminosis A is rare, with a reported average incidence of <10 cases per year from 1976 to 1987.[16] A randomized double-blind trial, in which 390 women who received 400,000 IU of vitamin A as a single dose were compared with 380 women who received placebo, suggested that dosing at this level is well tolerated by postpartum women.[92] It has been demonstrated that 100,000 IU of vitamin A in children aged 6â€“11 months and 200,000 IU of vitamin A every 3 to 6 months for children aged 12â€“60 months results in few side effects and is effective in reducing mortality.[15] The minimal dose required to produce toxicity in humans is not established. However, an animal study has shown that the median lethal acute dose in monkeys weighing between 1.0 and 1.8 kg is 560,000 IU (168 mg) per kg body weight.[119] In this study, all monkeys receiving > 300 mg/kg died, whereas none died at a dose of 100 mg/kg. Hepatoxicity can occur in humans following an acute ingestion of a massive dose of vitamin A (>600,000 IU).[105]

Hypervitaminosis A may occur more frequently secondary to chronic ingestions of vitamin A. Hepatotoxicity typically requires vitamin A ingestions of at least 50,000â€“100,000 IU/d for months or years.[6] , [105] One study found that in patients with vitamin A-induced hepatotoxicity, the average daily vitamin A intake was higher in patients who developed cirrhosis (135,000 IU/d) compared to patients who developed noncirrhotic liver disease (66,000 IU/d).[67] However, case reports have documented hepatotoxicity resulting from vitamin A doses as low as 25,000 IU/d,[67] , [105] a dose widely available in vitamin A preparations found in health food stores.

Pathophysiology

The mechanism of action for many of vitamin A's toxic effects may be at the nuclear level. Retinoic acid influences gene expression by combining with nuclear receptors.[122] Retinoids also influence expression of receptors for certain hormones and growth factors. Thus

they are able to influence growth, differentiation, and function of target cells.[117]

In epithelial cells and fibroblasts, retinoids affect changes in nuclear transcription, resulting in enhanced production of proteins such as fibronectin and decreased production of other proteins such as collagenase.[121] Excessive concentrations of retinoids lead to the presence of goblet cells, production of a thick mucin layer, and inhibition of keratinization. In addition, lipoprotein membranes have increased permeability and decreased stability, resulting in extreme thinning of the epithelial tissue.

In vitro studies in bone demonstrate that high doses of vitamin A are capable of directly stimulating bone resorption and inhibiting bone formation. This effect is secondary to increased osteoclast formation and activity and inhibition of osteoblast growth.[138 , 143 , 165]

Hepatotoxicity may develop secondary to an acute overdose or ingestion of â€œlowâ€• or â€œtherapeuticâ€• doses if taken over a prolonged time.[67 , 105] Ninety percent of hepatic vitamin A stores are located in the Ito, or fat-storing, cells of the liver, which are located in the perisinusoidal space of Disse, and are responsible for maintaining normal hepatic architecture.[79] Ito cells undergo hypertrophy and hyperplasia as vitamin A storage increases.[105] This results in transdifferentiation of the Ito cell into a myofibroblastlike cell that secretes a variety of extracellular matrix components, leading to narrowing of the perisinusoidal space of Disse, obstruction to sinusoidal blood flow, and noncirrhotic portal hypertension (Figure 41-1).[40 , 71 , 89 , 100 , 105 , 162] Continued ingestion of vitamin A and hepatic storage may lead to obliteration of the space of Disse, sinusoidal barrier damage, perisinusoidal hepatocyte death, fibrosis, and cirrhosis.[89 , 96 , 105 , 160]

Vitamin A toxicity is associated with idiopathic intracranial hypertension (IIH). Although vitamin A's role in the development of IIH is not definitively understood, serum concentrations of vitamin A are significantly higher in patients with IIH compared to healthy

controls.[94] In addition, cerebrospinal fluid (CSF) concentrations of vitamin A are significantly elevated in patients with IIH compared to patients with normal intracranial pressure (ICP) or patients with other causes of elevated ICP.[190] Unbound, circulating retinol and

retinyl esters are proposed to be capable of interacting with cell membranes and producing damage by membranolytic surface-active properties.[94] In the central nervous system (CNS), disruption of cell membrane integrity might lead to disruption of CSF outflow, thereby producing signs and symptoms consistent with IIH.[69 , 94 , 103 , 120]

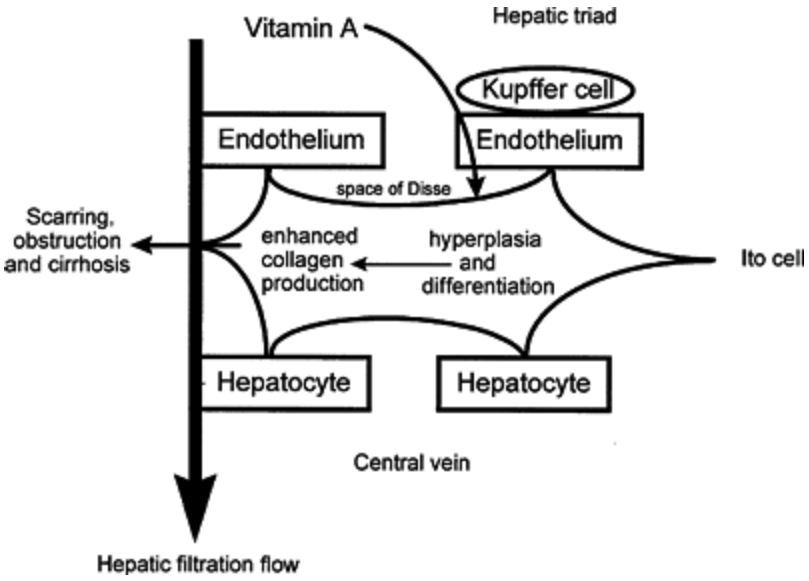


Figure 41-1. Schematic demonstration of hepatotoxicity resulting from excessive deposition of vitamin A in the Ito cells of the liver.

Clinical Manifestations

Hypervitaminosis A affects the skin, hair, bones, liver, and brain. The most common skin manifestations include xerosis, which is associated with pruritus and erythema, skin hyperfragility, and desquamation.[45 , 46 , 195] Retinoid toxicity may cause hair thinning and even diffuse hair loss in 10â€“75% of patients.[61 , 70 , 102] In addition, the

characteristics of the hair may change after regrowth. Hair sometimes becomes permanently curly or kinky.[10] Nail changes include a shiny appearance, brittleness, softening, and loosening.[55] Dryness of mucous membranes develops with chapped lips and xerosis of nasal mucosa, which sometimes is associated with nasal bleeding.[38]

Epidemiologic studies are consistent with bone loss and a resulting increase in fracture risk. In northern Europe, the region with the highest incidence of osteoporotic fractures, dietary intake of vitamin A is high. A study of this population demonstrated that the risk of first hip fracture was increased by 68% for every 1 mg increase in RE intake.[128] This study also showed that compared to intake <0.5 mg/d, intake >1.5 mg/d reduced bone mineral density by 10% at the femoral neck, 14% at the lumbar spine, and 6% for the total body, and doubled the risk of hip fracture. These findings are supported by other studies demonstrating an increased risk of hip fracture among women with elevated serum vitamin A concentrations and in women ingesting large daily amounts of vitamin A.[56 , 142] One study found that among women not taking supplemental vitamin A, a diet rich in vitamin A was also associated with an increased fracture risk.[56]

Other musculoskeletal findings include skeletal hyperostoses, most commonly affecting the vertebral bodies of thoracic vertebrae, extraspinal tendon and ligament calcifications, soft-tissue ossification, cortical thickening of bone shafts, periosteal thickening, and bone demineralization.[38 , 132 , 134] Many of these findings are apparent on radiographs. Patients often complain of bone and joint pain and muscle stiffness or tenderness. Hypercalcemia, with low parathyroid hormone (PTH) concentrations, is thought to be secondary to increased osteoclast activity and bone resorption.[23] Premature epiphyseal closure in children is reported.[151] Teratogenic effects include interference with skeletal differentiation and growth.[23]

The degree of hepatotoxicity appears to correlate with the dose of vitamin A and chronicity of use. With large doses, cirrhosis develops and may lead to portal hypertension, esophageal varices, jaundice,

and ascites.[41, 67, 105] Hepatotoxicity may be manifested by elevations in bilirubin, aminotransferases, and alkaline phosphatase concentrations.

Idiopathic intracranial hypertension, previously known as pseudotumor cerebri and benign intracranial hypertension, is characterized by elevated ICP in the absence of a focal lesion, infective process, or hydrocephalus. It occurs in patients with altered endocrine function, systemic diseases, impaired cerebral venous drainage, or ingestion of various xenobiotics, including excessive vitamin A[5] (Table 41-2). The syndrome is most common in young obese women, but the etiology remains unknown in the majority of cases. The first case of IIH associated with vitamin A toxicity was described in 1954.[66] However, the symptoms were first described in 1856 by an Arctic explorer who noted vertigo and headache after eating polar bear liver.[168] Patients typically present with headache and visual disturbances, including sixth nerve palsies, visual field deficits, and blurred vision, and have a normal mental status. Despite severe papilledema, visual loss often is minimal. However, blindness may result from optic atrophy.[118] Other symptoms of neurotoxicity include ataxia, fatigue, depression, irritability, and psychosis.[21]

Drugs
- Antibiotics: nalidixic acid, tetracycline, ampicillin, minocycline, nitrofurantoin, sulfamethoxazole, metronidazole
- Corticosteroid therapy (oral and intranasal) and cessation
- Griseofulvin
- Lithium
- Oral contraceptives and progestational drugs
- Phenothiazlnes
- Phenytoin
- Vitamin A

Toxins
- Lead

Anesthetics

Enflurane
Halothane
Ketamine
d -Tubocurare

TABLE 41-2. Drugs and Toxins Associated with Intracranial Hypertension

Isotretinoin is effective in the management of acne. However, its use is associated with teratogenecity. It is thought to interfere with cranial-neural-crest cells, which contribute to the development of both the ear and the conotruncal area of the heart and may cause malformed or absent external ears or auditory canals and conotruncal heart defects.[107] Although studies have not shown a teratogenic risk with topical preparations, case reports describe fetal malformations associated with their use during pregnancy.[11, 28, 97, 116, 167] In addition, mucocutaneous abnormalities, IIH, corneal opacities, hypercalcemia, hyperuricemia, musculoskeletal symptoms, liver function abnormalities, elevated triglyceride concentrations, and spontaneous abortion are reported.[3, 60, 65, 74, 75]

Treatment with tretinoin (all-*trans* -retinoic acid), followed by anthracycline and cytarabine, improves the complete remission rate and reduces the incidence of relapse in cases of acute promyelocytic leukemia.[54] Retinoic acid syndrome is the main adverse effect and may occur in up to 25% of patients who receive tretinoin without prophylactic measures. The syndrome is characterized by dyspnea, pulmonary effusions and infiltrates, fever, weight gain, renal failure, pericardial effusions, and hypotension.[53] Elevated leukocyte counts at diagnosis or rapidly increasing counts during tretinoin treatment predict the development of retinoic acid syndrome. Its etiology is thought to be related to cytokine release by maturing blast cells. Addition of dexamethasone to the treatment regimen decreases the incidence of this syndrome to approximately 15% and its mortality to 1%.[54]

Symptoms of an acute overdose often develop within hours to 2 days after ingestion.[132] Initial signs and symptoms include headache, papilledema, scotoma, photophobia, seizures, anorexia, drowsiness, irritability, nausea, vomiting, abdominal pain, liver damage, and desquamation.[132] Additional signs and symptoms are associated with chronic toxicity.[132] Nonspecific symptoms include fatigue, fever, weight loss, edema, polydipsia, dysuria, hyperlipidemia, anemia, and menstrual abnormalities.

Diagnostic Testing

An elevated serum vitamin A concentration is greater than 80 Âµg/dL. However, because the liver has a large storage capacity for excess vitamin A, hepatotoxicity may occur prior to an elevation in the serum concentration, which may be normal or even low, in the setting of an acute overdose. As the liver's storage capacity is overwhelmed, the serum concentration may rapidly rise in a nonlinear fashion. The diagnosis of vitamin A hepatotoxicity is supported by histologic evidence of Ito cell hyperplasia with fluorescent vacuoles on liver biopsy.[67] Laboratory testing should also include serum electrolytes, including calcium; liver function tests; and a complete blood cell count. Further evaluation should be guided by the clinical presentation and may include bone radiographs, computed tomography of the brain, and lumbar puncture.

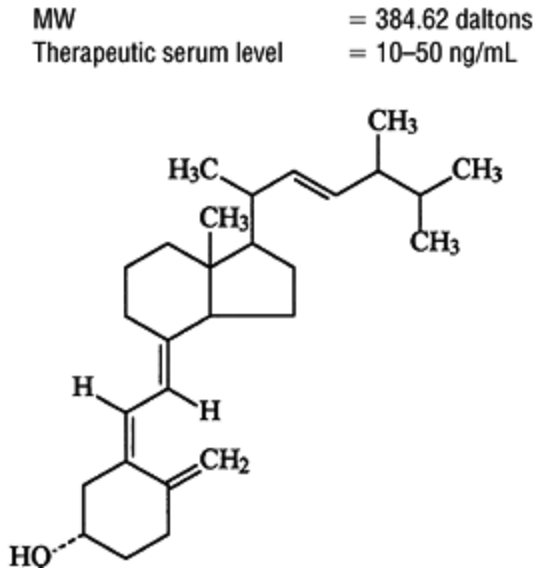
Treatment

Management of an acute, large overdose should begin with gastrointestinal decontamination. This can be accomplished with a dose of activated charcoal. In extremely large overdoses that are expected to produce significant toxicity, gastric lavage may be considered. Although most signs and symptoms of hypervitaminosis A resolve within 1 week of vitamin A discontinuation and with supportive care, papilledema and skeletal abnormalities may persist for several

months. Visual impairment secondary to optic atrophy may be a permanent sequela of vitamin A toxicity. Hypercalcemia should be treated with IV fluids, loop diuretics, and prednisone 20 mg/d.[20] Bisphosphonates may be beneficial in refractory cases.

IIH may require more aggressive therapy, similar to that of other causes of increased ICP. Depending on the severity of the syndrome, patients may require dexamethasone (0.25â€“0.5 mg/kg/d in children <40 kg and 12â€“16 mg/d in adults); an initial adult dose of 250 mg acetazolamide, which can be increased to 500 mg 3 times per day; 40 mg IV furosemide; and 1 g/kg mannitol.[168] Tapering doses of hydrocortisone or prednisone are alternatives to dexamethasone. Acetazolamide decreases CSF formation but may be associated with a transient increase in ICP. Patients with extremely high ICP may benefit from daily lumbar punctures with CSF drainage.

Vitamin D



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History and Epidemiology

Vitamin D is the name given to both cholecalciferol (vitamin D_2) and ergocalciferol (vitamin D_3). In humans, both forms of vitamin D have the same biologic potency. Vitamin D is used for the prophylaxis and treatment of rickets, osteomalacia, and osteoporosis, treatment of hypoparathyroidism, and skin conditions including psoriasis. Rickets, a disease of urban children living in temperate zones, was thought to result from the lack of a dietary factor or adequate sunshine. In 1919, two independent groups demonstrated that rickets could be prevented or cured by either the addition of cod liver oil to the diet or exposure to sunlight.[91 , 129] Vitamin D is found in other foods, including butter, cheese, and cream, which contain 12â€“50 IU/100 g; eggs, which contain 25 IU/100 g; and fatty fish, such as salmon and mackerel, which contain 150â€“550 IU/100 g and 1100 IU/g, respectively. Some foods typically are fortified with vitamin D, including cereals, bread, and milk.[84]

Vitamin D deficiency should not occur in individuals who are exposed to adequate sunlight and eat a well-balanced diet. Casual exposure of cutaneous tissues to ultraviolet light during the summer months should produce adequate vitamin D storage for winter months.[72] Total body sun exposure provides the vitamin D equivalent of 250 Âµg/d (10,000 IU/d).[185] The body only requires a total vitamin D supply of 100 Âµg/d (4000 IU/d).[185] Breast-fed infants may require supplemental vitamin D if they have limited exposure to sunlight because the vitamin D content of human milk is extremely low.[36] Other groups susceptible to vitamin D deficiency include the elderly, vegans, and persons without adequate sunlight exposure. The daily adequate intake of vitamin D is 5 Âµg/d (200 IU/d).[62] This dose approximates the vitamin D content of a half-teaspoon of cod liver oil.[145] These doses appear to prevent rickets and osteomalacia. However, larger doses may be required for treatment of osteoporosis or hypoparathyroidism.

Rickets has been eliminated as a major public health concern in children in Europe and North America since the fortification of milk with vitamin D. Outbreaks of vitamin D poisoning subsequently

occurred in Europe in the 1950s because of excessive fortification of milk and cereals to compensate for wartime nutritional deprivation of children.[42] This vitamin D poisoning led to a period of prohibition of vitamin D fortification of foods.[84] More recently, a study showed that milk and infant formulas rarely contain the amount of vitamin D stated on the label and may be either significantly underfortified or overfortified, leading to hypovitaminosis or hypervitaminosis D.[84] One case series demonstrated vitamin D toxicity in 8 patients who drank local dairy milk that was excessively fortified with vitamin D_3 .[95] Many cases of vitamin D toxicity are iatrogenic, resulting from oversupplementation of vitamin D and calcium given for treatment of hypoparathyroidism, osteoporosis, and osteomalacia without adequate patient followup.[39 , 111 , 147] Two reports describe vitamin D toxicity in families secondary to use of a highly concentrated vitamin D preparation in nut oil that was not intended for human consumption.[44 , 148] Another case report describes vitamin D poisoning secondary to contamination of table sugar with crystalline vitamin D_3 .[183] Vitamin D toxicity can occur secondary to vitamin D_3 exposure in the form of rodenticides (Chap. 104).

Pharmacology

Given adequate sunlight exposure, humans should not require exogenous sources of vitamin D because they can synthesize it in vivo. In addition, vitamin D itself is not biologically active but

must go through extensive metabolism to an active form, whether it is ingested from a food source or synthesized in the body. Vitamin D_3 is synthesized in the skin from 7-dehydrocholesterol (provitamin D_3) in a reaction catalyzed by ultraviolet B irradiation (Figure 41-2).[111] Vitamin D_3 then is bound to vitamin D-binding protein, a protein that also binds vitamin D from the diet, and afterward enters the circulation. In the endoplasmic reticulum of the liver, vitamin D_3 is metabolized to 25-hydroxyvitamin D [25(OH)D] by vitamin D-25-hydroxylase.[63] Once formed, 25(OH)D is again bound to vitamin D-

binding protein and transported to the proximal convoluted tubule in the kidney for hydroxylation to 1,25-dihydroxyvitamin D [1,25(OH)$_2$ D], or calcitriol, by 25(OH)D-1Î±-hydroxylase.[63] Once formed, 1,25(OH)$_2$ D is secreted back into circulation, bound to vitamin D-binding protein, and delivered to target cells where it binds to receptors.

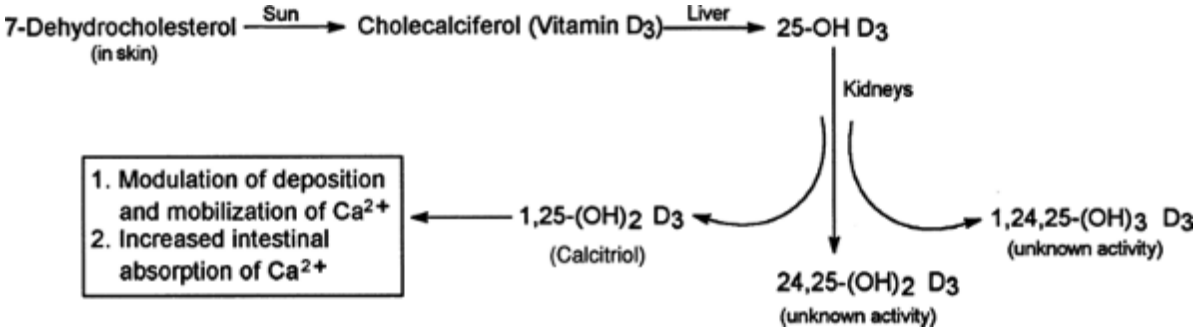


Figure 41-2. Schematic representation of the increased physiologic response to vitamin D resulting in increased calcium absorption and increased 25-hydroxyvitamin D.

Vitamin D might be more appropriately called a hormone rather than a vitamin because it is synthesized in the body, circulates in the blood, and then binds to receptors in order to evoke its biologic action. The primary role of vitamin D is regulation of calcium homeostasis via interactions with the intestines and bones. Protein-bound calcitriol is taken up by cells and then binds to a specific nuclear vitamin D receptor protein that, in turn, binds to regulatory sequences on chromosomal DNA.[111] The result is induction of gene transcription and translation of proteins that carry out the cellular functions of vitamin D. In the intestines, calcitriol increases the production of calcium-binding proteins and plasma membrane calcium pump proteins, thereby increasing calcium absorption through the duodenum.[98] In the bone, calcitriol stimulates osteoclastic precursors to differentiate into mature osteoclasts.[85] Mature osteoclasts, together with PTH, lead to mobilization of calcium stores from bone, thereby raising serum concentrations of calcium. Given sufficient serum concentrations of

calcium, calcitriol promotes bone mineralization by osteoblasts, resulting in increased deposition of calcium hydroxyapatite into the bone matrix.[85] Calcitriol also binds to a vitamin D receptor in the parathyroid glands, which leads to decreased synthesis and secretion of PTH.[137] The vitamin D receptor is actually present in most cells of the body.[161] Vitamin D receptors are found in lymphocytes, epidermal skin cells, and tumor cells. Binding of calcitriol can inhibit proliferation and induce terminal differentiation.[150] Although the role of vitamin D has not been elucidated in all cells, abnormalities present during vitamin D deficiency may help identify the function of vitamin D in various tissues.

Vitamin D deficiency results in hypocalcemia, leading to increased secretion of PTH, which acts to restore plasma calcium at the expense of bone. In children, this situation leads to rickets in which newly formed bone is not adequately mineralized and results in bone deformities and growth defects. Adults develop osteomalacia, a disease characterized by undermineralized bone matrix. Patients typically present with bone pain and tenderness and proximal muscle weakness. Bone deformities are limited to the advanced stages of disease.

Pathophysiology

The hallmark of vitamin D toxicity is hypercalcemia. Vitamin D in the form of $1,25(OH)_2$ D promotes calcium absorption from the gut and mobilization of calcium from bone. In hypervitaminosis D, the plasma concentration of 25(OH)D may be 20 times higher than normal, whereas the concentration of $1,25(OH)_2$ D remains normal, increased, or decreased.[63, 148] 25-Hydroxyvitamin D can mimic the action of $1,25(OH)_2$ D when it is present in excess and can bind to receptors usually specific for $1,25(OH)_2$ D.[63, 111] Alternatively, 25(OH)D, which has a higher affinity for vitamin D-binding protein compared to $1,25(OH)_2$ D, may preferentially bind to vitamin D-binding protein when it is present in elevated concentrations, displacing $1,25(OH)_2$ D

and allowing it to circulate in an unbound form, or loosely bound to albumin.[184] A study of patients with vitamin D toxicity who had normal or near-normal total $1,25(OH)_2$ D levels had elevated free $1,25(OH)_2$ D levels.[148] The availability of $1,25(OH)_2$ D to its receptors likely is increased, resulting in vitamin D toxicity.

The literature regarding the toxic dose of vitamin D varies, with little scientific data available for corroboration. The current â€œno observed adverse effect levelâ€• was conservatively set at 50 Âµg/d (2000 IU/d),[185] but this level did not take into account data showing that doses as high as 110 Âµg/d (4400 IU/d) and 2500 Âµg (100,000 IU) for 4 days did not result in adverse effects.[173, 180, 185] Case reports describe toxicity in the setting of vitamin D intake of 50,000â€“150,000 IU, or simply, doses in the milligram range, daily for prolonged periods.[39, 147]

Clinical Manifestations

Patients with vitamin D toxicity present with signs and symptoms characteristic of hypercalcemia.[111] Early manifestations include weakness, fatigue, somnolence, irritability, headache, dizziness,

muscle and bone pain, nausea, vomiting, abdominal cramps, and diarrhea or constipation. As the calcium concentration increases, hypercalcemia may induce polyuria and polydipsia. Diuresis results in salt and water depletion, further impairing calcium excretion. Severe hypercalcemia may present with ataxia, confusion, psychosis, seizure, coma, and renal failure. In addition, cardiac dysrhythmias result from a shortened refractory period and slowed conduction. ECG findings include increased PR intervals, widening of QRS complexes, QTc shortening, and flattened T waves.[139] Patients can develop metastatic calcification of the kidneys, blood vessels, myocardium, lung, and skin. Several patients with vitamin D toxicity have presented with anemia.[152, 163] Proposed mechanisms for anemia include a direct effect of vitamin D on hematopoietic cells and inhibition of

erythropoietin production.[152]

Diagnostic Testing

Hypervitaminosis D should be considered in patients presenting with signs and symptoms of hypercalcemia. Laboratory results may reveal hyperphosphatemia, given that vitamin D facilitates phosphate absorption in the small intestine, enhances its mobilization from bone, and decreases its excretion by the kidney.[124] The diagnosis should be suspected in children with nephrocalcinosis and hypercalcuria even if serum calcium and phosphorus concentrations are normal.[135]

Management

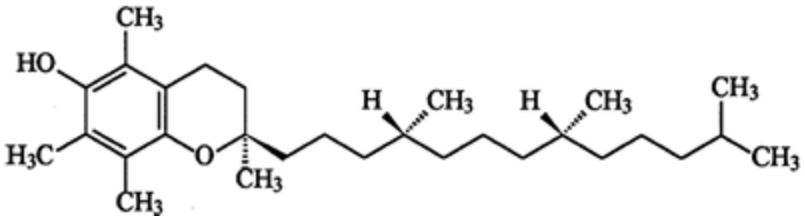
Treatment of hypercalcemia in patients with vitamin D toxicity should include discontinuation of vitamin D and calcium supplementation, maintenance of a low-calcium diet, and administration of adequate volumes of oral or IV fluid to increase calcium clearance.[111] Following rehydration, a loop diuretic can be added to promote calcium excretion.[111] Corticosteroids, in doses of hydrocortisone, 100 mg/d; or prednisone, 20 mg/d; improve hypercalcemia and hypercalcuria in vitamin D poisoning. Studies have attempted to explain this effect as being a result of either decreased intestinal calcium absorption or inhibition of bone resorption.[101, 176] Bisphosphonates, such as pamidronate and coldronate, have been used successfully in cases of severe hypercalcemia.[110, 156] These drugs inhibit bone resorption via actions on osteoclasts. Their use may preclude the need for hemodialysis in refractory cases of hypercalcemia. Calcitonin, a hypocalcemic hormone secreted by the thyroid gland that directly inhibits osteoclast activity, can be used to decrease bone resorption. Salmon calcitonin was successfully used to treat refractory hypercalcemia in a pediatric patient with vitamin D poisoning.[130]

Antioxidants (Vitamins E and C)

The antioxidants include vitamins E and C, and Î²-carotene. During the 1990s, the idea that antioxidants had a protective effect against atherosclerosis and carcinogenesis was widely promoted. This notion was based on the â€œoxidative-modification hypothesisâ€• of atherosclerosis, which proposes that atherogenesis is initiated by lipid peroxidation of LDLs.[43] Unregulated or prolonged production of cellular oxidants leading to oxidant-induced DNA damage is thought to be responsible for carcinogenesis.[104] Epidemiologic evidence seems to support the use of antioxidants for these indications.[106, 154, 172] However, several prospective, randomized, placebo-controlled clinical trials, designed to test for the effect of antioxidant vitamins on cardiovascular disease and cancer, have consistently shown that commonly used antioxidant regimens do not significantly reduce or prevent overall cardiovascular events or cancer.[26, 77, 81, 140, 178, 196]

Vitamin E

MW	= 430.69 daltons
Therapeutic serum level	= 0.5–2.0 mg/dL



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History

Vitamin E includes eight naturally occurring compounds in two classes, tocopherols and tocotrienols, which have differing biologic activities. The most biologically active form is RRR-Î±-tocopherol, previously known as d-Î±-tocopherol, which is the most widely

available form of vitamin E in food. Synthetic forms of vitamin E typically are composed of an approximately equal mixture of 8 stereoisomeric forms of Î±-tocopherol. The existence of vitamin E was first demonstrated in 1922.[50] Female rats deficient in a dietary principal were unable to sustain a pregnancy. Testicular lesions in male rats were described in deficiency states, and vitamin E was referred to as the â€œantisterility vitamin.â€•[122] Vitamin E was first isolated from wheat-germ oil in 1936.[49] The richest sources of vitamin E include nuts, wheat germ, whole grains, vegetable and seed oils, including soybean, corn, cottonseed, and safflower, and the products made from these oils. In general, animal products are poor sources of vitamin E.

Vitamin E deficiency occurs in patients with malabsorption syndromes, which may occur in the presence of pancreatic insufficiency or hepatobiliary disease, such as biliary atresia.[22] Patients with abetalipoproteinemia are at risk for vitamin E deficiency.[12] In this rare disease, absorption and transport of vitamin E are impaired secondary to a lack of chylomicron and Î²-lipoprotein formation. Manifestations of deficiency are variable but seem to have the most effect in organ systems that rely on vitamin E for normal functioning.[122] The clinical syndrome is primarily manifested by a peripheral neuropathy and spinocerebellar syndrome that improves with supplemental vitamin E.[131] Symptoms include ophthalmoplegia, hyporeflexia, gait disturbances, and decreased sensitivity to vibration and proprioception.[22]

Vitamin E is an essential nutrient. It is believed to be necessary for normal functioning of the nervous, reproductive, muscular, cardiovascular, and hematopoietic systems. Use of vitamin E has been proposed for a wide range of conditions. In most cases, scientific rationale for its use is lacking or is based on in vitro or animal data that have not been validated in humans or have demonstrated equivocal results.[22] As examples, vitamin E has been used for treatment of recurrent abortion, hemolytic anemias, claudication, wound healing, tardive dyskinesia, epilepsy, and adult respiratory

distress syndrome. In addition, much research over the past decade has focused

on the use of vitamin E for the prevention and treatment of cardiovascular disease and cancer, with disappointing results.[179]

Pharmacology

Vitamin E absorption is dependent on the ingestion and absorption of fat. The presence of bile also is essential. Vitamin E is passively absorbed in the intestinal tract into the lymphatic circulation by a nonsaturable process. Approximately 45% of a dose is absorbed in this manner and subsequently enters the bloodstream in chylomicrons, which are taken up by the liver. Vitamin E then is secreted back into the circulation, where it is primarily associated with LDLs. Vitamin E is distributed to all tissues, with the greatest accumulation in adipose tissue, liver, and muscle.

The primary biologic function of vitamin E is as an antioxidant. It prevents damage to biologic membranes by protecting polyunsaturated fats within membrane phospholipids from oxidation.[27] It accomplishes this task by preferentially binding to peroxyl radicals and forming the corresponding organic hydroperoxide and tocopheroxyl radical, which, in turn, interacts with other antioxidant compounds, such as ascorbic acid, thereby regenerating tocopherol. Vitamin E may be responsible for cell growth and proliferation by combating the inhibitory effects of lipid peroxidation.[131] Vitamin E may have a negative role in the regulation of cellular proliferation through its nonoxidant properties, such as inhibition of protein kinase C activity.[131]

Pathophysiology

In vitro studies demonstrate that vitamin E in high doses may have a prooxidant effect.[2, 25, 133] The prooxidant effect of vitamin E on

LDLs is related to the production of Î±-tocopheroxyl radicals, which normally are inhibited by other antioxidants such as vitamin C. High doses of vitamin E may displace other antioxidants, thereby disrupting the natural balance of the antioxidant system and increasing vulnerability to oxidative damage.[90] High doses of vitamin E may inhibit human cytosolic glutathione S-transferases, enzymes that are active in the detoxification of drugs and endogenous toxins.[182]

Clinical Manifestations

The RDA for vitamin E in adults is 15 mg/d Î±-tocopherol equivalents for men and women.[62] One IU is equivalent to 1 mg DL-Î±-tocopherol acetate. Human milk, in contrast to cow's milk, has sufficient Î±-tocopherol to meet the needs of breast-fed infants.[122] Supplementation should not be necessary in persons who consume a well-balanced diet. Large amounts of vitamin E, ranging from 400â€“800 IU/d for months to years, have been taken without apparent harm.[36] Vitamin E supplementation results in few obvious adverse effects, even at doses as high as 3200 mg/d.[17] In several species, the oral median lethal dose was 2 g/kg or more, and significant adverse effects were observed only when daily doses were >1 g/kg, equivalent to 200â€“500 mg/kg in humans.[132] However, a meta-analysis reveals that all-cause mortality may increase at doses â‰¥400 IU/d.[133]

Gastrointestinal symptoms, including nausea and gastric distress, were reported in patients who had received vitamin E 2000â€“2500 IU/d.[82 , 192] Diarrhea and abdominal cramps were reported in patients who received a dose of 3200 IU/d.[9] Reports of other adverse effects, including fatigue, weakness, emotional changes, thrombophlebitis, increased serum creatinine concentration, and decreased thyroid hormone concentrations, have not been reproduced in other case series or clinical trials.[132]

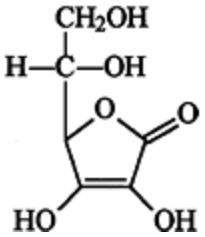
The most significant toxic effect of vitamin E, at doses exceeding 1000 IU/d, is its ability to antagonize the effects of vitamin K.[36]

Vitamin E appears to increase the epoxidation of vitamin K to its inactive form, thereby increasing the vitamin K requirement several-fold.[17 , 186] Although high oral doses of vitamin E typically do not produce a coagulopathy in normal humans with adequate vitamin K stores, coagulopathy may develop in vitamin K-deficient patients or those taking warfarin.[17 , 35 , 52 , 186] Animal studies demonstrate that absorption of both vitamins A and K is impaired by large doses of vitamin E.[22 , 157]

Use of an IV vitamin E preparation (E-Ferol) was associated with a severe epidemic of unexplained thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension, and metabolic acidosis in low-birth-weight infants in several neonatal intensive care units in the early 1980s.[24] Use of polysorbate 20 and polysorbate 80 for emulsification of lipids and fat-soluble vitamins in this IV vitamin E product was implicated as the cause of this syndrome, rather than vitamin E. The product was removed from the market and the syndrome disappeared. No cases developed with oral administration of vitamin E.

Vitamin C

MW = 176.12 daltons
Therapeutic serum level = 0.4–2.0 mg/dL



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History

Vitamin C, also known as *ascorbic acid* , is ingested in the form of vitamin supplements by 35% of the US population.[175] Approximately 91% of all people using vitamin supplements take vitamin C, making it the most widely consumed nutrient within this group of people.[36] Vitamin C has long been used as a â€œcureâ€• for the common cold. Interestingly, an extensive review of 14 studies of the role of vitamin C in the treatment of the common cold suggested that only 8 were valid investigations, and none of the studies demonstrated any therapeutic benefit.[29] Its function as an antioxidant has led to its use for the prevention and treatment of cardiovascular disease and cancer. Unfortunately, human data from clinical trials have failed to demonstrate that vitamin C significantly reduces or prevents overall cardiovascular events or cancer. Vitamin C may have a role as a reducing agent in the treatment of idiopathic methemoglobinemia. However, it is less effective than standard treatment with methylene blue and therefore not employed.[123] Vitamin C is popularly used to promote wound healing, treat cataracts, combat chronic degenerative diseases, counteract the effects of aging, and increase mental attentiveness and decrease stress.[36 , 132] However, little, if any, objective data demonstrate a benefit of treatment for many of these indications.[36]

Vitamin C has long been associated with prevention of scurvy.[123] In 1747, James Lind, a physician in the British Royal Navy, analyzed the relationship between diet and scurvy and confirmed the protective and curative effects of citrus fruits. Vitamin C was isolated from cabbage in 1928 and subsequently shown in 1932 to be the active antiscorbutic factor in lemon juice. It was given the name *ascorbic acid* to indicate its role in preventing scurvy. Other dietary sources of vitamin C include tomatoes, strawberries, and potatoes. Today, those at risk for developing scurvy include the elderly, alcoholics, chronic drug users, and others with inadequate diets, including infants fed formula diets with insufficient concentrations of vitamin C.[123] Symptoms include gingivitis, poor wound healing, bleeding, and

petechiae and ecchymoses. Musculoskeletal symptoms, consisting of arthralgia, myalgia, hemarthrosis, and muscular hematomas, develop in 80% of cases.[51] Children experience severe pain in their lower limbs secondary to subperiosteal bleeding.[51]

Pharmacology and Toxicokinetics

Following ingestion, intestinal absorption of vitamin C occurs via an active transport system that is saturable.[155] The absorptive capacity is reached with oral ingestions of approximately 3 g/d. When given as a single oral dose, absorption decreases from 75% at 1 g to 20% at 5 g. Vitamin C is distributed from the plasma to all cells in the body. Tissue uptake is also a saturable process.[132] Metabolic degradation of vitamin C to oxalate accounts for 30â€“40% of oxalate excreted daily.[73] Because metabolic conversion is saturable, large ingestions of vitamin C do not significantly increase oxalate production.[166] Only a small amount of vitamin C is filtered through the glomeruli, and tubular resorption, a saturable process that may compete with uric acid, usually is almost complete.[19] Plasma concentrations of vitamin C typically are maintained at approximately 1 mg/dL. The kidney efficiently eliminates excess vitamin C as unchanged ascorbic acid.

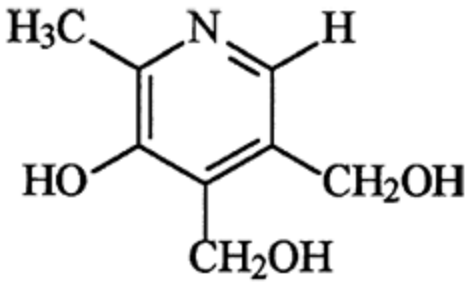
Vitamin C is a cofactor in several hydroxylation and amidation reactions by functioning as a reducing agent.[113 , 114] As a result, vitamin C plays an important role in the synthesis of collagen, carnitine, folinic acid, and norepinephrine. It also influences the processing of hormones such as oxytocin, antidiuretic hormone, and cholecystokinin. Vitamin C reduces iron from the ferric to the ferrous state in the stomach, thereby increasing intestinal absorption of iron. Vitamin C may be involved in steroidogenesis in the adrenals. Vitamin C also has a prooxidant effect in vivo.[149] This effect is not believed to occur at doses <500 mg/d but may occur in the setting of overdose.

Clinical Manifestations

The RDA for vitamin C in adults is 90 mg/d for men and 75 mg/d for women.[62] Vitamin C in the form of dietary supplements is commonly taken in doses of 500 mg/d. Higher doses are fairly well tolerated because excess vitamin C is not absorbed and does not undergo metabolic degradation to oxalate to a significant extent. Therefore, the possibility of oxalate nephrolithiasis should not be a significant clinical concern.[65] Reports of high urine oxalate concentrations likely were erroneous because of conversion of ascorbate to oxalate in alkaline urine samples left standing after collection.[189] Individual case reports documenting the presence of oxalate stones in the setting of vitamin C overdose have involved either IV administration or patients with chronic renal failure.[13, 64, 109, 125, 132, 177] A prospective study on the risk of kidney stones in men did not support an association between high daily vitamin C intake and stone formation.[37] Gastrointestinal tract effects of high doses of vitamin C may include localized esophagitis, given prolonged mucosal contact with ascorbic acid, and an osmotic diarrhea.[88, 188]

Vitamin B_6

MW = 169 daltons
Therapeutic serum level = 3.6–18 ng/mL



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History

Pyridoxine, pyridoxal, and pyridoxamine are related compounds that have the same physiologic properties. Although all three compounds are included in the term vitamin B_6 , the vitamin has been assigned the name *pyridoxine* . This vitamin was discovered in 1936 as the water-soluble factor whose deficiency was responsible for the development of dermatitis in rats.[123] In humans, deficiency is characterized by a seborrheic dermatitis around the eyes, nose, and mouth, cheilosis, stomatitis, glossitis, and blepharitis.[170] More importantly, pyridoxine deficiency is associated with seizures.

Pyridoxine is found in several foods, including meat, liver, whole-grain breads and cereals, soybeans, and vegetables.[123] The RDA for adults is 1.3 mg/d, and 1.7 mg/d for men >50 years and 1.5 mg/d for women >50 years.[62] Deficiency should not occur in humans who eat a well-balanced diet.[170]

Pyridoxine is popularly used as a component of bodybuilding regimens and for treatment of premenstrual syndrome and carpal tunnel syndrome.[1 , 47] High doses have been used for treatment of schizophrenia and autism with variable results.[57 , 112]

Pharmacology

All forms of vitamin B_6 are well absorbed from the intestinal tract. Pyridoxine is rapidly metabolized to pyridoxal, pyridoxal phosphate (PLP), and 4-pyridoxic acid.[197] PLP accounts for approximately 60% of circulating vitamin B_6 and is the primary form that crosses cell membranes.[123] Most vitamin B_6 is renally excreted as 4-pyridoxic acid, with only 7% excreted unchanged in the urine.[123 , 197] Experiments in anephric rats demonstrate an up to 10-fold increase in susceptibility to pyridoxine-induced neurotoxicity, suggesting a need for caution when prescribing pyridoxine to patients with renal failure.[115]

PLP is the active form of vitamin B_6 . It is a coenzyme required for the synthesis of Î³-aminobutyric acid (GABA), an inhibitory

neurotransmitter. Decreased GABA formation in the setting of pyridoxine deficiency may contribute to seizures.[123] Isoniazid and other hydrazines inhibit the enzyme responsible for conversion of pyridoxine to PLP.[86] Therefore, pyridoxine should be administered concomitantly with isoniazid. Seizures resulting from isoniazid overdose often are successfully treated with pyridoxine (Antidotes in Depth: Pyridoxine).

Pathophysiology

Interestingly, pyridoxine toxicity is also characterized by neurologic symptoms. The pathophysiology of pyridoxine neurotoxicity is not well defined. However, studies indicate that the mammalian peripheral sensory nervous system is vulnerable to large doses of pyridoxine.[164] Histopathology in dogs reveals sensory distal axonopathy with relative sparing of the cell body.[87] Peripheral sensory nerves may be particularly vulnerable to circulating toxins because of the permeability of their associated blood vessels.[164] Compared to the CNS, these nerves lack the bloodâ€“brain barrier. In addition, the nerves of the CNS may be relatively shielded from pyridoxine toxicity because pyridoxine is transported into the CNS by a saturable mechanism.[164]

Clinical Manifestations

Chronic overdoses of pyridoxine are associated with progressive sensory ataxia and severe distal impairment of proprioception and vibratory sensation. Touch, pain, and temperature sensation may be minimally impaired, and reflexes may be diminished or absent. These findings were first described in 1983 in a case series of 7 patients who were taking pyridoxine 2â€“6 g/d for 2â€“40 months.[164] Nerve conduction and somatosensory studies in these patients showed dysfunction in the distal sensory peripheral nerves. Nerve biopsy showed widespread, nonspecific axonal degeneration. This syndrome

has since been reported with pyridoxine doses as low as 200 mg/d.[146] In most cases, symptoms gradually improve over several months with abstinence from pyridoxine. However, symptoms may still progress for 2â€“3 weeks after pyridoxine discontinuation.[18]

Acute neurotoxicity may occur when a massive amount of pyridoxine is administered as a single dose or given over a few days.[4] Large overdoses of pyridoxine are associated with incoordination, ataxia, seizures, and death.[181] Administration of IV pyridoxine 2 g/kg in 2 patients resulted in permanent dorsal root and sensory ganglia deficits.[4]

Nicotinic Acid

MW	= 123 daltons
Therapeutic levels	= ?

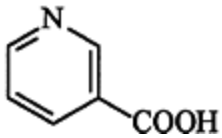

Figure. No Caption Available.

History

Nicotinic acid, or niacin, was discovered to be an essential dietary component in the early 1900s.[68] A deficiency of this vitamin, also known as vitamin B_3 , causes pellagra, which is characterized by dermatitis, diarrhea, and dementia. This disease had been prevalent for centuries in countries that heavily relied on maize as a dietary staple. It was determined that pellagra could be prevented by increasing dietary intake of fresh eggs, milk, and fresh meat, including liver.[123] Other food sources of nicotinic acid include fish, poultry, nuts, legumes, and whole-grain and enriched breads and cereals. Supplementation of flour with nicotinic acid in 1939 probably is responsible for the near eradication of this disease in the United

States. Chronic alcohol users are known to still get pellagra, likely secondary to malnutrition. The RDA of niacin is 16 mg/d for men and 14 mg/d for women.[62]

Niacin was introduced as a treatment for hyperlipidemia in 1955.[7] Nicotinic acid reduces triglyceride synthesis, with a resultant drop in very-low-density lipoprotein cholesterol and LDL cholesterol and a rise in high-density-lipoprotein cholesterol.[68] Therapy usually is started with single doses of 100â€“250 mg. Frequency of dose and total daily dose are gradually increased until a dose of 1.5â€“2.0 g/d is reached. If the LDL cholesterol concentration is not sufficiently decreased with this dosing regimen, the dose is further increased to a total dose of 3.0 g/d. These doses of niacin are 100-fold higher than the amount necessary to meet adult nutritional needs.[153]

Pharmacology and Toxicokinetics

Nicotinic acid is well absorbed from the intestinal tract and is distributed to all tissues. With therapeutic dosing, little unchanged vitamin is excreted in the urine. When extremely high doses are ingested, the unchanged vitamin is the major urinary component. Nicotinic acid ultimately is converted to nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADPH), which are the physiologically active forms of this vitamin. NAD and NADPH act as coenzymes for proteins that catalyze oxidation-reduction reactions that are essential for tissue respiration.[123]

Clinical Manifestations

The most common adverse effects associated with niacin use are vasodilatory side effects, which include cutaneous flushing and pruritus. These symptoms are mediated by prostaglandins and may occur at doses of 0.5â€“1.0 g/d.[127] Flushing occurs because of the predilection for the skin as a source of prostaglandin D_2 production

after niacin ingestion.[174] A single dose of aspirin taken 30 minutes before ingestion of niacin diminishes flushing.[194] Vasodilatory side effects have been noted in up to 100% of patients, particularly when given an immediate-release form of niacin.[127] Although tolerance to flushing usually develops over several weeks, 25% of patients discontinue niacin use because of vasodilatory symptoms.[127, 153]

Because rapid absorption of niacin seems to be related to development of flushing, time-release preparations of niacin were developed. Unfortunately, these preparations are more likely to produce gastrointestinal side effects, such as epigastric distress, nausea, and diarrhea.[127] In addition, niacin-induced hepatotoxicity occurs more frequently and is more severe in patients treated with modified-release niacin rather than immediate-release niacin.[32, 153] Elevated liver enzyme concentrations may occur with doses as low as 1 g/d, whereas symptoms of hepatic dysfunction occur at doses of 2â€“3 g/d.[127] These patients may have elevated serum bilirubin and ammonia concentrations and a prolonged prothrombin time. They may present with fatigue, anorexia, nausea, vomiting, and jaundice. In most cases, liver function improves following niacin withdrawal.[48, 127] Severe cases have progressed to fulminant hepatic failure and hepatic encephalopathy.[33, 83, 136] Niacin also causes amblyopia, hyperglycemia, hyperuricemia, coagulopathy, myopathy, and hyperpigmentation.[80]

Summary

Healthy adults consuming a well-balanced diet do not require vitamin supplementation. However, vitamins are popularly believed to be a panacea and are commonly taken in megadoses. Because the therapeutic index is large, toxicity generally does not develop unless very large doses are taken for sustained periods. Physicians should consider hypervitaminosis in the differential diagnosis when patients present with symptomatology consistent with a vitamin toxicity

syndrome. A thorough history, with emphasis on diet and prescribed and supplemental vitamin use, is important.

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Chapter 42
Essential Oils

S. Eliza Halcomb

A 2-year-old boy presented to the emergency department with altered mental status. His mother reported that the boy had developed a low-grade fever earlier that evening. He was given a bath and some ibuprofen. After the bath, the boy's grandmother rubbed him down with a â€œgenerousâ€• amount of eucalyptus oil. The child liked the smell and licked his arms. Shortly thereafter, he became lethargic and had a seizure.

Upon presentation to the emergency department, the child was sleepy but arousable. His vital signs and results of physical examination, laboratory studies, and head CT were all normal. He was hospitalized for observation overnight and had no further seizure activity. He was discharged home the next day with no further sequelae.

History and Epidemiology

â€œWhat got you in trouble?â€• says the

baldhead to t'other.

â€œWell I'd been selling an article to take the tartar off the teethâ€”and it does take it off, too, and generly the enamel along with itâ€¦â€•

--Mark Twain,[74]; Huckleberry Finn

Essential oils are a class of polyaromatic hydrocarbons extracted through steam distillation or cold pressed from the leaves, flowers, bark, wood, fruit, or peel of a single parent plant. These organic compounds are a complex mixture of chemicals with structures that give the oil its aroma, therapeutic properties, and occasionally cause toxicity. More than 500 oils exist and can be categorized into five chemical groups: terpenes, quinines, substituted benzenes, aromatic/aliphatic esters, and phenols and aromatic/aliphatic alcohols.

Use of plant-derived essential oils in the practice of herbal medicine has a long and colorful history, dating back thousands of years. The virtues of these extracts have been mentioned in ancient Egyptian and Greek medical literature and throughout the Bible.

Essential oils were used to treat everything from asthma to snakebites until the early 20th century. In America â€œIndian doctorsâ€• frequently sold these products, claiming they learned medicinal secrets from local Native American tribes. These remedies were advertised at medicine shows and demonstrated by troupes such as the famous Kickapoo Indian Medicine Company. The purpose of these traveling caravans was to sell patent medicines, which typically contained substantial quantities of ethanol, in addition to other substances of uncertain therapeutic value. A bottle of Kickapoo Oil sold at the beginning of the 20th century purportedly contained â€œcamphor, ether, capsicum, oil of cloves, oil of sassafras and myrrh.â€• Needless to say, many patients did rather poorly with the administration of these tonics,

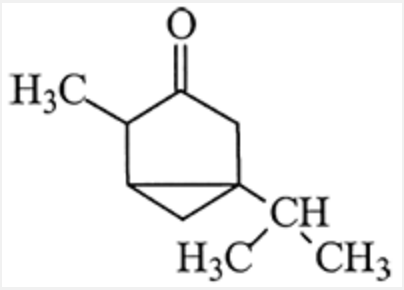
and the â€œdoctorsâ€• who sold them quite rightly earned a reputation for quackery.[76]

With the ascent of scientific research, many essential oil remedies fell from use. More recently, trends in globalization and natural healing have led to a popular resurgence in the use of essential oils in developed countries. Essential oils currently are marketed for use in aromatherapy and certain complementary medicines. The reintroduction of these agents into mainstream society has highlighted the need for research and toxicity studies to ensure that appropriate decision making and care can be provided to exposed patients.

Absinthe; Oil of Wormwood

History

Absinthe is an emerald green liqueur made from the extract of the wormwood plant *Artemisia absinthium.* The earliest references to wormwood date to 1500 B.C., when its antihelminthic properties were described. It is thought that Napoleon's soldiers popularized the drink upon their return from Algeria, where they had added wormwood extract to their wine to avoid helminthic infections during the war.[35]



Thujone

Absinthe reached its pinnacle of popularity by the late 19th century in Europe. Famous artists and authors, including Lautrec, Van Gogh, Baudelaire, Wilde, and Hemingway, sat for hours in the cafes of Paris, drinking the green liqueur and romanticizing its aphrodisiac effects. However, recognition of the devastating side effects led the French, Swiss, and American governments to ban its sale by the early 1900s.[35] Absinthe is still sold in its dethujonized form, Pernod.

Many people have speculated on the cause of Vincent Van Gogh's bizarre behavior. Some have concluded that his fondness for absinthe may have contributed to his seizures and psychotic episodes.

Toxicokinetics

The toxic component in oil of wormwood is thujone, a monoterpene ketone, which exists in Î±- and Î²-diastereoisomeric forms.[34] After oral absorption, both isomers undergo species-specific hydroxylation reactions by the cytochrome P450 system,

followed by glucuronidation in the hepatocyte, leading to production of several renally eliminated nontoxic metabolites.[34]

Pathophysiology

The Î±-stereoisomer is generally accepted to be the more toxic of the two isomers and the parent compound antagonizes the Î³-aminobutyric acid $(GABA)_A$ receptor at the picrotoxin site on the chloride channel, leading to neuroexcitation that may manifest as hallucinations or seizure activity, presumably in a dose dependent fashion.[34] Interestingly, ethanol enhances GABA activity and may have a protective effect by reducing seizure activity in mice.[34]

Thujones are implicated in the development of porphyrialike syndromes by inducing the synthesis of 5-aminolevulinic acid synthetase, leading to increased porphyrin production. This finding suggests that individuals with defects in heme synthesis may unmask a porphyrialike syndrome upon ingestion of thujones.[10]

Clinical Features

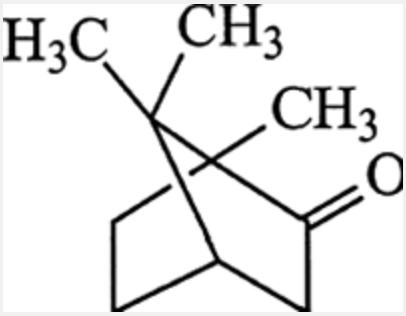
Case reports of toxicity reflect a recent resurgence in the popularity of the absinthe liquor, which has reappeared on the market in several European countries and is available on the Internet. Clinical features of acute toxicity are similar to those of ethanol intoxication, including euphoria and confusion, which may progress to restlessness, visual hallucinations, and delirium. Chronic abusers may suffer from seizures, hallucinations, and erratic behavior.[4]

Rhabdomyolysis and acute renal failure have occurred following ingestion of oil of wormwood intended for preparation as absinthe.[80] The etiology of the rhabdomyolysis has not been elucidated.[80]

Camphor

History

One of the first western references to camphor is found in Marco Polo's description of his travels.[26] Camphor was traded widely throughout Asia. Historically it was used as a rubefacient, antiseptic, decongestant, and moth repellent. It gained immense popularity as a liniment during the American Civil War, and the US government signed a contract with China to buy the entire camphor output of Formosa (Taiwan).



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The French introduced camphor to Europe in 1879.[24] Vincent Van Gogh's epileptiform illness may have been exacerbated by his continuous exposure to camphor. Camphor belongs to the terpene family and is capable of causing central nervous system (CNS) toxicity.[35] Camphor oil is extracted from an evergreen tree from the Laurel family *Cinnamomum camphora*,[17] which is native to eastern China, Japan, and Taiwan. It is primarily used today in nasal decongestant ointments such as Vicks Vapo-Rub, although in the recent past it was widely used in moth repellents (Chap. 99).

Toxicokinetics

Camphor is a monoterpene ketone, which is rapidly absorbed from the gastrointestinal (GI) tract and then undergoes extensive first-pass metabolism. After hydroxylation and glucuronidation in the liver, its inactive metabolites undergo urinary excretion.[59,71]

Pathophysiology

Camphor toxicity is reported after its ingestion, inhalation, and nasal administration. It is rapidly absorbed from the GI tract or through mucous membranes. Camphor is highly lipid soluble and readily crosses the bloodâ€“brain barrier and placenta. Seizure activity is common postingestion, although the specific mechanism of action is not elucidated. Cellular respiration is inhibited by camphor and similar compounds, resulting in increased excitability of neuronal tissue.[63] Other studies suggest that camphor binds noncompetitively to nicotinic acetylcholine receptors, inhibiting an intracellular influx of calcium and sodium, although the investigations fail to explain how this process would be epileptogenic.[55]

Children seem particularly prone to hepatotoxicity because of the relative immaturity of their hepatic enzyme systems, and they may develop hepatotoxicity resembling Reye syndrome.[37] The fetus is thought to be susceptible to toxicity through the same mechanism. Several cases of camphor use as an abortifacient and a single case of fetal demise after ingestion are reported.[58,81]

Clinical Features

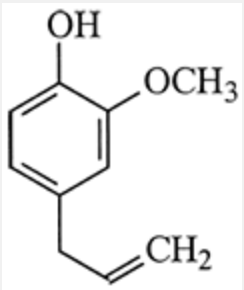
Camphor ingestion results in rapid onset of nausea and vomiting, followed by headache, agitation, and seizure activity.[16] Symptom onset usually occurs within minutes of ingestion. Seizures can occur in isolation without antecedent gastrointestinal effects.[5] Inhalational and dermal exposures typically result in local

irritation.

Oil of Clove

History

Cloves once were considered one of the world's most important commodities second only to nutmeg in Medieval and Renaissance Europe. Clove oil is extracted from the plant *Syzygium aromaticum*, also known as *Eugenia aromatica.* This evergreen plant is native to the islands of the Malaccan Straits. Its unopened buds, when dried, are known as cloves. Eugenol, the main constituent of clove oil, has been used for centuries as a remedy for toothache and in multiple dental products.[8]



Eugenol

Toxicokinetics

Eugenol, a phenol, is the principal component of clove oil. Very little available data on the metabolism of eugenol is available. An in vitro study found that incubation of isolated rat hepatocytes

with eugenol resulted in a glucuronic acid conjugate, although other conjugates with sulfate and glutathione were found.[69]

Pathophysiology

Little is known about the pathophysiology of eugenol toxicity. Intravenous infusion and intratracheal instillation

of eugenol in rats has led to the development of hemorrhagic pulmonary edema, which is thought to result from oxidative damage.[42,83]

In vitro studies of hepatic cell cultures incubated with eugenol demonstrated marked glutathione depletion, covalent bonding of conjugates to cell proteins, and cell death. These findings indicate that a reactive intermediate might be formed, leading to toxicity.[69]

Nerve conduction studies performed with frog sciatic nerves demonstrated that eugenol blocked impulse conduction irreversibly. Eugenol has been demonstrated to inhibit peripheral sensory nerve conduction at low doses, but has been associated with CNS manifestations at higher doses.[40]

Clinical Features

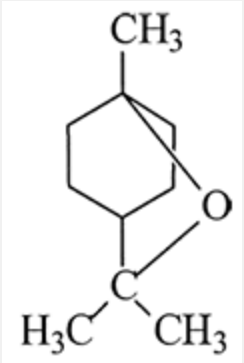
A case report on the neurotoxicity of eugenol described a 24-year-old woman who spilled a small amount of clove oil on her face in an attempt to relieve a toothache. The topical spillage resulted in permanent infraorbital anesthesia and anhidrosis.[36] Likewise, inhibition of the pharyngeal reflex by inhalation of clove cigarettes has been reported to cause aspiration pneumonitis.[30]

Inadvertent oral administration of 1â€“2 teaspoons of clove oil resulted in marked CNS depression, metabolic acidosis, and elevation of aminotransferases in 2 children.[32,41]

Oil of Eucalyptus

History

The eucalyptus tree is native to Australia. Its extracts were historically used as an aboriginal fever remedy. In 1778, the Surgeon-General of the First Fleet arrived in Australia and noted that these unusual trees produced a gumlike resin, which he distilled into a quart of oil and sent back to England for further examination. The introduction of eucalyptus oil to the west led to an increased demand for the product to relieve the symptoms of the common cold and influenza. Eucalyptol is found in many nonprescription cough preparations and is widely used for treatment of upper respiratory infections because of its purported antiinflammatory effects.[38] Although oral administration of eucalyptol-containing products rarely causes toxicity, ingestion of eucalyptus oil has resulted in morbidity and mortality.



Eucalyptol

Toxicokinetics

Eucalyptus oil contains up to 70% eucalyptol, a monocyclic terpene compound with an ether bridge between carbons 1 and 8. Eucalyptol, also known as 1,8 cineole, is rapidly absorbed from the gastrointestinal tract. It undergoes oxidation in the liver to form hydroxycineole, and subsequently undergoes further glucuronidation and excretion.[79] In rats, the main urinary metabolites have been characterized as 2-hydroxycineole, 3-hydroxycineole, and 1,8-dihydroxycineol-9-oic acids.[45] Rabbits excrete 2-exo-hydroxycineole and 2-endo-hydroxycineole, as well as 3-exo-hydroxycineole and 3-endo-hydroxycineole, in the urine after oral administration of eucalyptol.[51]

The lowest lethal doses reported are 4â€“5 mL[46] in adults and 1.9 g eucalyptus oil in a 10-year-old boy.[52] However, ingestion of higher doses in another case series caused less severe effects.[78] Ingestion of <1 teaspoon (5 mL) of eucalyptus oil has resulted in severe toxicity.[1,6,23]

Pathophysiology

The mechanism of toxicity is unclear because little toxicity seems to be associated with eucalyptol.[20]

Clinical Features

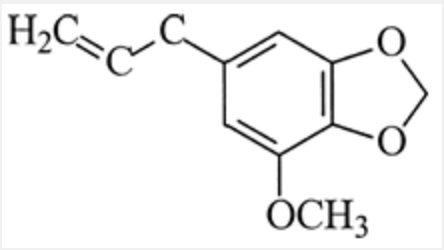
Symptoms develop rapidly and include headache and lightheadedness progressing to CNS depression. Serious poisoning is marked by respiratory depression and vomiting, which heighten the risk of aspiration.[62,70]

Oil of Nutmeg

History

During the Middle Ages, spices were prized for their medicinal and preservative qualities. Chief among these spices was nutmeg,

which, after silver and gold, was the most valued commodity in the western world. In addition to its soporific and emetic properties, nutmeg was purported to be a prophylactic against the plague. Nutmeg has been used unsuccessfully as an abortifacient and abused as a hallucinogen.



Myristicin

In 1510, a European explorer named Ludovico de Varthema described seeing the nutmeg tree flourishing in the Indonesian archipelago on the Bandas Islands, which was the only place on Earth that the spice could be found. This discovery spawned a gold rush of sorts, with intense competition among the great navies of Europe to dominate the spice trade.[61]

Toxicokinetics

Nutmeg oil is extracted from the fruit of the evergreen tree *Myristica fragrans.* Its main active ingredient is thought to be myristicin, although other putative toxins derived from the extraction process include mace, eugenol, and other terpenes.[57] Case reports of toxicity suggest that patients become symptomatic 3â€“6 hours after ingestion of 1â€“3 whole nuts or 1â€“2

tablespoons of ground nutmeg. Myristicin is oxidized in the hepatic P450 system to 5-allyl-1-methoxy-2,3-dihydroxybenzene,[84] which then undergoes glucuronidation and urinary excretion.

Pathophysiology

Animal studies have suggested that myristicin-induced CNS toxicity may result from increased serotonin concentrations in the brain.[72] Myristicin has been shown to inhibit monoamine oxidase,[73] which theoretically could lead to an adverse reaction if combined with another monoamine oxidase inhibitor. Another in vitro experiment showed that myristicin was converted to the amphetamine derivative 3-methoxy-4,5-methylene dioxyamphetamine,[12] which may explain its euphoric effects. Other animal studies have demonstrated fatty degeneration of the liver.[77]

Clinical Features

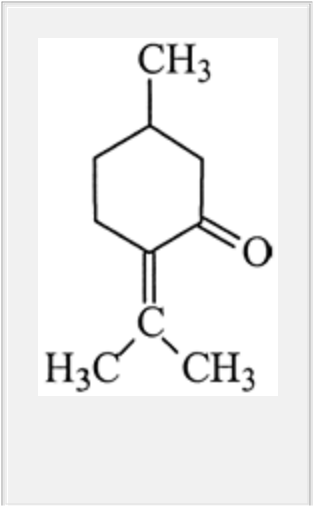
CNS effects tend to be the predominant clinical features of nutmeg poisoning. Nutmeg toxicity may mimic anticholinergic toxicity, with flushing, dryness, tachycardia, hypertension, agitation and altered mental status.[56] One feature that may help differentiate anticholinergic toxicity from nutmeg ingestion is that the pupils often are small.

Escalating doses result in increasing drowsiness that may progress to coma. Abdominal pain is frequently reported, but nausea and vomiting are uncommon. The toxic syndrome typically resolves within 24 hours, although resolution may be delayed.[28] A single fatality is reported in the literature.[19]

Oil of Pennyroyal

History

References to pennyroyal oil date back to antiquity when Pliny the Elder wrote about its insect repellent effects in book 20 of his masterpiece *The Natural History.* Its scientific name *Mentha pulegium* is derived from the Latin *pulex*, which means flea. Both the fresh plant and smoke from the burning leaves were used as early insect repellents. Over the centuries this essential oil also developed a reputation for being an abortifacient and an emmenagogue.[11] The 16th-century English herbalist Gerard noted, â€œPennie Royall boiled in wine and drunken, provoketh the monthly terms, bringeth forth the secondine, the deade childe and unnatural birth.â€• [18] An early American 19th-century pamphlet recommended a recipe that included drinking a pint of pennyroyal water to induce abortion.[67] The toxic effects of pennyroyal were first described in a case report to *The Lancet* in 1897.[2] Today, Internet searches for pennyroyal oil lead to multiple web sites where women relate their experiences with the substance for inducing abortion. The Seattle-based grunge band Nirvana, whose lead singer wrote the song â€œPennyroyal Teaâ€• for the aptly titled album In Utero, immortalized the oil with the following lyrics:



Pulegone

Sit and drink pennyroyal tea

Distill the life inside me.

Toxicokinetics

The active ingredient in pennyroyal oil is R-(+)-pulegone, a monoterpene commonly found in mint oils. Toxicity predominately results from ingestion of pennyroyal for the purposes of inducing abortion, although cases of oil administration to children with gastrointestinal complaints are reported.[7] Toxicity is noted in mice when 300â€“500 mg/kg is administered, and a human fatality was reported at an approximate dose of 500 mg/kg.

After ingestion, pulegone is metabolized by the P450 system in the liver to methofuran and other reactive metabolites, which in turn are excreted in the urine.

Pathophysiology

The reactive metabolites of pulegone bind to cell proteins, disrupting normal cellular function and resulting in significant cellular damage.[3] Methofuran also appears to be associated with pennyroyal-induced pulmonary toxicity, which is manifested as bronchiolar necrosis.[27]

Electrophilic reactive metabolites of pulegone deplete hepatic glutathione concentrations by reacting with the nucleophilic cysteinyl sulfhydryl group on glutathione, further worsening hepatotoxicity.[68] This hepatotoxicity is manifested as centrilobular necrosis, which occurs in both mouse and human specimens.[27]

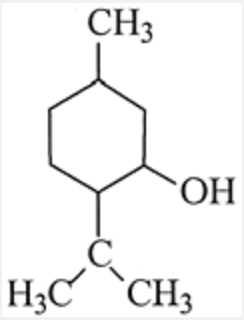
Clinical Features

Case reports in the literature describe a variety of symptoms after ingestion of pennyroyal oil. The most common symptoms of significant toxicity seem to include abdominal discomfort, nausea, vomiting, dizziness, syncope, and coma. Ingestion of 5â€“10 mL has been associated with coma and seizure activity, and ingestion of 15 mL may cause death.[3,7,65] Early symptoms are manifested by gastrointestinal and CNS toxicity,[7] followed by the development of hepatic and renal dysfunction.[65,75] In fatal ingestions, patients have developed disseminated intravascular coagulation and hepatic failure manifested as purpuric rash, epistaxis, vaginal bleeding, and oozing at venipuncture sites.[3,65,75]

Oil of Peppermint

History

Plants in the mint family have been used as medicinal herbs for centuries. One of the first known references to the medicinal qualities of mint comes from the Ebers Papyrus, an ancient Egyptian pharmacopoeia dating back to 1552 B.C. In this document, mint is mentioned as one of the recommended remedies for indigestion and nausea. According to ancient Greek mythology, Hades, the god of the underworld, fell in love with the beautiful nymph Minthe. The affair was short-lived, however, as Hades' jealous wife Persephone turned Minthe into a plant. Hades tempered the curse on the nymph by making the plant fragrant. Peppermint oil is extracted from the plant *Mentha piperita* and is widely used in flavorings and aromatherapy.



Menthol

Toxicokinetics

Menthol, the active ingredient in peppermint oil, is a cyclic terpene alcohol that is rapidly absorbed from the GI tract when ingested. In the liver, menthol undergoes hydroxylation to form *p*-menthane-3,8-diol and 3,8-dihydroxy-*p*-menthane-7-carboxylic acid by the P450 microsomal enzyme system. These metabolites subsequently are glucuronidated by UDP (uridine diphosphate)-glucuronyl transferase and excreted in the urine.[21]

Pathophysiology

Menthol's unique cooling property adds to its commercial value and is one of the most studied features of the

oil. Electrophysiologic investigations have shown that menthol has a dose-dependent effect on calcium concentrations across cell membranes. Inhibition of calcium efflux results in depolarization and, in turn, increases electrical discharges from cold receptors.[21] The increased electrical activity in the trigeminal nerve is thought

to be responsible for the subjective impression that menthol has a decongestant effect on the nasal passages.[21] Research has shown that menthol actually increases nasal congestion and causes an inhibition of upper airway muscle reflexes.[50]

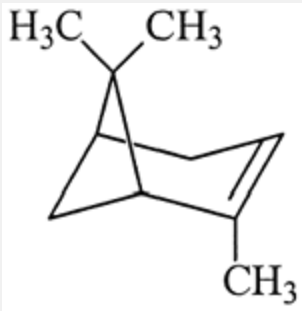
Clinical Features

Rare case reports of menthol toxicity appear in the literature. The reported symptoms of toxicity include CNS effects, such as ataxia, confusion, and coma,[53] and gastrointestinal distress, such as nausea and vomiting.[49,60]

Oil of Pine

History

Pine oil and turpentine are distilled from the wood of pine trees. Turpentine has been historically used as a solvent and paint thinner, whereas pine oil is used as a disinfectant.



Î±-Pinene

Toxicokinetics

The main active ingredient in pine oil is Î±-pinene, a monoterpene hydrocarbon that is absorbed via the GI tract or through inhalation. The lipophilicity of this compound results in its accumulation in adipose tissue and slow metabolism. The primary modes of metabolism include hydration, hydroxylation, and acetylation reactions, after which inactive metabolites undergo renal excretion.[39]

Pathophysiology

Pine oil and turpentine are volatile hydrocarbon compounds with low viscosity. Inhalational injury is common when low-viscosity hydrocarbons are ingested or inhaled, because of inhibited surfactant production in the alveoli.[13] Household cleaning products containing pine oil used as additives to increase the solution's viscosity tend not to cause inhalational injury. However, significant risk of pulmonary injury is associated with turpentine ingestion and inhalation.[25]

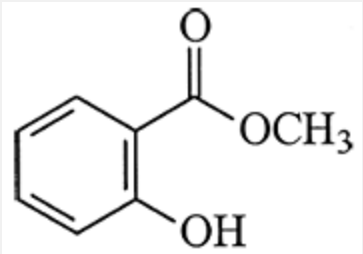
Clinical Features

Pine oil ingestion results in a characteristic pine odor on the breath,[82] whereas turpentine ingestion reportedly causes the urine to smell of violets.[54] Significant ingestions may result in CNS depression that progresses from headache, dizziness, and blurry vision to lethargy and coma.[14] Aspiration resulting in pneumonitis, acute lung injury, and acute respiratory distress syndrome reportedly causes development of pneumatocoeles.[13,82] Inhalational exposure to turpentine fumes causes increased airway resistance and irritation of the oral mucosa in study subjects.[22] Further details on the management of hydrocarbon aspiration are given in Chap. 102.

Oil of Wintergreen

History

European botanists became fascinated by medicinal plants upon the discovery of the New World. John Bartram established the first botanical garden in the United States in 1728 and was named the â€œBotanizer Royal for Americaâ€• in 1765. His collection included the *Gaultheria procumbens*, a fragrant ground cover plant whose leaves were steamed. The distilled product, oil of wintergreen, was used topically to relieve the symptoms of rheumatism.[9] Oil of wintergreen is found in topical preparations worldwide, such as Tiger Balm and Ben-Gay, which are used to treat myalgias. The active ingredient in oil of wintergreen is methyl salicylate, which has a pleasant smell and taste, posing a significant hazard to the pediatric population.



Methyl Selicylate

Five milliliters of oil of wintergreen is equivalent in salicylate content to 7 g aspirin, and numerous case reports of fatalities after even small ingestions are reported.[29,47,64]

Toxicokinetics

Methyl salicylate is absorbed from the GI tract. Dermal absorption occurs,[48] and reportedly causes significant toxicity.[15,33] Once absorbed, methyl salicylate enters the circulation and is transported to the liver, where it undergoes hydrolysis to form salicylic acid. The salicylic acid undergoes conjugation with glycine and glucuronic acid, forming salicyluric acid, salicyl acyl, and phenolic glucuronide.[43] Salicylates are predominantly excreted by the kidney as salicyluric acid (75%), free salicylic acid (10%), salicylic phenol (10%) and acyl (5%) glucuronides, and gentisic acid (<1%).[44]

Pathophysiology

An extensive discussion of salicylate pathophysiology is given in Chap. 35.

Clinical Features

Oil of wintergreen overdose can result in a toxic syndrome identical to that of salicylate poisoning, characterized by nausea, vomiting, tinnitus, hyperpnea, and tachypnea. Patients often present with diaphoresis and mental status changes. Severe toxicity is associated with seizures, cerebral edema, acute lung injury, coma, and death. Further details on the laboratory tests and treatment of salicylate toxicity are given in Chap. 35.

Diagnostic Testing

Laboratory studies are of limited value in essential oil toxicity. Generally, blood or urine concentrations of the active ingredients are not available in a meaningful time frame. However, the patient's clinical status should determine which laboratory studies are to be ordered. Patients who present with altered mental status or seizures warrant a complete evaluation, including a head CT

and lumbar puncture to address other serious potential etiologies.

In patients who present with respiratory distress, chest radiographs and continuous pulse oximetry are warranted.

A few of the essential oils require specific studies:

- *Absinthe:* Laboratory studies should include a complete blood count (CBC), chemistry panel, creatine phosphokinase concentration, and glucose monitoring in patients who present with seizures. Urinalysis should be performed to evaluate for myoglobinuria.
- *Camphor, Nutmeg:* Useful laboratory studies include a chemistry panel to evaluate hydration status and liver enzyme concentrations (nutmeg and chronic camphor exposure).
- *Pennyroyal:* CBC and liver function studies, including the aminotransferases, bilirubin, and prothrombin time, and partial thromboplastin time, are indicated.
- *Wintergreen:* Salicylate concentrations and acidâ€“base status should be determined.

Treatment

Treatment of symptomatic essential oil toxicity is generally supportive, including administration of intravenous fluids and supplemental oxygen. A dose of activated charcoal may be helpful in alert patients with an intact airway. Benzodiazepines are the mainstay of treatment in patients who present with agitation and seizures.

A few of the essential oils require specific treatment:

- *Absinthe:* If rhabdomyolysis is present, hydration and urinary alkalinization may be appropriate, depending on the clinical

severity.

- *Clove:* In patients who exhibit signs of hepatotoxicity, *N*-acetylcysteine (NAC) should be administered. Although no definitive studies on NAC use in this patient population are available, the suggestion that NAC is protective in the rat model,[69] combined with the safety profile of this antidote, probably warrant its use in the setting of eugenol-induced hepatotoxicity.
- *Pennyroyal:* Patients who present with a recent history of pennyroyal ingestion should undergo gastric decontamination with gastric lavage and administration of activated charcoal. NAC therapy is warranted following significant pennyroyal oil ingestions, given the depletion of hepatic glutathione stores.[3,31] Administration of NAC should continue until the patient's clinical status improves or hepatotoxicity resolves. NAC should be administered in the same doses used for acetaminophen toxicity because no trials have demonstrated the optimal dose in the setting of pennyroyal poisoning. If no signs of hepatic or renal toxicity develop, the traditional 20-hour course of intravenous NAC should suffice. If oral NAC is administered, a 24- to 36-hour period of administration should prevent hepatotoxicity, given the 1- to 2-hour half-life of pennyroyal and its metabolites.[3] In asymptomatic patients with minimal ingestions, a brief observation period of 3â€“6 hours is sufficient. An animal study demonstrated that treatment of mice with a combination of disulfiram and cimetidine prior to pennyroyal administration, diminished the hepatotoxic effects, but whether these treatments would be beneficial in human toxicity is uncertain.[66]

Summary

Essential oils are increasingly being used as an alternative form of

medical therapy. In general, the topical use of these products is associated with minimal toxicity. However, ingestion or prolonged inhalation of essential oils may result in significant morbidity and mortality. Suspected cases of essential oil toxicity should be reported to the regional poison center to enhance our very limited epidemiologic understanding of essential oil toxicity.

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Chapter 43
Herbal Preparations

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A 21-year-old woman, 5â€“6 weeks pregnant by dates, presented to the complaining of a 2-day history of abdominal pain and bilious vomiting. Sh from an herbalist several abortifacients, including â€œslippery elmâ€• pov â€œblue cohoshâ€• tincture for ingestion, and â€œparsleyâ€• and â€œes previous 4 days, she had ingested daily approximately 15 cups of slippery cohosh. She had used the parsley and slippery elm douches the day befo having any medical illness or allergies, or using any conventional medica

On examination, the patient was flushed and diaphoretic. Her vital signs Hg; pulse, 148 beats/min; respiratory rate, 24 breaths/min; rectal tempe sounds were normal, and her lungs were clear to auscultation. She had t muscles. The gynecologic examination was unremarkable. Neurologic exa weakness. Her pupils were equal, reactive, and normal size. Laboratory concentrations and complete blood count, were normal. The electrocardio tachycardia without conduction abnormalities. Urinalysis revealed high co was admitted to the hospital for intravenous hydration. Sonography reve Following appropriate advice regarding her desire to terminate her pregn

she was discharged home without complications the following day.

The patient's clinical presentation suggests poisoning by a nicotinelike ag use of an herbal preparation and the development of illness suggests the constituent of one or more of the herbs. Although the popularity of herba to the belief that they are safe, one of the herbal products used by this Blue cohosh (*Caulophyllum thalictroides*) is also known as squaw root a native American herb found in the woods of eastern North America. Histo American Indians to facilitate childbirth. It continues to be used today as antirheumatic, emmenagogue, and abortifacient.[11] The oxytocic activity o by the glycosides caulosaponin and caulophyllosaponin, which are derivat The plant also contains the nicotinelike alkaloid methylcytisine, which has nicotine.[11] Many other herbal preparations are popularly used as abortifa black cohosh, cantharidin, compound Q, ergots, feverfew, juniper, mugwo rue, sage, and white cohosh.

Definition

The botanical definition of the term *herb* is specific for certain leafy plant herbal preparations often include nonherb plant materials, even animal ar terms, herbals include any â€œnaturalâ€• or â€œtraditionalâ€• remedy, defined. Although these products often are called *medications* , this term misleading. Many herbal preparations purportedly are used for their nor properties (ie, they help the body return to a normal state by resisting s Because many herbal users and herbalists do not consider herbal prepara term *herbal medicine* by the clinician may convey a different, and perhap reasons, it may be inappropriate and without benefit to refer to these pr

Herbal preparations are a subset of alternative medical therapies. These interventions that are neither widely taught in medical schools nor genera Alternative medical therapies are divided into several major domains: alt Ayurveda, homeopathy), mindâ€“body interventions (e.g., prayer, hypnos herbal preparations, diet therapies), manipulative and body-based metho chiropractic, massage), and energy therapies (eg, therapeutic touch).[118] conjunction with conventional medical therapies, alternative medical thera *complementary* or *integrative* medical therapies.[117]

For regulatory purposes, herbal preparations are recognized by the Food a type of dietary supplement, which reflects their classification as nutrients not all dietary supplements are herbal preparations. Many nonherbals, su supplements, and food additives, are also dietary supplements (Chaps. 3

The study of herbal preparations is complicated by the lack of standardiz of common,

proprietary, and botanical names may increase the confusion. A single pla common names, in addition to its botanical name. For example, *Datura* s weed, Angel's trumpet, datura stramonium, apple of Peru, Jamestown we Likewise, a common name for a plant, such as gordolobo, may refer to s *Verbascum thapsus* and *Gnaphalium macounii* .[79] The mandrake refers no alkaloidâ€“containing *Mandragora officinarum* but also the podophyllum- Thus, accurate classification of herbal preparations is very difficult, which

Historical Background

Since ancient times and perhaps since prehistoric times, people of all cul to treat disease and promote health.[41] A 60,000-year-old Iraqi burial site plants, suggesting very early historical usage.[151] The earliest surviving w the Egyptian Ebers papyrus, circa 1500 B.C., which lists dozens of medici In India, the *Vedas* , epic poems written in approximately 1500 B.C., cor preparations of the time. In China, the *Divine Husbandman's Classic* , wr 252 herbal preparations. In ancient Europe, herbal medicines were the ma century, the Greek physician Dioscorides wrote one of the first European which listed 600 herbals and was translated into many languages. Shaman Americas, Africa, Australia, and Asia continue to include herbals for spirit on oral traditions passed from generation to generation.

During the Scientific Revolution, European scientists began to isolate puri use as medicinal agents. In 1804 and 1832, morphine and codeine were i plant *Papaver somniferum* .[139] In the mid-18th century, Edward Stone de of the Royal Society of Medicine the successful use of the bark of the wil (fever).[81] In 1829, salicin, the active ingredient of the willow bark, was salicylate was marketed in 1875 as a treatment for rheumatic fever and

success of this drug led to the synthesis of acetylsalicylic acid in 1899. Tl
cetyl-*spiric* acid), is said to have been derived from *Spiraea* , the plant g
was prepared. Even today, plant preparations still are being investigated
drugs. Sweet wormwood (*Artemisia annua* , qing hao) was first described
in 168 B.C.[89] In 1971, the active parent compound artemisinin was first
Artemisinin, in the form of combination based therapy, now is considered
drug-resistant malaria.[108] Prescriptions from plant-derived medicines repr
prescriptions dispensed in the United States.[1 , 168] At least 60% of non
one or more natural products as ingredients.[48]

Today, herbal preparations continue to be the dominant form of healing i
the high cost of â€œwesternâ€• medical treatment and the scarcity of
personnel.[47 , 93 , 96 , 109] The World Health Organization estimates that 4
world population, use herbal preparations for some aspect of primary he
world, herbal preparation usage has undergone a resurgence.[54] In 1991,
of respondents had used herbal preparations in the prior year.[54] The sam
determined that reported herbal usage in the previous year increased to
2002 and 2004 revealed that 14% and 19% of the population used at le
preceding week and past 12 months, respectively.[7 , 86] Factors attributed
cost and ease of purchase compared to prescription medications, consur
with conventional therapies, and the perception that herbals are better a

Herbal preparations and other dietary supplements are no longer sold exc
are readily available for sale in mainstream outlets such as grocery store
practitioner's offices, mail order companies, the Internet, and even gasoli
preparations in the United States were estimated at approximately $4 billi
18% per year.[16] In 1998, several US pharmaceutical companies launched
the self-reported increase in herbal usage in consecutive surveys, actual
The boom period of the 1990s was followed by reversals in the early 200
2000 and declined by 21% and 14% in 2001 and 2002, respectively.[12 , 1
to recent negative publicity concerning the dangers associated with ephedr
of specific popular herbal preparations, such as ginkgo and St. John's wo

Although the FDA does not classify these preparations as medications, they
preventing or treating medical illness. Despite reports of toxicity associate
evaluation of herbal efficacy or safety is required. Because patients often

as medications, they may not provide a history of usage unless they are survey, 21.7% of respondents reported using herbal preparations. For 15. preparation was being used specifically to treat aspects of the patient's seven percent of herbal users reported that their physicians were unawar usage.[76] A survey of outpatients in a veteran's affairs hospital revealed t at least 1 dietary supplement with prescription medications. Of those taki potential for drugâ€“dietary supplement interactions compared to the re medications.[131]

Herbal preparation use appears to vary greatly, depending on the commu Mississippi and southwestern West Virginia reported that 71% and 73% herbal preparations in the past year.[32 , 33 , 44] Among Chinese Americans Americans in west Texas, herbal preparation use was reported to be very respectively.[104 , 132] Herbal preparations use appears to be higher among AIDS, rheumatoid arthritis, and cancer.[85 , 87 , 167] In the United States, preparation usage is associated with multiple factors, including concurren and cultural influences.

Given their pharmacologic constituents, it is not surprising that herbal pr treatment of certain medical

conditions. Saw palmetto may be as effective as finasteride in the treatm hyperplasia.[172] Glucosamine and chondroitin may be useful in the treatm Chinese herbal medicines may be effective in the treatment of irritable b associated with preliminary studies having systematic flaws that limit the scientific evidence is required to prove their effectiveness by current sci

In 1998, Congress established the National Center for Complementary an the National Institutes of Health to stimulate, develop, and support resea alternative medicines.[105] In 2002, an NCCAM-funded study revealed that effective in treating depression than was placebo.[80] A sampling of currer *Ginkgo biloba* for delaying the progression of dementia (phase 3), glucos of osteoarthritis (phase 3), shark cartilage for treatment of lung cancer (of hepatic disease (phase 2), valerian root for treatment of insomnia (pha migraine headaches, echinacea for treatment/prevention of upper respirat cohosh for treatment of menopausal hot flashes (phase 2), pycnogenol fo

2), and Ayurvedic medicine for treatment of type II diabetes mellitus (ph

Regulation of Herbal Preparations

Very little proactive federal regulation of the herbal industry exists. In 19 Supplement Health and Education Act (DSHEA), which reduced the FDA's dietary supplements.[58] Dietary supplements include vitamins, minerals, he product that had been sold as a â€œsupplementâ€• before October 15, new ingredient intended for use in dietary supplements requires notificatio 75 days in advance of marketing. The FDA must review within this time ingredient is reasonably expected to be safe under the intended condition contained in dietary supplements were in use prior to 1994, the vast maj subject to premarket safety evaluations. After marketing, if the FDA dete supplement is unsafe, the agency can warn the public, suggest changes t the manufacturer to recall the product, recall the product, or ban the pro

On several occasions the FDA has urged manufacturers to stop producing unsafe products. In July 2001, the FDA warned dietary supplement manu containing aristolochic acid because of nephrotoxicity and to remove comf because of hepatotoxicity. In November 2001, the FDA warned the manu phenylpropanolamine, caffeine, yohimbine, diiodothyronine, usnic acid) to marketplace because of reports of associated hepatotoxicity. In 2002, the healthcare providers of the risk of hepatotoxicity associated with the use However, the FDA did not ban the development of kava-containing product States. In March 2004, the FDA â€œwarnedâ€• dietary supplement man androstenedione or face enforcement actions.[162] To ban a dietary supple must prove that the product is unsafe. In April 2004, the FDA â€œbanned supplements containing ephedra. This was the first prohibition of any sup

Because the law requires the FDA to consider dietary supplements food p production methods are governed by the Current Good Manufacturing Pra However, these regulations only ensure that foods, and thus dietary supp sanitary conditions; they do not guarantee the purity, safety, or efficacy o pharmaceuticals. In fact, 2 studies suggest that many herbal preparations quantities of the listed herb. In one study of 54 ginseng products, 60% o pharmacologically insignificant amounts of ginseng and 25% contained no

echinacea preparations determined that 10% of preparations contained n assayed species was consistent with labeled content in 52% of the sample standard described by the label.[62]

Herbal products can be marketed without any proof of testing for efficacy claims to cure or prevent a specific disease is not permitted unless appro affects the â€œbody's structure or functionâ€• are permissible. Substanti challenged by regulators,[160] but their methodology and requirements are corroborated by a study evaluating herbal advertising on the Internet. The sites marketing dietary supplements made 1 or more health claims withou these sites, 55% made specific claims to treat, prevent, or cure specific

In March 1999, the FDA implemented new dietary supplement labeling ru must provide a statement of identity (eg, ginseng); net quantity of conte structureâ€“function claims with disclaimers that the product has not beer for use; supplements fact panel (list of serving size, amount, and active and name and place of business of manufacturer, packer, or distributor. I dietary supplement manufacturers not to make pregnancy-related claims o the FDA sent warning letters to 8 companies for making unsubstantiated the use of dietary supplement products for weight loss. In addition, it ser dietary supplements suggesting that it may take enforcement action agai â€œintent on starting a program of inspection of retail establishments to unsubstantiated claims in their labeling.â€• Finally in November 2004, th for dietary supplements. First, the FDA intends to change its regulatory with other agencies to improve the evidentiary base it uses to make safe dietary supplements. Second, the FDA announced a meeting to seek public evidence manufacturers should provide the FDA in a new dietary ingredie intends to fully implement the DHSEA by asking for comments on what t require to substantiate a structureâ€“function claim under DHSEA.[163]

Background of Herbal Toxicology

Awareness of the widespread use of herbal preparations in the United Sta physician seeks information about the use of these products only after t Some well-publicized examples of toxicity from herbal preparation usage

poisoning from contaminated Paraguay tea in New York City in 1994;[22] , bradycardia following consumption of *Jin Bu Huan* tablets in Colorado in agranulocytosis with 1 death following consumption of *Chui Fong Tou Ku* Although few studies have examined this issue, most herbal preparations to be safe. From 1983â€“1989, the National Poisons Unit, London, receiv exposures to herbal extracts, of which 270 (25.2%) patients were sympt to demonstrate a probable association between exposure and effect in only Hong Kong in 1990, Chinese herbal medicines and proprietary medicines a medical admissions despite their use by 40â€“60% of the population. W for 4.4% of acute medical admissions.[36] , [37] In the United States, a mul reported in 2003 collected 2253 calls involving dietary supplements inclu exposures were determined to be caused by dietary supplement and were seizures, 8 cases of coma, and 9 cases of hepatotoxicity.[129] The overall supplement cases was greater compared to outcomes of other poison ce However, in developing countries where herbal usage is much greater, re preparation usage also is much higher. In South Africa, traditional medicin poisonings and were responsible for 51.7% of all deaths from acute poisc

Pharmacologic Principles

The pharmacologic activity of herbal preparations (plant containing) can b classes: volatile oils, resins, alkaloids, glycosides, and fixed oils.[153]

- Volatile oils are aromatic plant ingredients. They are also called eth evaporate at room temperatures. Many are mucous membrane irritant (CNS) activity. Examples of herbs containing volatile oils include penn catnip (*Nepeta cataria*), chamomile (*Chamomilla recutita*), and garli
- Resins are complex chemical mixtures of acrid resins, resin alcohols, resenes. These substances are often strong gastrointestinal irritants. include dandelion (*Taraxacum officinale*) elder (*Sambucus* spp), and *racemosa*)
- Alkaloids are a heterogeneous group of alkaline, organic, and nitrog compound usually is found throughout the plant. This class consists c toxic compounds. Examples of alkaloid-containing herbs include aconi

goldenseal (*Hydrastis canadensis*), and jimson weed (*Datura stramo*

- Glycosides are esters that contain a sugar component (glycol) and a one or more sugars during hydrolysis. They include the anthroquinor and lactone glycosides. The anthroquinones (senna [*Cassia acutifolia* irritating cathartics. Saponins (licorice [*Glycyrrhiza lepidota*] and gir *quinquefolius*]) are mucous membrane irritants, cause hemolysis, ar glycosides found in apricot, cherry, and peach pits release cyanide. L [*Dipteryx odorata*]) have anticoagulant activities. Cardiac glycosides (Chap. 62) are found in foxglove (*Digitalis* spp) and oleander (*Nerium*
- Fixed oils are esters of long-chain fatty acids and alcohols. Herbs co as emollients, demulcents, and bases for other agents. Generally, they of all herbal preparations. Examples include olive (*Olea europaea*) a

Factors Contributing to Herbal Toxicity

The toxicity of a plant may vary widely and depends on conditions such as developmental stage at which the plant is collected.[79] The pyrrolizidine a varies widely from month to month and year to year.[79] In some cases, or prepare an herbal preparation are responsible for its toxicity. For exampl comfreyâ€“pepsin capsules varies from 270 to 2900 mg/kg, depending on used in the preparation.[78] The area in which the plant is collected may a from Gardner Canyon, Arizona, may contain up to 18% pyrrolizidine alkal recorded for any *Senecio* plant species (normal concentration is 0.5%). F storage may affect its toxicity. The toxicity of *Crotalaria* decreases with s pyrrolizidines.

Few poisonings likely result from the inherent toxicity of the herbal, beca active ingredient and the known safety of the chosen herb (Table 43-1). from the misuse, misidentification, misrepresentation, or contamination o poisonings from lead, cadmium, mercury, copper, zinc, and arsenic are a usage.[37 , 46 , 50 , 52 , 130 , 133 , 138] High levels of these elements may re manufacturing process of some herbal or patent medications (ready-made Chinese herbalists). In some cases, as with cinnabar (mercuric sulfide) a these ingredients are intentionally included for purported medicinal bene

contain pharmaceutical medications, such as acetaminophen, aspirin, an Many of these medicines are not listed on the packaging and may not eve States. For example, 4 cases of agranulocytosis followed consumption of preparation that contains aminopyrine (which is not approved for nonpres and phenylbutazone (which was withdrawn) but

which are not listed on the packaging.[142] Both aminopyrine and phenylbu agranulocytosis.

Cardiac Toxins

Ch'an Su

Serum digoxin, potassium

Digoxin Specific Fab

Foxglove

Serum digoxin, potassium

Digoxin Specific Fab

Oleander

Serum digoxin, potassium

Digoxin Specific Fab

Squill

Serum digoxin, potassium

Digoxin Specific Fab

Central Nervous System Toxins

Henbane

None

Physostigmine

Jimson weed (Datura)

None

Physostigmine

Mandrake

None

Physostigmine

Gastrointestinal Toxins

Aloe

Serum electrolytes

Potassium repletion

Buckthorn

Serum electrolytes

Potassium repletion

Cascara

Serum electrolytes

Potassium repletion

Fo-Ti

Serum electrolytes

Potassium repletion

Senna

Serum electrolytes

Potassium repletion

Metals

Ag, As, Au, Cd, Cr, Cu, Hg, Pb, Th, or Zn

Abdominal radiograph

Metal chelators

Hematologic Toxins

Dong Quai

PT

Vitamin K_1

Tonka bean

PT

Vitamin K_1

Woodruff

PT

Vitamin K_1

Hepatotoxins

Pennyroyal oil

AST/ALT

N-Acetylcysteine

Pyrrolizidine Alkaloids

AST/ALT

None available

Salicylates
Medicated oils, etc.
Serum salicylate
Sodium bicarbonate, multiple-dose activated charcoal, hemodialysis
Cellular Toxins
Apricot pits (cyanide)
Lactate
Cyanide antidote kit
Autumn crocus (colchicine)
WBC, BUN
? Glutamic acid
Elder (cyanide)
Lactate
Cyanide antidote kit
Periwinkle (vincristine)
WBC, BUN
? Glutamic acid
Podophyllum (podophyllin)
WBC, BUN
? Glutamic acid
Miscellaneous
Licorice
Serum potassium
Potassium repletion
Quinine
ECG, potassium
Sodium bicarbonate, magnesium

Herbal Preparation Suggested Laboratory Analysis Antidote

TABLE 43-1. Laboratory Analysis and Treatment Guidelines for S
Their Critical Contaminants

Classification of Toxicity

Herbal preparations are associated with a wide variety of toxicologic mar addition, many individual herbal preparations are associated with multiple better understand these effects, it may be useful to organize herbal toxi

Indirect Health Risks

Herbal usage may adversely impact health by altering previous conventi A patient may discontinue or become less compliant with previous therap Alternatively, the addition of an herbal preparation may affect the pharma bioavailability or clearance of concurrently used medications, with resultin Coadministration of St. John's wort, an inducer of CYP3A4, with the prote metabolized by this enzyme, may result in decreased plasma indinavir c decreased antiretroviral activity.[136]

Direct Health Risks

Direct health risks include pharmacologically predictable and dose-depen toxic reactions, long-term toxic effects, and delayed toxic effects. For exa the suggested dose, causes tachydysrhythmias and hypotension. Idiosyncr predicted on the basis of principal pharmacologic properties. For example in anaphylaxis in a small subset of patients with probable allergies to the effects result only after chronic usage. For example, long-term use of he muscular weakness from hypokalemia. Delayed toxic effects include carc example, prolonged consumption of *Aristolochia* causes urothelial cancers

TABLE 43-2. Selected Herbal Preparations, Popular Use,

Top-Selling Herbal Supplements

The top-selling herbal supplements (food, drug, and mass-market retail ou are listed below in order of sales.[14]

- Garlic (*Allium sativum*) ($34,509,288)â€”Garlic has been used as a times. As an herbal, it is used for treatment of infections, hypertensio cells of garlic contain the odorless, sulfur-containing amino acid de sulfoxide, also known as *alliin.* When crushed, alliin is converted to has antibacterial and antioxidant activity and gives the herb its chara effects of garlic extracts include contact dermatitis, gastroenteritis, n constituents of garlic, such as ajoene, possess antiplatelet effects. Co risk of bleeding in individuals who are also taking antiplatelet agents
- Ginkgo (*Ginkgo biloba*) ($32,998,528)â€”This herbal contains ginkgo *ginkgolides* , that are reputed to have antioxidant properties, inhibit circulation. It is a popular supplement for Alzheimer disease and peri major study in 2002 failed to find any improvement in cognitive func without cognitive impairment.[152] Ginkgo in appropriate doses appears increase the risk of bleeding in individuals who are also taking antipl [110 , 126]
- Echinacea (*Echinacea purpurea, angustifolia*) ($32,448,966)â€”Echin and is a popular herbal remedy for cold and flu symptoms. Echinacea doses.[67] Rare individuals develop allergic reactions when taking echi
- Soy (*Glycine max*) ($28,252,518)â€”Soy contains 2 popularly adver isoflavones. Diets high in soy protein are associated with decreased lipoprotein concentrations. Soy isoflavone supplements (genisten, dai estrogens) that currently are suggested as alternative remedies for t There is current concern regarding how high levels of isoflavones will cancer in postmenopausal women.

- Saw palmetto (*Serenoa repens*) ($23,053,036)â€”Saw palmetto is a benign prostatic hypertrophy. Saw palmetto inhibits 5-Î±-reductase. Sa appropriate doses.[110 , 126]
- Ginseng (*Panax ginseng*) ($21,686,192)â€”Ginseng is the common of the genus *Panax*. *Panax ginseng* is native to Korea, China, Japan, the common ginseng species in North America and grows abundantly regions of Canada and the United States. Ginseng preparations have b respiratory illnesses, gastrointestinal disorders, impotence, fatigue, a effectâ€•). It is regarded as a tonic and panacea (hence the name *Pa* Its only recognized use in the United States is as an external demulc good example of the complexity of the biochemistry and pharmacologi components of ginseng are called *ginsenosides* and include panaxin, sapogenin, and ginsenin. Its general metabolic effects include decreas cholesterol concentrations; increasing erythropoiesis, hemoglobin prod the gut; increasing blood pressure and heart rate; GI motility; and C syndrome (GAS), which consists of hypertension, nervousness, sleepl been described following long-term use of ginseng.[63 , 148] Ginseng us anticoagulant effect.[82 , 177]
- St. John's wort (*Hypericum perforatum*) ($14,969,575)â€”St. John's for treatment of depression and as topical remedy for cuts, bruises, a popular as an AIDS treatment because of the lack of clinical efficacy.[6 hyperforin and hypericin. Its antidepressant properties likely derive fr inhibit the reuptake of serotonin, dopamine, norepineprine, Î³-aminob major study in 2002 demonstrated that St. John's wort is ineffective toxicity appears limited to photosensitization reactions. St. John's wor with medications metabolized by this enzyme (eg, indinavir, oral co John's wort is a weak monoamine oxidase inhibitor, raising concerns serotonin reuptake inhibitors.[136]
- Black cohosh (*Cimicifuga racemosa*) ($12,333,188)â€”Black cohosh of premenstrual syndrome and as an estrogen replacement therapy a perimenopausal symptoms. It also is used as a treatment for arthritis cohosh appears to be safe in appropriate doses.[77]
- Cranberry (*Vaccinium macrocarpon*) ($11,857,782)â€”Cranberry is a

urinary tract infections. Cranberry appears to be safe in appropriate

- Valerian (*Valeriana officinalis*) ($8,120,329)â€”Valerian is a popular and is also used as a sleeping aid. Valerian appears to be safe in ap potentiate sedation in patients taking sedative-hypnotics.[126]
- Milk thistle (*Silybum marianum*) ($7,762,350)â€”Milk thistle contain for treatment of liver dysfunction. It appears to be safe.
- Evening primrose (*Oenothera biennis*)â€”Evening primrose contain prostaglandin E_1 precursor. This herbal is a popular remedy for treat diabetes, eczema, and rheumatoid arthritis. Evening primrose appears This herbal may lower the seizure threshold in epilepsy.
- Kava kava (*Piper methysticum*) ($4,423,427)â€”Kava kava is a pop and muscle relaxant. Kavalactones are the active ingredients. Kava ka patients taking sedative-hypnotics.[110] Long-term use of kava at high and yellowish discoloring of the skin, ataxia, hair loss, partial loss of weight reduction. The dermatologic signs of excessive kava use are k *kavaism* and usually are reversible with discontinuation of use.[123] In hepatoxicity, including 4 deaths associated with the consumption of k

reported worldwide.[106] Consequently, sales of kava were restricted i Canada, Switzerland, Japan, New Zealand, Singapore, and France.[69] not restricted sales of kava but issued a consumer advisory in March

Toxicity of Specific Herbal Preparations

Cardiovascular Toxins

Aconite

Aconites (caowu, chuanwu, and fuzi) are the dried rootstocks of the *Acon* usually is derived from *Aconitum carmichaelii* (chuan wu) or *A. kuznezoff* States, aconite is derived from *A. napellus*, commonly known as *monksh* most toxic part of the plant, When ingested, both cardiac and neurologic

far more common in Asia, especially China.[40] In Hong Kong, it is respons poisonings from Chinese herbal preparations.[35 , 38 , 40]

Aconite toxicity is caused by C19 diterpenoid-ester alkaloids, including a hypoaconitine.[19] Mechanistically, aconitine increases sodium influx throug inotropy while delaying the final repolarization phase of the action poten excitation.[73] Sinus bradycardia and ventricular dysrhythmias can occur.[39] minutes to 4 hours after ingestion. Paresthesias of the oral mucosa and e nausea, vomiting, diarrhea, and hypersalivation, and then by progressive may occur with doses as low as 5 mL aconite tincture, 2 mg pure aconite, of value in treating bradycardia or hypersalivation.[156] Although no antido suggest the use of amiodarone, flecainide, bretylium, lidocaine, and proc tachydysrhythmias.[156 , 176] Pharmacologic principles support the use of t case of aconite-induced refractory tachydysrhythmias was successfully ma device.[57] In a case series of 2 aconite-poisoned patients, use of charcoa removal was described as reversing aconite-induced ventricular dysrhyth

Ch'an Su

Ch'an su is a traditional herbal remedy derived from the secretions of the the toad *Bufo bufo gargarizans* or *Bufo melanosticus.* This remedy is trad congestive heart failure.[91] Ch'an su contains two groups of toxic compo consisting of bufadienolides and the hallucinogenic compound bufotenin. are similar to cardioactive steroid poisoning, including gastrointestinal syr also marketed as an aphrodisiac for its purported topical anesthetic effects â€œStone,â€• â€œLove Stone,â€• â€œBlack Stone,â€• and â€œRock H New York City, several fatalities were associated with the ingestion of Ch' aphrodisiac.[24] Severe toxic reactions or death are reported after mouthir eating an entire toad, toad soup, or toad eggs.[17] Assays for serum digox bufadienolides but may qualitatively assist in making a presumptive diagr digoxin-specific Fab was successfully used to treat Ch'an su poisoning an for any suspected case of Ch'an su cardiotoxicity or other cardioactive st

Central Nervous System Toxins

Absinthe

Wormwood (*Artemisia absinthium*) extract is the main ingredient in absi outlawed in the United States in 1912. This volatile oil is a mixture of Î±- Both tetrahydrocannabinol and thujone have an affinity for a common CNS similar oxidative metabolic pathways.[175]

Chronic absinthe use caused absinthism, which was characterized by ps deterioration, and seizures. The most famous victim of absinthism may ha thought to have suffered from this disorder in the later part of his life.[4] A now is used for flavoring vermouth and pastis. A case of wormwood-indu acute renal failure was described involving a patient who purchased and essential oil of wormwood from the Internet, assuming it was absinthe li supportive.

Anticholinergic Agents: Henbane, Jimson Weed

Many plants contain the belladonna alkaloids: atropine (DL-hyoscyamine), hyoscine). They may still be used therapeutically for treatment of asthma included in herbal teas.[34] Signs and symptoms of anticholinergic poisonin bowel sounds, urinary retention, dry mouth, flushed skin, tachycardia, ar usually require only supportive care and CNS sedation with intravenous physostigmine reverses anticholinergic poisoning; however, its use should to severely symptomatic cases because inappropriate use may cause seiz

Ephedra

Members of the genus *Ephedra* are generally erect evergreen plants rese include sea grape, ma-huang, yellow horse, desert tea, squaw tea, and M long history of use as stimulants and for management of bronchospasm. and, in some species, pseudoephedrine.[159] In large doses, ephedrine ca insomnia, dizziness, palpitations, skin flushing, tingling, vomiting, anxiety psychosis. The treatment is similar to that for other CNS stimulants (Chap reports of adverse events associated with ephedra use submitted to the F considered â€œprobableâ€• or â€œpossiblyâ€• related to ephedra use. commonly reported adverse effect (17 cases), followed by palpitations or

cases), and seizures (7 cases). Ten reported cases resulted in death. Thi disability.[71] In 2002, the FDA banned the sale of ephedra-containing die herbal preparations, such as bitter orange *(Citrus aurantia)* , contain ep are still widely available.[115 , 125] Exposures may result in cardiovascular

Khat

A common form of drug abuse in East Africa involves chewing the leaves a) plant and swallowing the juice.[53 , 101] Khat is used by herbalists to tre gastric ulcers. The two active compounds in khat are cathine (norpseudo aminopropiophenone), the more active stimulant (an extensive discussion

Broom
Cytisus spp
Smoke for relaxation
Sparteine
Sedative-hypnotic
California poppy
Eschscholtzia californica
Smoke as marijuana substitute
Alkaloids and glucosides
Euphoriant
Catnip
Nepeta cataria
Smoke or tea as marijuana substitute
Nepetalactone
Euphoriant
Ch'an Su
Bufo bufo gargarizans
Bufo bufo melanosticus
Smoke or lick for hallucinations
Bufotenin
Hallucinogen
Cinnamon

Cinnamomum camphora
Smoke with marijuana
?
Stimulant
Cloves
Syzgium aromaticum
Smoke in cigarette/â€œkreteksâ€•
Eugenol
Euphoriant
Damiana
Turnera diffusa
Smoke as marijuana substitute
?
Stimulant/hallucinogen
Goldenseal
Hydrastis canadensis
Ingest to mask detection of opioid, marijuana, or cocaine in urinary drug â€”
No evidence
Hops
Humulus lupulus
Smoke or tea as sedative and marijuana substitue
Humulone, lupulone â†’ methylbutenol
Sedative (mild)
Hydrangea
Hydrangea paniculata
Smoke as marijuana substitute
Hydrangin, saponin
Stimulant
Ibogaine
Tabernanthe iboga
Stimulant, hallucinogen
Ibogaine
Hallucinogen

Juniper
Juniper macropoda
Smoke as hallucinogen
?
Hallucinogen
Kava kava
Piper methysticum
Smoke or tea as marijuana substitute
Kava lactones
Hallucinogen
Kola nut
Cola spp
Smoke, tea, or capsules as stimulant substitute
Caffeine, theobromine, kolanin
Stimulant
Lobelia
Lobelia inflata
Smoke or tea as marijuana substitute
Lobeline
Euphoriant
Mandrake
Mandragora officinarum
Tea as hallucinogen
Atropine, scopolamine
Hallucinogen
Mate
Ilex paraguayensis
Tea as stimulant
Caffeine
Stimulant
Mormon tea
Ephedra nevadensis
Tea as stimulant
Ephedrine

Stimulant
Morning glory
Ipomoea violacea
Seeds have hallucinogens
D-lysergic acid amide (ergine)
Hallucinogen
Nutmeg
Myristica fragrans
Tea as hallucinogen
Myristicin
Hallucinogen
Passion flower
Passiflora incarnata
Smoke, tea, or capsules as marijuana
Harmala alkaloids
Stimulant (mild)
Periwinkle
Catharanthus roseus
Smoke or tea as euphoriant
Indole alkaloids
Hallucinogen
Prickly poppy
Argemone mexicana
Smoke as euphoriant
Protopine, bergerine, isoquinolones
Analgesic
Snakeroot
Rauwolfia serpentina
Smoke or tea as tobacco substitute
Reserpine
Tranquilizer
Thorn apple
Datura stramonium
Smoke or tea as tobacco substitute or hallucinogen

Atropine, scopolamine
Hallucinogen
Tobacco
Nicotiana spp
Smoke as tobacco
Nicotine
Stimulant
Valerian
Valeriana officinalis
Tea or capsules
Chatinine, velerine alkaloids
Tranquilizer
Wild lettuce
Lactuca sativa
Smoke as opium substitute
Unknown
Analgesic (mild)
Wormwood
Artemisia absinthium
Smoke or tea as relaxant
Thujone
Analgesic
Yohimbe
Pausinystalia yohimbe
Smoke or tea as stimulant
Yohimbine
Hallucinogen (mild)
Adapted from Siegel RK: Herbal intoxication. JAMA 1976;236:473â€“476.

Labeled Ingredient Scientific Name Usage Active Ingredients

TABLE 43-3. Constituent Psychoactive Xenobiotics in Herbal Prep

Nicotinic Agents: Betel Nut, Blue Cohosh, Bro Tobacco

Betel (*Areca catechu*) is chewed by an estimated 200 million people wor herbal, it used as a digestive aid and as a treatment for cough and sore arecoline, a direct-acting nicotinic agonist. The betel leaf also contains a capable of producing sympathomimetic reactions Arecoline is a bronchoc methacholine, and may exacerbate bronchospasm in asthmatic patients c betel nut toxicity is supportive. Long-term use of betel nut is associated carcinoma of the oral mucosa.[122]

Many other herbal preparations have nicotinic effects. Examples of plants include blue cohosh, methylcytisine; broom, L-sparteine; chestnut, esculir tobacco/nicotine.

Other herbals possessing CNS activity include valerian (sedation), kava k (seizures), nutmeg (hallucinations),[171] mace (hallucinations), and iboga

Gastrointestinal Toxins

Goldenseal

Goldenseal (*Hydrastis canadensis*) originally was used by the Cherokees dye and an internal remedy.[64] Today, it is used as an astringent, as a re gastrointestinal tract disorders, and as treatment for menorrhagia. Golden presence of illicit drugs on urinary drug screens, although multiple studie the results of urinary drug screens.[42 , 118 , 128] This myth originated in *the Pike* (1900), which was written by the internationally

known plant pharmacist Uri Lloyd. In this novel, one of the major charact poisoning with strychnine but is posthumously exonerated with evidence in goldenseal) and morphine cross-react to produce a positive color assay of this herbal is thought to be safe, but ingestion of large amounts can paralysis, and respiratory failure. In those cases, the patient should rece care.

Hepatotoxins

Pennyroyal

Pennyroyal oil is a volatile oil extract from the leaves of *Mentha pulegium* Herbalists use pennyroyal oil as an abortifacient and to regulate menstruat flea/mosquito repellant and as a fragrance. The abortive effect is thought contraction of the uterus.[155] Pennyroyal usually is ingested as a strong te the oil itself. It is cited as the causative agent in several well-documente ingestion of as little as 15 mL of the oil.[2,6] The postulated mechanism i glutathione depletion from the cyclohexanone pulegone and its cytochrom CYP2C19)-dependent toxic metabolites that include menthofuran.[88] On a matter of the midbrain is reported in both a fatal human exposure and in pulegone depletes hepatic glutathione stores, *N*-acetylcysteine treatment in Depth: *N*-Acetylcysteine). In an animal model, pretreatment with cy (CYP1A2, CYP2C19) and disulfiram (CYP2E1) reduced pulegone-induced reasonable to consider use of cytochrome P450 inhibitors in the treatme however, evidence of clinical benefit in humans currently is lacking.

Pyrrolizidine Alkaloids

Pyrrolizidine alkaloids are hepatotoxins found in many plants, including *H* and *Symphytum* .[135,140] Examples of other plants and products contair borage (*Borago officinalis*), coltsfoot (*Tussilago farfara*), and T'u-san-ch

The alkaloids undergo metabolism to pyrroles, which serve as biologic al hepatic sinusoidal hypertrophy and venous occlusion, resulting in hepatic hepatomegaly, cirrhosis, and possibly hepatic carcinoma. Chronic low dos resulting in pulmonary artery hypertension and right ventricular hypertro tea, prepared from the leaves of the *Crotalaria* plant, is considered an er Epidemics have also occurred in Afghanistan and India, where ingestion *Heliotropium* and *Crotalaria* seeds resulted in reports of 1632 and 60 ca respectively.[112,157] In western countries, ingestion of herbal products led to several cases of hepatic venoocclusive disease.[135] Treatment of he supportive but may require liver transplantation in severe cases.

Other Hepatotoxins

Several herbal preparations are associated with hepatotoxicity.[94] These p
(*Larrea tridentata*),[23,65] germander (*Teucrium chamaedrys*),[95] impilia
(*Atractylis gummifera*), and sassafras (*Sassafras albidum*).[147]

Metals

Poisonings by metals, including arsenic, cadmium, lead, and mercury, ma
various types of herbal preparations[28,29,46,141] (Chaps. 85, 87, 91,
ceasing consumption of the herbal product and use of an appropriate che

Hai ge fen (clamshell powder) contamination with copper, chromium, arse
case reports.[72,103] Pay-loo-ah, a red and orange powder used by the Hm
remedy, was contaminated with lead.[25] Ayurvedic remedies, based upon
often intentionally contain metals such as gold, silver, copper, zinc, iron,
Ghasard, Bola Goli, Kandu, and Moha Yogran Guggulu, traditional Indian
associated with lead poisoning.[28,146] One fatality from lead poisoning fr
reported from the United States.[28] In one study, 20% of surveyed Ayurv
and sold in stores in the Boston area contained potentially harmful levels

Azarcon (lead tetroxide) and Greta (lead oxide) are used by an estimate
families for treatment of *empacho*. In Spanish, *empach* o means â€œblo
any type of chronic digestive problem, including diverse symptoms such
vomiting, anorexia, apathy, and lethargy.[30,33] Azarcon and Greta are fi
varying from 70% to >90%.[15,31]

Herbal balls, hand-rolled mixtures of herbs and honey produced in China,
and mercury contamination.[56] Examples include An Gong Niu Huang Wan,
Chiang Ya Wan.

Renal Toxins

Aristolochia

An epidemic of renal failure in Belgium was linked to the substitution of *A*
birthwort, heartwort, and fangchi, for another Chinese herbal, *Stephania*

weight-loss regimen.[165, 166] Of 70 identified cases of renal fibrosis, 30 failure. Aristolochic acid in *Aristolochia* causes renal fibrosis which typica 12â€“24 months after the initial injury. Patients with *Aristolochia* -induce increased risk for developing urothelial cancer.[121]

Miscellaneous

Chamomile Tea

Chamomile tea is a popular herbal drink made from chamomile flower he occur in patients allergic to ragweed, asters, chrysanthemums, or other r , [21] Such reactions are rare but can be life threatening. The patient need highly atopic to experience a cross-reaction.

Rattlesnake Capsules

Rattlesnake capsules are a common Mexican folk remedy used to treat c These capsules contain dried, pulverized rattlesnake powder and are sold vibora de cascabel, polvo de

vibora, and carne de vibora, without prescriptions. Infection with *Salmone* ingestion.[10, 43, 124, 143, 169]

Chinese Patent Medications

Chinese patent medicines, a component of traditional Chinese medicine, formulated into tablets, capsules, syrups, powders, ointments, and plaster by poorly regulated Chinese pharmaceutical agencies and are highly susc contamination (Table 43-4). They are often sold by nonherbalists at con incomplete documentation of ingredients, and, typically, they are not label California Department of Health Services investigated 260 Asian patent r determined that 32% contained undeclared pharmaceutics or heavy meta determined that 24% of 2609 samples collected were contaminated by at

Jin Bu Huan is a traditional Chinese preparation used as a sedative and a an isoquinoline alkaloid L-tetrahydropalmatine (L-THP), is responsible for

Bu Huan. In 2 case reports, 3 pediatric patients developed life-threatenin developed hepatitis while using Jin Bu Huan.[26, 27] Hepatotoxicity may be structurally similar to the hepatotoxic pyrrolizidine alkaloids.[173] Although in these cases indicate that *Polygala chinensis* was the plant source for L L-THP. Plants from the genera *Stephania* and *Corydalis* are also known as appreciable amounts of L-THP. The product implicated in the case reports by the manufacturer.

Nan Lien Chiu Fong Toukuwan (now withdrawn from the market) was fou phenacetin, phenylbutazone, indomethacin, mefenamic acid, diazepam, mercuric sulfide, lead, and cadmium, depending on the manufacturer.[38] S were reported following ingestion of this preparation.[142] Dr. Tong Shap Y contain theophylline.[38] Leng Pui Kee cough pills were found to contain b

Ansenpenaw Tablets
Chung Lien Drug Works (Hankow, China)
Mercuric chloride
Bezoar Sedative Pills
Lanzhou Fo Ci Pharmaceutical Factory (Lanzhou, China)
Mercuric chloride 2% or 10%
Compound Kangweiling
Wo Zhou Pharmaceutical Factory (Zhe Jiang, China)
Centipede (scolopendra) 10%
Dahuo Luodan
Beijing Tun Jen Tang (Beijing, China)
Centipede (scolopendra)
Danshen Tabletco
Shanghai Chinese Medicine Works (Shanghai, China)
Borneol
Fructus Persica Compound Pills
Lanzhou Fo Ci Pharmaceutical Factory (Lanzhou, China)
Cannabis indica seed
Fuchingsung-N Cream
Tianjin Pharmaceutical Corp. (Tianjin, China)
Fluocinolone acetanide

Kwei Ling Chi
Changchun Chinese Medicines and Drugs Manufactory (Chang Chun, China
Mercuric chloride
Kyushin Heart Tonic
Kyushin Seikyaku Co., Ltd. (Tokyo, Japan)
Toad venom, borneol
Laryngitis Pills
China Dzechuan Provincial Pharmaceutical Factory (Chengtu Branch, China
Borax 30%, toad-cake 10%
Leung Pui Kee Cough Pills
Leung Pui Kee Medical Factory (Hong Kong)
Dover's powder (opium powder)
Lu-Shen-Wan
Shanghai Chinese Medicine Works (Shanghai, China)
Toad secretion
Nasalin
Kwangchow Pharmaceutical Industry Co. (Kwangchow, China)
Centipede 5%
Nui Huang Chieh Tu Pien
Tung Jen Tang (Beijing, China)
Borneo camphor
Nui Huang Xiao Yan Wan Bezoar Antiphlogistic Pills
Soochow Chinese Medicine Works (Kiangsu, China)
Realgar 19.23%
Pak Yuen Tong Hou Tsao Powder
Kwan Tung Pak Yuen Tong Main Factory (Hong Kong)
Scorpion 10%
Po Ying Tan Baby Protector
Po Che Tong Poon Mo Um (Hong Kong)
Camphor 20%
Superior Tabellae Berberini HCl
Min-Kang Drug Manufactory (I-Chang, China)
Berberini HCl
Watson's Flower Pagodo Cakes

A.S. Watson & Co., Ltd. (Hong Kong)
Piperazine phosphate
Xiao Huo Luo Dan
Lanzhou Fo Ci Pharmaceutical Factory (Lanzhou, China)
Aconite 42%
From Appendix E. Alternative Medicine: Expanding Medical Horizons. A rep
Health on alternative medical systems and practices in the United States.
workshop on alternative medicine. Chantilly, Virginia. Sept. 14â€“16, 19

Product Name Manufacturer Toxic Xenobiotics

TABLE 43-4. The 20 Most Popular Asian Patent Medicines That C

Tung Shueh (black ball) contains diazepam and mefenamic acid and is a
nephritis.[51] Gan Mao Tong Pian, an herbal cold remedy, contains phenylb
in one child.[119] Chui Feng Su Ho Wan, which contains *Glycyrrhiza glabra*
induced torsade de pointes in an elderly woman.[38]

Several Chinese patent medicines contain the mercurials cinnabar (mercu
chloride). Tse Koo Choy and Qing Fen, which contain calomel, are associa
poisoning.[84]

Many Chinese medicated oils contain oil of wintergreen, which is methyls
intended for external use, it is a common practice to ingest a few drops u
general tonic or specific remedy. Examples of medicated oils include White
wintergreen, 30% menthol, 6% camphor), Red Flower Oil (67% oil of wi
Kwan Loong Medicated Oil (menthol 25%, methylsalicylate 15%, camphor

Herbal Preparations and AIDS Therapies

Many patients infected with human immunodeficiency virus (HIV) have tu
hope of finding less toxic therapy than the conventional modalities current
positive patients in a university-based AIDS clinic, 22% used 1 or more h
period.[85] Twenty-four percent of these patients were unable to state whic
effects included dermatitis, nausea, vomiting, diarrhea, thrombocytopenia

mental status, hepatotoxicity, and electrolyte imbalances. Twenty percent were unaware of their use of herbs. A more recent study reported that m were taking alternative medicines, and 24% of AIDS patients were taking botanicals.[66]

Current popular herbal preparations and dietary supplements for treatmer include *Lactobacillus acidophilus* , adrenal cortex, aloe vera, *Artemisia* , *A* blue-green algae, cat's claw, *Chlorella* , coenzyme Q10, colloidal silver, (DHEA), echinacea, elderberry, evening primrose oil, flaxseed oil, garlic, glucosamine, glutamine, glutathione, glycyrrhizin, grapeseed, green tea, palmetto, Siberian ginseng, and silymarin and are used for treatment of

Treatment

A specific treatment strategy should emphasize identification of the specif patient, concurrent medication(s), and medical illness(es). Because herba depending on the preparation used, careful examination may be aided by preparation. In most cases, supportive care and discontinuation of the h Some herbal toxicities require specific laboratory analysis and therapy (Ta

All adverse events associated with herbal preparations should be reported or to FDA MedWatch by phone at 1-800-FDA-1088 or online at http://w

Summary

The popularity of herbal preparations is expected to increase in the fores users will suffer no ill effects, both herbal users and clinicians should be pharmacologically active and have the potential for toxicity. They may in to increase the toxicity of the medication or decrease its therapeutic effe conditions may have increased risk for toxicity when using herbal prepar

Herbal users should be aware that these preparations are poorly studied. for most preparations. No standards exist for their manufacture, quality, not contain the purported amount of the active ingredient. Some herbal p active ingredient. Herbal products are reported to be adulterated with pr contaminants such as heavy metals.

Many herbal stores are staffed by untrained personnel who may dispense unfounded claims concerning their products.[134] Herbalists (eg, Chinese h remedies with the potential for serious toxicity as the result of improper improper preparation of the herbal product by the herbalist or herbal use herbalists may be unaware of the potential for toxicity of their product.

Clinicians should be familiar with herbal preparations and their potential effects. This is especially important because standard herbal reference te on the management of poisoning or other adverse effects.[70] Every patien assessing the concurrent or recent past use of herbal preparations.

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Chapter 44
Athletic Performance Enhancers

Susi U. Vassallo

Case

A 17-year-old boy presented to the emergency department complaining of chest pain while he was playing basketball. The patient stated that he had basketball court at his high school and had experienced chest discomfort rest. Because of the chest discomfort, the patient decided a few minutes instead of playing more basketball. He again developed chest pain with w ceased his activities. He went home and reported the experience to his m mother brought her son to the emergency department and was present at history obtained in the presence of his mother revealed that this was the had experienced chest discomfort. No one in his family had died suddenly family history of structural cardiac abnormalities. Upon questioning, the drug use but stated that he took vitamin supplements. He denied anabolic he had been considering taking growth hormone to grow taller and bigge examination was remarkable for a well-developed, well-conditioned muscu athletic physique of normal height. Vital signs were as follows: blood pres pulse 60 beats/min; respiratory rate 14 breaths/min; temperature 98.6Â examination was unremarkable. Electrocardiogram and chest radiograph w

patient asked to be discharged to complete his mid-term examinations ar exercise regimen. An echocardiogram was planned for the following day.

The desire to improve athletic performance in a scientific manner is a re development. The emphasis on, and study of, human physical and menta centered on the importance of manual work and military service. The role inconsequential, except for its potential in improving military preparedne comes from the Dutch word *doop* , a viscous opium juice used by the an

Public interest in extraordinary athletic achievement fuels the modern-da performance enhancement in sports. In spite of the prohibition of doping, they would use a banned substance to win if they would not be caught.[15]

History and Epidemiology

Controversy surrounding the systematic use of performance-enhancing dru participating athletes has marred many sporting events. Since the Interr Committee (IOC) began testing for drugs during the 1968 Olympic games have been sanctioned and even stripped of their Olympic medals because for banned substances. However, from a public health perspective, the us enhancing drugs among athletes of all ages and abilities is a far more se highly publicized cases involving a few world-class athletes. The majority epidemiology of performance-enhancing substances have investigated an steroid use. *Androgenic* means masculinizing and *anabolic* means tissue *process* stimulates protein synthesis, promotes nitrogen deposition in lean decreases protein breakdown.[248] Studies of high school students documen seniors have used anabolic steroids, and 35% of these individuals were n organized athletics.[32] Others find rates of androgenic steroid use in adol from 3%â€“19%.[124 , 112 , 182 , 243 , 247 , 248] According to the 2005 surv Collegiate Athletic Association (NCAA), 1.2% of college athletes use anab use ephedrine.[161] The Drug Enforcement Agency (DEA) reported that 30â androgenic anabolic steroids and human growth hormone sold illegally do purport.[61]

Sudden Death in Athletes

Sudden unexpected death in athletes younger than 35 years is underesti
According to the IOC, 2 of 100,000 athletes between 12 and 35 years of
cardiac death each year. In the general population of young nonathletes,
times lower, or 0.7 individuals per 100,000. During the 5-year period fror
fewer than 60 cases of sudden cardiac death among high school athletes
approximately 12 per year in the United States.[142, 149] In December 200
a panel of experts to develop a consensus paper to be known as the *Lausa*
paper provides the scientific basis for preventing sudden death of athlete

The leading cause of nontraumatic sudden death in young athletes is mos
cardiac anomalies.[140] In autopsy studies of athletes with sudden death,
cardiomyopathy is the most common structural abnormality, followed by
anomalies.[142]

Traumatic causes of sudden death include head and spinal cord injuries,
players and pole vaulters, vertebral artery rupture and subarachnoid hem
the neck by

hockey pucks, and commotio cordis from blunt impact to the chest wall.[14
Medical causes of sudden death other than cardiac causes include heat st
sickle cell trait, and asthma.[76, 116, 144, 229] Many unexpected deaths in
young competitors have occurred in the absence of obvious medical or tr
these cases, the use of performance-enhancing drugs is linked to the deat
erythropoietin (EPO), introduced in Europe in 1987, may have contributed
of deaths in young European endurance athletes over the next few years.
In young healthy athletes experiencing cerebrovascular events or myocar
temporal link between the use of cocaine, ephedrine, or performance enh
anabolic androgenic steroids suggests a role for these xenobiotics as pre
adverse events[142] (Chap. 74).

Principles

Performance enhancers can be classified several ways for the purposes of
categorize agents according to the expected effect of the drug. For exam
increase muscle mass, whereas others decrease recovery time, increase e
presence of other drugs. However, one drug may have several expected

diuretics may be used to mask the presence of other agents by forcing th may be used to reduce weight. Clenbuterol is an anabolic agent, but it als because of its Î²2 -adrenergic agonist effects. Bromontan is another stimul a masking agent. Depending on the xenobiotic, it is used either before c future performance or during competition to improve immediate results.[2

According to the World Anti-Doping Agency (WADA) World Anti-Doping Co method constitutes doping and can be added to the prohibited list if it me following three criteria: it enhances performance; its use presents a dang health; and it is contrary to the spirit of sport[245] (Table 44-1).

Some of the substances on the WADA 2005 Prohibited List are used to tr frequently encountered in athletes.[244] Many athletes have sought to expl test by claiming the substance was prescribed for a medical condition, suc modafinil, a stimulant, for the sleep disorder narcolepsy. However, some medical conditions that may require treatment. For example, the prevalen increasing in athletes. At least 10â€“15% of Olympic athletes have exer , [216] Salbutamol (albuterol) is the most commonly used asthma medicine adrenergic agonists are commonly used for treatment of asthma, these a during and out of competition. In the Olympics, use of inhaled Î²2 -adren an abbreviated Therapeutic Use Exemption (TUE). With the TUE, the inhal if the athlete provides medical justification for therapeutic necessity and investigations performed to establish the diagnosis of asthma. Neverthele concentration (free salbutamol concentration plus glucuronide level > 100 considered a positive test and an adverse finding unless the athlete prove value results from therapeutic use of the drug.[244] Systemic administration such as prednisone, is not permitted. Topical preparations of glucocortico

Substances (S) and Methods (M) Prohibited at All Times (In- and Out-of-

- S1. Anabolic Agents
- S2. Hormones and Related Substances
- S3. Î²-Adrenergic Agonists
- S4. Agents with Antiestrogenic Activity
- S5. Diuretics and Other Masking Agents
- M1. Enhancement of Oxygen Transfer
- M2. Chemical and Physical Manipulation

M3. Gene Doping

Substances and Methods Prohibited In-Competition

In addition to S1 to S5 and M1 to M3 above, the following categories a competition:

S6. Stimulants

S7. Narcotics

S8. Cannabinoids

S9. Glucocorticosteroids

Substances Prohibited in Particular (P) Sports

P1. Alcohol

P2. Î²-Adrenergic Antagonists

Specified Substances[a]

Ephedrine

Cannabinoids

All Inhaled $Î²_2$ -Adrenergic Agonists, Except Clenbuterol

Probenecid

All Glucocorticosteroids

All Î²-adrenergic antagonists

Alcohol

[a] In certain circumstances, a doping violation involving specified substance reduced sanction, provided the athlete establishes that the use was not i performance.

TABLE 44-1. Abbreviated Summary of World Anti-Doping Agency List[244]

Anabolic Xenobiotics

Androgenic Steroids

Androgenic anabolic steroids (AAS) increase muscle mass, lean body weig nitrogen retention.[155] Testosterone is the prototypical androgen, and mo steroids are synthetic testosterone derivatives. The androgenic effects of responsible for male appearance and secondary sexual characteristics suc

of body hair and subsequent deepening of the voice.

In the 1970s and 1980s, federal regulation of anabolic steroids was under Food and Drug Administration (FDA). Because of increasing media reports anabolic steroids in sports, particularly by high school students and ama enacted the Anabolic Steroid Control Act of 1990, which amended the Co Act and classified anabolic steroids as schedule III. Schedule III implies th currently accepted medical use in the United States and has less potential drugs categorized as schedule I or II. The Anabolic Steroid Control Act of steroid precursors, such as androstenedione and dihydrotestosterone, to t substances that are considered illegal without a prescription. Possession

or other metabolic precursors called *prohormone drugs* is considered a f by jail. Distributing these substances is a felony that may result in up to the first offense. Nevertheless, anabolic steroids are still available illicitly and over the Internet from international marketers, veterinary pharmace some legitimate US manufacturers (Table 44-2). The US FDA estimates t AAS amounts to $300â€“500 million annually.[46]

Physiology and Pharmacology

The Leydig cells of the testis produce 95% of endogenous male testoster comes from the adrenal glands. Normally 4â€“10 mg testosterone and 1â androstenedione are produced daily in men. Women secrete approximatel testosterone and 2â€“4 mg androstenedione daily from their ovaries and

Testosterone is rapidly degraded in the liver. The plasma half-life is less Therefore, in order to create a substance that is useful clinically, testoste the 17-hydroxy position, forming a hydrophobic compound that can be ad vehicle for gradual release.[12] Most of these esters of testosterone must b intramuscularly to avoid extensive first-pass hepatic metabolism associate administration.[14] The alternative to esterification at the 17-hydroxy positi position. Alkylated androgens can be administered orally because they are hepatic metabolism. These agents, more commonly used by athletes, are majority of complications associated with AAS use[12] (Table 44-2).

17Î±-Alkyl Derivatives (Oral)

Ethylestrenol

Maxibolin

Fluoxymesterone

Halotestin

Methandrostenolone

Dianabol

Methyltestosterone

Oxandrolone

Anavar

Oxymetholone

Anadrol

Stanozolol

Winstrol

17Î²-Ester Derivatives (Parenteral)

Boldenone

Equipoise, Equibold, Vebenol

Nandrolone decanoate

Durabolin, Decadurabolin

Nandrolone phenpropionate

Durabolin, Hybolin

Testosterone esters

Testosterone cypionate

Testex, Sten

Testosterone enanthate

Testoviron, Delatestryl

Testosterone ester combination

Depotest, Sustenon

Testosterone heptylate

Theramex

Testosterone propionate

Testex, Testopel

Trenbolone

Finajet

Transdermal Testosterone Preparations

Buccal gel

Striant

Dermal gel, ointment

AndroGel, Testim

Transdermal reservoir patch

AndroDerm

Generic Nomenclature Representative Trade Names

TABLE 44-2. Synthetic Testosterone Derivatives/Anabolic Androg

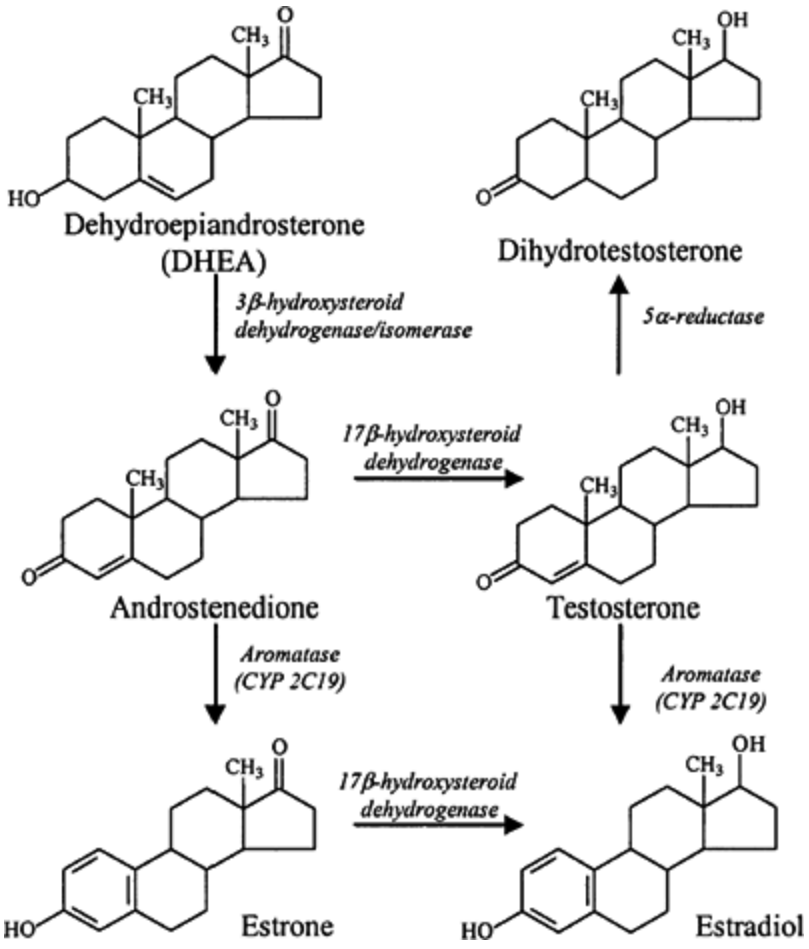

Figure 44-1. Metabolic pathways of dehydroepiandrosterone (DHEA).

Antiestrogens and Antiandrogens

In sports, the general purpose of taking androgens is to increase the ana avoid the unwanted side effects of feminization, such as gynecomastia, c secondary sexual characteristics such as facial hair and deepening voice. that completely dissociates the desired from the undesired effects has no Therefore, athletes are directed on the use of agents to manipulate the r androgen metabolism and decrease unwanted side effects by combining antiestrogenic or antiandrogenic activity. Such xenobiotics are divided in such as anastrozole (Arimidex) and aminoglutethimide (Cytadren), select modulators (SERMs) such as tamoxifen and raloxifene, and other antiest such as clomiphene (Clomid). These agents are prohibited for all athletes indirectly increasing gonadotropin release, is most commonly used by ath endogenous testosterone upon discontinuation of androgenic anabolic st such as the 5Î±-reductase inhibitor cyproterone acetate, prevent masculi athletes (Figure 44-1). Internet web sites have extensive discussions on substances as part of the AAS regimen for muscle building.

Administration

Approximately 50% of AASs are taken orally. The remainder is administe injection, with one fourth of intramuscular AAS users sharing needles.[62] needles and syringes exchanged in a needle-exchange program in Wales steroids.[171] Unlike therapeutically indicated regimens, which consist of fix intervals, athletes typically use AASs in cycles of 6 to 8 weeks.[12] For exa use steroids for 2 months and then abstain for 2 months. Cycling is based individual preferences

and not on any validated protocol. *Stacking* implies combining the use of time, often with both oral and intramuscular administration. To prevent *p* developing tolerance, to any one drug, some athletes who take AASs use different AASs simultaneously. The doses used are frequently hundreds of

scientifically based therapeutic recommendations.[2 , 242] *Pyramiding* impli a low dose, increasing the dose many times, and then tapering once aga may require several months to be totally excreted, whereas water-soluble only days to weeks to be cleared by the kidney. Water-soluble testosteror â€œbridging therapy.â€• *Bridging* refers to the practice of halting the a lasting alkylated testosterone formulations so that urine analyses at a spe evidence of use, while injections of shorter-acting testosterone esters are orally administered alkylated formulations. This strategy, which was used German Democratic Republic, is documented in a review of the subject b research of previously classified records.[75] Clearance profiles for testoste determined for each athlete. In general, the daily injection of testosteron when termination of the more readily detectable synthetic alkylated test was necessary to avoid a positive doping test. These daily injections of were halted 4â€“5 days before competition. Testosterone-to-epitestosteror determined upon the athletes' departure to a sporting event. A few days European Swimming Championships, the urine samples of 4 female swimn Olympic Gold medals) had T/E ratio > 6. Corrupt officials involved in dopi values would decrease to acceptable levels in time for the event, based o athletes' clearance of testosterone esters. Epitestosterone propionate inj to bring the T/E ratio back to < 6:1, the acceptable ratio at that time.[75] > 4:1 is considered positive.[244]

Clinical Manifestations of Androgenic Anab

Musculoskeletal

Without question, supraphysiologic doses of testosterone, when combined training, increase muscle strength and size.[23] The most common muscul of steroid use are tendon and ligament rupture.[77 , 99 , 129 , 134]

Hepatic

Hepatic subcapsular hematoma with hemorrhage is reported.[201] Peliosis h blood-filled sinuses in the liver that may result in fatal hepatic rupture, c with alkylated androgens and may not improve when androgen use is sto

This condition is not associated with the dose or duration of treatment.[12] Cyproterone acetate is a chlorinated progesterone derivative that inhibits reportedly causes hepatotoxicity.[12 , 81 , 85]

Infectious

Local complications from injection include infected joints,[71] cutaneous ab *Candida albicans* endophthalmitis.[241] Injection of steroids using contamin to transmission of infectious diseases such as HIV and hepatitis B and C.[1 [204 , 207] Severe varicella may occur in long-term AAS users.[110]

Dermatologic

Cutaneous side effects are common and include keloid formation, sebace seborrheic furunculosis, folliculitis, and striae.[203] Acne is associated with sometimes is referred to as â€œgymnasium acne.â€•[43 , 175] A common and gynecomastia occurs. The production of sebum is an androgen-deper dihydrotestosterone is active in sebaceous glands.[12]

Endocrine

Conversion of AAS to estradiol in peripheral tissues results in feminizatior Gynecomastia may be irreversible. AAS use causes negative feedback inh gonadotropin-releasing hormone, luteinizing hormone, and follicle-stimula the hypothalamus. This process results in testicular atrophy and decreas which may be reversible. In females, menstrual irregularities and breast AAS use causes virilization in females.[220]

Cardiovascular

Cardiac complications include acute myocardial infarction and sudden car [107 , 136 , 138 , 151] Autopsy examination of the heart may reveal biventri extensive myocardial fibrosis, and contraction-band necrosis. Myofibrillar hypertrophy of the interventricular septum and left ventricle are present. and use of AAS impair diastolic function by increasing left ventricular wal models and in vitro myocardial cell studies show similar pathologic chang

[227 , 228] Doppler echocardiography shows that several years after streng using AAS, concentric left ventricular hypertrophy remains, compared to athletes not using AAS.[227] Growth hormone may potentiate the effects of increase concentric remodeling of the left ventricle.[115] In addition to dire vasospasm or thrombosis may occur.[152] Alkylated androgens lower the c density lipoprotein (HDL) cholesterol and may increase platelet aggregati Thromboembolic events such as pulmonary embolus,[59 , 83] central nervou events such as stroke,[119 , 120 , 206] carotid arterial occlusion,[128] cerebral popliteal artery entrapment,[133] and poststeroid balance disorder occur.[26

Neuropsychiatric

Distractibility, depression or mania, delirium, irritability, insomnia, hostili lability, and aggressiveness (â€œroid rageâ€•) may occur.[17 , 79 , 178 , 1 neuropsychiatric effects do not appear to correlate with plasma AAS con Withdrawal symptoms from AAS include decreased libido, fatigue, and m

Cancer

An association between AAS use and development of cancer has been ob animals.[191] Testicular and prostatic carcinomas are reported in more freq [82 , 190] Hepatocellular carcinoma,[111 , 165] peliosis hepatis, and cholangio [91] Wilms tumor and renal cell carcinoma are reported in young AAS users

Specific Anabolic Xenobiotics

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a precursor to testosterone (Figure 4 by the FDA in 1996, this drug subsequently was marketed as a nutritiona available for purchase without a prescription.[220] DHEA is converted to a then to testosterone by the enzyme 17Î²-hydroxysteroid dehydrogenase.[Administration of androstenedione in dosages of 300 mg/d increases test concentrations in some men and women.[132]

Women with adrenal insufficiency given DHEA replacement at a dose of 50 months demonstrated increased serum concentrations of DHEA, androste and dihydrotestosterone. Serum total and HDL cholesterol concentrations decreased. Some women experienced androgenic side effects, including gr hirsutism.[10] Sense of well-being and sexuality increased in men and wome treatment.[10 , 157 , 158] The neuropsychiatric effects of DHEA have been d animals. Increased hypothalamic serotonin, anxiolytic effects, antagonism aminobutyric acid type A ($GABA_A$) receptor, and agonism of the *N* -met receptor are demonstrated.[10 , 140 , 153]

Clenbuterol

Clenbuterol is a $Î²_2$ -adrenergic agonist that decreases fat deposition and breakdown in animal models.[6 , 41] Clenbuterol is also a potent *nutrient p* term implying it can increase the amount of muscle and decrease the am per pound of feed given to cattle and other animals.[78 , 189] Use of clenbu is illegal. Nevertheless, the consumption of veal liver contaminated with resulted in sympathomimetic symptoms and positive urine tests in affect Clenbuterol increases the glycolytic capacity of muscle and causes hyper growth of fast-twitch fibers.[141 , 251] $Î²_2$ -Adrenergic receptors are present and may mediate the anabolic effect of this class of drugs. Athletes typica 60â€“100 Âµg/d clenbuterol and in some cases as much as 600 Âµg/d. C characterized by the typical symptoms of sympathomimetic overdose[40] , Several drug users became ill when they used a substance they thought v was determined to contain only clenbuterol.

Other $Î²_2$ -adrenergic agonists, such as oral albuterol, have similar anab however, the half-life of oral albuterol is much shorter, making it less att agent.[156] The half-life of clenbuterol is approximately 27 hours, whereas albuterol is 3â€“6 hours. Inhalational use of $Î²_2$ -adrenergic agonists has demonstrated to share the anabolic properties associated with parenteral [235]

Peptides and Glycoprotein Hormones

Creatine

Creatine is an amino acid formed by combining the amino acids methioni glycine. It is synthesized naturally by the liver, kidneys, and pancreas. Cr protein-containing foods such as meat and fish.[154] In its phosphorylated f the resynthesis of adenosine triphosphate (ATP) from adenosine diphosph Supplemental creatine bound to phosphorous acts as a substrate to dona formation of ATP.[219] Because ATP is the immediate source of energy for creatine is used by athletes to increase energy during short, high-intensi than 2.5 million kg of creatine is consumed annually in the United States. have admitted to using creatine as part of their training nutritional regim by athletes at all levels. Creatine supplementation increases total creatine muscle by up to 20%.[33 , 93] Numerous studies demonstrate improved pe creatine supplementation, particularly in sports requiring short, high-inte [, 126 , 150 , 231]

Creatine is found in skeletal muscle and in the heart, brain and kidney. T stored primarily as phosphorylated creatine (PCr) and the remainder as f Consuming carbohydrates with creatine supplements increases total creatir skeletal muscle.[93] This process explains why creatine is marketed in com carbohydrate. Human endogenous creatine production is 1 g/d, and norm meat and fish offer another 1 to 2 g/d as dietary intake. From 1â€“2 g o daily by irreversible conversion to creatinine.[237]

Creatine supplementation is most commonly accomplished with creatine r of 20â€“25 g/d can increase the skeletal muscle total creatine concentrati Creatine uptake in skeletal muscle occurs via the creatine transporter pro sarcolemma. Creatine stores do not increase in some individuals despite supplementation. Creatine transporter expression and activity, as well as influence the uptake of creatine and the effect of creatine loading on ath [211 , 214]

One adverse effect of creatine supplementation is weight gain, which is t primarily from water retention.[95 , 150] However, evidence indicates that r partially responsible for the weight gain associated with long-term creatir was the most commonly reported side effect of creatine use in one study

athletes. Other complaints were muscle cramping and dehydration, althou no complaints.[113]

Creatine supplementation increases urinary creatine and creatinine excreti serum creatinine concentrations by 20%.[95, 114] Long- and short-term cr supplementation does not appear to have an adverse effect on renal func patient who had been taking creatine 5 g/d for 4 weeks developed inters improved with cessation of creatine use. Whether ingestion of creatine ca unknown.[125] A young man with focal segmental glomerular sclerosis deve creatinine concentration and decreased glomerular filtration rate (GFR) w supplementation was started. The values returned to baseline upon cessa supplementation.[181] The possibility of developing decreased renal functior concern. Ingestion of large amounts of creatine may result in formation substance *N* -nitrososarcosine, which induces esophageal cancer in rats.[8]

Human Growth Hormone

Human growth hormone (hGH) is an anabolic peptide hormone secreted b pituitary gland. It causes its anabolic effect by stimulating protein synthe growth and muscle mass in children. Recombinant human growth hormon since 1984. It is commonly used therapeutically for children with growth daily doses of 5â€“26 Âµg/kg body weight.[232]

Growth hormone secretion is stimulated by growth hormone-releasing hor by somatostatin. Growth hormone receptors occur in many tissues, includ of hGH to hepatic receptors causes secretion of insulinlike growth factor-1 potent anabolic effects and is the mediator responsible for many of the a

Human growth hormone is released in a pulsatile manner, mainly during stimulates hGH release, and more intense exercise causes proportionately [, 51, 220]

Amino acids such as ornithine, L-arginine, tryptophan, and L-lysine, incre through an unknown mechanism and often are ingested for this purpose.[5]

Human growth hormone stimulates protein synthesis and tissue growth b and increased movement of amino acids into tissue. The effects on increa

size are well proven in growth hormone-deficient individuals, but studies c resultant increase in strength related to the increase in muscle size.[49, 1 hormone improves muscle and cardiac function, increases red cell mass capacity, stimulates lipolysis, normalizes serum lipid concentrations, and subcutaneous fat. It also improves mood and sense of well-being.[49, 50,

Growth hormone is used by athletes for its anabolic potential. As an agent particularly attractive because laboratory detection is difficult. In one surv gyms used hGH for body building.[70] In another survey of adolescents, 5% had used hGH.[188] Recombinant human growth hormone (rhGH) was found Chinese swimmers at the 1998 World Swimming Championships and of cy France in 1998, suggesting use of hGH by elite athletes.[238] Pituitary-derive illicitly sold as recombinant growth hormone on the black market.

Human growth hormone administration may cause myalgias, arthralgias, syndrome, and edema.[106] The effects of hGH on skeletal growth depend c preadolescence, excessive hGH may cause increased bony growth and gig excessive hGH may cause acromegaly.[228, 230] Growth hormone may cau and hyperglycemia. Skin changes, such as increased melanocytic nevi and occur.[174] Lipid profiles may be adversely affected. HDL concentrations are associated with increased risk of coronary artery disease.[252] Because hGH parenterally, there is risk of transmission of infection.[137] The illicit sale c pituitary-derived growth hormone is associated with a risk of Creutzfeldt Long-term users of hGH may be at increased risk for prostate cancer beca complications associated with IGF-1.[90]

Insulinlike Growth Factor

IGF-1 is a peptide chain structurally related to insulin. Parenteral adminis approved for clinical treatment of dwarfism and insulin resistance. Childre antibodies to recombinant growth hormone may respond to IGF-1.

IGF-1 is produced in the liver and many other cell types. A recombinant Human growth hormone is the primary stimulus for release of IGF-1, alth nutrition play a role.[193] The effects of growth hormone are primarily med binds principally to the type I IGF receptor, which has 40% homology wit

and a similar tyrosine kinase subunit.[223] IGF-1 also binds to insulin recep 1% of insulin's affinity for the insulin receptor. IGF-1 increases glucose u the movement of glucose into cells, increasing amino acid uptake and st synthesis.

The actions of IGF-1 can be classified as either anabolic or insulinlike.[193] and DHEA increase IGF-1 levels.[157]

Side effects are similar to those associated with use of growth hormone a acromegaly. Other effects include headache, jaw pain, edema, and altera A potentially serious side effect of IGF-1 is hypoglycemia. High endogeno are associated with an increased risk for prostate cancer.[38]

In one group of 189 weightlifters, 14.3% had taken what they believed to knowledge of the substance, and most said they would consider using it i studies on the efficacy of IGF-1 in improving the conditioning of athletes attractive to female athletes because it does not cause virilization.[220]

Insulin

Insulin is used by body builders for its anabolic properties. It has been c magazinesâ€• as â€œthe most powerful anabolic hormone on the planet identified anabolic androgenic steroid users in 1 gym, 5 (25%) who had r take insulin reported using it to increase muscle mass.[186] These individua had injected insulin from 20â€“60 times over the 6 months prior to the s was to inject 10 U regular insulin and then eat sugar-containing foods af

Insulin inhibits proteolysis and promotes growth by stimulating movement acids into muscle and fat cells. It increases the synthesis of glycogen, fat proteins[53] (Chap. 48).

Two cases of hypoglycemia have been reported in body builders using ins 80 U regular insulin in both thighs every hour over a 3- to 4-hour period eating large amounts of carbohydrates on each of the previous 2 days. On presentation, he had injected 320 U regular insulin over the previous 4 h The patient had a seizure at the gym and arrived comatose in the emerg serum glucose concentration was 18 mg/dL.[183] Another young body build posthypoglycemic encephalopathy after using intravenous insulin.[66]

Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) is a glycoprotein that stimulates t in men. In women, hCG is secreted by the placenta during pregnancy. Hu gonadotropin may be used by male athletes to prevent testicular atrophy androgen administration.[121] Analysis of hCG in 740 urinary specimens of abnormal concentrations in 21 individuals. This finding prompted the IOC l 1987.[31 , 51] Presently, distinguishing exogenous hCG administration from early pregnancy is not possible, so the urine samples of women are not t

Very small amounts of hCG are normally present in men and nonpregnan measurement is made by immunoenzymatic assay. The decision limit, the which the test is considered positive, is set at 5 IU/mL urine. Trophoblast nontrophoblastic tumors can increase hCG concentrations, and this possib considered in the evaluation of elevated urinary hCG concentration.[57]

Although administration of hCG causes an increase in the total testostero ratio is unchanged because epitestosterone production also is stimulated.

Oxygen Transport

Erythropoietin (EPO)

EPO induces erythropoiesis by a receptor-mediated mechanism that stimu develop into mature red blood cells (RBCs). EPO has been available since human erythropoietin (rhEPO). Its use in international competition has b 1990. Because EPO increases exercise capacity and hemoglobin production athletes, often with additional iron supplementation, for these purposes. increased hematocrit occur several days after administration.[80 , 167] EPO oxygen uptake by 6â€“7%, an effect that lasts approximately 2 weeks af administration is completed.[64]

Two EPO analogs exist. Darbopoietin, also known as *new erythropoiesis-s* (NESP), differs from EPO by 5 amino acids. It has a much longer half-life

weekly.[169] Another protein known as synthetic erythropoiesis protein (SEP protein structure to EPO. The protein polymers created in this molecule h immunogenicity, fewer biologic contaminants, and more predictable pha

EPO is secreted primarily by the kidney, although some is produced by o the liver. The mean half-life of EPO is 4.5 hours following IV administratic subcutaneous administration.[195]

In patients with renal failure who are on dialysis, a typical dose is approx weight given 3 times per week.[100 , 195] EPO enhances endothelial activati reactivity and increases systolic blood pressure during submaximal exerc effects, in addition to the increase in hemoglobin, increase the risk for t hypertension, and hyperviscosity syndromes.[21 , 148 , 167] Evidence indicat rhEPO might pose a risk for decreased endogenous EPO production and of reticulocytosis and anemia.[36 , 167]

Increases in hematocrit subsequent to EPO use are believed to have cont of a number of competitive cyclists in Europe. Nineteen Belgian and Dutch uncertain causes between 1987 and 1990.[63] The 1998 Tour de France wa discovery of widespread EPO use by members of several different cycling

An EPO overdose occurred in a patient who self-administered 10,000 U/d of time as a result of a dosing error. The patient presented to the hospita with a plethoric appearance, blackened toes, decreased pulses, and a her Emergent erythropheresis was performed and resulted in rapid reduction improvement in the patient's condition.[250] Another report of deliberate of an unknown dose of rhEPO resulted in a hematocrit of 70%. The patier emergently with phlebotomy and intravenous hydration and improved.[30]

Artificial Oxygen Carriers

Artificial oxygen carriers are blood substitutes that supplement the oxyge RBCs.[202] Artificial oxygen carriers fall into two categories: hemoglobin-ba (HBOC) and perfluorocarbon (PFC) emulsions. Athletes may experiment w to increase endurance.

Hemoglobin can be genetically engineered or obtained from cattle or outc hemoglobin may serve as a source for human HBOC products. Hemoglobin

subunits, 2 Î±-chains and 2 Î²-chains. When removed from erythrocytes, unstable and dissociates into dimers. Therefore, hemoglobin must be stab variety of methods before an exogenous therapeutic agent is created. Th modification of hemoglobin by polymerization, conjugation, or cross-linki of human purified hemoglobin with glutaraldehyde, surface conjugation of polyethylene glycol, or linking of recombinant hemoglobin with short pepti hemoglobin stabilization. The life of HBOCs is much shorter than that of hemoglobin has a half-life of 12 hours, and surface-modified hemoglobin In comparison, erythrocytes may survive 120 days. In 1 report, healthy suffered no ill effects from infusion of Hemopure, a product of purified b cross-linked to glutaraldehyde.[106] HBOCs cause vasoconstriction resulting and pulmonary pressures.[202 , 217]

The differences in molecular weights of native hemoglobin and stabilized determined by size-exclusion high-performance liquid chromatography, whi primary methods of doping analysis for HBOCs.[233]

Perfluorocarbons

PFCs are synthetic oxygen-carrying compounds that can be used as RBC liquids, which are composed of 8â€“10 carbon atoms with fluorine substit serve as excellent solvents for gases.[92] In 1966, it was shown that mice fully submerged in PFCs infused with oxygen.[42] Compared to RBC transfus without risk of infection, require no cross-matching, and do not increase PFCs are stable at room temperature and have a shelf life of greater thar that make them convenient to use.

Several cyclists have been hospitalized for illnesses that were possibly as Symptoms included transient back pain, malaise, flushing, and fever of s duration.[92] Dose-related thrombocytopenia is transient and occurs 3â€“4 administration.[209]

PFCs increase vascular tone, which may cause hypertension. Both system vascular resistance is increased.[92] For unclear reasons, intravenous infusi can cause cardiac arrest.[224] Allergic reactions are reported to the egg yo [, 163 , 202]

Because PFCs are perceived by the immune system as foreign substances cleared by the reticuloendothelial system. The plasma half-life is approxin accumulate in the liver and spleen and are slowly transported to the lung. months to years, the PFCs are eliminated unchanged in the expired air an expired air by thermal conductance or in blood by using gas chromatogra spectrometry.[224 , 202]

Autotransfusion

Infusion of autologous or heterologous blood for the purpose of increasing known as *blood doping.* Blood doping was used in the Olympic Games as Finnish steeplechaser. During subsequent summer and winter Olympics, cyclists, and skiers acknowledged their use of this practice. The US cyclin using blood transfusions in the 1984 Olympics. Subsequently, the IOC ba

Blood doping is beneficial in endurance athletes. Infusion of 400 mL pack runners increased the total RBC concentration and substantially improved km races.[29] Blood doping also increases the speed performance of cross preparatory technique involves the removal of 1000 mL blood, the immed plasma volume, and the freezing and storage of RBCs. After 5â€“6 weeks return to normocythemia), reinfusion of frozen RBCs resulted in increase from 45% to 49%, 5% increase in oxygen utilization, and increased endu Reinfusion of packed RBCs resulted overnight in an increase in maximal e 23% and increased maximal oxygen uptake by 9%. These improvements increase in hemoglobin concentration.[65]

Altitude acclimatization, which is considered an acceptable practice by WA improvements in performance similar to the banned practice of blood do athletes living at sea level are at a disadvantage in their training compar at high altitudes. One problem with altitude training is that exercise capac intensity of the training is decreased until acclimatization occurs. This offs beneficial effects of altitude training. Many athletes avoid this by â€œlivir lowâ€• or by training in an oxygen rich environment while acclimatizing t increase in hemoglobin due to altitude acclimatization resulted in a 6% in oxygen uptake and 25% increase in endurance capacity upon return to se

Stimulants

Caffeine

Caffeine is a CNS stimulant that causes a feeling of decreased fatigue ar performance[69 , 170] (Chap. 63). These changes may occur through seve mechanisms, including increased calcium permeability in the sarcoplasmic enhanced contractility of muscle, phosphodiesterase inhibition and subse nucleotides, adenosine blockade leading to blood vessel dilation, and inh Caffeine is no longer prohibited by the WADA 2005 Prohibited List World Caffeine and pseudoephedrine are included in a monitoring program that WADA to detect patterns of misuse for substances that are no longer on

Amphetamines

The beneficial effects of amphetamines in sports result from their ability t pain.[55] Initial studies of soldiers showed they could march longer and ign took amphetamines.[225] In one study of college students, resting and max strength, acceleration, and anaerobic capacity increased. However, althou fatigue decreased, lactic acid continued to accumulate and maximal oxyg unchanged.[39] Other studies have shown no significant effects on exercise (Chap. 73).

Sodium Bicarbonate

Sodium bicarbonate loading, known as *soda loading* , has a long history o racing.[16] Sodium bicarbonate may buffer the lactic acidosis caused by ex delaying fatigue and enhancing performance.[86]

During high-intensity exercise, metabolism becomes anaerobic and lactic Intracellular acidosis is said to contribute to muscle fatigue by reducing t muscle contractile apparatus to calcium.[172] Several studies demonstrated performance when sodium bicarbonate was ingested 2â€“3 hours before The study dose was 0.2â€“0.3 g/kg body weight of sodium bicarbonate, $NaHCO_3$ per day. The effects of sodium bicarbonate are greatest when pe

longer than 4 minutes because anaerobic metabolism contributes more to production and energy from aerobic metabolism diminishes.[86 , 88] Adverse bicarbonate loading include diarrhea, abdominal pain, and possible hype

An animal model demonstrated that intracellular acidosis, occurring as a production, reversed muscle fatigue.[3 , 172] Previously, intracellular acidosis contribute to muscle fatigue by reducing the sensitivity of the muscle co calcium, decreasing the force of muscle contraction. However, the mecha excitationâ€“contraction is complex. Because it permeates membranes eas important for maintaining and stabilizing the muscle fiber resting membra pH. Because of this characteristic, a large sodium current is needed to o stabilization and produce an action potential. In intracellular acidosis, m to the chloride ion is reduced, the resting membrane potential is no longe inward sodium influx is needed to produce an action potential. The excita tubule system is therefore increased by acidosis, protecting against musc

Diuretics

The World Anti-Doping Code bans diuretic use.[244] Diuretics are used in sp athlete must achieve a certain weight to compete in discrete weight class weight loss, body builders find that diuretic use gives greater definition to skin draws tightly around the muscles.[1] Diuretics also result in increased thereby diluting the urine and making more difficult the detection of othe xenobiotics.[34 , 56] Diuretic use in a body builder caused hyperkalemia ar 60).

Miscellaneous Xenobiotics

Chromium Picolinate

Chromium acts as a cofactor to enhance the action of insulin.[94] It is foun grains, raisins, apples, and mushrooms.[219] It is sold as chromium picolin acid is thought to enhance chromium absorption.[219] In people who are c chromium supplementation results in increased glycogen synthesis and g Studies have not shown an increase in strength or a change in body com

metabolism when chromium is administered in a controlled fashion.[5, 52] from chromium picolinate doses > 200 Âµg/d.[48] A 24-year-old body build rhabdomyolysis after ingesting 1200 Âµg chromium picolinate, 6-24 times recommended dose of 50â€“200 Âµg, over 48 hours.[147]

Renal failure developed in one patient who took chromium picolinate 600 weight reduction, which is 12â€“45 times the usual intake of dietary chron recommended supplementation dose.[240] Another individual who took 120 chromium picolinate for the previous 4 months for weight loss presented dysfunction, anemia, thrombocytopenia, and hemolysis. Chromium plasma 2â€“3 times normal (Chap. 88). Other causes of the abnormalities were laboratory parameters improved with cessation of chromium ingestion.[37]

Laboratory Detection

Enormous amounts of energy and money are expended to determine the performance-enhancing substances. Nevertheless, the average percentage tests analyzed by the IOC accredited laboratories between the years 1993 1.8%.[230] WADA implemented a worldwide testing program before the 200 Sydney, Australia. In the program, 2846 tests were conducted on athletes 27 different sports. Unannounced out-of-competition testing was performed an Olympic event and began 2 weeks before the games started. The first urine testing for EPO use was introduced in Sydney and represented the f sampling for the detection of previously undetectable performance-enhanc targeted the sports at high risk for EPO use, primarily endurance events. teams of independent observers were involved in monitoring all aspects o process.[164] In the 2004 Olympics in Athens, Greece, approximately 3500 and yielded 30 positive test results. For the first time, drug testing in At unannounced tests during the games and even subsequently when the at home. In previous Summer Olympics, only the top four finishers were te the competition.

Analysis of samples on the international level is performed by a limited r laboratories. The majority of tests are performed on urine, with careful p requirements regarding handling of samples. From the first moment the a

a sample is requested for testing, the athlete must at all times remain wi chaperone who is an official of the anti-doping association. This official d athlete urinating to produce the sample. The athlete must report to the within 60 minutes for a no-advance-notice sample and within 24 hours fo sample collection. The sample is collected in â€œtamper-evidentâ€• con Documentation identifying the athlete is completed but not included with sample is delivered to the laboratory such that the integrity, identity, and sample are assured.[245] Attention must be paid to proper storage of spec bacterial metabolism may increase urinary steroid concentrations.[24 , 60]

Upon the sample's arrival at the testing laboratory, the integrity of the s including the code, seal, visual appearance, density, and pH. Registration completed, and the sample is divided into two aliquots. All testing is done and any positive results are confirmed on the second aliquot. The aliquots referred to as sample A and sample B. Sample preparation is difficult and

Capillary gas chromatography is the most important technique currently Gas chromatography typically is combined with mass spectrometry for de of substances.[160] Analysis of the urine by gas chromatography-mass spe current standard for detection of anabolic androgenic steroids.[34] Such an amount of reference data.[35]

The complexity of the laboratory testing is illustrated in the discovery of undetectable by standard sport doping tests of urine. In the summer of 2 was provided anonymously to the United States anti-doping authority. The the University of California Los Angeles (UCLA) Olympic Analytical Labora furor, now known as the BALCO scandal, resulted in the implication of m athletes in sports doping. BALCO is the acronym for the Bay Area Labora company that provides vitamins and nutritional supplements to athletes.

Through a painstaking process of analyses, an impurity in the substance i identified as a derivative of the AAS norbolethone. â€œA hypothesis for which fit all the dataâ€• resulted in the discovery and synthesis of a new tetrahydrogestrinone (THG).[35] THG has characteristics that differentiate i anabolic steroids. According to the report describing the discovery, synth THG, this new chemical was not a known pharmaceutical or a known vet

Detection of exogenously administered peptide hormones is difficult becau similarity to endogenous substances. Research continues in this area, as report using monoclonal antibodies to detect administration of rhGH.[246] E measured by a monoclonal anti-EPO antibody test, which does not distinq endogenously produced and exogenously administered recombinant EPO. methods of EPO detection are used, such as measurement of hemoglobin

Previously, some sports-governing bodies, such as the International Cyclir International Skiing Federation, selected a hematocrit of 50% in men and action level above which an athlete may be disqualified for presumed EPO normal hematocrit values vary greatly among athletes. Several studies ha hematocrits above the action values of 50% in men and 47% in women a From 3â€“6% of athletes who did not use EPO had hematocrits > 50%.[23 living and training at altitudes between 2000 and 3000 m above sea level hematocrit values > 50%.[234] Other studies confirm the increased hemato training at altitudes from 1000â€“6000 m.[19 , 198 , 199 , 234]

Although many endurance athletes may have increased blood volume, the lowered because of the increased plasma volume, which exceeds the RBC dilutional pseudoanemia is sometimes called *sports anemia* .[205] Additionall measurements are affected by hydration status, upright versus supine po and they demonstrate an approximately 3% diurnal variation.[197] Because among individuals, postural effects, and the ease of manipulation through indirect detection of EPO use by hematocrit measurement is fraught with

The ratio between serum soluble transferrin receptors (sTfr) and ferritin h indirect method for detection of EPO use. Soluble transferrin receptor is r progenitors. EPO stimulates erythropoiesis and causes an increase in

sTfr and a decrease in ferritin.[84] Individuals with other causes of polycyt erythropoiesis also can exhibit increased ratios and be falsely accused of hematocrit with sTfr > 10 Âµg/mL and sTfr-to-serum protein ratio > 153 an indirect measurement of EPO use.[11]

A combination of multiple indirect markers of altered erythropoiesis for d was developed at the 2000 Olympics in Sydney, Australia.[167] Current EPO â€œON-model,â€• and recent, but not current, use of EPO is known as

Five variables predict current rhEPO use: reticulocyte count, serum EPO hematocrit, and percentage of macrocytes. The 3-variable combination of reticulocyte count, and serum EPO concentration was the best mechanism rhEPO use.[167] A major drawback to this method is the instability of these blood so that confirmatory testing of the split blood sample is impossible.

The two isoforms of EPO, recombinant and endogenous, have different c compositions causing differing molecular charges.[169] An immunoblotting advantage of these different net charges, and the proteins can be separa when they are placed in an electric field.[131] Subsequently, by isoelectric obtains an image of EPO patterns in the urine.[130] The technique is difficul WADA considers a positive urine test result by this method definitive, eve testing of indirect markers.[169] Because of darbopoietin's structural similar detection techniques also are effective for darbopoietin.[169]

Masking Agents

Some agents are available for the sole purpose of interfering with urine are added to the urine. Examples include â€œKlear,â€• which is 90% m Seal tea, which produces colored urine.[28] Other commercially available p â€œXxtra Clean,â€• which contains pyridinium chlorochromate, and â€œ contains glutaraldehyde. Such adulterants are easily detected.

Any chemical or physical manipulation done with the purpose of altering t or blood sample is prohibited by WADA.[244] For example, use of intraveno substitution is prohibited. The list of prohibited masking agents includes epitestosterone, probenecid, plasma expanders such as albumin, dextran, starch, and Î±-reductase inhibitors such as finasteride and dutasteride.[24 urinary excretion of the glucuronide conjugates of AAS. A number of urin to contain probenecid at the 1987 Pan American Games, leading to subse probenecid by the IOC.[47 , 236]

Gene Doping

The discovery of the genetic codes for some diseases has made gene the conditions, such as muscular dystrophy, a reality. It is now conceivable t

be used to enhance athletic performance. For example, insertion of a ger produce a desired effect, such as large muscles or increased body produc advantageous substances such as testosterone or growth hormone. In an EPO lead to erythropoiesis and genes for IGF-1 produce increased muscle Myostatin, which belongs to a family of proteins that control growth and tissues in the body, inhibits skeletal muscle growth.[200] Mutations of the result in muscle hypertrophy. A report of an extremely muscular baby bor the myostatin gene illustrates the potential effect of gene alterations on The mother of this infant was a professional athlete, and other members known for their strength.[200]

A gene is introduced into the body by direct injection of DNA or by introc of a virus vector containing the altered DNA.[226] As of 2005, gene doping WADA prohibited list. Gene doping is defined as â€œthe non-therapeutic genetic elements, or of the modulation of gene expression, having the ca athlete performance.â€•[244]

Summary

Although the press spotlights a few world-class athletes, the vast majorit performance-enhancing substances are not in the public view. Some indi consequences. The knowledgeable clinician will identify these health effect and educate susceptible individuals on the risks of using performance-er

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Chapter 45
Food Poisoning

Michael G. Tunik

Cases 1 and 2

A 30-year-old woman and her 32-year-old husband, who were on a scuba Puerto Rico, had a local dinner consisting of rice, beans, a large red sna fruit preserves, and wine. That night, approximately 5 hours after dinner, by abdominal discomfort and nausea. These symptoms were followed by Although they were unsure of the order of events, a throbbing headache, numbness of the arms, legs, and mouth ensued. Each patient described f pain with â€œdeep aches in the joints.â€• The woman stated that when warm washcloth to rub on her â€œfreezing skin,â€• the warm washcloth distressing symptom of temperature misinterpretation lasted for 2 days. during the early morning hours, but the nausea and diarrhea continued f crampy, abdominal pain persisted for approximately 4 days. The following spoke to some of the local inhabitants. Many of them described similar s appear after they ate a large fish, such as sea bass, red snapper, groupe

Because so many people had the same symptoms, the couple did not see their return to the mainland 10 days later, they had no clinical or physic

The most common causes of foodborne disease are bacteriaâ€”*Salmonella Clostridium perfringens, Staphylococcus aureus, Campylobacter* spp, *Bacil Escherichia coli, group A Streptococcus, Clostridium botulinum, Vibrio ch* virusesâ€”hepatitis A, E, F, and G, Norwalk virus; parasitesâ€”*Entamoeba lamblia, Trichinella spiralis* ; fishborne toxinsâ€”scombrotoxin, ciguatoxin chemicalsâ€”heavy metals, monosodium glutamate; and plantsâ€”mushro

Foodborne Poisoning with Neurologic Sym

The differential diagnosis of patients with foodborne poisoning presenting symptoms is vast (Tables 45-2 and 45-3). Many of these cases are icht toxins from the muscles, viscera, skin, gonads, and mucous surfaces of t toxicity follows consumption of the fish blood or skeleton. Shellfish poison considered. Most episodes of poisoning are not species specific, although toxicity from Tetraodontiformes (puffer fish), Gymnothoraces (moray eel), and other species) are recognized.

Deep-sea fish, eels, mussels, clams, and crabs are all implicated in diarrl cases of ciguatera poisoning, the major symptoms usually are neurotoxic, gastrointestinal (GI) symptoms are minor. Scombroid poisoning, which is common, is not associated with neurologic manifestations, but facial flush dysphagia are its major signs and symptoms.

Knowing where the fish was caught often is helpful for the diagnosis, bu of foods and rapid worldwide travel can complicate the assessment. Trave Pacific islands, as well as individuals traveling within the United States, h ciguatera poisoning.[88] In geographically disparate regions of Canada,[120] from domoic acid intoxication caused by ingestion of cultivated mussels f Island.

In the differential diagnosis of foodborne poisons presenting with neurolo activities other than eating must always be considered. In particular, spo their activities in high-risk areas (Florida, California, and Hawaii), and oft risk periods (May through August). In the process, they may sustain a bit stingray tail), or laceration (from a deltoid or pectoral fin spine of a lion can cause consequential marine toxicity (Chap. 116).

Ciguatera Poisoning

Ciguatera poisoning is one of the most commonly reported vertebrate fis accounting for almost half of the reported cases in the United States.[36] It water, bottom-dwelling shore reef fish living around the globe between 35 south latitude, including tropical areas such as the Indian Ocean, the Sou Caribbean. Hawaii and Florida report 90% of all cases occurring in the Ur commonly during May through August.[91]

More than 500 fish species are involved, with the barracuda, sea bass, pa grouper, amber jack, kingfish, and sturgeon the most common sources. T the comparably large size of the fish involved.

Large fish (4â€“6 lb or more) become vectors of ciguatera poisoning in a complex feeding patterns inherent in aquatic life. Ciguatoxin can be found protozoa, and the free algae dinoflagellates. These plankton members of

phylum Protozoa are single-celled, motile, flagellated, pigmented organis photosynthesis. Photosynthetic dinoflagellates such as *Gambierdiscus tox* within the dinoflagellates are the origins of ciguatoxin.[45, 71, 96] These d main nutritional source for small herbivorous fish. Because these small fis source for larger carnivorous fish, the ciguatoxin becomes increasingly co flesh, adipose tissue, and viscera of larger and larger fish.[10]

Salmonella
32,610
357
13
Escherichia coli [a]
3,260
84
8
Clostridium perfringens
2,772
57
0

Other parasitic
2,261
13
0
Other viral
2,104
24
0
Shigella
1,555
43
0
Staphylococcus aureus
1,413
42
1
Norwalk virus
1,233
9
0
Hepatitis A virus
729
23
0
Bacillus cereus
691
14
0
Other bacterial
609
6
1
Campylobacter
539

25
1
Scombrotoxin
297
69
0
Ciguatoxin
205
60
0
Streptococcus, group A
122
1
0
Listeria monocytogenes
100
3
2
Clostridium botulinum
56
13
1
Glardia lamblia
45
4
0
Vibrio parahaemolyticus
40
5
0
Other chemical
31
6
0

Yersinia enterocolitica
27
2
1
Mushroom poisoning
21
7
0
Brucella
19
1
0
Trichinella spiralis
19
2
0
Heavy metals
17
4
0
Streptococcus, other
6
1
0
Shellfish
3
1
0
Vibrio cholerae
2
1
0
Monosodium glutamate
2

1
0
[a] The fatality rate of *E. coli* 0157:H7 increased dramatically in the late 1

Etiology	Cases	Outbreaks	Deaths

TABLE 45-1. Epidemiology[36] of Foodborne Poisoning Reporte (1993â€“1997)

Anticholinergic poisoning
Bacterial food poisoning
Bends type I, II, III (caisson disease)
Botulism
Carbon monoxide
Diphtheria
Eaton-Lambert syndrome
Encephalitis
Metals
Migraine
MSG (monosodium glutamate)
Myasthenia gravis
Organic phosphorous compounds
Plant ingestions (poison hemlock, buckthorn)
Poliomyelitis
Tick paralysis

TABLE 45-2. Differential Diagnosis of Possible Foodborne Poisoni Neurologic Symptoms

Ciguatoxin is heat stable, lipid soluble, acid stable, odorless, and tasteles toxin is a large (molecular weight 1100 daltons) complex ester that does is stored in its tissues.[91, 95] The molecule binds to the sodium channel i increases the sodium permeability of the channel.[9, 149] Multiple ciguatoxi the same fish, perhaps explaining the variability of symptoms and differi

can be afflicted after they eat fresh or properly frozen fish prepared by a boiling, baking, frying, stewing, or broiling. The appearance, taste, and s fish usually are unremarkable. The majority of symptomatic episodes beg ingestion, 75% within 12 hours, and all but 4% within 24 hours.[10] Sympto onset of diaphoresis; abdominal pain with cramps, nausea, vomiting; pro and a constellation of dramatic neurologic symptoms.[165] Headaches are c loose, painful teeth may occur. Typically, peripheral dysesthesias and pa predominate. Watery eyes, tingling, and numbness of the tongue, lips, th occur. A strange metallic taste is frequently reported. A reversal of tem is reported, but the pathophysiology remains to be elucidated.[25] Myalgias, lower extremities, arthralgias, ataxia, and weakness are commonly expe and symptoms of dyspareunia and vaginal and pelvic discomfort may occu sexual intercourse with men who are ciguatoxic.[87] Ciguatoxin may be tra milk[18] and can cross the placenta.[118] Vertigo, seizures, and visual disturl vision, manifestations of scotomata, and transient blindness) are describ

Bradycardia and orthostatic hypotension are described.[55] The GI sympto within 24â€“48 hours; however, cardiovascular and neurologic symptoms several days to weeks, depending on the amount of toxin ingested. Delay include protracted itching and hiccoughs. Although deaths are reported, n documented in the United States.[36] Mortality is a result of respiratory pa apparently managed without adequate life support.

Laboratory analysis using an enzyme-linked immunosorbent assay (ELISA) toxin can be performed; alternatively, high-pressure liquid chromatograph The original mouse bioassay was the standard, but the method was slow, destruction of animals, and did not differentiate the variants in ciguatoxi immunobead assay test being developed for field use will allow testing of laboratory processing of the toxin-containing tissues.[9, 69, 117] A useful and management using laboratory testing is excluding other diagnostic p determining the need for, or extent of, specific therapeutic interventions.

Initial treatment for victims of ciguatoxin poisoning includes standard sup toxic ingestion.[165] In most patients, elimination of the toxin is accelerate and diarrhea (70%) have occurred. Administration of activated charcoal m benefit. In patients with significant GI fluid loss through vomiting and/or

fluid and electrolyte repletion is essential. The orthostatic hypotension ma intravenous fluids, atropine, and Î±-adrenergic agonists.

IV mannitol may produce a decrease in neurologic and muscular dysfunc associated with ciguatera. GI symptoms are less responsive to mannitol.[1] randomized

controlled trial, mannitol failed to produce any greater improvement in sy 0.9% sodium chloride solution.[137] Mannitol should be used with caution b hypotension. Vascular reexpansion and cardiovascular stability should be priorities.

Ciguatera
2â€“30 h
*Months to years
t, p, n, v, d
Large reef fish: amber jack, barracuda, snapper, parrot, sea bass, mora source)
*Ciguatoxin
**Increased sodium channel permeability
Clinical, mouse bioassay, immunoassay
*Supportive, mannitol, amitripyline
Tetrodotoxin
Minutes to hours
*Days
p, r, â†“bp
n, v, d
Puffer fish, *fugu,* blue-ringed octopus, newts, horseshoe crab
*Tetrodotoxin
**Blocks sodium channel
*Clinical
**Respiratory support
Neurotoxic shellfish poisoning
15 min to 18 h
*Days

b, t, n, v, d, p
Mussels, clams, scallops, oysters, *P. brevis:*
â€œred tideâ€•
*Brevetoxin
**â†‘ Sodium channel permeability
Clinical, mouse bioassay of food, HPLC
Paralytic shellfish poisoning
30 min
*Days
r, p, n, v, d
Mussels, clams, scallops, oysters, *P. catanella, P. tamarensis*
*Saxitoxin
**Decreases sodium channel permeability
Clinical, mouse bioassay of food, HPLC
*Respiratory support
Amnestic shellfish poisoning
15 min to 38 h
*Years
a
n, v, d, p, r
Mussels, possibly other shellfish; *N. pungens;*
*Domoic acid
**Glutamate analog
Clinical, mouse bioassay of food, HPLC
*Respiratory support
Botulism
12â€“73 h
v, d, r, w
Home-canned foods, ? honey, corn syrups, *C. botulinum*
*Botulinum toxin
**Binds to presynapse, blocks acetylcholine release
Clinical immunoassay
*Antitoxin, respiratory support
n = nausea; v = vomiting; d = diarrhea; p = paresthesias; r = respirator

bronchospasm; t = temperature reversal sensation; a = amnesia; â†“bp =
weakness.

Onset/Duration*	Symptoms	Toxin Source/Toxin*/Mechanism**	

TABLE 45-3. Common Foodborne Neurologic Diseases (Prim
Symptoms)

Admission to the hospital for cautious supportive care is essential when t
uncertain or when volume depletion or any consequential manifestations
differential diagnosis includes botulism, organic phosphorus compound po
potentially life-threatening processes (Tables 45-2 and 45-3). The etiolo
must be rapidly identified to provide specific therapy, if available. Diapho
clinical finding and an important factor in the differential diagnosis. Late i
ciguatera poisoning, amitriptyline 25 mg orally twice daily may alleviate
may persist up to 1 year.

Ciguateralike Poisoning

Moray, conger, and anguillid eels carry a ciguatoxinlike neurotoxin in the
and gonads that does not affect the eel itself. The toxin has a complex e
be structurally very similar to ciguatoxin and is heat stable.[113] These sam
ichthyohemotoxin that is resistant to drying but can be destroyed by heat
(65Â°C). Individuals who eat these eels may manifest neurotoxic sympto
that occurring with ciguatoxin, or they may show signs of cholinergic toxi
hypersalivation, nausea, vomiting, and diarrhea. Shortness of breath, mu
cutaneous eruptions may occur. These findings may be present in additio
symptoms.[65] Management is supportive. Mortality is related to the compl
neurotoxicity, such as seizures and respiratory paralysis.

Scombroid Poisoning

Scombroid poisoning originally was described with the Scombroidae fish (
dark-meat marine tuna, albacore, bonito, mackerel, and skipjack). Howev

commonly ingested vectors identified by the Centers for Disease Control are nonscombroid fish, such as mahi mahi and amber jack.[35] All of the i live in temperate or tropical waters. Ingestion of bluefish in New Hampsh cause of scombroid poisoning in 5 people,[46] and mackerel was the likely reported from a prison. The incidence of this disease probably is far grea perceived. This type of poisoning differs from other fishborne causes of ill entirely preventable if the fish is properly stored after it is removed from

Scombroid poisoning results from eating cooked, smoked, canned, or raw fish all have a high concentration of histidine in their dark meat. *Morganel* and *Klebsiella pneumoniae* , commonly found on the surface of the fish, decarboxylase enzyme that acts on a warm (not refrigerated), freshly kil histidine to histamine, saurine, and other heat-stable substances. Althoug suggested as the causative toxin, chromatographic analysis demonstrates found as histamine phosphate and saurine is merely histamine hydrochlo *saurine* originated from saury, a Japanese dried fish delicacy often assoc intoxication. The extent of spoilage usually correlates with histamine co concentrations in healthy fish are < 0.1 mg/100 g fish meat. In fish left the concentration rapidly increases, reaching toxic concentrations of 100 12 hours.

The appearance, taste, and smell of the fish usually are unremarkable.[5] F abnormal â€œhoneycombingâ€•

character or a pungent, peppery taste that may be a clue to its toxicity (C within minutes to hours after eating the fish, the individual experiences a burning sensation of the mouth, dysphagia, headache, and, of particula scombroid poisoning, a peculiar flush characterized by an intense diffuse neck, and upper torso.[78] Rarely, pruritus, urticaria, angioedema, or bron Nausea, vomiting, dizziness, palpitations, abdominal pain, diarrhea, and develop.[58 , 78 , 83 , 105]

The prognosis is good with appropriate supportive care and parenteral ar diphenhydramine. H_2 -Receptor antagonists such as cimetidine or ranitidin alleviating symptoms.[16] The toxic substance should be removed or absorb Inhaled B_2 -adrenergic agonists and epinephrine may be necessary if bro

prominent. Patients usually show significant improvement within a few ho

Elevated serum or urine histamine concentrations confirm the diagnosis. I remains, isolation of causative bacteria from the flesh is suggestive but r capillary electrophoretic assay makes rapid histamine detection possible.[1 concentrations > 50 mg/100 g fish meat is considered hazardous by the U Administration (FDA). Isoniazid may increase the severity of the reaction inhibiting enzymes that break down histamine.[72 , 159]

The patient may be reassured that he or she is not allergic to fish if othe experience a similar reaction to eating the same fish at the same time, or can be preserved and tested for elevated histamine concentrations. If this available, an anaphylactic reaction to the fish must be considered. Table differential diagnosis of flushing, bronchospasm, and headache. Because consume alcohol with fish, alcohol must be considered an independent va

The differential diagnosis of the scombrotoxic flush apart from a disulfira ingestion of niacin or nicotinic acid, carcinoid syndrome, Zollinger-Ellison pheochromocytoma. The history and clinical evolution usually establish th

Anaphylaxis (anaphylactoid)	
Minutes to hours	
Urticaria, angioedema, bronchospasm, hypotension	
Allergensâ€”nuts, eggs, milk, fish, shellfish, peanuts, soy	
Oxygen, epinephrine, $Î²_2$ -adrenergic agonist,	
Corticosteroids, volume expansion, H_1 H_2 histamine blockers	
MSG (monosodium glutamate)	
Minutes	
Flushing, â†“ BP, palpitations, facial pressure, headaches, bronchospasm	
Shivering (children)	
Flavor enhancer in Chinese and other foods	
Oxygen, $Î²_2$ -adrenergic agonists, volume expansion, avoidance	
Metabisulfites	
Minutes	
Flushing, low BP, bronchospasm	
Preservative used in wines, salad (bars), fruit, juice, shrimp	

	See Anaphylaxis, Avoidance			
	Scombroid			
	Minutes to hours			
	Flushing, â†“ BP, urticaria, headache, pruritis, GI symptoms			
	Large fishâ€”poorly refrigerated; tuna, bonito, albacore, mackerel, mahi			
	See Anaphylaxis, Avoidance			
	Tyramine			
	Minutes to hours			
	Headache, hypertension (INH or MAOI) increases risk			
	Wines, aged cheeses			
	Avoidance			
	As for hypertension, migraines			
	Tartrazine			
	Hours			
	Urticaria, angioedema, brochospasm			
	Yellow coloring			
	Food additive			
	See Anaphylaxis, Avoidance			

INH = isoniazid; â†“BP = hypotension; MAOI = monoamine oxide inhibito

Onset Symptoms/Signs Cause Therapy

TABLE 45-4. Common Foodborne Disease Symptoms: Flushing Headache (Primary Presenting Symptoms)

Shellfish Poisoning

Healthy mollusks living between 30Â° north and 30Â° south latitude inges quantities of dinoflagellates. These dinoflagellates are the major source o during the â€œnon-Râ€• months (May through August) in the northern this time, these dinoflagellates are responsible for the â€œred tidesâ€• t California to Alaska, from New England to St. Lawrence, and across the w Europe.[102] The number of toxic dinoflagellates may be so overwhelming t and humans who walk along the beach may suffer respiratory symptoms

toxin.[104]

Ingestion of shellfish, including oysters, clams, mussels, and scallops, co dinoflagellates or algae may cause neurotoxic, paralytic, and amnestic sy dinoflagellates most frequently implicated are *Ptychodiscus brevis* (forme *breve*), the diatom causing neurotoxic shellfish poisoning; *Protogonyaulax Protogonyaulax tamarensis* , which cause paralytic shellfish poisoning; ar the diatom implicated in amnestic shellfish poisoning. Proliferation of thes a red tide, but shellfish poisoning may occur even in the absence of this

Paralytic shellfish poisoning is caused by saxitoxin. Saxitoxin blocks the sodium channel in a manner identical to tetrodotoxin (see below). The s usually are clams, oysters, mussels, and scallops. A higher number of sh associated with more severe symptoms. Symptoms usually occur within 3 ingestion. Neurologic symptoms predominate and include paresthesias and mouth and extremities, a sensation of floating, headache, ataxia, vertigo paralysis, and cranial nerve dysfunction manifested by dysphagia, dysart transient blindness. GI symptoms are less common and include nausea, pain, and diarrhea. Fatalities may occur as a result of respiratory failure, 12 hours after symptom onset. Muscle weakness may persist for weeks.

Treatment is supportive, but with early intervention for respiratory failur and cathartics were used to remove unabsorbed toxin from the GI tract b necessary

or efficacious.[22 , 93 , 109 , 142] Activated charcoal may be given. Antibodi have reversed cardiorespiratory failure in animals,[12] but this therapy has humans. Assays for saxitoxin include a mouse bioassay, ELISA, and HPLC. interlaboratory accuracy,[161] but the differences in saxitoxin derivatives r an analytic test difficult.[8 , 89]

Neurotoxic shellfish poisoning (NSP) is caused by brevetoxin. Brevetoxin, *Krenia brevis* (previously *Gymnodium brevis*), is a lipid-soluble, heat-sta similar to ciguatoxin. It acts by stimulating sodium flux through the sodiu nerve and muscle.[6 , 26] NSP is characterized by gastroenteritis with asso symptoms. GI symptoms include abdominal pain, nausea, vomiting, diarrh burning. Neurologic features include paresthesias, reversal of hot and co

sensation, myalgias, vertigo, and ataxia. Other symptoms may include h tremor, dysphagia, bradycardia, decreased reflexes, and dilated pupils. P occur. The combination of bradycardia and mydriasis is unusual. The incu hours (range 15 minutesâ€“18 hours). GI and neurologic symptoms app Other manifestations of brevetoxin toxicity include respiratory irritation, bronchospasm, which occur when *P. brevis* is aerosolized by wave action Duration of symptoms averages 17 hours (range 1â€“72 hours).[109]

Brevetoxins can be assayed using mouse bioassay, ELISA, and, more rec radioimmunoassay (RIA) and reconstituted sodium channels.[122 , 158] Trea and severe respiratory depression is very uncommon. Therapy includes re from the environment and the administration of bronchodilators. NSP is n

Amnestic shellfish poisoning is caused by domoic acid. The etiologic agent structural analogue of glutamic and kainic acids produced by the diatom *N* documented outbreak occurred in Canada in 1987, when 107 individuals mussels harvested from cultivated river estuaries on Prince Edward Islan Other outbreaks are possible because a similar diatomâ€”*Pseudonitzschia* isolated in shellfish from other areas.[53] Pelican deaths caused by domoic were reported in 1991. Canada instituted monitoring for domoic acid afte death of 400 sea lions in California in 1998 was linked to domoic acid fro *pungens f multiseries* .[138]

Amnestic shellfish poisoning is characterized by GI symptoms of nausea, cramps, and diarrhea, and by neurologic symptoms of memory loss and, seizures, hemiparesis, ophthalmoplegia, purposeless chewing, and grimac include unstable blood pressure and cardiac dysrhythmias. The onset of s ingestion of mussels is 5 hours (range 15 minutesâ€“38 hours). The mort death most frequently occurring in older patients, who suffer more sever symptoms. Ten percent of victims may suffer long-term antegrade memor motor and sensory neuropathy. Postmortem examinations has revealed ne hippocampus and amygdala.[153]

Tetrodon Poisoning

This type of fish poisoning involves only the order Tetraodonti-formes. Alt

fish is not restricted geographically, it is eaten most frequently in Japan, South America, and Australia.[65] Cases in Florida and New Jersey have be Approximately 100 freshwater and saltwater species of this order exist, ir pufferlike fish such as the globe fish, balloon fish, blowfish, and toad fish found in these fish is also isolated from the blue-ringed octopus[49] and th mollusc.[168] It has also caused fatalities from ingestion of horseshoe crab (a local variety of puffer fish) is considered a delicacy, but special licensir prepare this exceedingly toxic fish. In 1989, the FDA legalized the import However, prior to exportation from Japan, the fish must be laboratory tes two Japanese organizations to be tetrodotoxin free. In addition, certain newts (*Taricha* , notophthalmus, triturus, and cynops), particularly *Taricha* Oregon, California, and southern Alaska, can be fatal when ingested. Most salamanders with bright colors and rough skins contain toxins.[20]

Tetrodotoxin is a heat-stable (except in alkaline milieu), water-soluble, aminoperhydroquanizole found mainly in the fish skin, liver, ovary, intest muscle.[65 , 133] The ovary has a high concentration of the toxin and is mo during the spawning season. Tetrodotoxin is detected by mouse bioassay. heated to 212Â°F (100Â°C) in acid, distinguishing it from saxitoxin. Tetro detected using fluorescent spectrometry[8] or detected in the urine of into a combination of immunoaffinity chromatography with fluorometric HPLC. produced by inhibition of sodium channels and blockade of neuromuscula

Symptoms of tetrodon poisoning typically occur within minutes of ingesti diaphoresis, dysesthesias, and paresthesias of the lips, tongue, mouth, fa evolve rapidly. Buccal bullae and salivation may develop. Dysphagia, dys vomiting, and abdominal pain may ensue. Generalized malaise, loss of c fasciculations, and an ascending paralysis (with risk of respiratory paralys hours. Other cranial nerves may be involved. In more severe toxicity, hy In some studies, mortality has approached 50%.[145]

Therapy is supportive. Removal of the toxin and prevention of absorption measures. Supportive respiratory care emphasizing airway protection, inc necessary, is extremely important.

Less Common Poisonings: Echinoderms

The sea urchin usually causes toxicity by contact with its spinous process delicacy also is toxic upon ingestion. When the sea urchin is prepared as containing gonads should be removed because they contain an acetylcho causes profuse salivation, abdominal pain, nausea, vomiting, and diarrhea considered edible by some individuals, although an asteriotoxin with sap produces nausea and vomiting is reported.

Prevention of Marine Foodborne Disease

Careful evaluation of the symptoms and meticulous reporting to local and departments, as well as to the CDC, will allow for more precise analysis o poisoning from contaminated or poisonous food or fish. Many states and developed rigorous health codes with regard to harvesting

certain species of fish in certain areas at certain times. A review of food reported to the CDC over a 5-year period may be representative of the n food poisoning in the United States (Table 45-1). Some examples of acti foreign health agencies in controlling epidemics of fishborne food poisonir

- In 1972, the 3230-km Massachusetts coastline was noted to be unsaf harvesting. A health emergency was declared because of a red tide bl confiscated shellfish and prohibited the marketing, export, and servin
- The health code of Miami, Florida, prohibits the sale of barracuda and fillets from large and potentially toxic fish containing ciguatoxin.
- The Japanese closely regulate preparation and selling of the puffer fi requiring that preparers receive special training and licensing.
- The Canadian government marks the location and time of harvesting mussels are tested for the presence of domoic acid.[53 , 120]

Case 3

A 4-year-old child presented to the emergency department (ED) with a 1 diarrhea, vomiting, and intermittent abdominal pain. The family became

and mucus appeared in the stool after 4 days. At that time, blood tests a obtained at another hospital. Antipyretics were prescribed for fever, and hydration were given. No antibiotics or other therapy was offered, and th other symptoms began to resolve. The parents again became concerned v child appeared pale, was more irritable than usual, had a decreased urine uninterested in eating at a favorite fast-food restaurant. The child was bro evaluation after a brief generalized seizure. The child was otherwise heal medical history, other medication use, or ingestions. The child was atter

Physical examination revealed an afebrile child with blood pressure 125/80 beats/min; and normal respiratory rate. The child appeared pale and irrit the physical examination was significant for a systolic flow murmur on c mild abdominal pain without rebound or guarding, and a liver edge palpab right costal margin. No meningeal signs were evident, and the neurologic nonfocal. Laboratory studies were significant for a white blood count 22, 25%, and platelet count 80,000/mm^3 . A peripheral blood film revealed helmet cells. Serum sodium concentration was 128 mEq/L; potassium 5.9 nitrogen (BUN) 40 mg/dL; creatinine 2.2 mg/dL; and alanine aminotransf Coagulation studies and cerebrospinal fluid analysis were normal.

Foodborne Poisoning Associated with Gas Anemia, Thrombocytopenia, and Azotemia

This constellation of findings is typical for the hemolytic uremic syndrome frequently caused by a bacterial gastroenteritis. The most common organ *coli* O157:H7.[63] Other bacteria producing a Shigalike toxin can cause the xenobiotics also implicated as causes of HUS include estrogen-containing mitomycin C, cyclosporin A, and radiation therapy.[121] Other nontoxicologic clinical picture include autoimmune disease, Kawasaki syndrome, and ba leading to disseminated intravascular coagulopathy and shock.

Laboratory findings typically include microangiopathic hemolytic anemia, acute intrinsic renal failure. Other laboratory findings include hyperkalem hyponatremia, and hypocalcemia. Liver aminotransferase concentrations m pancreatic involvement may produce hyperamylasemia, elevated lipase c

hyperglycemia.

Most children with HUS are younger than 6 years, and many are younger begins with a prodrome of diarrhea 90% of the time. The diarrhea lasts fe frequently becomes bloody. Abdominal pain because of colitis is common. findings include vomiting, altered mental status (irritability or lethargy), fever. At the time of presentation, many children have oliguria or anuria. children present with a generalized seizure at the onset of HUS.[141] Postdi endemic in Argentina.[97] Frequent epidemics occur in North America, and describe the association of enterohemorrhagic *E. coli* (EHEC) or *E. coli* O postdiarrheal HUS.[21, 101, 114, 115, 126, 163] Postdiarrheal HUS occurs the summer months, matching the peak incidence of positive stool culture common source of the organism).[66] Food products from cattle (ground be cheese) and water contaminated with fecal material are common sources Contaminated water used in gardens and unpasteurized apple cider have diarrhea and HUS as a result of EHEC.[14, 40]

EHEC, including *E. coli* O157:H7, produces a toxin similar to the toxin pro *dysenteriae* type I, referred to as Shigalike toxin (SLT) or verotoxin.[52] Th mechanism for SLT damage is intestinal absorption, bloodstream access t endothelium, intracellular adsorption via glycolipid receptors, ribosomal in death.[151] In animal models, organ damage is more severe if endothelial c concentrations of globotriaosylceramide receptors, which have a high bind toxin. Other organs with these receptors include the renal, GI, and centr which may explain the pattern of organ damage in children with HUS. En and other pathologic processes, including platelet and leukocyte activation coagulation cascade, and the production of cytokines, occur.[75, 160] More exists; SLT-1, SLT-2, and variants of SLT-2 structure have been identifie

Detection of *E. coli* O157:H7 through stool culture early in the course of recovery decreases after the first week of illness.[121, 151] *E. coli* O157:H produces SLT; therefore, if stool cultures are negative, enzyme immunoas polymerase chain reaction (PCR) tests can be used to detect SLT in the s no longer be identified by culture.[23]

Treatment of HUS should focus on meticulous supportive care, with fluid the priority. Peritoneal dialysis or hemodialysis should be instituted early

hyperkalemia, acidosis, and fluid overload. Red blood cells are transfused hemoglobin concentrations > 6 g/dL and platelets to maintain hemostasis invasive procedures. Hypertension should be treated with short-acting ca (nifedipine 0.25â€“0.5 mg/kg/dose orally) and

seizures with benzodiazepines. Many therapies have been used for HUS, fibrinolytics, IV immunoglobulin, fresh-frozen plasma, vitamin E, and ant has been obviously beneficial, and some have been deleterious.[156] Plasma used in nondiarrheal HUS and in recurrent HUS after renal transplants. In antibiotics did not change the course or outcome of children with postdia analysis also found no increased risk of antibiotic therapy.[130] Antiâ€“SLT-2 protected mice from SLT-2 toxicity, but IV immunoglobulin with SLT-2 ac outcome in children with HUS. A doubleâ€“blind, placebo controlled study synthetic SLT receptors attached to an oral carrier did not change the m morbidity of HUS syndrome.[157]

The mortality from HUS with good supportive care is approximately 5%; a suffer end-stage renal disease or cerebral ischemic events and chronic r Prolonged anuria (> 1 week) or oliguria (> 2 weeks) or severe extrarenal markers for higher mortality and morbidity.[121]

Strategies to prevent the spread of *E. coli* O157:H7 and subsequent HUS education on thorough cooking of beef to a well-done temperature of 170 pasteurization of milk and apple cider, and thorough cleaning of vegetabl measures include education of clinicians to consider *E. coli* O157:H7 in p diarrhea and routine capability of microbiology laboratories to culture *E.* provide for EIA or PCR determination of SLT. Public health departments s surveillance systems to identify early outbreaks of *E. coli* O157:H7 infect

Staphylococcus spp
2â€“6 h
+
+
+
-
-

Prepared foods: meats, pastries, salads
Heat-stable enterotoxin
Supportive
Volume expansion
Bacillus cereus
Type I
1â€“6 h
+
+
+
-
-
Fried rice
Heat-labile toxins
Supportive

Volume expansion
Type II
12 h
+
-
+
-
-
Meats, vegetables
Heat-labile toxins

Anisakiasis
1â€“12 h
+
+
-
-
-
Raw fish, sushi, Eustrongyloides, minnows, salmon, cod, herring, squid, t
Intestinal larvae
Endoscopy
Laparotomy
Removal
Clostridium perfringens
8â€“24 h
+
=
+
=
-
Poultry, heat-processed meats
Heat-labile enterotoxin
Volume expansion
Salmonella spp
8â€“24 h
=
=
+
=
+
Poultry, egg
Pets (turtles, lizards, chicks)
Bacteria, endotoxin (bacteremia)
Antibiotics

E. coli
24â€“72 h

Water, food
Enterotoxin, heat stable
Volume expansion
Enterotoxigenic

+
=
+
-
+
Enteric contact
Electrolytes
Invasive

+
-
+
+
+
Raw produce
Bacteria (invasive)
Antibiotics
Hemorrhagic

+
+
+

+
=
Under cooked beef
Unpasteurized milk
Shigalike toxin
Renal, hematologic support
Vibrio cholera
24â€“72 h
=
=
+
-
=
Water, food
Enteric contact
Enterotoxin
Heat labile
Electrolyte replacement, antibiotics
Shigella spp
24â€“72 h
+
=
+
+
=
Institutional food handler
Household, preschool, enteric contact
Bacteria
Endotoxin
Antibiotics
Campylobacter jejuni
1â€“7 d
+
+

+
=
+
Milk, poultry
Unchlorinated water
Bacteria
Heat-labile enterotoxin
Antibiotics
Yersinia spp
1â€“7 d
+
+
+
=
+
Pork, milk, pets
Bacteria
Enterotoxin
Antibiotics
A = abdominal pain; V = vomiting; Di = diarrhea; Dy = dysentery; F = f

Symptoms

Etiology Onset A V Di Dy F Source Pathogenesis Thera

TABLE 45-5. Common Foodborne Disease: Gastrointestinal (Pr
Symptom)

Foodborne Poisoning Associated with Diarr
Elevated Temperature

The initial differential diagnosis for acute diarrhea involves several etiolc (bacterial, viral, parasitic, and fungal), structural (including surgical), m toxin induced, and food induced. The differential diagnosis is described in

An elevated temperature may be caused by invasive organisms, including *Shigella* spp, *Campylobacter* spp, invasive *E. coli, Vibrio parahaemolyticus* as well as some viruses. Episodes of acute gastroenteritis not associated caused by organisms producing toxins, including *S. aureus, B. cereus, C.* enterotoxigenic *E . coli* , and viruses.[30]

Fecal leukocytes typically are found in patients with shigellosis, salmone enteritis, typhoid fever, invasive *E. coli* colitis, *V. parahaemolyticus* , *Yers* and ulcerative colitis. In all of these conditions, except typhoid fever, the primarily polymorphonuclear; in typhoid fever, they are mononuclear. No noted in cholera, viral diarrhea, noninvasive *E. coli* diarrhea, or nonspeci

The timing of diarrhea onset after exposure or the incubation period can differentiating the cause. Extremely short incubation periods of less than *Staphylococcus* , *B. cereus* (type I), enterotoxigenic *E. coli* ,[30 , 99 , 152] a enterotoxins, as well as roundworm larvae ingestions. Intermediate incub 8â€“24 hours are found with *C. perfringens* , *B. cereus* (type II enteroto *coli* ,[44 , 106] and salmonella. Longer incubation periods are seen in other acute gastroenteritis (Table 45-5).

The three most likely etiologies of diarrhea are infectious, xenobiotics, a three etiologies are not mutually exclusive. The differential diagnosis mus these groups. When the time from exposure to onset of symptoms is brief nonbacterial infectious etiologies (viral, parasitic, fungal, and algal) excep invasion by roundworm larvae can be eliminated. The possibility of a bac enterotoxin production should be considered (Table 45-5).[30 , 51]

Epidemiology

Epidemiologic analysis is of immediate importance, particularly when GI than one person in a group. The questions raised in Table 45-6 must be available, an infectious disease consultant or infection control officer shou assistance. Alternatively, assistance from state and local health departme Often only the CDC or state health department has the resources to inve

presumptive diagnosis in an outbreak. Sophisticated techniques such as matching the organism in the food by phage type with a food handler, ma phage type with other persons, isolating 10 or more organisms per gram [47] or PCR identification of bacterial or plasmid DNA are potentially useful possible using the laboratory and personnel available in most hospitals.[23] metabolic, and functional causes often can be eliminated. As in these dise significant grouping of cases nor a limited clinical history is characteristic such as *Trichinella spiralis* (trichinosis), *Toxoplasma gondii* (toxoplasmosis (giardiasis) must be considered, although acute GI symptoms usually are

Staphylococcus Species

In cases of suspected food poisoning with a short incubation period, the assess the risk for staphylococcal causes. The usual foods associated wit production include milk products and other proteinaceous foods, cream-fi potato and chicken salads, sausages, ham, tongue, and gravy. Pie crust c maintaining the temperature of the cream filling and occasionally permitt even during refrigeration.[4] A routine assessment must be made for the p the hand or nose of any food handlers involved. Unfortunately, â€œcarrie enterotoxigenic staphylococci are difficult to recognize because they usual appear healthy.[70] A fixed association between a particular food and an ill helpful epidemiologically but rarely occurs clinically. Factors such as envi resistance, nature of the agent, and dose make the results surprisingly v

1. Is the occurrence of the disease in a large group significant enough t foodborne disease (two or more cases)?
2. Is the symptomatology in affected individuals well defined and simila
3. Is the onset, time, and duration of illness similar among affected gro (incubation)?
4. What are the possible modes of transmission (ie, contact, food, wate
5. Is there a relationship between the time of exposure of the group and transmission?
6. Do attack rates differ for age, gender, or occupation?
7. Can it be determined which foods were served and to whom?

Can the items which were not eaten by those who did not become ill

8. What is the food-specific attack rate?
9. How was the food procured? How was it stored?
10. Was cooking technique adequate?
11. Was personal hygiene acceptable?
12. Was there animal contamination?

TABLE 45-6. Epidemiologic Analysis of Gastrointestinal Disease

Although patients with staphylococcal food poisoning rarely have a signif elevation, 16% of patients in a review of 2992 documented cases had a s fever.[70] Abdominal pain, nausea followed by vomiting, and diarrhea domi findings. Diarrhea does not occur in the absence of nausea and vomiting. period is 4.4 hours with a mean duration of illness of 20 hours. Two sta food poisoning incidents involving large numbers of people have been rep people attended a public event in Brazil. Within hours of food consumptio suffered nausea, emesis, diarrhea, abdominal pain, and dizziness. Of thes presented to and overwhelmed local emergency departments, 396 (20%) intensive care units), and 16 (young children and elderly) died.[143] In anc individuals became ill with symptoms of diarrhea, vomiting, dizziness, chi after they ate cheese or milk.[144] Staphylococcus enterotoxin was found in by the patients in both reports.

Most enterotoxins are produced by *S. aureus* coagulase-positive species. initiate an inflammatory response in GI mucosal cells and lead to cell de enterotoxins may have a dramatic effect on the emesis center in the brai organ systems. Discrimination of unique *S. aureus* isolates from foodborn made using restriction fragment length polymorphism analysis by pulsed- electrophoresis and PCR techniques. [164]

Salmonella Species

Salmonella enteritidis infections are of great concern in the United States outbreaks define very special problems. In the 1980s, recurrent outbreak grade A eggs or food containing such eggs occurred. In the past, such ou

enteritis were attributed to infection of the egg with salmonella (from the through cracks in the shell. More recently, outbreaks have involved nonc eggs.[107] In these cases, presumably the salmonella has infected the eggs formed. In either case, people who consume raw or undercooked eggs are salmonella enteritis. Raw eggs can be found as ingredients of chocolate sauce, eggnog, egg creams, caesar salads, and

homemade ice cream. Whole, partially cooked eggs may be eaten as sunn eggs.[28] The second group of outbreaks was associated with raw milk,[123] popular in certain communities. Inadequate microwave cooking may caus These outbreaks are of great concern because they frequently involve m salmonella infections.[41] Drinking pasteurized milk may not be protective. salmonellosis resulting in more than 16,000 culture-proven cases was trac dairy. The probable cause of the outbreak was a transfer line connecting milk containment tanks.[129]

Additional concern has developed over the widespread use of antibiotics i poultry, and manure-fertilized vegetables now frequently contain resistant place virtually the entire population at risk.[41 , 129] Household pets known also places families at risk. Chicks, turtles, and iguanas carry salmonella transmit the organism to household contacts, including infants, who are a invasive diseases.[1]

Campylobacter jejuni

Campylobacter jejuni , a curved Gram-negative rod, is a major cause of organism is most commonly isolated in children younger than 5 years and years. Campylobacter enteritis outbreaks are more common in the summe temperate climates. Although most cases of Campylobacter enteritis are are associated with contaminated food and water. The most frequent sou in food are raw or undercooked poultry products[48] and unpasteurized mil common reservoir, and small outbreaks are associated with contamination pecking on milk-container tops.[146] Contaminated water supplies are also Campylobacter enteritis involving large numbers of individuals.[17] *C. jejur* cooking of food, pasteurization of milk, and chlorination of water prevent

The incubation period for Campylobacter enteritis varies from 1â€“7 days Typical symptoms include diarrhea, abdominal cramps, and fever. Other s headache, vomiting, excessive gas, and malaise. The diarrhea may contai frequently leukocytes are present on microscopic examination.[68] Illness u days (range 1â€–8 days). Rarely, symptoms last for several weeks. Seve include lower GI hemorrhage, abdominal pain mimicking appendicitis, a reactive arthritis, and meningitis. The organism may be detected using P techniques.[57] Treatment is supportive, consisting of volume resuscitation quinolone antibiotics in more severe cases.[30]

Group A Streptococcus

Bacterial infections not usually associated with food or food handling occ transmitted by food or food handling. Streptococcal pharyngitis can be tr prepared by an individual with streptococcal pharyngitis.[42]

Clostridium botulinum

In the last 3 decades, a median of 4 cases of foodborne botulism, 3 case and 71 cases of infant botulism have been reported annually to the CDC.[1 and vegetables, as well as commercial fish products, are among the comm botulism. The incubation period usually is 12â€–36 hours; typical symptor GI symptoms, followed by malaise, fatigue, diplopia, dysphagia, and rapic muscle incoordination.[90] In botulism, the toxin is irreversibly bound to t junction, where it impairs the presynaptic release of acetylcholine.[84] The must be made immediately, and aggressive respiratory therapy must be i is to survive. Additional therapeutic measures include administering antito Antidotes in Depth: Botulinum Antitoxin). The differential diagnosis of b myasthenia gravis, atypical Guillain-BarrÃ© syndrome, tick-induced paral chemical ingestions (see Tables 46-1 and 46-2).

Yersinia enterocolitica

Yersinia enterocolitica is a Gram-negative coccobacillus that causes enter children and young adults. Typical clinical features include fever, abdomir

which usually contains mucus and blood.[7, 150, 162] Other associated syn nausea, vomiting, anorexia, and weight loss. The incubation period may be more. Less common features include prolonged enteritis, arthritis, pharyn involvement, and rash. Yersinia is a common pathogen in many animals, pigs. Sources of human infection include milk products, raw pork product pets, and person-to-person transmission[24, 64, 92] Infections may be dia cultures of food, stool, blood, and, less frequently, skin abscesses, phary cultures from other organ tissues (mesenteric lymph nodes, liver). Yersini with PCR.[74] Therapy usually is supportive; however, patients with invasiv bacteremia, bacterial arthritis) should be treated with IV antibiotics. Fluo third-generation cephalosporins are highly bacteriocidal against *Yersinia*

Listeria monocytogenes

Listeriosis transmitted by food usually occurs in pregnant women, their fe immunocompromised individuals (corticosteroid use, malignancy, diabetes, infection).[13, 29, 34, 136] Typical food sources include unpasteurized milk, feta, and undercooked chicken. Individuals at risk should avoid the usual evaluated for listeriosis if typical symptoms of fever, severe headache, m pharyngitis develop. Treatment with IV ampicillin or trimethoprimâ€“sulfa indicated for systemic listerial infections.

Xenobiotic-Induced Diseases

Careful assessment for possible foodborne pesticide poisoning is essential aldicarb contamination has occurred in hydroponically grown vegetables contaminated with pesticides.[62] Eating malathion-contaminated chapatti a resulted in 60 intoxications and 1 death in one outbreak[39] (Chap. 109).

The possibility of unintentional acute heavy-metal ingestion must be cons poisoning most typically occurs when very acidic fruit punch is served in Antimony, zinc, copper, tin, or cadmium in a container may be

dissolved by an acid food or juice medium. Insecticides, rodenticides, ars preparations can be mistaken for a food ingredient. These poisonings usua

of signs and symptoms after exposure.

Mushroom-Induced Disease

Some species produce major GI effects. *Amanita phalloides* , the most p usually causes GI symptoms as well as hepatotoxic effects with a delay t manifestations. The rapid onset of symptoms suggests some of the gast mushrooms (Chap. 113).

Intestinal Parasitic Infections

The popularity of eating raw fish, usually from Japanese restaurants, has reported intestinal parasitic infections. The etiologic agents typically are (*Eustrongyloides anisakis*) and fish tapeworms (*Diphyllobothrium* spp). S anisakiasis, or eustrongylidiasis, that are localized to the stomach typicall after raw fish is eaten, whereas symptoms of lower intestinal involvement days or weeks. Typical gastric or intestinal symptoms include nausea, vo crampy abdominal pain that may mimic a gastric ulcer. Typical lower int include abdominal cramping and, with perforation of the intestinal wall by localized abdominal pain, rebound, and guarding, which may mimic an ac (appendicitis). In some cases, the symptoms include anaphylaxis with or pain. Without an adequate dietary history (of eating raw fish), the diagno impossible to establish. Therapy would be directed toward the most likely (gastric ulcer or appendicitis). Diagnosis usually is established on visual i (on endoscopy, laparotomy, or pathologic examination), which typically are fish that may contain *Eustrongyloides* include minnows (*Fundulus* spp.) a *Anisakis simplex* and *Pseudoterranova decipiens* are Anisakidae that may types of frequently consumed raw fish, including mackerel, cod, herring, yellowfin tuna, and squid. Reliable methods of preventing ingestion of live freezing â€“4Â°F (â€“20Â°C) for 60 hours or cooking at 140Â°F (60Â°C) 98 , 128 , 134 , 166

Diphyllobothriasis (fish tapeworm disease) is caused by eating uncooked f parasite. Hosts include, but are not limited to, herring, salmon, pike, and symptoms are less acute than with intestinal roundworm ingestions and u

weeks after ingestion.[37] Signs and symptoms include nausea, vomiting, flatulence, abdominal distension, diarrhea, and anemia (megaloblastic). Dia history of ingesting raw fish and on identification of the tapeworm proglo Treatment with niclosamide, praziquantel, or paromomycin usually is effe

Another foodborne toxin with GI symptoms is associated with eating rehe Chinese restaurants. *Bacillus cereus* type I is the causative organism, ar and toxin production causes consequential early onset nausea and vomiti toxin causes liver failure.[100] *Bacillus cereus* type II has a delayed onset symptoms, including diarrhea.[54]

Monosodium Glutamate

The so-called â€œChinese restaurant syndromeâ€• is induced by ingestio glutamate (MSG); L-sodium glutamate. Individuals present with burning, headache, flushing, chest pain, GI symptoms usually limited to nausea ar infrequently, life-threatening bronchospasm[3] and angioedema.[148] Intensity symptoms are dose related, with significant variation in individual respons ingested.[135 , 169] MSG causes â€œshudder attacksâ€• or a seizurelike sy children. Absorption is more rapid following fasting, and the typical burni spread over the back, neck, shoulders, abdomen, and occasionally the thi rarely prominent. Symptoms usually can be prevented by prior ingestion symptoms do occur, they usually last approximately 1 hour. The syndrome patrons of Chinese restaurants. It is a reaction to MSG, which is used fre restaurants. MSG is also marketed as an effective flavor enhancer.[11] Man canned soups contain heavy doses of MSG.

MSG (regarded as â€œsafeâ€• by the FDA) can cause other acute and l symptoms. The pathophysiology has not been clarified, although studies receptors.

Spicy Food

Certain religious or cultural customs, such as eating bitter herbs at a Pas wasabi[147] at a sushi bar, are associated with syncope. The precipitant in horseradish. Despite severe oropharyngeal or abdominal pain, no hemat

or fever is noted with horseradish. Gastric mucosal contact with pepperor (capsaicin) may produce a similar syndrome.[61]

Anaphylaxis and Anaphylactoid Presentatic

Some foods and foodborne toxins may cause allergic or anaphylacticlike are also referred to as â€œrestaurant syndromesâ€•[139] (Table 45-4). T syndromes complicates a patient's future approach to safe eating. Isolatir essential so that the risk can be effectively assessed. Manufacturers of p provide an unambiguous listing of ingredients on package labels. Sensitiv parents) must be rigorously attentive.[131 , 170] Those with severe reaction by the immediate availability of epinephrine and antihistamine. Attempts reactions to dairy products by avoiding dairy-containing foods may fail. N contain flavor enhancers of a dairy origin (eg, partially hydrolyzed sodium cause morbidity and death in allergic individuals.[56] Individuals with know frequently fail to carry prescribed spring-injected epinephrine syringes, b allergen is easily identifiable and avoidable.[77] Food additives to consider anaphylaxis include antibiotics, aspartame, butylated hydroxyanisole (BH hydroxytoluene (BHT), nitrates or nitrites, sulfites, and parabens esters.[9] preservatives is limited, and agents such as sulfites are so ubiquitous tha guacamole, cider, vinegar, fresh or dried fruits, wines, or beers do or do sensitizing agents may be difficult.

Illegal Food Additives

Medications are given to animals to increase their health and growth. Cle agonist, has been administered to cattle raised for human consumption. T cause toxicity in humans who eat contaminated animal meat. Tachycardia

nausea, epigastric pain, headache, muscle pain, and diarrhea were preser patients. Other findings included hypertension and leukocytosis.[125] No de reported, but use of antibiotics, $\hat{I}^2_2$ agonists, and other growth enhancers safety concerns and laws against their use, because these practices incre

Vegetables and Plants

Plants, vegetables, and their diverse presentations often are involved in
, 80 , 85 , 86 Edible plants and plant products may be poorly cooked or pre
contaminated. Extensive discussion is given in Chap. 114 .

Food Poisoning and Bioterrorism

The threat of terrorist assaults has received increased attention and is di
and 127 . Food as a vehicle for intentional contamination with the intent
suffering or death has occurred in the United States.[38 , 82 , 155] In the fi
laboratory workers suffered GI symptoms, primarily severe diarrhea, caus
served in the staff break room, which had been purposefully contaminate
type II.[82] Four workers were hospitalized; none had reported long-term
strain is a rare one to cause endemic disease; the identical strain, as ide
gel electrophoresis, was found in 8 of the symptomatic workers, in the pa
break room, and in the laboratory's stock culture of *S. dysenteriae* . This
purposeful poisoning of food eaten by laboratory personnel. The person r
motive remain unknown.

The second case series describes a large community outbreak of food poi
Salmonella typhimurium .[155] The outbreak occurred in the Dalles, Oregon
1984. A total of 751 people suffered salmonella gastroenteritis. The outbr
intentional contamination of restaurant salad bars and coffee creamer by
religious commune using a culture of *S. typhimurium* purchased before th
poisoning. A criminal investigation found a salmonella culture on the relig
grounds that contained *S. typhimurium* identical to the salmonella strain
poisoning victims, as identified by using antibiotic sensitivity, biochemical
restriction endonuclease digestion of plasmid DNA. More than 1 year of i
needed before this purposeful salmonella outbreak was linked to terrorist
the delay in identifying the outbreak as a purposeful food poisoning inclu
motive; (2) no claim of responsibility; (3) no pattern of unusual behavior
(4) no disgruntled restaurant employees identified; (5) epidemic exposur
multiple time points for contamination, suggesting a sustained source of
a single act; (6) no previous event of similar nature as a reference; (7)
seemed more likely (eg, repeated unintentional contamination by restaura

fear that the publicity necessary to aid the investigation might generate activity.

The delay in publication of the event (almost 10 years) also resulted from activity. The activity of the Japanese cult Aum Shinrikyo and its use of b appears to have provided the motivation to release this publication in the purposeful food poisoning patterns can be identified more quickly in the

The third report describes a disgruntled employee who contaminated 200 l supermarket with a nicotine-containing insecticide.[38] Ninety-two people b sought medical care. Symptoms included vomiting, abdominal pain, rectal case of atrial tachycardia.

The capacity for infecting large numbers of people with foodborne agents obtain and disperse is clearly exemplified by two specific outbreaks: the outbreak in Oregon, and the apparently unintentional salmonella outbreak 16,000 culture-proven cases traced to contamination in 1 Illinois dairy w cause of the outbreak was a transfer line connecting raw and pasteurized tanks.[129] These events emphasize the vulnerability of our food supply and ensuring its safety and security because the potential for purposeful cont widespread morbidity is an ever-present problem.

Summary

The diversity of etiologies for food poisoning involves almost all aspects concerns center around the natural toxicity of a product such as a plant c contamination of which can occur in the field, during factory processing, preparation or storage. These events may be intentional or unintentional, our approaches to general nutrition and society. The current debates abo role in food preparation and protection range from bacteria such as *E. co* Creutzfeldt-Jacob disease (bovine encephalopathy) to genetically altered corn. Future discussions of food poisonings and interpretations of the imp problems may dramatically alter our food sources and their preparation.

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Chapter 46
Botulism

Lewis R. Goldfrank

Neal E. Flomenbaum

A 27-year-old woman was in excellent health until 3 days before admission, when her family gathered for dinner following her mother-in-law's funeral. Shortly thereafter, the patient began experiencing dysphagia and dysarthria and seemed generally anxious. She saw her family physician, who prescribed diazepam. The day prior to her admission, the patient became dyspneic. She began to communicate by writing when talking became impossible. Writing soon became difficult, and the patient complained of having trouble walking and lifting her head. She would not eat and vomited food when she was force-fed. She then began to look straight ahead without moving her eyes.

The next day she was taken to the nearest hospital, where the physicians in attendance noted the peculiarity of the symptoms, the fact that she was taking diazepam, and the temporal relationship to the funeral of her mother-in-law. The family physician was called from the emergency department and told of

the new symptoms that had developed during the previous 2 days. The physician reassured the emergency staff that this was â€œanxietyâ€•; and the woman was discharged.

Shortly after the patient returned home, she became increasingly dyspneic and cyanotic, and then had a cardiopulmonary arrest. Her husband initiated cardiopulmonary resuscitation (CPR) until the paramedics arrived. The paramedics continued CPR and brought her to the hospital.

Physical examination on admission revealed an apneic, intubated, comatose young woman with blood pressure 90/40 mm Hg; pulse 80 beats/min; ventilated respiratory rate 14 breaths/min; rectal temperature 97.0Â°F (36.1Â°C). Her left pupil was 4 mm in diameter, her right pupil was 3 mm, and both pupils were sluggishly responsive to light.

The heart and lungs were unremarkable. The abdomen was soft, and bowel sounds were diminished. The stools were negative for occult blood. There was no response to painful stimuli or cold-water caloric testing. Her upper extremities were flaccid, with absent reflexes. The patient had increased extensor tone in her legs, 2+ patellar reflexes, ankle clonus, and generalized myoclonic jerks.

Cerebrospinal fluid (CSF) examination was normal as was edrophonium (Tensilon) testing. An electromyogram (EMG) demonstrated increased muscle action potentials with rapid repetitive stimulation and posttetanic potentiation.

Botulism was diagnosed, and the patient was given 2 vials of trivalent botulinum antitoxin. However, her condition steadily deteriorated and she died 3 days after admission. Postmortem examination revealed cerebral edema and herniation. Examination of stomach contents revealed undigested mushrooms, from which *Clostridium botulinum* toxin type B was isolated.

Because of the patient's presentation, the mother-in-law's

hospitalization was reviewed: Twelve days before the daughter-in-law's first symptoms, the mother-in-law experienced nausea, vomiting, abdominal cramps, and distension, and she was treated with an antiemetic. Three days later, she complained of a dry throat, dysphagia, and chest pains. Two days after that, she had dyspnea. When an electrocardiogram (ECG) revealed inverted T waves in the precordial leads and occasional premature ventricular contractions, she was hospitalized to â€œrule out myocardial infarction.â€•

The day after the mother-in-law's admission, she was even more dyspneic and stuporous. She was also noted to have dilated, sluggishly reactive pupils. She was intubated and became more alert. However, upon extubation the next day, she developed respiratory distress and required reintubation. A tracheostomy was performed, but she became febrile and died 2 days later.

Following the daughter-in-law's hospitalization and death, the body of the mother-in-law was exhumed. An autopsy revealed bronchopneumonia, an enlarged heart, and mushroom fragments in the small intestines. The mushroom fragments yielded *C. botulinum* toxin type B.

When the diagnosis of botulism was first considered and before the mushrooms were implicated, all family members who had been at the funeral meal were admitted to the hospital for observation. At that time, a third member of the family reported having difficulty swallowing. This woman was the only other family member who had eaten mushrooms at the funeral meal. She was given 1 vial of trivalent botulinum antitoxin, and her symptoms resolved in 3 days. Her stool specimens later revealed *C. botulinum* toxin type B. Twenty days after she was given the antitoxin, the woman developed severe arthralgias and fever suggestive of serum sickness.

At the time of presentation, many of the other family members were understandably anxious. Some complained of dry throat,

headache, or tingling in their extremities, although none had eaten any of the mushrooms, and none had stools positive for *C. botulinum* toxin type B. Most were discharged from the hospital within 24â€“48 hours.[48]

A carefully obtained history revealed that the mother-in-law canned her own peppers, eggplant, artichokes, and mushrooms without using a pressure cooker. When the remaining canned foods were obtained from the mother-in-law's house and examined, only the mushrooms were found to contain *C. botulinum* toxin type B.

Epidemiology

Botulism has been recognized since the end of the 18th century. This classic foodborne poisoning was directly linked to inadequate preservation of varied forms of sausages that more than 200 years ago led to religious, legal, and culinary edicts to protect health. The term *botulism* is derived from the Latin word â€œbotulusâ€• for sausage, demonstrating the epidemiologic link. All clostridial species are ubiquitous, and bacteria and spores are present in soil, seawater, and air.[97] Botulism outbreaks can occur anywhere in the world[112] and have been reported from such diverse areas as Iran, the former Soviet Union, Japan,[71] France, Belgium, Portugal,[53] Scandinavia, and Canada.[68]

Approximately 1.25 cases of foodborne botulism per 10 million people occur annually in the United States.[56] The etiologies of botulism are 72% infant, 24% foodborne, 3% wound, and 1% adult type.[92] When botulism is diagnosed, multiple cases per occurrence do not necessarily follow. In a series of hundreds of outbreaks involving more than 400 persons in total, approximately 70% involved only 1 person, 20% involved 2 persons, and only 10% involved more than 2 persons (mean 2.7 cases per outbreak).[118] When only sporadic patients were affected, they were more severely ill, with 85% requiring intubation, compared

to only 42% requiring intubation in multiperson outbreaks.[118] It is suggested that diagnosis in the index case may lead to appropriate rapid therapeutic intervention for associated cases. It also is possible that these index cases may have been exposed to the greatest amount of toxin and, therefore, had the shortest incubation period. Conversely, a lack of symptoms in others does not necessarily reassure that an individual was not exposed or ultimately will not develop serious sequelae.

Although only 4% of foodborne botulism is associated with food purchased in restaurants, restaurant-related outbreaks usually affect large numbers of individuals and account for > 40% of all reported cases.[56] Over the last 50 years, commercial food processing has accounted for only 7% of reported cases, with vegetables (peppers, beans, mushrooms, tomatoes, and beets, with or without meat) thought to be the causative agents in approximately 70%, meat in 17%, and fish in 13% of cases related to processed food. Home-processed food accounted for 65.1% of outbreaks, whereas 27.9% of outbreaks were of unknown origin.[25]

Concern has been raised regarding minimally processed foods (eg soft cheeses) that lack sufficient quantities of intrinsic barriers to botulinum toxin production, such as salt and acidifying agents.[80] These foods become high-risk sources of botulism when refrigeration standards are violated. The US Food and Drug Administration (FDA) continuously reviews recommendations for appropriate measures to process such foods.[108 , 109] Common home-canning errors responsible for cases include failure to use a pressure cooker and allowing food to putrefy at room temperature.

Outbreaks of botulism are associated with specialty foods consumed by different ethnic groups: chopped garlic in soy oil by Chinese in Vancouver, British Columbia;[68 , 100] fried lotus rhizome solid mustard in Japan;[71] uneviscerated salted fishâ€"called *kapchunka* â€"eaten by Russian immigrants in New York City;[22 , 106] and the same food-called *faseikh* â€"eaten by Egyptians in

Egypt.[114] Other outbreaks have involved fermented salmon eggs, seal and raw whale *muktuk* (skin and pink blubber layer) consumed by Inuits and Native Americans in Alaska,[27, 113] and heat shrink-wrapped meat roll *(Matambre)* consumed in Argentina.[112]

Over the last 50 years, the botulism case fatality rate was 17% toxin type A, 7.4% toxin type B, 15.5% toxin type E, and 18.6% toxin type unknown.[25] As expected, case fatality data have continuously improved, with a fatality rate of 5.8% reported for all types in the most recent analysis.[25] Approximately 67% of patients with toxin type A require intubation, compared to 52% of patients with toxin type B, and 39% with toxin type E botulism.[118] Although the median incubation period for all patients is 1 day, it ranges from 0â€“7 days for toxin type A, 0â€“5 days for toxin type B, and 0â€“2 days for toxin type E.[118] Physicians may need to respond more rapidly to a potential epidemic of toxin type E, but they should be prepared for greater complication rates associated with toxin type A.[118] The improvement in case fatality rates for all botulism toxin types probably represents increasing awareness of the problem associated with earlier diagnosis, appropriate and early use of antitoxin, and better and more easily accessible life support techniques.

Awareness of evolving trends and unusual presentations or locations of botulism and instituting preventive education are important. Although 90% of toxin type E outbreaks have occurred in Alaska because of home-processed fish or meat from marine animals,[30, 56] 1 incident occurred in New Jersey.[23] In the past decade, 3 cases of botulism involved members of the Native American church after they ingested a ceremonial tea that was made from the buttons of dried, alkaline-ground peyote cactus that were prepared in a water-covered refrigerated jar. The resultant alkaline and anaerobic milieu presumably fostered the growth of toxin from naturally occurring spores.[44]

In recent times, concern about the use of botulinum toxin as a biologic weapon has increased. Interest in the adverse consequences of therapeutic botulinum toxin injections also has developed.[8] In ways unimaginable since the first edition of this chapter was published, the medical and public health issues associated with terrorism and botulinum toxin unfortunately only increase the relevance of this chapter in the 21st century (Chap. 127).

Characteristics of *Clostridium Botulinum, Clostridium Butyricum* , and *Clostridium Baratii*

Clostridium botulinum is actually a group of spore-forming, anaerobic, Gram-positive bacilli. Although often classified as a single species, the genus *Clostridium* consists of at least 4 distinct genetic variants that produce 7 homologous neurotoxic proteins that cause botulism: *C. botulinum* , which produces toxin types A, B, and E; *Clostridium baratii* , which produces toxin type F; *Clostridium butyricum* , which also produces toxin type E, and *Clostridium argentinense* , which produces toxin type G.[45 , 92] Rare instances of both adult and infant botulism are attributed to *C. baratii* and *C. butyricum* .[43 , 64 , 72 , 77] This rarity of toxin type F may be exaggerated because of the only recent additional capacity of most laboratories to determine the presence of *C. baratii* and other clostridial species producing toxin type F.[43] Toxin types A through G, with CÎ± and CÎ², have been identified to date. In the United States, toxin type A is found west of the Mississippi,[58] toxin type B is found east of the Mississippi, particularly in the Allegheny range, and toxin type E is found in the Pacific northwest.[24 , 97] Toxin types A and B typically are found in poorly processed meats and vegetables. Toxin type E is commonly found in raw or fermented marine fish and mammals. Toxin type G has

not been associated with naturally occurring disease. Toxin types C and D cause disease in birds and mammals.

Although botulinum toxins have slightly different mechanisms of action, the ultimate pathophysiology and clinical syndromes are identical. All botulinum spores are dormant and highly resistant to damage. They can withstand boiling at 212Â°F (100Â°C) for hours, although they usually are destroyed by 30 minutes of moist heat at 248Â°F (120Â°C).

Factors that promote germination of spores in food are pH > 4.5, sodium chloride content < 3.5%, or a low nitrite concentration. Most viable organisms produce toxin in an anaerobic milieu with temperatures > 80.6Â°F (27Â°C), although some strains produce toxins even when conditions are not optimal. *C. botulinum* organisms can produce toxin type E at temperatures as low as 41Â°F (5Â°C). To prevent spore germination, acidifying agents such as phosphoric or citric acid are added to canned or bottled foods that have a low acid content, such as green beans, corn, beets, asparagus, chili peppers, mushrooms, spinach, figs, olives, and certain nonacidic tomatoes. As opposed to the spores, the toxin itself is heat labile and can be destroyed by heating to 176Â°F (80Â°C) for 30 minutes or to 212Â°F (100Â°C) for 10 minutes. At high altitudes, where the boiling point of water may be as low as 202.5Â°F (94.7Â°C), a minimum of 30 minutes of boiling may be required to destroy the toxin. Under high-altitude conditions, pressure cooking at 13â€“14 lb of pressure often is necessary to achieve appropriate temperatures to destroy the toxin.

Food contaminated with *C. botulinum* toxin types A and B often does not look or smell normal and appears putrefied because of the action of proteolytic enzymes.[42] In contrast, because toxin type E organisms are saccharolytic and not proteolytic, food contaminated with toxin type E may look and taste normal.[9]

Pathophysiology

Botulinum toxin is the most poisonous substance known. The LD_{50} for mice is 3 million molecules injected intraperitoneally. The human oral lethal dose is 1 Âµg/kg.[85] The toxin is a protein consisting of a single polypeptide chain, with a molecular weight (MW) of 900,000 daltons, which includes a 750,000 MW nontoxic protein and a 150,000 MW neurotoxic component. To become fully active, the single-chain polypeptide 150,000 MW neurotoxin must undergo proteolytic cleavage to generate a dichain structure with a heavy chain (MW 100,000) that is linked by a disulfide bond to a light chain (MW 50,000). It appears that the single polypeptide chain toxin and the dichain form both are resistant to gastrointestinal degradation.[59] Because the toxin is often demonstrated only in the stool, determining what percentage of the toxin actually is absorbed is difficult.[33 , 34] The botulinum toxin binds to serotype specific receptors on the mucosal surfaces of gastric and small intestinal epithelial cells, where endocytosis followed by transcytosis permits release of the toxin on the serosal cell surface.[51 , 60] The dichain form of the molecule is responsible for all clinical manifestations.[45 , 96] The dichain form binds rapidly and irreversibly to the neuronal cell membrane and is taken up by endocytosis. The heavy chain is responsible for cell-specific membrane binding to acetylcholine-containing neurons.[74] Once inside the cell, the light chain acts as a zinc-dependent endopeptidase to cleave polypeptides that are essential components of the neurotransmitter release apparatus, thereby inhibiting exocytosis.[85] Different botulinum toxin types share the same mechanism of cell entry, but three groups of botulinum toxin types appear to have distinct mechanisms of preventing acetylcholine release, which may be responsible for their variable toxicity.[94] Different light chains specifically cleave different members of the SNARE family. Toxin types B, D, F, and G act on vesicle-associated membrane protein (VAMP)/synaptobrevin

localized on the synaptic vesicle, toxin types A and E cleave synaptosomal associated protein (SNAP)-25, and toxin type C cleaves both presynaptic plasma membrane proteins syntaxin and SNAP-25 (Figure 46-1).[51] Regardless, cholinergic transmission at all acetylcholine-dependent synapses in the peripheral nervous system is impaired. However, the central nervous system and axonal conduction are not affected. The duration of action of the toxin types may vary, depending on the components of the neurotransmitter release apparatus that are disrupted. The persistence of clinical effect may result from the individual cleavage product, the intraneuronal biological half-life of the toxin, or both. Current evidence indicating intraneuronal toxin metabolism or elimination is inadequate.[96]

Signs and Symptoms

Foodborne Botulism, Adult Type (In Vitro)

Although botulism is the most dreaded of all food poisonings, the initial phase of the disease (which occurs the first day following ingestion) often is so subtle that it goes unnoticed. Further compromising the care of exposed individuals is the fact that botulism often is misdiagnosed on the first visit to a physician.[19] , [119] Conversely, when gastrointestinal symptoms are striking and food poisoning is suspected, the differential diagnosis should include other acute poisonings, such as metals, plants, mushrooms, and the common bacterial, viral, and parasitic agents discussed in Chap. 45 .

Because physicians so infrequently encounter the disease (especially compared to other much more common diseases in the differential diagnosis), initiation of appropriate management often is seriously delayed (Table 46-1). This is particularly true of toxin

type E botulism, which typically initially causes much more prominent gastrointestinal signs than neurologic signs.[9] The differences in the appearance of food and initial clinical symptoms associated with the various serotypes may be related to the presence of proteolytic enzymes in toxin types A and B and saccharolytic enzymes in toxin types E and C botulism. The index case of an epidemic or an isolated case often is misdiagnosed at a stage when the risk of morbidity and mortality still could be substantially diminished.

Early gastrointestinal signs and symptoms of botulism include nausea, vomiting, abdominal distension, and pain. A time lag (from 12 hours to several days, but typically not more than 24 hours) may or may not be observed before one or more of the following signs and symptoms appear: constipation, dry or sore mouth and throat, dysphonia (typically manifested by a nasal quality to the voice), dysarthria, dysphagia (at times predominant and severe); blurred vision with impaired accommodation, diplopia, descending, bilaterally symmetric motor paralysis beginning with abducens (VI) or oculomotor (III) nerve palsy (frequently resulting in strabismus); mydriasis (often fixed); respiratory insufficiency; and urinary retention. Although many of these initial signs and symptoms are anticholinergic in nature, mental status and the remainder of the neurologic examination remain normal.

The Centers for Disease Control and Prevention (CDC) case definition for foodborne botulism is established in a patient with a

neurologic disorder manifested by diplopia, blurred vision, bulbar weakness, and symmetric paralysis in whom

- Botulinum toxin is detected in serum, stool, or implicated food samples or
- *C. botulinum* is isolated from stool, or

- A clinically compatible case is epidemiologically linked to a laboratory-confirmed case of botulism[24]

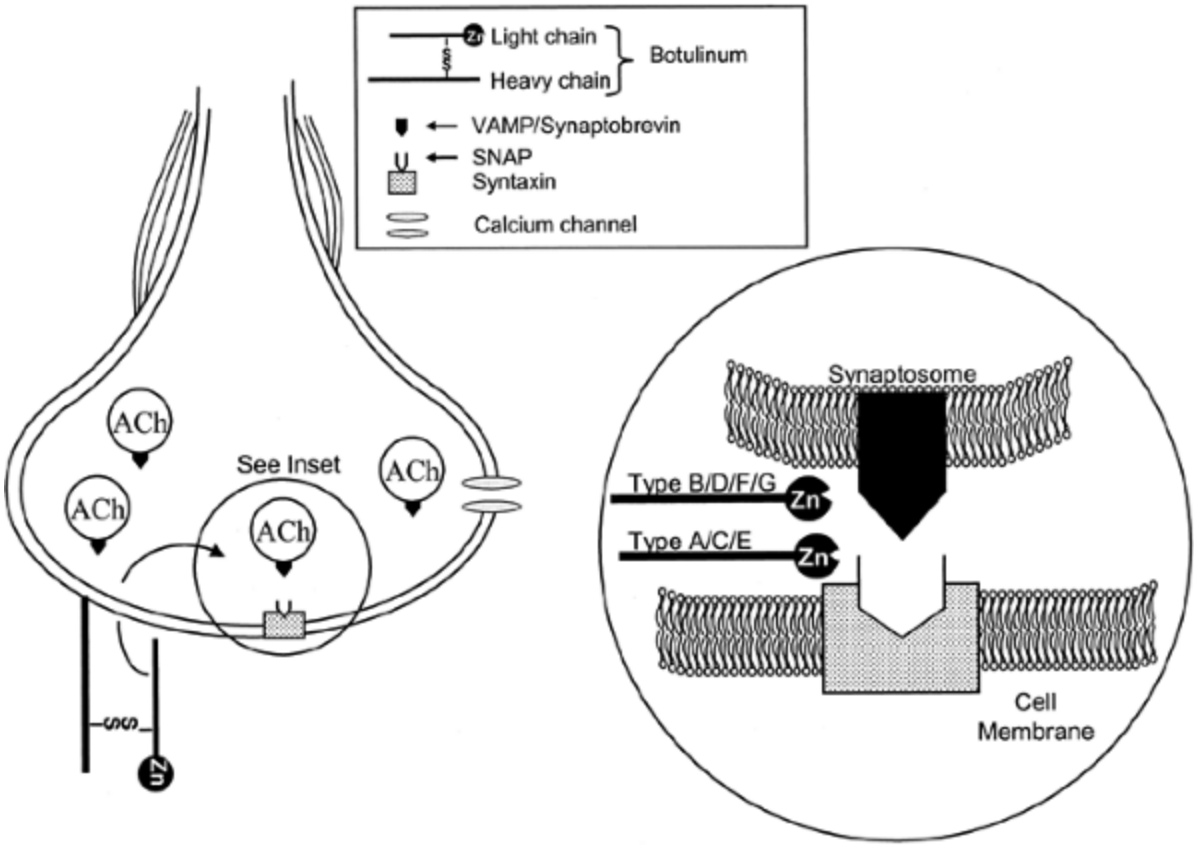

Figure 46-1. Botulinum toxin consists of two peptides linked by disulfide bonds. The heavy chain is responsible for specific binding to acetylcholine (ACh)-containing neurons. Following binding to the cell surface, the entire complex undergoes endocytosis and subsequent translocation of the light chain into the nerve cell cytoplasm. The light chain contains a zinc-requiring endopeptidase that cleaves proteins required by the docking/fusion complex critical to neuroexocytosis. Botulinum toxin type B targets both vesicle-associated membrane protein (VAMP)/synaptobrevin, a docking protein located on the acetylcholine-containing synaptic vesicles (synaptosome). Botulinum toxins types A and E proteolyse synaptosomal associated protein (SNAP), a component of the presynaptic cell-membrane docking complex (associated with

syntaxin). After these important components of the docking complex are destroyed, neurotransmitter release cannot proceed, resulting in clinical findings consistent with acetylcholine deficiency.

When lateral rectus palsy, ptosis, and sluggish pupillary reactivity occur, respiratory insufficiency usually follows. As weakness progresses, deep-tendon reflexes may diminish. The pulse frequently is normal or slow, and temperature in adults typically remains normal. The absence of a tachycardia is surprising in the presence of other typical anticholinergic findings. The normal mental status and temperature in the presence of ophthalmoplegia and generalized muscle weakness (nicotinic findings) that occur with botulism, but not with antimuscarinic poisoning, should lead the clinician to rapidly suspect or diagnose botulism and institute appropriate management for the patients affected by this life-threatening toxin.[107] When suspicion of disease is high and the vital capacity is < 30% of predicted, intubation should be strongly considered.[104] The most difficult and frequently encountered problem in correctly diagnosing botulism is differentiating between botulism and the Miller Fisher variant of the Guillain-BarrÃ© syndrome (Table 46-2).

Infant Botulism (In Vivo Infant Intestinal Colonization)

First described in California[6 , 46 , 50] in 1976, several thousand cases of infant botulism have now been confirmed across the world. Interestingly, 95% of these cases are reported in the United States.[31 , 72] Although infant botulism is reported from approximately half of the states in the United States and all inhabited continents except Africa,[31] 50% of reported cases originate from California, Utah, Pennsylvania, and New Mexico.[117] In California, aggressive surveillance and educational efforts with

infant botulism have been practiced since 1976, which may explain in part the disproportionate distribution of cases.[5]

Aminoglycoside poisoning
Postanesthetic paralysis, intraoperative exposure
Anticholinergic poisoning
Mydriasis, vasodilation, fever, tachycardia, ileus, dry mucosa, altered mental status
Buckthorn (*Karwinskia humboldtiana*)
Rapidly progressive ascending paralytic neuropathy with quadriplegia
Carbon monoxide poisoning
Headache, nausea, altered sensorium, tachypnea, elevated carboxyhemoglobin concentration
Diphtheria (polyneuritis)
Exudative pharyngitis, cranial polyneuropathy (late), cardiac manifestations, hypotension
Eaton-Lambert syndrome
Neoplasm, ophthalmoplegia (rare), no respiratory paralysis, increased strength following sustained contractions, posttetanic facilitation on electromyography, calcium channel-blocking antibodies
Elapidae (coral snake) envenomation
Euphoria, light-headedness, fasciculations, tremor, weakness, salivation, nausea, vomiting followed by bulbar palsy, paralysis including slurred speech, diplopia, ptosis, dysphagia, dyspnea, respiratory compromise
Encephalitis
Fever, mental status abnormalities, seizures, elevated CSF protein, pleocytosis
Food poisoning (other bacterial)
Rapid onset of disease, absence of cranial nerve findings
Guillain-BarrÃ© syndrome (Miller Fisher variant)

Acute inflammatory demyelinating polyneuropathy, areflexia, paresthesias, ataxia, elevated CSF protein without cells, denervation, prolonged nerve conduction velocity on electromyography

Hypermagnesemia

Respiratory compromise, diffuse flushing, weakness, thirst

Inflammatory myelopathies (acute myelitis, transverse myelitis, necrotic myelopathy)

Complete (transverse) or incomplete spinal syndrome: posterior column myelopathy with ascending paresthesias or ascending spinothalamic findings or Brown-Sequard syndrome; typically follows viral illness, back pain, progressive paraparesis, asymmetric ascending paresthesias in legs; CSF: 5â€“50 lymphocytes/mm^3 , elevated creatine kinase concentrations

Multiple sclerosis

Weakness, visual blurring (optic neuritis), sensory disturbances, diplopia, ataxia; lesions separated in space and time; mononuclear cell pleocytosis in CSF; evoked response testing: slow or abnormal conduction in visual, auditory, somatosensory, or motor pathways; abnormal MRI with a paramagnetic dye (gadolinium)

Myasthenia gravis

Aggravation of fatigue with exercise, recurrent paralysis, positive edrophonium test, acetylcholine receptor antibodies

Organic phosphorus compound poisoning

Salivation, lacrimation, urination, defecation, fasciculations, bronchorrhea, delayed neuropathy

Paralytic shellfish poisoning

Incubation < 1 h, dysesthesias, paresthesias, impaired mentation, respiratory paralysis

Poliomyelitis

Fever, GI symptoms, asymmetric neurologic findings

CSF pleocytosis, elevated CSF protein

Polymyositis

Insidious onset, proximal limb weakness, dysphagia, muscle

tenderness, cramping, â†‘ESR, electromyography: fibrillation and sharp waves
Stroke syndrome (midbrain)
Asymmetric focal paralysis, abnormal brain neuroimaging (CT, MRI)
Tetanus
Cranial nerve defects (rare), spasticity, rigidity
Thallium poisoning
Constipation, cranial neuropathy, ascending sensory neuropathy, Mees lines, alopecia
Tick (*Dermacentor* spp): related paralysis
Ataxia, progressive large muscle weakness, ascending paralysis, absence of paresthesias, normal CSF analysis, presence of an embedded tick and resolution upon removal

Condition Diagnostic Findings

TABLE 46-1. Differential Diagnosis of Conditions Commonly Confused with Botulism

Fever
Absent
May be present
May be present
Motor
Pupils
Dilated or unreactive (50%)
Normal
Normal
Ophthalmoplegia
Present (early)
Present (late)
Present (early)
Paralysis

Descending
Ascending
Descending
  Deep tendon reflexes
Diminished
Absent
Absent
  Ataxia
Absent
Present
Present
Sensory
  Paresthesias
Absent
Present
Present
Laboratory
  CSF protein
Normal
Elevated (late)
Elevated (late)

Botulism	Guillain-BarrÃ© Syndrome	Miller Fisher Variant of Guillain-BarrÃ©

TABLE 46-2. Differentiating Botulism from Guillain-BarrÃ© Syndrome

Infant botulism is the most common form of botulism in the United States, and 99% of these cases are from botulinum neurotoxin type A or B.[72] Affected children are always younger than 1 year (usually 1â€“3 months) and characteristically have normal gestations and births. The first signs of infant botulism are constipation; difficulty with feeding, sucking, and swallowing;

feeble crying; and a â€œfloppyâ€• baby with diffuse, decreased muscle tone. The decreased muscle tone is particularly apparent in the limbs and neck. Ophthalmoplegia, loss of facial grimacing, dysphagia, diminished gag reflex, poor anal sphincter tone, and respiratory failure are present, but fever and enteric symptoms do not occur. The differential diagnosis of infant botulism initially includes dehydration, failure to thrive, hypotonia, sepsis, and a viral syndrome. Conversely, many of the signs and symptoms of infant botulism and many of the syndromes cited in Table 46-1 are relevant to the evaluation of sick children, or children with the rarer neurologic, myopathic, and congenital syndromes that occur in the first year of life.[50] Because the

toxin in infant botulism is absorbed gradually as it is produced, the onset of clinical manifestations of botulism may be less abrupt than in severe cases of foodborne botulism caused by large amounts of preformed toxin absorbed over a brief period of time. A single case of foodborne botulism associated with home-canned baby food was reported in a 6-month-old infant.[4]

Only certain children are susceptible to infant botulism. As opposed to the better-understood foodborne botulism variants, infant botulism may result from ingestion of *C. botulinum* organisms in food or following the inspiration or ingestion of organism-laden aerosolized dust. Some infants may be immunologically unprepared for spore control, a deficiency that allows subsequent germination and toxin development within their gastrointestinal tracts and subsequent gut absorption. Also, an infant's gastrointestinal tract lacks bile acids and gastric acid, which when present may inhibit clostridial growth in older children and adults. Approximately 70% of infant botulism cases occur in breast-fed infants, even though only 45â€“50% of all infants are breast-fed. Bacterial growth associated with breast-feeding may favor *Bifidobacterium* development, whereas formula-fed infants are rapidly colonized by *Coliforme* spp, *Enterococcus* spp, and

Bacteroides spp. All three of the species colonizing formula-fed infants may inhibit *C. botulinum;* conversely, the absence of these typical organisms in breast-fed infants may facilitate *C. botulinum* multiplication.[46]

Epidemiologic studies indicate that ingestion of honey was associated with 34.7% of hospitalized cases of infant botulism worldwide. Moreover, of all nutritional items tested as possible epidemiologic sources, only honey was found to contain *C. botulinum* spores.[6] When *C. botulinum* spores were isolated from honey implicated in cases of infant botulism, the same toxin type was isolated from the infant and, as noted previously, no preformed toxin was isolated. The epidemiologic link to honey is debated, because similar clostridial organisms are found in household dust, yard dirt, and the honey ingested.

Previous studies suggested a correlation between the presence of both *C. botulinum* organisms and toxin and sudden infant death syndrome (SIDS).[98] However, in a prospective study of 248 infants with SIDS, *C. botulinum* was not found on stool culture of any of the children.[20] Cases of infant botulism must be managed in the hospital, preferably in a pediatric intensive care unit for at least the first week, when the risk of respiratory arrest is greatest. In 1 study, approximately 80% of children with botulism required intubation for reduced vital capacity, and 25% of these children had frank respiratory compromise.[87] In a group of 57 affected infants 18 days to 7 months of age managed during the decade ending in the mid-1980s, 77% were intubated and 68% required mechanical ventilation. In the subsequent decade ending in the late 1990s, investigators from the same institution found that 61.7% of 60 infants required endotracheal intubation for a mean of 21 days.[2] Better understanding of disease progression with close observation permitted a decrease in intubations and complications. In this study, the investigators also demonstrated that airway complications such as stridor, granuloma formation, and subglottic stenosis were common, yet tracheotomy was

infrequently performed. Loss of airway protection was the best indicator of patients who required aggressive management.[88] The survival rate in infant botulism is approximately 98%.[88]

Several children with infant botulism sustained unexpected respiratory arrests,[7] often associated with procedures such as lumbar punctures or radiographic examinations. However, it appears that the cardiopulmonary status was often unintentionally compromised during these procedures.[54]

Wound Botulism (In Vivo)

Wound contamination previously was considered an uncommon cause of botulism. The first case of wound botulism was not reported until 1943, and the total number of wound-related cases identified by the CDC to date is approximately 100. The â€œclassicâ€• presentation of wound botulism is that of a patient injured in an automobile crash who sustains a deep muscle laceration, crush injury, or compound fracture treated with open reduction. The wound typically is quite dirty and usually associated with inadequate dÃ©bridement, subsequent purulent drainage, and local tenderness, although the wound may appear unremarkable in other cases. Four to 18 days later, cranial nerve palsies and the other neurologic findings typical of botulism may appear.[65] Other signs of food-related botulism, such as the gastrointestinal manifestations, usually are absent. Most of the recent cases of wound botulism are associated with subcutaneous injection of heroin.

In wound botulism, fever may be prominent and associated with the abscess, sinusitis, or other tissue infection presumed to harbor the clostridial organisms. Although in some cases the patients may require management for wound-related problems, in other cases, the wounds appear clean and uninfected. No particular vehicle, vector, or pathophysiologic etiology for wound botulism has been identified. Recognition of wound botulism as a potential

complication of wound infections is essential for appropriate early and aggressive therapy.

In a small series of parenteral drug-using patients with botulism in New York City, the most prominent symptoms were dysphagia, dysarthria, and dry mouth. In these patients and 3 other clinically comparable patients with botulism, the CDC investigators were not able to find any organism or toxin in serum, stool, or skin lesions.[57]

Cocaine[76, 101] and heroin,[19] particularly subcutaneously injected â€œblack tar heroin,â€• are associated with an increasing number of wound botulism cases.[73, 83, 115] The markedly increased frequency associated with black tar heroin use appears to be related, at least in part, to physical characteristics such as its viscosity, its potential to facilitate anaerobic growth and spore germination, and its ability to devitalize tissue or inhibit wound resolution.[11]

Adult Infectious Botulism (In Vivo Adult Intestinal Colonization)

This fourth class of botulism includes any patient older than 1 year in whom a particular food source cannot be implicated. Until the recent recognition of â€œtherapeutic botulism,â€• adult infectious botulism was the rarest form of botulism, with only 15 cases reported by 1997.[41, 64] Some cases of in vivo adult intestinal colonization may represent a variant form of infant botulism.[67]

There is a well-documented case of an adult female with botulism resulting from the ingestion of a food source contaminated with *C. botulinum* type A organisms and no preformed toxin.[29] In this case, the combination of a long incubation period with toxin present in the serum and stool for 3 weeks after exposure and the absence of disease in the patient's spouse who shared the food suggested in vivo intraluminal elaboration of toxin. This patient

was a very unusual host in that she had a history of peptic ulcer disease treated with truncal vagotomy, antrectomy, and a Billroth I anastomosis. She had received perioperative antibiotics 5 weeks prior to the development of botulism. All of these factors may have compromised the gastric and bile acid barrier, gut flora, and motility, thus allowing spore germination, altered bacterial growth, and

toxin development. Other cases of adult infectious botulism occurred in patients after ileal bypass surgery and Crohn disease,[12] jejunoileal bypass for obesity,[38, 63] gastroduodenostomy,[63] vagotomy and pyloroplasty,[63] and necrotic volvulus.[56] The general risk factors favoring organism persistence and *C. botulinum* colonization include recent antibiotic therapy, achlorhydria (surgically or pharmacologically induced), and previous intestinal surgery.

In a single case report, production of endogenous antibody to botulinum toxin was demonstrated.[41] A 67-year-old man with long-standing Crohn disease who had undergone terminal ileum and right colonic resection presented with abdominal pain. Prior to admission, the patient had experienced several episodes of diplopia. After admission, systemic paralysis developed. The patient had a prolonged recovery after receiving two courses of equine trivalent botulinum antitoxin and 81 days of antibiotic treatment. A mouse assay performed to determine the persistence of any previously administered antitoxin prior to administering additional antitoxin identified a particularly high level of antitoxin specific to toxin type A but not toxin type B. An enzyme-linked immunosorbent assay (ELISA) test performed to distinguish equine from human antitoxin antibodies demonstrated an endogenous human antitoxin response to the toxin. This response points out a distinct characteristic of adult infectious botulism, as other investigators have shown that antitoxin immunity does not develop in patients with foodborne botulism.[85]

Therapeutic and Inadvertent Botulism (In Vitro)

The fifth and most recently recognized form of botulism is purely iatrogenic. Currently doses ranging between 10 and 100 ng botulinum toxin type A (BotoxÂ® or DysportÂ® [available in Europe]) or botulinum toxin type B (MyoblocÂ®) are used therapeutically.[21] The initial therapeutic use of botulinum toxin involved injections into extraocular muscles under electromyographic control as a treatment for blepharospasm or as a supplement to corrective strabismus surgery.[49] Its use is supported by animal investigation[105] and suggested by clinical experience[49] indicating that the neurotoxinâ€"at the smallest effective clinical dosesâ€"would not diffuse from the injection site, avoiding the risk of excessive local or systemic complications. Currently used without intensive monitoring, these agents are used to cause the temporary weakness necessary to treat facial nerve disorders and to eliminate frown lines, achalasia, dysphagia, dystonia, torticollis, axillary hyperhidrosis, migraine headaches, obesity, spasticity, voice and speech disorders (spasmodic dysphonia), and chronic anal fissures.[18,61]

The relative potencies of commercially available botulinum toxins are quite variable[69,81,90] (Table 46-3). The doses of botulinum toxin selected are measured in functional units corresponding to the median lethal doses (LD_{50}) used for female Swiss Webster mice weighing 18â€"20 g. The units of each marketed agent are distinctly different and may confuse the clinician, leading to inadvertent botulinum toxin poisoning.[21] The potential for clinician confusion may be substantial when switching from type A to type B botulinum toxin. For example, 1 U BotoxÂ® equals 50 U MyoblocÂ®, which represents 100 U botulinum toxin A per vial and 5000 U botulinum toxin B per vial, respectively.[17] The approximate estimate of quantities of type A botulinum toxin

causing disease by different routes of administration are given in Table 46-3 .

Doses range widely depending on the size of the muscle to be treated, the degree of weakness required, and the commercial preparation of the toxin.[42] These injections irreversibly block the local neuromuscular junction. The affected muscles then weaken by atrophy over a 3-week period but recover within 2â€“4 months as nerve transmission is restored through sprouting of new nerve endings and functional connections at motor endplates.[1,85] Repetitive doses of botulinum toxin may be indicated to prolong duration of action for several months.[42,49,55]

Intravenous
0.09â€“0.15 Âµg (90â€“150 ng) = 0.001 Âµg/kg
Inhalation
0.70â€“0.90 Âµg (700â€“900 ng) = 0.01 Âµg/kg
Intramuscular
7.0 Âµg (7000 ng) = 0.1 Âµg/kg
Intraperitoneal
7.5 Âµg (7500 ng) [approximate, equals] 0.1 Âµg/kg
Oral
70 Âµg (70,000 ng) = 1 Âµg/kg
1 U BotoxÂ® = lethal intraperitoneal dose in mice
1 U BotoxÂ® = 2.5 ng botulinum toxin type A
100 U BotoxÂ®/vial powder for reconstitution for intramuscular use[68,79]
1 U BotoxÂ® [approximate, equals] 3â€“5 U Dysportâ‰ˆ[107]

Route of Exposure	Dose

TABLE 46-3. Botulinum Toxin Type A (Crystalline)[36,83,88] Very Approximate Human LD_{50}

Although one early marketing assumption was that the neurotoxin

did not diffuse from the injection site,[79] botulinum toxin does diffuse into local tissues and adverse effects typically occur locally.[79] Systemic manifestations are of concern when an inadvertent, excessive, or misdirected dose of toxin is administered. In addition, a number of studies demonstrate that even appropriately injected doses result in neuromuscular junction abnormalities throughout the body, infrequently producing autonomic dysfunction without muscle weakness.[39 , 52 , 70] Several cases of iatrogenic botulism characterized by asthenia, diplopia, and severe generalized muscle weakness with widespread EMG abnormalities have resulted from therapeutic doses of botulinum toxin injected intramuscularly.[10 , 13 , 110]

In a large series of 107 patients treated successfully for spasmodic torticollis, 44% of all treatments resulted in dysphagia. Of this subgroup, several patients developed stridor and/or aspiration and required hospitalization.[3]

Following repeated injections of therapeutic doses of botulinum toxin, patients typically develop neutralizing antibodies that subsequently may limit the toxin's efficacy and lead to increased use of a different toxin type.[16] In Japan and the United Kingdom, a preparation of botulinum toxin type F is also used when antibodies to type A develop.[93] Some studies[14] suggest that animals receiving type F botulinum toxin have a more transient and reversible weakness than that associated with types A and B. Interestingly, however, recurrent episodes of foodborne botulism occurring in one individual suggest that repeated exposure to clinically significant quantities of toxin do not result in long-term immunity.[85]

Diagnosis

Routine laboratory studies, including CSF analysis, are normal in patients with botulism. Specific tests that are uncommonly used but are particularly helpful in diagnosing botulism include the

following.

Tensilon Test

Edrophonium (Tensilon) is a rapidly acting anticholinesterase used to diagnose myasthenia gravis and occasionally used to differentiate myasthenia gravis from botulism. This drug prevents metabolism of

the available acetylcholine, permitting continued reaction with the reduced number of postsynaptic acetylcholine receptors in myasthenia gravis. An IV injection of 10 mg is prepared and then 1â€“2 mg is administered slowly to avoid the nausea and vomiting commonly associated with larger doses. The remainder of the edrophonium is given over the next 5 minutes. The strength of patients who have myasthenia gravis but not botulism dramatically improves within 30â€“60 seconds, and the improvement lasts 3â€“5 minutes. In rare cases, early in the course of botulism, limited improvement in strength occurs that is far less dramatic than that seen in patients with myasthenia gravis.[75] Anticholinesterase drugs, such as edrophonium, have no effect on the toxin's action but may affect patients clinically if some cells can still release acetylcholine. Because acetylcholine release is impaired in botulism, prevention of its metabolism is of limited importance.

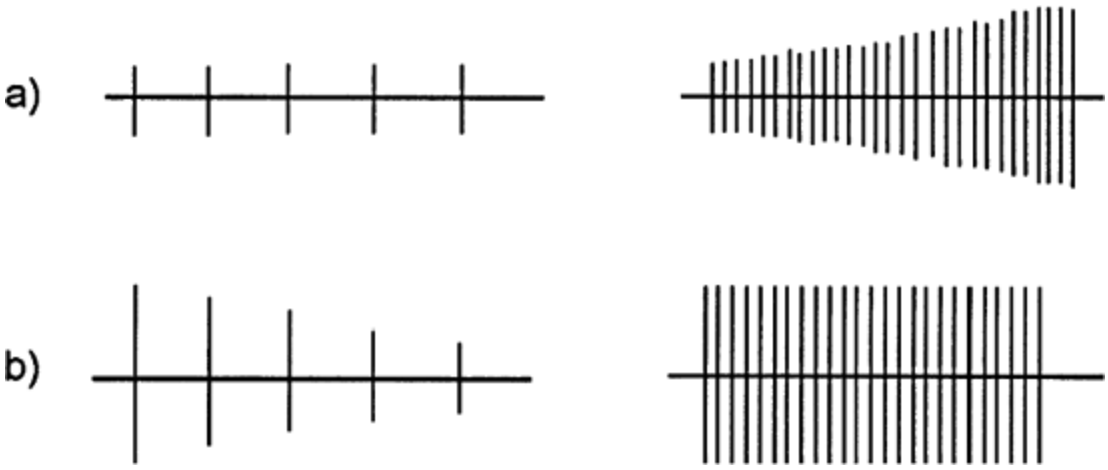

Figure 46-2. Electromyographic findings. Schematic representations of repetitive nerve stimulation at low (5/sec) and high (50/sec) frequencies. In botulism (a), repetitive stimulation produces a small-muscle action potential that facilitates (increases in amplitude) at higher frequencies. This effect results from increased acetylcholine release with high-frequency stimulation because of increased intracellular calcium concentration. In contrast, myasthenia gravis (b) is associated with a normal muscle action potential amplitude and a decremental response at low-frequency stimulation with a normal response at high-frequency stimulation. Myasthenia gravis, a disorder of the muscle endplate, produces this decremental response at low frequencies because the natural reduction in acetylcholine response with subsequent stimulation falls below threshold.[75, 111]

Electromyography

The EMG pattern in all forms of botulism is characterized by brief, small, abundant motor-unit action potentials (BSAPs; or low-amplitude, short-duration potentials) (Figure 46-2). Motor nerve conduction velocity remains normal because axon conduction is not affected. Normal sensory nerve amplitudes and latencies are found. Primary muscle diseases also produce normal conduction velocity and a BSAP pattern, but in botulism, serum concentrations

of muscle enzymes and muscle biopsy are normal. Another typical EMG finding of botulism is an increment in small compound muscle action potential (CMAP) amplitude directly related to acetylcholine release following repetitive stimulation at 20â€“50 Hz. Posttetanic facilitation may be noted in cases of botulism and in other entities such as Eaton-Lambert paraneoplastic syndrome, aminoglycoside-associated paralysis, and hypermagnesemia. Although not pathognomonic, EMG findings interpreted in light of the total clinical presentation can help establish the diagnosis of botulism.[75, 111]

Toxin type
A, B, E, F, G in humans; C, D in animals
A, B, C, F
A, B
A
Route
Ingestion
Ingestion
Wound, abscess (sinusitis)
Ingestion of bacteria and spores
Specimens
Stool: positive for bacteria/spores and toxin
Stool: positive for bacteria/spores and toxin for up to 8 weeks after recovery
Wound site: Gram stain, aerobic and anaerobic cultures; positive for bacteria/spores
Stool: positive for bacteria/spores and toxin
Toxin in serum
Yes
Yes
Yes
Yes
Toxin, bacteria/spores in food
Yes (all)

Bacteria/spores: yes
Toxin: no
No
Bacteria/spores: yes
Toxin: no
Family and friends
At risk if same foods were eaten
Unaffected
Unaffected (unless shared needle or drug)
Unaffected
All toxin and positive presence of bacteria/spores refer to *C. botulinum* .

Classification	Foodborne	Infant	Wound	Adult Infectious

TABLE 46-4. Epidemiologic and Laboratory Assessment of Botulism

Laboratory Testing

Samples of serum, stool, vomitus, gastric contents, and suspected foods should be subjected to anaerobic culture (*C. botulinum*) and toxin mouse bioassay (botulinum toxins) (Table 46-4). A medication list for the patient should accompany each sample to exclude any other potential xenobiotics that might be toxic to the mice. The serum samples must be collected prior to initiation of antitoxin therapy. If wound botulism is suspected, serum, stool, exudate, dÃ©brided tissue, and swab samples should be collected. For infant botulism, feces and serum samples also should be obtained. Infants who are constipated may require an enema with nonbacteriostatic, sterile water to facilitate collection. All enema fluid and stool should be sent for analysis. The specimens should be refrigerated (not frozen) and examined and tested as soon as

possible after collection. The earlier the specimens are collected after the onset of illness, the more likely the toxin assay will be positive.[113] Later in the course of illness, stool culture more likely will be positive.

Although polymerase chain reaction studies can determine the presence of *C. botulinum* in food, this test is not yet available to determine the presence of *C. botulinum* in human specimens.[34, 103] Stool, serum, or suspected food samples can be used for a mouse neutralization bioassay. Although botulinum poisoning normally is lethal within 6â€“24 hours, in mice, illness or death may not occur for up to 4 days. The mouse bioassay is the most sensitive diagnostic technique, detecting as little as 0.03 ng of botulinum toxin.[84] The materials are injected into the mouse peritoneum, and

subsequent paralysis and death of the mouse are considered to be a positive test. Control animals receive portions of the specimen materials that have been boiled to destroy the toxin or previously incubated with antitoxin to achieve neutralization. Stool specimens are incubated anaerobically and then subcultured on an egg yolk agar to search for lipase-producing Gram-positive anaerobic rods.[56]

Approximately 60â€“70% of botulism cases reported since 1950 had an identifiable toxin type. Because isolation of *C. baratii* and *C. butyricum* from food and stool requires techniques that deviate from the usual laboratory protocols, it is conceivable that some of the 30â€“40% of unconfirmed and suspect botulism cases result from the more recently appreciated and more rarely sought after species.[43]

Treatment

Supportive Care

Respiratory compromise is the usual cause of death from botulism. To prevent or treat this complication, hospital admission of the patient and of all individuals with suspected exposure to a possible source is mandatory. Careful continuous monitoring of respiratory status using parameters such as vital capacity, peak expiratory flow rate, negative inspiratory force (NIF), pulse oximetry, and the presence or absence of a gag reflex is essential to determine the need for intubation or tracheostomy, as the patient begins to manifest signs of bulbar paralysis.[87] The most reliable, readily obtainable test is the NIF, which can be used in most institutions to determine the need for intubation. A reverse Trendelenburg positioning at 20â€“25Â° with cervical support has been suggested to be beneficial by enhancing diaphragmatic function, but the clinical application to seriously ill patients has not been validated.[8] This approach may reduce the risk of aspiration while decreasing the pressure of abdominal viscera on the diaphragm, with resultant improvement in ventilatory effort.

Gastric Decontamination

An attempt should be made to remove the spores and toxin from the gut. Although most patients present after a substantial time delay, the etiologic agent may still be present hours or even days later. Activated charcoal should be a routine part of supportive care, because it adsorbs *C. botulinum* type A toxin in vitro and probably also the other botulinum toxin types.[40] Gastric lavage or emesis should be initiated only for an asymptomatic person who has very recently ingested a known contaminated food. If a cathartic is chosen, sorbitol is the preferable agent because other agents such as magnesium salts may exacerbate neuromuscular blockade. Theoretically, whole-bowel irrigation may have a role in decontamination, particularly if there is concern about initiating emesis, but interventions other than activated charcoal have not been evaluated under these circumstances.

Wound Care

Thorough wound dÃ©bridement is the most critical aspect in the management of wound botulism and should be performed promptly.[47, 56] Antibiotic therapy alone is inadequate, as evidenced by several case reports of disease despite antibiotic therapy. Aminoglycoside antibiotics[84] and clindamycin[89] should not be used because they may exacerbate neuromuscular blockade.

Botulinum Antitoxin

Botulinum antitoxins types AB (bivalent) and ABE (trivalent) are available. The type-specific antitoxins are ineffective against any other antigen. In humans, the efficacy of the type-specific antitoxin to type B strain toxin is unknown, whereas the type-specific antitoxins to A and E probably are beneficial.[104]

A 45-year-old woman with presumed botulism was administered bivalent (AB) botulinum antitoxin, but her condition deteriorated. Four days later, the culture demonstrated type F botulinum toxin, and the CDC released heptavalent experimental botulinum antitoxin.[77] Minimal improvement in strength may have resulted. Some debate in the literature exists as to whether type E antitoxin has partial neutralizing potential against type F antitoxin. Currently no human experiences validate this hypothesis, which might lead to use of trivalent (ABE) antitoxin if type F botulinum antitoxin were unavailable.[43, 64]

Antitoxin can prevent paralysis but does not affect already paralyzed muscles.[37] This finding is supported by the sustained duration of weeks to months of toxin type A and B in tissue after therapeutic injection in humans and animals. For greatest effectiveness, trivalent antitoxin must be used immediately upon consideration of the disease in both symptomatic and asymptomatic individuals recently exposed to a presumptive food source.[92] Botulinum antitoxin types AB should be used for

presumptive wound botulism.

In a review of 132 cases of type A foodborne botulism, a lower fatality rate and a shorter course of illness were demonstrated for patients who received trivalent antitoxin, even after controlling for age and incubation period.[104] The earlier a patient received antitoxin, the shorter was the clinical course. In addition, no respiratory arrests occurred more than 5 hours after antitoxin was administered. In view of the high mortality rate associated with foodborne botulism and the limited statistical data, the antitoxin should be given IV to all exposed patients. Two studies on the use of antitoxin in the presence of wound botulism demonstrate that the longer the delay to antitoxin administration, the more prolonged the requirement for ventilatory support and the poorer the outcome.[28]

Although specific foods tend to correlate relatively well with botulinum type, trivalent antitoxin (7500 U type A, 5500 U type B, and 8500 U type E) should be used. An entire 10-mL vial of trivalent antitoxin should be given IV as a 1:10 vol/vol dilution in 0.9% sodium chloride over several minutes. If epidemiologic investigation identifies the organism, subsequent type-specific antitoxin therapy can be instituted if the product is available. Because antitoxin is an equine globulin preparation, hypersensitivity testing for horse serum has sometimes been recommended. However, this testing is of no value because the predictive value is limited and antitoxin therapy is essential. Epinephrine should always be readily available to treat anaphylaxis. The overall rate of adverse reactions, including hypersensitivity and serum sickness,[15] is 9â€“17%, with an incidence of anaphylaxis as high as 1.9%[9 , 66] (Antidotes in Depth: Botulinum Antitoxin).

Guanidine, 4-Aminopyridine, and 3,4-Diaminopyridine

Guanidine is no longer recommended for treatment of botulism, because its merits were not substantiated[35] (see previous editions of

this text for a more extensive discussion). Several studies[82] and case reports[32] have proposed that 4-aminopyridine and 3,4-diaminopyridine are effective in improving neuromuscular transmission by enhancing acetylcholine release from the motor nerve terminal.[82] In a rat botulinum toxin type A model, 3,4-diaminopyridine restored neuromuscular function and enhanced animal survival.[95] The therapeutic efforts for those with Eaton-Lambert syndrome and the successful animal results all suggest that further investigative efforts are necessary. It is suggested that 4-aminopyridine's potential for inducing seizures at therapeutic doses limits its clinical usefulness. The fact that 3,4-diaminopyridine does not substantially cross the bloodâ€“brain barrier, resulting in limited CNS manifestations, makes this agent appropriate for further investigation.

Penicillin

Penicillin G is one of many drugs with excellent in vitro efficacy against *C. botulinum* and is useful for wound management.[102] However, penicillin has no role in the management of botulism caused by preformed toxin, nor has it been shown to prevent gut spores from germinating. For these reasons, penicillin is not considered useful in infant and adult infectious botulism, and it is not by itself considered adequate for wound botulism.

Treatment and Prevention of Infant Botulism

Whether botulinum antitoxin or antibiotics have a role in infant botulism is unclear. Cases of children surviving without either

antitoxin or parenteral antibiotics are documented. Currently, antitoxin is not recommended because circulating toxin is believed to be present at very low concentrations, and antitoxin has no effect on toxin-producing organisms in the gut.[50, 53, 86] Therefore, antitoxin is not expected to halt syndrome progression. Moreover, in fully recovered children, both toxin and spores can be found in the stools for months despite use of oral or parenteral antibiotics and/or antitoxin administration. Human-derived botulism immune globulin (BIG) is an investigational new drug available for IV treatment only as part of an FDA-approved â€œopen label administrationâ€• study by the California Department of Health Services[5, 26, 36, 66] (Antidotes in Depth: Botulinum Antitoxin).

Measures used to prevent infant botulism include limiting exposure to spores by thoroughly washing foods and objects that might be placed in a child's mouth. In addition, honey should not be given to infants younger than 6 months.

Prognosis

The prolonged and variable period of recovery that occurs after exposure to botulinum toxin is directly related to the extent of neuromuscular blockade and neurogenic atrophy and the regeneration rates of nerve endings and presynaptic membrane.[62] If the patient has excellent respiratory support during the acute phase and receives adequate parenteral nutrition, residual neurologic disability may not occur. Although the initial course may be protracted, near total functional recovery can follow within several months to 1 year. Common long-term sequelae include dysgeusia (Chap. 21), dry mouth, constipation, dyspepsia, arthralgia, exertional dyspnea, tachycardia, and easy fatigability.

The long-term status of 13 patients who survived a toxin type B botulinum outbreak was characterized 2 years later by persistent dyspnea and fatigue, although surprisingly, pulmonary function

tests had returned to normal in all patients.[115] Inspiratory muscle weakness persisted in 4 of 13 patients. Maximal oxygen consumption and maximal workload during exercise were diminished in all patients, and all had more rapid shallow breathing and a higher dyspnea score than controls. The reasons for premature exercise termination may be multifactorial. Although persistent respiratory muscle weakness may be an explanation, most dyspnea and fatigue appeared to be related to reduced cardiovascular fitness, leg fatigue, and diminished nutrition.[116] Nevertheless, because long-term prognosis can be so good, early recognition of the disease and supportive care are essential.

Pregnancy

At least 3 cases of botulism occurring during pregnancy have been reported. One case occurred during the second trimester,[78] and 2 cases occurred during the third trimester.[99] Although botulinum toxin or *C. botulinum* was isolated in the mother in 2 of the botulinum cases prior to administration of antitoxin therapy, no detectable toxin was isolated from the neonates in either of the third-trimester cases. The large MW of the neurotoxin (150,000 daltons) makes passive diffusion through the placenta unlikely,[45] and, although theoretically possible, no active transport system has been identified.[99] None of the three neonates had neurologic evidence of botulism. Appropriate care of the mother and preparation for maternal complications of delivery appear to assure the best potential outcome for a normal infant.

Epidemiologic and Therapeutic Assistance

Whenever botulism is suspected or proven, the local health department should be contacted. The health department should report to the CDC Emergency Operations Center at 770-488-7100.

The center, which is available 24 hours per day, 7 days per week, pages the Foodborne and Diarrheal Diseases Branch Medical officer. The CDC can provide or facilitate diagnostic, consultative, and laboratory testing services, access to bivalent or trivalent botulinum antitoxin, and assistance in epidemiologic investigations. All foods that possibly are responsible for the illness should be preserved for epidemiologic investigation. The merits of this surveillance and antitoxin release system were demonstrated in Argentina,[112] where the CDC assisted in establishing comparable principles that are nation specific, including local stocking of antitoxin and establishing mechanisms for distribution, emergency identification, response, and laboratory confirmation for suspect cases. Expansion of this system to other nations will enhance worldwide botulism surveillance for foodborne botulism and for potential terrorist dissemination of botulinum toxin.[91]

Summary

Botulism remains one of the rarest poisonings while its etiologies have become increasingly diverse. The incidences of wound botulism and the adult infectious form of botulism have increased dramatically. Previously unrecognized complications of therapeutic botulinum toxin now permit a better understanding of the effects of the toxin and an appreciation of its risks. The international experience with botulism epidemics has allowed the CDC to enhance epidemiologic surveillance and to prepare for the possible use of botulinum toxin as a biologic weapon. Further treatment strategies are being developed to include an $F(ab€²)_2$ despeciated heptavalent immune globulin, a human BIG, a recombinant vaccine, and other creative advances (Antidotes in Depth: Botulinum Antitoxin).

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Antidotes in Depth

Botulinum Antitoxin

Lewis R. Goldfrank

Equine Immunoglobulins

The production of antitoxin is complex, requiring almost 2 years to immunize healthy horses against botulinum toxin. The resultant immunoglobulin product, which is then defibrinated, digested, dialyzed, and purified as a 20% protein antitoxin,[5] can be lyophilized and preserved.[24] Bivalent (serotypes A and B) and trivalent (serotypes A, B, and E) botulinum antitoxin are the equine immunoglobulin preparations available in the United States. The bivalent (AB) preparation is used for patients with presumed wound botulism. The trivalent product is reserved for patients with foodborne botulism.

Botulinum antitoxin is distributed from the 9 regional centers of the Centers for Disease Control and Prevention (CDC) on a named patient basis, after a probable diagnosis of botulism is established. Each 10-mL vial of the currently available trivalent botulinum antitoxin contains 7500 IU (2381 US units) of type A botulinum antitoxin, 5500 IU (1839 US units) of type B antitoxin, and 8500

IU (8500 US units) of type E antitoxin.[9] The proportion and quantity of types A, B, and E antitoxin are assumed to be adequate to neutralize the quantities of circulating toxins in a typical case of botulism.[5,9]

Evidence substantiating the efficacy of types A and E antitoxin is available,[14,28] but the efficacy of type B antitoxin has not been established in clinical trials.

Currently only limited data are available on the relationship of dose and route of administration, the amount of circulating antitoxin found in treated patients, the toxin-neutralizing capacity of this material, and the half-life of the antitoxin. Peak serum concentrations of antitoxin are 10â€“1000 times higher than the concentrations of antitoxin calculated to be necessary to achieve toxin neutralization.[10] Ninety percent of the activity of the equine antitoxin administered was detected when all the circulating toxin was neutralized.[16] The half-life for antitoxin persistence in a single patient was calculated at 6.5, 7.6, and 5.3 days for antitoxin types A, B, and E, respectively.[10] The prolonged half-life of the antitoxin, and the exceedingly small quantities of toxin measured, explain the limited decrease in antitoxin titers following toxinâ€“antitoxin binding.

In the presence of disease, 1 vial of the antitoxin is administered slowly IV, over several minutes, as a 1:10 vol/vol dilution in 0.9% sodium chloride solution. Subsequent doses can be given IV every 2â€“4 hours, depending on the progression of clinical findings.[5,9]

Like many other heterologous proteins, administration of this horse serum-derived preparation results in substantial adverse effects.[15] Each patient treated during the initial decade during which antitoxin was available (1967â€“1977) was studied to determine both hypersensitivity reaction rates and the efficacy of the antitoxin in treating botulism. The overall rate of adverse reactions, including hypersensitivity and serum sickness, was 9â€“17%, with an incidence of anaphylaxis as high as 1.9%.[2,18]

However, the doses of antitoxin used in that era were substantially larger than those currently used. Because of the lethality of botulinum toxin, the risk of adverse drug reaction for the antitoxin is considered acceptable for anyone with presumed illness and for anyone potentially exposed to the toxin. Pregnancy is not a contraindication to antitoxin administration, and antitoxin has been used successfully in these circumstances.[23,28]

Anaphylaxis should be anticipated, and the clinician should be prepared to treat this complication immediately with epinephrine. The smaller quantities of botulinum antitoxin used for botulism present a far smaller risk for serum sickness[2] than do the larger amounts of antivenom used to treat snake envenomation. The risk of serum sickness from the refined serum proteins in botulinum antitoxin is approximately 4â€“10%.[3,9]

Patients who received antitoxin within the first 24 hours after exposure had a shorter clinical course of botulism without regression of symptoms, but a comparable mortality rate to those who received antitoxin later.[29] Reduced mortality can only be demonstrated in animal models.[20] Morbidity and mortality studies are difficult to perform for a disorder that is so rare and often recognized at a delayed stage, when the toxin already is tightly bound to the neuromuscular junction. Also, most of the reported case series involve patients who received varying degrees of supportive care, further making evaluation or comparison unreliable.

Investigations: Despeciated Immune Globulins

$F(ab'â€²)_2$ â€œdespeciatedâ€• heptavalent (against toxin types A, B, C_1, D, E, F, and G) botulism immune globulin (dBIG) is currently under investigation and available from the CDC.[22] This equine immune globulin[7] is extensively purified to eliminate

fibrinogen, plasminogen, and other proteins. Pepsin is used to remove the Fc fragment of the immunoglobulin in order to reduce the potential for allergic manifestations, should reexposure to equine protein occur.[12] The single-dose vials available contain > 4000 IU of serotypes A, B, C, E, and F and > 500 IU for serotypes D and G.[22] When given prior to exposure, this $F(ab€^2)_2$ immunoglobulin protected mice from inhaled toxin at doses 10 times that of the LD_{50} and was still fully protective when given after exposure but prior to the onset of clinical signs.[13]

Although 10 of 45 patients given dBIG in the Egyptian type E botulism outbreak manifested adverse reactions, 9 were considered mild and 1 episode was classified as serum sickness.[12] In this botulism epidemic, the incidence of adverse effects of dBIG was comparable to those of numerous other internationally available botulinal antitoxins. Although followup of individuals was limited, the agent appeared to be as safe as other commercially available antitoxins. Further investigations with regard to safety and efficacy are necessary.

Human Immunoglobulins

Human-derived preparations of type E antitoxin were developed as 5000 IU per 2-mL vials for intramuscular use. This human-derived

type E botulinum antitoxin was dosed between 1000 and 5000 IU based on the estimated quantity of toxin ingested for 100 Egyptians who presumably had ingested botulinum toxin-contaminated, uneviscerated, salted, mullet fish.[8,32] The safety of the human-derived preparation allowed for repetitive dosing in any individual, if clinical findings developed.[7] This regimen was based on the premise that effective treatment could be achieved by delivering small antitoxin doses prior to tissue binding of circulating toxin.

Human-derived botulism immune globulin (BIG) was developed for

use in the treatment of infant botulism. This pentavalent (types A, B, C, D, and E) immune globulin is harvested by plasmapheresis from human donors who received multiple immunizations with pentavalent botulinum toxoid.[21,30] A longer biologic half-life, with a prolonged effective level, should be possible with BIG.[14] Both of these effects are substantial clinical advantages, particularly for the infant form of botulism, where toxin is slowly and continuously produced in the intestine and absorbed. Use of a human immune globulin obviously avoids the risk of hypersensitivity that is associated with foreign equine proteins. Results of the orphan-drug infant botulism prevention clinical trial of the human BIG suggest many advantages over the current equine antitoxin therapy.[1,6] BIG became available for clinical trials in California in 1991.[6]

Human BIG was used successfully in a 3-year-old child who developed altered gut microbial flora and botulism following bone marrow transplantation.[25] This case is a relatively rare example of infant type (in vivo intestinal colonization) botulism, in a 3-year-old child.

Other Investigatory Modalities

A pentavalent toxoid vaccine (types A, B, C, D, and E) was developed at the US Army Medical Research Institute of Infectious Diseases (USAMRID) at Fort Detrick, Maryland, and has been studied for more than 40 years.[4,16] Its use remains investigational and is suggested only for laboratory personnel who work with *Clostridium botulinum* or for those who might be first responders in the case of terrorism.[26] An additional monovalent toxoid type F vaccine was manufactured for the US Army and has been tested by USAMRID.[11,17]

Recombinant vaccines,[4,27] recombinant monoclonal antibodies, recombinant oligoclonal antibodies,[19] and drugs that act as metalloproteinase inhibitors (thereby preventing toxin uptake) are

all currently under investigation by the Department of Defense.[7]

Summary

Consultation with a regional poison center and local health department and ultimately between the health department and the CDC at 770-488-7100, 24 hours per day, 7 days per week (or other comparable agencies in other parts of the world) provide improved access to rapid diagnostic tests for botulism and effective therapeutic modalities. Earlier disease recognition and the currently organized public health approach appear to be responsible for decreasing morbidity and increasing survival after typical foodborne botulism.[24,31] Results of current research on infant botulism will demonstrate whether sufficient circulating toxin is present in that variant to be amenable to antitoxin treatment. Antitoxin may be useful if, as suggested, a low level of absorbed toxin is present in these disorders.[16] After these issues are clarified, providing adequate treatment for the infant form of botulism, which has become the most prevalent form of botulism, may be possible.

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Chapter 47
Anticonvulsants

Suzanne Doyon

Carbamazepine
4â€“12
17â€“51
Ethosuximide
40â€“100
283â€“708
Gabapentin
2â€“15*
12â€“88
Lamotrigine
1â€“< 5
â ‰ ¤19.5
Phenobarbital
15â€“40
65â€“172
Phenytoin
10â€“20
40â€“79

Valproic acid
50â€“120
347â€“833
*Proposed.

Therapeutic serum concentrations

Drug	*mg* /L	Âµmol/L

A 45-year-old man with a history of alcoholism, posttraumatic stress disc was brought to the emergency department (ED) after ingesting unknown gabapentin. He was suffering from depression, and he had ingested all of hours prior to presentation.

Upon arrival to the ED, the patient was unresponsive. His vital signs were pulse 110 beats/min; respiratory rate 12 breaths/min; temperature 98.6Â all extremities to deep pain. His head was atraumatic with 3-mm pupils t Gag reflex was absent. Examination of his lungs, heart, and abdomen wer track marks, cyanosis, or edema. Deep-tendon reflexes were symmetrical extension was present.

The patient was endotracheally intubated and connected to a ventilator. A concentration was 70 mg/dL, and 50 mL of 50% dextrose was administer mental status. The electrocardiogram (ECG) revealed sinus tachycardia wi nasogastric tube was inserted, and 75 g activated charcoal was instilled.

Serum ethanol and acetaminophen concentrations were negative. Initial s was 236 mg/L, serum ammonia concentration 45 Âµmol/L (normal 9â€“3 concentration 19 mg/L.

The patient was admitted to the intensive care unit (ICU). Four hours lat concentration was 810 mg/L and serum ammonia 82 Âµmol/L. Multiple do administered. Hemoperfusion was considered but was not instituted. The was 933 mg/L and serum ammonia 141 Âµmol/L. An intravenous (IV) load started, followed by a maintenance dose of 1 g every 4 hours IV for 24 l unchanged. Approximately 18 hours postingestion, the valproic acid conce The 28-hour valproic acid concentration was 481 mg/L, serum ammonia 3 concentration

2.7 mg/L. The patient's mental status improved, but he developed a fever He remained intubated and mechanically ventilated. Two days later, his p 30,000/mm^3 from the admission value of 156,000/mm^3 . There were no expanding hematoma developed at an arterial puncture site. He responde His liver enzymes remained normal throughout his hospital stay. The pat his complete blood cell count normalized 3 days later. He was discharged with psychiatric support.

History and Epidemiology

The prevalence of seizures in the United States is 3%. Historically, seizure methods, including barbiturates, bromides, ketogenic diets, fluid restriction or irritable cortical foci. The first truly effective therapy was introduced in bromides was noted to sedate patients and significantly reduce their seiz to treat seizures in 1912. Consequently, sedation was erroneously believed seizure therapy.

The search for nonsedating anticonvulsive agents led to the introduction o the anticonvulsants introduced subsequently, such as primidone, had chem phenobarbital. After 1965, benzodiazepines, carbamazepine, and valproic gained wide use as anticonvulsants. These anticonvulsants were the only when the US Food and Drug Administration approved numerous new anti gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiram zonisamide.

Anticonvulsants are also currently used for treatment of mood disorders, trigeminal neuralgia, bruxism, migraine headaches, drug withdrawal synd

In a review of more than 5000 patient suicides, anticonvulsants were imp suggesting a fairly high rate of suicidal ideation among people with acces last decade, as reported in the American Association of Poison Control Ce Surveillance System (TESS) data, a shift occurred from predominantly ca exposures to VPA and newer anticonvulsants. VPA is involved in 44% of anticonvulsants (Chap. 130).[160]

This chapter reviews the toxicity and management of overdoses with ant

benzodiazepines and barbiturates are discussed in Chap. 72 .

Pharmacology

A *seizure* is defined as the clinical manifestation of excessive neuronal ac system (CNS). It is accompanied by various degrees of motor, sensory, result from 1 of 4 cellular mechanisms: sustained repeated firing of the conductance, increased excitatory neurotransmission (eg, glutamic acid), c inhibitory neurotransmitters (eg, Î³-aminobutyric acid [GABA]).

Correspondingly, the mechanisms of action of anticonvulsants fall into 1 c channel inhibition, calcium channel inhibition, inhibition of excitatory amir Frequently, more than 1 mechanism accounts for a drug's anticonvulsive

During seizures, a high-frequency pattern of neuronal firing is detected. T normal physiologic neuronal activity. Voltage-gated sodium channels are neuronal firing that occurs in epilepsy. Under the influence of anticonvuls channels remain partially open, but their functionality is hindered by pers gate. The sodium channels cannot recover from inactivation and are preve frequencies. Phenytoin, carbamazepine, VPA, lamotrigine, topiramate, ox felbamate all attach themselves to the batrachotoxin binding site (or adja and prolong the channel's recovery from inactivation[91 , 99 , 159 , 162] At channel blockade is selective. At toxic concentrations, selectivity is lost a spontaneous sodium channels are inhibited. For several of these medicati occurs.

Voltage-gated calcium channels are multisubunit complexes that are broa high-voltage groups. The low-voltage group encompasses the T-type calc and ethosuximide inhibit flow of calcium through these channels, thus red the *pacemaker current* .[50 , 115 , 125] The high-voltage group consists of th Calcium entry into presynaptic nerve terminals is regulated by these cha inhibits the N-type calcium channels.[90 , 125]

The *N* -methyl-D-aspartate (NMDA) receptor is the glutamate receptor of respect to development of seizures. When stimulated by glutamate, the N gated ion channel that permits entry of Na^+ and Ca^{2+} into the neuronal c glutamateâ€“NMDA interaction is protective against seizures.[99] Felbamate

glutamate antagonists at the NMDA receptors.[59] More specifically, felbama insensitive glycine recognition site on the NMDA receptor[98] (Chap. 14). phenytoin inhibit glutamate release by binding to presynaptic Na^+ channe as opposed to the NMDA glutamate receptor subtype, and blocks Na^+ ent

GABA acts through fast chloride-permeable ionotropic $GABA_A$ receptors a coupled $GABA_B$ receptors.[3] Pharmacologic enhancement of GABA receptor effective approach to epilepsy. Anticonvulsants may interact with the GAB kinetics of GABA itself. Vigabatrin irreversibly inhibits GABA transaminase responsible for GABA metabolism.[52] VPA may have similar effects.[99] Tiaga transporter GAT-1 and thereby prevents reuptake of GABA into presynap [120] Despite its design as a GABA agonist, gabapentin does not mimic GAB poorly understood. Gabapentin may increase GABA release from vesicles [56] or inhibit the L-type high-voltage calcium channel.[62] Figure 47-1 sum

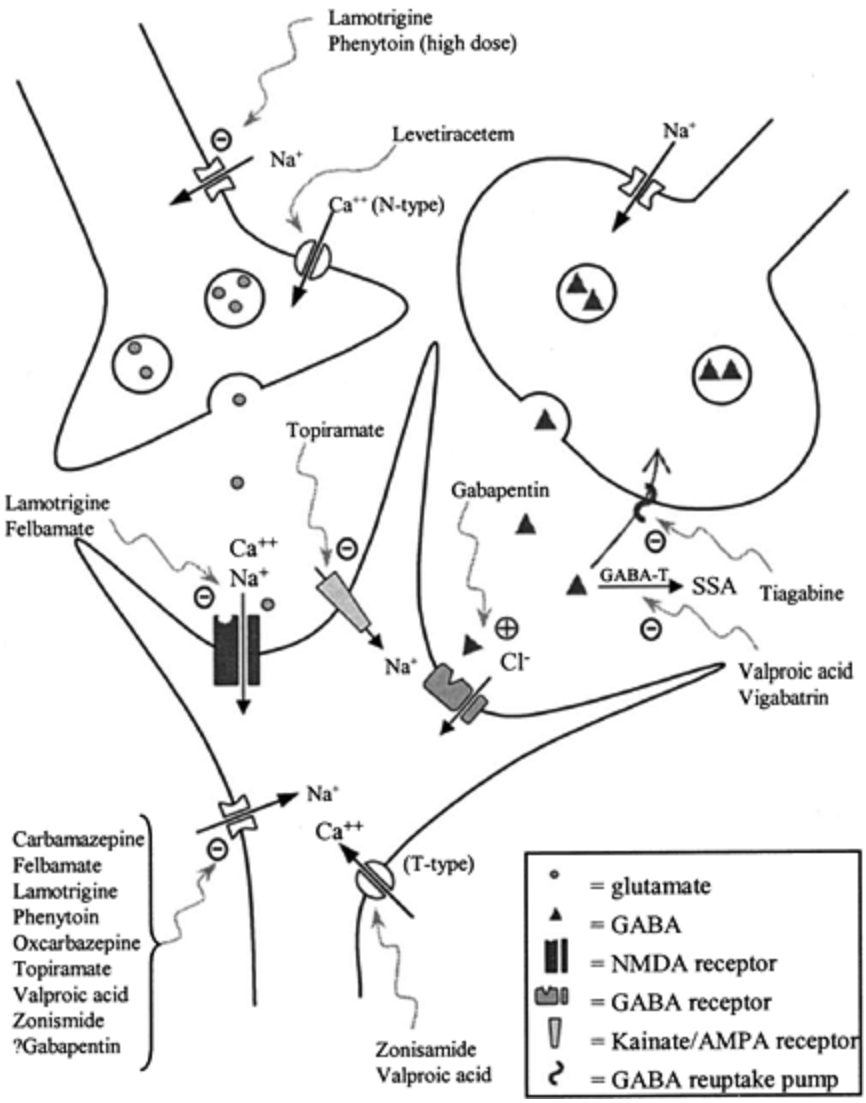


Figure 47-1. Mechanism of action of anticonvulsants. SSA = succinic aci transaminase.

Phenytoin/Fosphenytoin

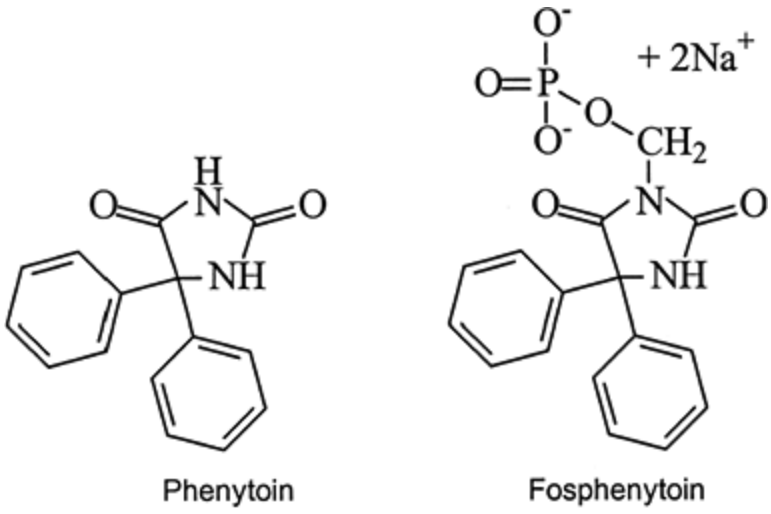


Figure. No Caption Available.

Phenytoin, introduced in 1938, is still a first-line anticonvulsant for treatr except absence seizures.[95] It has no role in the treatment of toxin-relate withdrawal syndrome.[22] It is nonsedating in therapeutic doses and theref GABAergic anticonvulsants for long-term management of epilepsy.

Fosphenytoin, a water-soluble phenytoin derivative introduced in 1997, wa apparent shortcomings of parenteral phenytoin, such as its poor water so intramuscular injection. Its clinical utility derives from the rapid achiever concentrations, its potential for intramuscular administration, and its lower cardiotoxicity.[13 , 99]

Pharmacokinetics and Toxicokinetics

Phenytoin is a weak acid (pK_a 8.3) that is highly protein bound and is ra Single-dose oral therapeutic loading using 18 mg/kg phenytoin capsules is incomplete in 36% of patients at 8 hours.[112] In very large oral overdose be delayed even more, up to several days.[21 , 30] Some authors suggest p absorption in the colon because of its lipophilic properties.[148] Phenytoin d the gastrointestinal tract.[21]

Phenytoin is extensively bound to serum proteins, mainly albumin. Only t biologic membranes and exert pharmacologic action. A significant fraction

neonates, uremic patients, and other patients with hypoalbuminemia.[55] L
phenytoin is excreted unchanged in the urine. The remainder is metabolize
phenytoin metabolite, a parahydroxylphenyl derivative, is inactive but is b
hypersensitivity reaction associated with phenytoin administration.[78] The
saturable enzyme kinetics explains the relationship between phenytoin do
steady state. At phenytoin concentrations below 10 mg/L, elimination usu
half-life ranges between 6 and 24 hours. At higher concentrations, zero-c
dependent elimination) occurs as a result of saturation of the hydroxylati
elimination half-life increases to 20â€“60 hours.[99 , 24] Therefore, the app
phenytoin is progressively prolonged as plasma concentration increases[99]

Fosphenytoin (1.5 mg fosphenytoin = 1 mg phenytoin) is a water-soluble
phenytoin. It is available in a water-based parenteral formulation that cor
a pH of 8â€“9. Fosphenytoin is converted entirely to phenytoin by circula
minutes of IV injection. Peak phenytoin concentrations are reached 30 m
injection. The loading dose, expressed in phenytoin equivalents (PE), is th
47-1).

Clinical Manifestations

Acute phenytoin toxicity produces predominantly neurologic dysfunction th
and vestibular systems. Phenytoin concentrations greater than 15 mg/L u
nystagmus, concentrations greater than 30 mg/L are associated with ata
50 mg/L are associated with lethargy, slurred speech, and pyramidal an
[101] CNS concentrations correlate best with free serum phenytoin concent
seizures on extremely rare occasions, usually in the setting of acute over
seizures.[149] Young children and the elderly may present with atypical ma
example, phenytoin-induced chorea and opisthotonic posturing are reporte
children.[101]

Cardiotoxicity resulting from oral overdoses of phenytoin has not been re
phenytoin impairs myocardial contractility, decreases peripheral vascular

myocardial conduction. In a large case series, IV phenytoin was associated
hemodynamic complications.[40] Deaths following IV administration of phen
[164] These complications correlate with rate of administration and total dos

ascribed to the diluents used in the IV preparation of phenytoin, that is, ethanol (10%).[103] Propylene glycol in particular depresses myocardial tis vascular resistance (Chap. 53). However, fosphenytoin, which does not c diluent, also impairs cardiac conduction and contractility. Two reports of 5â€“10 times in excess of the required dose, administered to young infa in bradycardia, hypotension, and asystole.[83 , 127] Still, the water solubilit therapeutic IV administration, and fosphenytoin can be infused at a maxim is 3 times that of phenytoin.[13]

Carbamazepine
3â€“24 in overdose
4â€“12
0.8â€“1.8
75
1
CBZ 10,11-epoxide
6â€“20 overdose
4.9â€“11.5 chronic
Felbamate
4
30â€“50
0.75
25
40
None
20â€“23
Gabapentin
3
2.7â€“4
0.8
0
100
None
5â€“7
Lamotrigine

2.5
4â€“18
1.2
55
10
None
14â€“50
Levetiracetam
1â€“2
10â€“70
0.7
10
66
None
5â€“8
Phenytoin
5â€“24 in overdose
10â€“20
0.6
> 90
< 5
None
6â€“60
Tiagabine
1â€“2
5â€“70 ng/mL
1
96
< 5
None
5â€“9
Topiramate
1â€“4
4.5â€“30

0.5â€“0.8
15
60
None
20â€“30
Valproic acid
1â€“24 in overdose
50â€“120
0.1â€“0.2
> 90
< 5
2-en-VPA
3-OHVPA
3-keto VPA
6â€“18
Vigabatrin
4
20â€“80
0.8
0
100
None
4â€“8
Zonisamide
4â€“6
6.7â€“40
1.2
40â€“60
< 5
None
60

[a] After therapeutic oral administration, unless otherwise stated. From references [1,5,8,51,53,77,89,99,102,118,119].

	Time to Peak Plasma Concentrationa(h)	Therapeutic Serum Concentrations (mg/L)	Vd (L/kg)	Plasma protein binding (%)	Urina elimina unchan (%)

TABLE 47-1. Pharmacokinetics of Anticonvulsants[a]

Intravenous phenytoin is commonly associated with local irritation. Extrava necrosis, possibly necessitating surgical intervention.[26 , 40 , 75] These cor from the propylene glycol diluent and pH. The risk of fosphenytoin-induce its water solubility.

Chronically elevated phenytoin concentrations may result in gingival hyp behavioral changes, and encephalopathy. Hyperactivity, confusion, lethar the behavioral changes. Chronic use of phenytoin is associated rarely wi produce hepatotoxicity, which may or may not be part of the anticonvul (AHS, discussed below under Anticonvulsant Hypersensitivity Syndrome).

Diagnostic Testing

Serum phenytoin concentrations should be performed in all cases of pher unpredictable absorption, phenytoin concentrations should be repeated a concentrations are 10â€“20 mg/L. Because of the switch to zero-order e concentrations may take days or weeks before they return to the therape

Patients with impaired or decreased protein-binding capacity can develop concentrations within the therapeutic range. Patients at greatest risk incl hypoalbuminemic, hyperbilirubinemic, and uremic patients, and patients with VPA, salicylates, and sulfonamides because these agents displace ph sites. In such patients, determination of the free phenytoin fraction is he reliably with the CSF concentrations than does the total phenytoin conce fraction can be measured directly by a number of analytical methods, in followed by gas chromatography or enzyme-multiplied immunoassay tech free phenytoin concentrations are 1.0â€“ 2.1 mg/L.

Equation 47-1 approximates the total phenytoin concentration that would measured serum phenytoin concentration and measured albumin concen

$$[\text{Phenytoin}] = \frac{[\text{Measured phenytoin}]}{(0.25 \times [\text{Measured albumin}]) + 0.1.}$$

(Eq. 4

Management

The treatment of patients with acute or chronic phenytoin overdoses ren related deaths are rare, even after massive overdoses. Because the use (MDAC) reduces the elimination half-life of intravenously administered phe it is recommended in patients in whom serial serum concentrations are i elevated.[96] Aggressive lowering of the serum phenytoin concentration may patient, and MDAC should be used cautiously in these patients. Given the hemodialysis and hemoperfusion are of little benefit in the management toxicity.[71 , 81]

Severe ataxia mandates careful evaluation of patients because of concern determinations are necessary because of the unpredictable absorption an Patients admitted to the hospital after oral phenytoin

overdoses do not require routine cardiac monitoring because they do not cardiovascular complications.[42 , 163]

Phenytoin-induced agranulocytosis can be treated successfully with admi stimulating factor.[152]

Hypotension, cardiac dysrhythmias, and dyskinesias during IV administrati transient and usually resolve spontaneously in 30â€“60 minutes unless c phenytoin infusion for a few minutes and administering a bolus of 250â€“ solution generally is sufficient for treatment of hypotension in an adult. R initial rate is recommended.[140] Prolonged periods of cardiopulmonary resu cases of fosphenytoin- or parenteral phenytoin-induced dysrhythmias, in other tissues thereby permitting time for the cardiotoxicity to resolve.[83 ,

The management of extravasation is discussed in Chap. 6 .

Carbamazepine/Oxcarbazepine

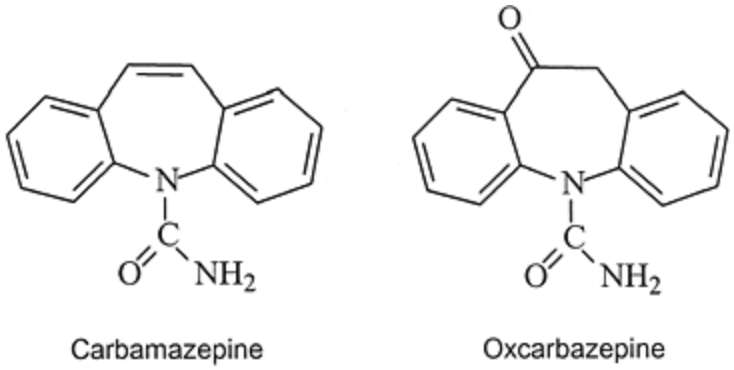


Figure. No Caption Available.

Carbamazepine, which was introduced in 1947, is structurally related to Carbamazepine is a first-line therapy for seizures and may be especially epilepsy.[95] Oxcarbazepine is a keto-analog of carbamazepine, which funct

Pharmacokinetics and Toxicokinetics

Carbamazepine is lipophilic agent with slow and unpredictable absorption rapid distribution to all tissues. Peak concentrations may not be reached large overdose or an overdose of sustained-release preparations.[33 , 37 , weak anticholinergic properties and can decrease gastrointestinal motility, Hence, no simple relationship exists between the dose of carbamazepine

Carbamazepine is metabolized primarily by CYP3A4 to carbamazepine 10, pharmacologically active. This quantifiable metabolite is further degraded carbamazepine-diol, a largely inactive compound.[73] The enzymes respons carbamazepine are not considered saturable.[41] Elimination of carbamazepi weeks of therapy because of autoinduction, and the half-life on chronic Therefore, the dose must be increased gradually over a 2- to 4-week peri mg/kg for adults and 20â€“70 mg/kg for children. Children require a high the drug more rapidly. During chronic therapy, the elimination half-life is The elimination half-life after single acute overdoses is unpredictable and and 47-2).

Carbamazepine
1A2
2C9
None
73, 144
2C8
3A subtype
2C9
3A4
Levetiracetam
None
None
None
119
Phenobarbital
2C9
2C
None
4
2C19
3A
Phenytoin
2C9
2C subtype
None
79
2C19
3A subtype
Tiagabine
3A4
None
None
1
Topiramate

None

2C19
118
Valproic acid
2A6

2C9
8
2C9
2C19

Metabolized by	Induction	Inhibition	References

TABLE 47-2. Anticonvulsants and Cytochrome (CYP) System

Oxcarbazepine is rapidly converted to the pharmacologically active 10 metabolite before conjugation and renal elimination. It is a less potent in

Clinical Manifestations

Acute carbamazepine toxicity is manifest by neurologic signs and sympto cardiovascular effects. The initial neurologic disturbances include nystagm patients with a large overdose, fluctuations in level of consciousness is c [63, 135, 137, 161] Carbamazepine toxicity may cause seizures both in nor with underlying epilepsy. The mechanism underlying carbamazepine-induc understood.[63, 115] In some cases, an increase in seizure frequency, una symptoms, is the only presenting symptom of carbamazepine toxicity. St acute carbamazepine toxicity.[139, 143, 154] In 1 case series, 55% of adu concentrations > 40 mg/L developed seizures.[63] Children may experience concentrations.[142]

Cardiovascular effects include sinus tachycardia, which occurs in 35% of o anticholinergic mechanism, hypotension with myocardial depression, and abnormalities.[49 , 63 , 84] High concentrations of carbamazepine may cause of the action potential in cardiac tissue.[147] In a large case series of carb incidence of QRS complex prolongation (> 100 msec), 50% incidence of (msec), and no cases of terminal 40-msec axis deviation of the QRS comp These abnormalities can be delayed for as long as 20 hours and may occ [70 , 151]

The toxicity of carbamazepine in children differs slightly from that in adu incidence of dystonic reactions, choreoathetosis, and seizures and have a electrocardiographic abnormalities.[12 , 142 , 150]

Chronic carbamazepine overdose can result in headaches, diplopia, or at are common.[130] Vasopressin secretion can be stimulated at high carbam hyponatremia (syndrome of inappropriate antidiuretic hormone)[47] (Chap.

Diagnostic Testing

A serum carbamazepine concentration should be obtained in all cases of exposure. Because of erratic absorption, the concentrations should be rep closely monitored until a downward trend is observed. Therapeutic conce Patients receiving multiple anticonvulsants may not tolerate high concent should be maintained at 4â€“8 mg/L. Concentrations > 40 mg/L tend to respiratory depression, and cardiotoxicity.[63] Carbamazepine may cross-rea tricyclic antidepressants (Chap. 7).[46]

Carbamazepine
None
Doxycycline, felbamate, haloperidol, lamotrigine, ?methadone, oral contr tiagabine, valproic acid, warfarin
Allopurinol, cimetidine, danazol, diltiazem, fluoxetine, fluvoxamine, gemf lamotrigine, macrolides, nefazodone, nicotine, propoxyphene, protease i Benzodiazepines, felbamate, isotretinoin, phenobarbital, phenytoin, primic Felbamate

Carbamazepine, epoxide, phenytoin, valproic acid
Carbamazepine
Valproic acid, gabapentin
Carbamazepine, phenytoin
Gabapentin
Felbamate
None
None
Antacids
Lamotrigine
Carbamazepine
None
Valproic acid
Antituberculous agents, carbamazepine, phenobarbital, phenytoin
Levetiracetam
None
None
None
None
Oxcarbazepine

Oral contraceptives

Phenobarbital
Valproic acid metabolites
Carbamazepine, corticosteroids, doxycycline, estradiol, griseofulvin, lamo
quinidine, theophylline, valproic acid, warfarin
Acetazolamide, chloramphenicol, CNS depressants, dextropropoxyphene,
MAOIs, valproic acid
Ammonium chloride, antacids, folic acid, pyridoxine, warfarin
Phenytoin
N-acetyl-P-benzo quinoneimine (NAPQI), oral anticoagulants, phenobarbit
Amiodarone, carbamazepine, cardioactive steroids, corticosteroids, cyclos

doxycycline, furosemide, haloperidol, influenza vaccine, levodopa, methad
contraceptives, phenothiazines, quinidine, theophylline, tiagabine, tolbuta
Allopurinol, amiodarone, chloramphenicol, chlorpheniramine, clarithromyci
disulfiram, ethosuxamide, felbamate, fluconazole, fluoxetine, fluvoxamine,
methylphenidate, metronidazole, miconazole, omeprazole, phenylbutazone
tolbutamide, tolazamide, topiramate, valproic acid, warfarin
Antacids, antineoplastics carbamazepine, calcium, diazepam, diazoxide, et
influenza vaccine, loxapine, nitrofurantoin, phenobarbital, phenylbutazone
sulfisoxazole, sulcrafate, theophylline, tolbutamide, valproic acid, vigaba
Tiagabine
Valproic acid

Carbamazepine, phenytoin
Topiramate
Phenytoin, digoxin
Oral contraceptives
None
Carbamazepine, phenytoin, valproic acid
Valproic acid
Felbamate, lamotrigine, phenobarbital, primidone
Carbamazepine, tiagabine
Cimetidine, felbamate, ranitidine
Antacids, carbamazepine, chlorpromazine, felbamate, INH, methotrexate,
primidone, salicylates
Vigabatrin
None known
Phenytoin
None
None
Zonisamide
?Phenytoin, ?carbamazepine
None
None

Phenytoin, carbamazepine, barbiturates
From references [1,5,8,53,79,102,118,144].

Increases Concentrations of	Decreases Concentrations of	Toxicity Enhanced by

TABLE 47-3. Anticonvulsant Drug interactions

The contribution of active metabolites to the toxicity of carbamazepine m receiving multiple anticonvulsants, especially combination therapy with VP clinical toxicity with carbamazepine concentrations within the therapeutic concentrations of the circulating carbamazepine-10,11-epoxide metabolite attributed to the additive inhibitory effects of VPA and lamotrigine on the Carbamazepine-10,11-epoxide concentrations in the 1â€“10 mg/L range carbamazepine/carbamazepine-epoxide ratio usually is > 1.7 and is appro monotherapy.[117]

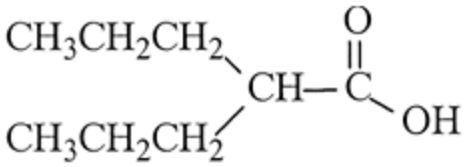
Oxcarbazepine is detected on the carbamazepine assay and concentrations

Management

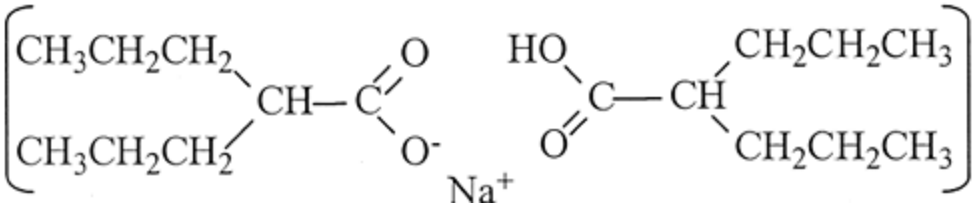
MDAC has a therapeutic role in the management of patients with carbama particularly helpful by reducing enterohepatic circulation.[109,154] Concreti suspected when serum concentrations rise or symptom occurrence is dela occurrence of QRS or QTc abnormalities is recommended. Although not f bicarbonate should be administered if the QRS duration exceeds 100 ms seizures usually respond to benzodiazepines.

Because carbamazepine is poorly water soluble, hemodialysis is relatively be associated with a 20% reduction in serum carbamazepine concentratio improvement.[49] Success with use of high-efficiency hemodialysis and ver reported.[7,136] It must be emphasized that MDAC remains as effective a less invasive, and is associated with comparable outcomes.[154]

Valproic Acid



Valproic acid



Divalproex Sodium

Valproic acid (di-*n* -propylacetic acid [VPA]), a simple branched-chain car of a broad spectrum of seizure disorders, ranging from simple and compl partial and myoclonic seizures. It is widely used as a mood stabilizer in t psychiatric illnesses, especially bipolar affective disorders for which it is a prophylaxis. VPA inhibits voltage-gated sodium channels and inhibits GAE

Pharmacokinetics, Toxicokinetics, and Pa

VPA is available in soft gelatin capsules, in syrup form, as enteric-coated in sprinkle capsules that can be added to food. An IV form is available. I tolerated.

VPA is almost 100% absorbed from the gastrointestinal tract. Peak concer hours, except for enteric-coated and probably extended release preparatio for up to 24 hours.[14 , 58] VPA is 90% protein bound at therapeutic conce decreases as the VPA concentration increases (Table 47-1).

VPA metabolism is complex. It is extensively metabolized (95%) by hepa using uridine diphosphate glucuronosyltransferase enzymes and Î²-oxidatio glucuronic acid and then oxidized in 1 of 2 ways: mitochondrial Î²-oxida

Nine different metabolites are isolated. The 3 Î²-oxidation metabolites are metabolites are quantitatively less important.[38] Mitochondrial Î²-oxidation VPA involves activation and linkage to coenzyme A (CoA) followed by tra in the mitochondrial matrix[87] (Figure 47-2 and Table 47-4).

VPA decreases carnitine stores through a number of different mechanisms excretion via formation of valproylcarnitine, which is renally excreted. S ATP-dependent carnitine transporter located on the plasma membrane. Th mitochondrial CoA. Mitochondrial CoA trapping (or depletion) decreases AT negatively affects the carnitine transporter.[121] Because of the reductions fatty acids arriving to the liver for metabolism

via Î²-oxidation cannot be transported effectively into the mitochondria ar cytoplasm. This process accounts for the development of fatty liver assoc

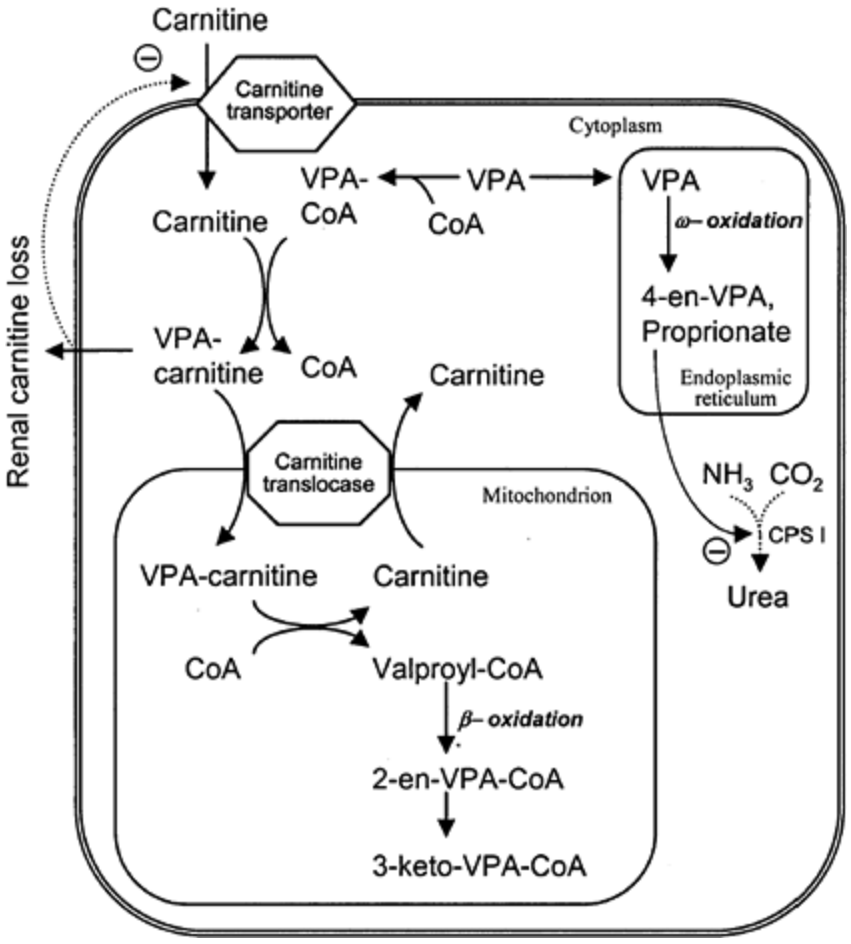


Figure 47-2. Valproic acid metabolism by the hepatocyte. Valproic acid, to coenzyme A (CoA) by acyltransferase I and subsequently transferred = carnitine) is shuttled into the mitochondrion where, after transfer back undergoes Î²-oxidation yielding several metabolites. These metabolites se the Î²-oxidation of other fatty acids. This process may lead to a Reyelike Alternatively, valproylcarnitine may diffuse from the cell and be renally el uptake of carnitine. In either case, the cellular depletion of carnitine shi microsomal Ï‰-oxidation. This pathway forms 4-en-valproate, a putative severe hepatotoxicity associated with valproic acid. Ï‰-Oxidation product carbamoylphosphate synthase I (CPS I), the initial step in the urea cycle

Carbamazepine

Diploplia, dizziness, sedation, headache, nausea, hyponatremia, hypocalc dysrhythmias

Agranulocytosis, aplastic anemia, hepatotoxicity, photosensitivity, Stevens syndrome, morbilliform rash, thrombocytopenia, pseudolymphoma, myoc hypersensitivity syndrome

Felbamate

Irritability, insomnia, anorexia, nausea, headache

Fulminant hepatic failure, pancreatitis, aplastic anemia, psychosis

Gabapentin

Sedation, dizziness, diplopia, ataxia sedation

Dystonic movements, asterixis

Lamotrigine

Dizziness, tremor, diplopia, ataxia, Sedation

Agranulocytosis, rashes, erythema multiforme, Stevens-Johnson syndrome anticonvulsant hypersensitivity syndrome

Levetiracetam

Dizziness, asthenia, sedation

Psychosis

Phenytoin

Anorexia, nausea, aggression, ataxia, cognitive impairment, depression, neonatal hemorrhage, gingival hypertrophy, coarse facies, acne, hirsutis osteomalacia, hypothyroidism, vitamin deficiencies, teratogenicity

Blood dyscrasias, lupus syndrome, reduced IgA, pseudolymphoma, peripl
intracranial hypertension, rashes, Stevens-Johnson syndrome, Dupuytren
teratogenicity, gingival hyperplasia, aplastic anemia, anticonvulsant hyp
Tiagabine
Dizziness, asthenia, tremor, diarrhea
Spontaneous ecchymoses
Topiramate
Sedation, dizziness, diplopia, metabolic acidosis, weight loss, paresthesi

Valproic acid
Anorexia, nausea, tremor, alopecia, peripheral edema, rashes, sedation,
Pancreatitis, hepatotoxicity, thrombocytopenia, hyperammonemia, encep
Vigabatrin
Sedation, weight gain, behavioral changes
Psychosis
Zonisamide
Sedation, ataxia

From references [1,5,8,53,57,60,61,66,79,102,118,126,130,144].

Predictable Idiosyncratic

TABLE 47-4. Adverse Events Associated with Anticonvulsants

Mitochondrial CoA is essential to the formation of *N*-acetylglutamate, an
synthetase I (CPS I). CPS I is the primary enzyme responsible for incorpo
cycle. In the absence of adequate mitochondrial CoA stores, CPS I activity
accumulates. Evidence indicates that CPS I is directly inhibited by VPA. I
effect of carnitine depletion and/or CPS I inhibition is suppression of hep
accumulation of ammonia.

Clinical Manifestations

Overdoses of VPA result in symptoms varying from lethargy to coma asso
Nystagmus, ataxia, and tremor typically do not occur. The neurotoxicity o

of acute overdose in patients chronically taking VPA.[67]

Metabolic complications following acute VPA overdoses include hypernatr acidosis, hypocarnitinemia, and hyperammonemia.[3 , 4 , 74] Metabolic acid overdoses and is a poor prognostic sign.[43 , 105] It results from accumulat carboxylic, and proprionic acids.[3 , 27 , 58 , 104 , 105 , 127]

Bone marrow suppression occurs 3â€“5 days following acute massive over by pancytopenia.[3 , 27 , 127] These hematopoietic disturbances usually reso days.

Pancreatitis, hepatotoxicity, and renal insufficiency are rare manifestations Chronic VPA therapy may lead to hepatotoxicity secondary to the aforem fatty acid metabolism rather than, as with other anticonvulsants, a hype findings may vary from asymptomatic elevation of aminotransferase conc Microvesicular steatosis, in which the hepatocyte cytoplasm contains large appearance on liver biopsy.[15 , 36]

Valproate-induced hyperammonemic encephalopathy (VHE) is characterized confusion or lethargy, focal or bilateral neurologic signs, and increased se accompanied by elevated VPA concentrations. The etiology is uncertain, b concentrations coupled with elevated concentrations of some of the more be responsible.[156]

Diagnostic Testing

Serum VPA concentrations should be obtained in all cases of VPA exposur obtained every 4â€“6 hours and closely monitored until a downward tren concentrations are 50â€“100 mg/L, although some clinicians use higher

All 9 VPA metabolites can be measured in the urine. The 4-en-VPA conce indicating excessive Ï‰-oxidation. The Î²-oxidation metabolite 2-en-VPA r inhibition of Î²-oxidation and/or carnitine depletion. Concentrations of th 1â€“3 days following acute ingestion, signaling the return to normal Î²-o

Electrolytes, blood gases, and serum lactate and serum ammonia concent patients. Hyperammonemia (> 80 Âµg/dL or > 35 Âµmol/L) occurs in 16 chronic VPA therapy.[29 , 111 , 156]

An inverse correlation exists between serum carnitine concentrations and patients receiving chronic VPA therapy.[111] Free serum carnitine concentra acylcarnitine/free carnitine ratio > 0.4 are indicative of carnitine deficien measurement of drug-induced hypocarnitinemia.

Management

Supportive management is sufficient to ensure complete recovery in most Discontinuation of all medications that likely affect VPA metabolism is als

MDAC reduces the half-life of VPA from a mean of 12 hours to 4.8 hours whom serum concentrations are continuously rising.[43] Although VPA is ex theoretically not amenable to MDAC, the percentage of bound VPA decrea 29%) as the concentration increases.[43]

In vitro studies suggest that naloxone has GABA antagonistic properties, endogenous opioid system, and may inhibit the effects of VPA on GABA r describe rapid resolution of CNS symptoms in VPA-overdosed patients fo naloxone.[2 , 142] These patients had minimally elevated VPA concentrations however, showed no effect in patients with much higher VPA concentratio experience does not support the routine use of naloxone for reversing VP not recommended.

Carnitine should be administered if evidence indicates the presence of hy hepatotoxicity.[32] The loading dose is 100 mg/kg IV over 30 minutes (max IV over 10â€“30 minutes every 4 hours until clinical improvement occurs

Hemodialysis and hemoperfusion increase VPA clearance but should be res rapid deterioration, evidence of hepatic dysfunction, apparent continued a VPA concentrations > 1000 mg/L.[58 , 104]

Gabapentin

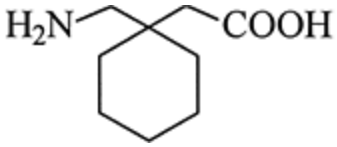


Figure. No Caption Available.

Gabapentin is a cyclohexane derivative of GABA approved as adjunctive t partial seizures with and without secondarily generalized seizures in adult postherpetic neuralgia. It is currently used as a treatment for posttraum disorders, mood disorders, bruxism, migraine prophylaxis, neuropathic pair neurologic disturbances.

Pharmacokinetics and Toxicokinetics

The bioavailability of gabapentin is approximately 60% in the therapeutic and easily crosses the bloodâ€“brain barrier. Dosage adjustments are nec renal function (creatinine clearance < 60 mL/min). It is not metabolized b function oxidase system[99] (Table 47-1).

Clinical Manifestations

Sedation, ataxia, movement disorders,[17 , 122] slurred speech, and gastro following acute gabapentin overdose.[45 , 76] In a case series of 20 patien lethargy, ataxia, and gastrointestinal symptoms developed in less than 5 hours.[76]

In 1 case report of chronic overdose in a patient with renal failure, trem were noted. The serum concentration was 85 mg/dL. Symptoms were sel dose adjustment.[155]

Catatonia following abrupt withdrawal of gabapentin is described.[129]

Diagnostic Testing

The preferred method for gabapentin analysis is high-pressure liquid chr concentration for seizure control is generally 2â€“15 mg/L, although the evolving. Because gabapentin is not appreciably protein bound, this rang

gabapentin.

Management

The treatment of patients with gabapentin overdose is largely supportive. to limit absorption. No specific antidote exists, but in 1 case report, an e dose of flumazenil, a benzodiazepine receptor antagonist devoid of GABA case report, flumazenil is not recommended for the management of gaba persistent neurologic symptoms must be admitted to the hospital. Hemod generally required, except in severely symptomatic patients with significa supportive care is sufficient in most instances.

Lamotrigine

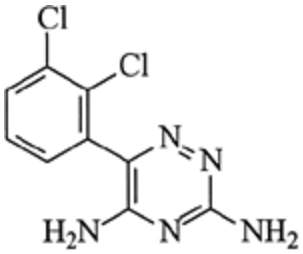


Figure. No Caption Available.

Lamotrigine is approved as an adjunctive medication for treatment of par patients. It also is approved for maintenance treatment of bipolar mood

Pharmacokinetics and Toxicokinetics

The bioavailability of lamotrigine is 98%. It is metabolized predominantly 2-*N* -glucuronide. The elimination half-life is approximately 25 hours but c phenytoin and carbamazepine, which can induce glucuronidation, and can because of competition with lamotrigine for the same step in the glucur reduced clearance of lamotrigine occurs in patients with Gilbert syndrome glucuronidation). Lamotrigine does not affect the cytochrome P450 system except when it is administered concomitantly with carbamazepine, when i of the carbamazepine epoxide metabolite.[53]

Clinical Manifestations

Neurologic manifestations such as lethargy, ataxia, nystagmus, and gast described following lamotrigine overdose. Coma, seizures, and cardiac co occur.[11,16,88,110] The 2-*N*-methyl metabolite of lamotrigine causes C

Chronic overdoses of lamotrigine result in multiorgan involvement, includ elevated hepatic aminotransferase and serum creatinine phosphokinase c findings represent AHS etiologically is unclear. All abnormalities resolved

Diagnostic Testing

Lamotrigine concentrations can be measured by high-performance liquid greater than 18 mg/L are potentially toxic.

Management

Activated charcoal should be administered. Supportive care and ECG mor Lamotrigine-induced seizures should be treated with benzodiazepines.[18] M hemodialysis and hemoperfusion are available.

Topiramate

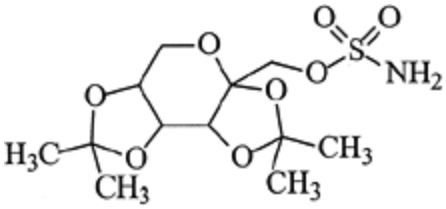


Figure. No Caption Available.

Topiramate is a sulfamate-substituted monosaccharide approved as adjunc partial-onset seizures. It also is approved for migraine prophylaxis, infant seizure disorders in infants and children. Although the precise mechanism blocks sodium channels, enhances the action of GABA, and diminishes the

receptor stimulation.[118] Topiramate's sulfamate moiety weakly inhibits ca the CA-II and CA-IV isoforms present in the kidney and CNS.[35 , 138]

Pharmacokinetics and Toxicokinetics

Topiramate is readily bioavailable. Only 20% of the dose is hepatically r hydrolysis, and glucuronidation; the remaining 80% of the drug is elimina plasma elimination half-life is long[68] (Table 47-1).

Clinical Manifestations

Lethargy, ataxia, nystagmus, myoclonus, coma, seizures, and status epil topiramate overdose.[25 , 44 , 141] Echolalia and repetitive mouthing are r metabolic acidosis resulting from inhibition of renal cortical CA may be pr serum chloride, as well as hypokalemia (2.0â€“3.2 mEq/L). Metabolic acid ingestion and can persist for days.[25 , 44 , 94 , 116 , 153]

Diagnostic Testing

Topiramate concentrations are performed by liquid or gas chromatograph between 4 and 30 mg/L. A death with a postmortem concentration of 170 chemistry and/or arterial blood gas analysis should evaluate for hyperch metabolic acidosis.

Management

Activated charcoal and supportive care are recommended. Severe hyperc be treated with sodium bicarbonate 1â€“2 mEq/kg intravenously. Howeve sodium bicarbonate may impair the anticonvulsive effect of topiramate.[25] topiramate can be significantly affected by hemodialysis, resulting in 4- t rates.[48] Hemodialysis is generally recommended in patients who overdose associated neurologic impairment, electrolyte abnormalities that have not therapy, or renal insufficiency.

Tiagabine

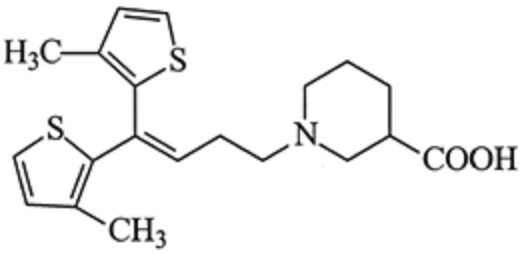


Figure. No Caption Available.

Tiagabine inhibits the presynaptic reuptake of GABA and is approved as a and secondarily generalized seizures. It is also being prescribed for a va

Pharmacokinetics and Toxicokinetics

Tiagabine is quickly and completely absorbed within 2â€“3 hours of inges easily crosses the bloodâ€“brain barrier.[69] It is metabolized by the CYP3 The elimination half-life is reduced by 50% in patients taking enzyme-in has no effect on the CYP450 system.[82 , 89]

Clinical Manifestations

Lethargy, facial myoclonus (grimacing), nystagmus, and posturing are des on tiagabine. Seizures and status epilepticus are reported at very high s previously healthy toddler developed 3 seizures after an unintentional ov tiagabine concentrations were 530 ng/mL.[72] A patient presented in status be noncompliant with therapy until a tiagabine concentration of 1870 ng/r overdose determined.[113] Stimulation of the presynatpic $GABA_B$ receptors the underlying mechanism for tiagabine-induced seizures.[124]

Symptoms generally persist for 12â€“24 hours, and permanent neurologic [, 72 , 113]

Diagnostic Testing

Tiagabine concentrations are performed by high-performance liquid chr Therapeutic tiagabine concentrations are 5â€“70 ng/mL.

Management

Activated charcoal and supportive care are recommended. Seizures respor benzodiazepines. Refractory status epilepticus should be treated with barbi hemodialysis and hemoperfusion are available.[20 , 72 , 113]

Levetiracetam

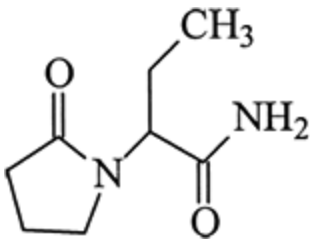


Figure. No Caption Available.

Levetiracetam is approved as an â€œadd-onâ€• medication for the mana mechanism of action remains incompletely understood, although it inhibit Research has illustrated both a neuroprotective and an antiinflammatory

Pharmacokinetics and Toxicokinetics

The bioavailability of levetiracetam approaches 100%. The major metabo hydrolysis. There are no active metabolites. Dosage adjustments are nec renal function (creatinine clearance < 60 mL/min).[119]

Clinical Manifestations

In 1 reported case of levetiracetam overdose, lethargy, coma, and respir Nystagmus was absent. Symptoms persisted for 24 hours.[9]

Diagnostic Testing

Levetiracetam concentrations can be assessed using gas chromatography 3â€“70 Âµg/mL.[119]

Management

Activated charcoal should be administered. Supportive care is recommende hemodialysis and hemoperfusion are available.

Other Anticonvulsants

Vigabatrin

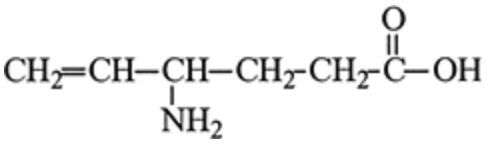


Figure. No Caption Available.

Vigabatrin, or vinyl GABA, is a stereospecific irreversible inhibitor of GA vigabatrin has a short elimination half-life, its duration of action is 24 hc necessary in patients with impaired renal function.[52] Agitation, coma, and after acute ingestion.[31 , 85]

Chronic toxicity may result in psychosis, dizziness and tremor, which usua as depression and psychosis.[85] Treatment of vigabatrin toxicity is largely best treated with IV benzodiazepines. Some cases of mild vigabatrin-indu withdrawal of the medication.[85]

Felbamate

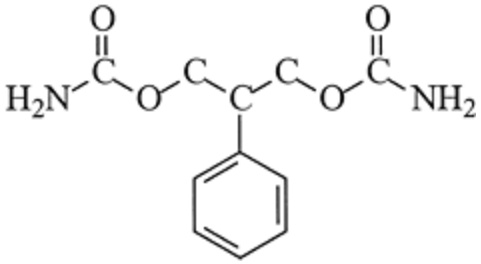


Figure. No Caption Available.

Felbamate is a phenyl dicarbamate derivative structurally similar to mepr adverse effects, including hepatic failure and aplastic anemia, it is a thera of seizures. It is absorbed quickly, and 50% of an ingested dose is excre Mild lethargy and gastrointestinal symptoms are reported following acute reversible renal failure following an acute overdose are reported.[123] Treat largely supportive.

Zonisamide

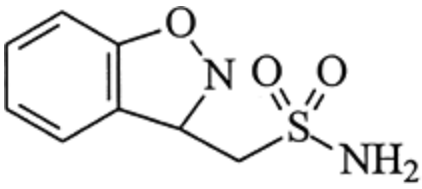


Figure. No Caption Available.

Zonisamide is structurally similar to other current anticonvulsants. It inh T-type calcium channels, and possibly CA. Somnolence is a commonly re experience with zonisamide is limited. In one case report, status epileptic attributed to zonisamide overdose despite a minimally elevated concentra 10â€“40 mg/L).[145]

Anticonvulsant Hypersensitivity Syndrome

Ill defined since it was first described in 1950, AHS is a disorder that occ 1000â€“10,000 exposures to anticonvulsants. AHS is traditionally associat anticonvulsants such as phenytoin, carbamazepine, phenobarbital, and pr the inclusion of the nonaromatic lamotrigine as a causative agent. The in regardless of gender and ethnic origin. Data suggest

a genetic defect in drug metabolism. First-degree relatives of patients with developing this syndrome.[78 , 157]

AHS occurs most frequently within the first 2 months of therapy and is nc concentration. The pathophysiology of AHS is related to accumulation res

detoxification by the enzyme epoxide hydrolase of arene oxide metabolite These reactive arene oxides bind to macromolecules and cause cellular ap form neoantigens that may trigger an immunologic response. Interestingly to cause other serious dermatologic reactions, such as Stevens-Johnson s necrolysis. The pathophysiology of lamotrigine-induced hypersensitivity sy unknown; only a small proportion undergoes CYP450 metabolism.[132 , 134

AHS is defined by a triad of fever, rash, and internal organ involvement. malaise, and pharyngitis (including tonsillitis). A skin eruption characteriz into a pruritic and confluent papular rash primarily involving the face, tru tender lymphadenopathy usually follows. Severely affected cases develop rash usually spares the mucous membranes. Multiorgan involvement usual syndrome. The liver is the most frequently affected organ, although invol cardiac muscle (myocarditis), lungs (pneumonitis), renal system (nephriti thyroiditis followed by hypothyroidism) are rare but possible. Liver distur aminotransferase concentrations to fulminant hepatic failure.[78 , 157

Leukocytosis is present and consists of a large number of atypical lymph biopsies reveal perivascular lymphocytic infiltration, spongiotic or lichenoi of edema.[157] Lymph node histology reveals benign hyperplasia, atypical l laboratory abnormalities include a positive rheumatoid factor, antinuclea DNA smooth muscle antibodies, cold agglutinin, and hypogammaglobinem novel, easy, fast, objective lymphocyte toxicity assay is being studied.[108

Prompt discontinuation of the offending agent is essential to prevent syr be admitted to the hospital and receive methylprednisolone 0.5â€“1 mg/k Other promising therapies include use of IV immunoglobulin.[97 , 133 , 157

In 1 case study, 90% of patients with AHS showed in vitro cross-reactivit anticonvulsant.[40] Based on this evidence, avoidance of phenytoin, carba primidone, lamotrigine, and potentially oxcarbazepine is recommended. topiramate, tiagabine, and levetiracetam are safer alternatives.[140]

Summary

All anticonvulsant drugs produce CNS symptoms when taken in overdose. findings is difficult. Lethargy, sedation, ataxia, and nystagmus occur follo

anticonvulsants. Coma occurs following substantial overdose of all anticc Seizures, including status epilepticus, may occur with carbamazepine, ph overdoses.

Hemodynamic instability and abnormal electrocardiograms are rare findi and possibly topiramate can cause QRS prolongation. Electrolyte abnorm with VPA and topiramate. Topiramate is uniquely associated with hyperc

Except for VPA overdoses, no specific antidotes exist for overdoses of a alone usually yields beneficial outcomes. Administration of activated char because of its safety and efficacy. Anticonvulsant-induced seizures are tr barbiturates. Patients with VPA overdoses in most cases should receive removal is rarely necessary and should be reserved for patients with sev topiramate overdoses and associated electrolyte abnormalities, hemodyna deterioration. Overdoses and toxicity associated with the newer anticonv so few data are available. However, most reported patients do not appea consequences.

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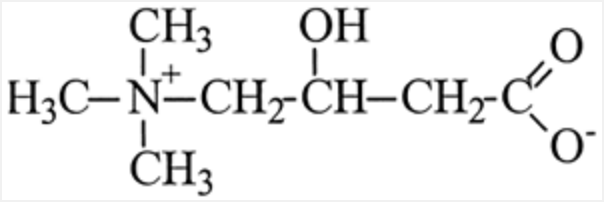
Antidotes in Depth

L-Carnitine

Mary Ann Howland



L-Carnitine

L-Carnitine (levocarnitine) [R-3-carboxy-2-hydroxy-*N,N,N*-trimethyl-1-propanaminium, inner salt or 3-hydroxy-4-(*N,N,N*-trimethylaminobutyrate] is an amino acid that is vital to

mitochondrial utilization of fatty acids. It is an orphan drug approved by the FDA for treatment of L-carnitine deficiency secondary to valproic acid toxicity, resulting from inborn errors of metabolism, associated with hemodialysis, and for zidovudine (AZT)-induced mitochondrial myopathy and pediatric cardiomyopathy.

L-Carnitine decreases valproic acid-induced hyperammonemia and limits valproic acid-induced hepatic toxicity. L-Carnitine should be administered IV to symptomatic patients to circumvent the low bioavailability from oral administration.

History

L-Carnitine is found in mammals, in many bacteria, and in very small amounts in most plants.[27] Carnitine was first discovered in 1905 in extracts of muscle, and its name is derived from *carnis*, the Latin word for flesh.[15] Over the next 25 years, its chemical formula and structure were identified, and in 1997 its enantiomeric properties were confirmed.[27] Carnitine was formerly known as vitamin BT.

Chemistry

Carnitine can exist as either the D or L form. Only the L isomer is found endogenously, is active, and should be used therapeutically. L-Carnitine ($C_7H_{15}NO_3$) has a molecular weight of 161 daltons. It is a water-soluble amino acid derivative that belongs to the same chemical family as choline. At physiologic pH, L-carnitine contains both a positively charged quaternary nitrogen ion and a negatively charged carboxylic acid group.[11]

Fatty acids provide 9 kcal/g and are an important source of energy for the body, especially for the liver, heart, and skeletal muscle. The utilization of fatty acids as an energy source requires L-carnitineâ€“mediated passage through both the outer and inner

mitochondrial membranes to reach the mitochondrial matrix where Î²-oxidation occurs (Figure 47-2). Enzymes in the outer and inner mitochondrial membranes (carnitine palmitoyltransferase and carnitine acylcarnitine translocase) catalyze the synthesis, translocation, and regeneration of L-carnitine.[23] Binding of L-carnitine to fatty acid occurs through esterification at the hydroxyl group on the chiral carbon.[11] The L-carnitine regenerated in the mitochondrial matrix is able to translocate in the opposite direction, from the matrix and through the inner membrane back to the space between the outer and inner membrane. The fatty acyl-coenzyme A (CoA) undergoes Î²-oxidation in the mitochondrial matrix, generating acetyl-CoA that then enters the citric acid cycle.

L-Carnitine Homeostasis

Approximately 54â€“87% of endogenous L-carnitine is derived from the diet; the remainder is synthesized.[27] Meat and dairy products are the primary dietary sources. Although most plants supply very little L-carnitine, avocado and fermented soy products are exceptionally rich in this amino acid. The remainder of the carnitine needed by the body is synthesized from trimethyllysine. This amino acid, found largely in skeletal muscle, is converted to trimethylammoniobutanoate (Î³-butyrobetaine) and then carried to the liver and kidney for hydroxylation to L-carnitine.[15] Synthesis of L-carnitine in the liver and kidney occurs at a rate of approximately 2 Âµmol/kg/d and is regulated by the amount of diet-derived trimethyllysine.[15,27] L-Carnitine is filtered by the kidneys, and tubular reabsorption keeps L-carnitine serum concentrations in the normal range.

Pharmacokinetics of Exogenous L-Carnitine

Our current understanding of L-carnitine pharmacokinetics is largely derived from three major studies.[7,14,31] L-Carnitine is not bound to plasma proteins. Vc (volume of distribution of the central compartment) is 0.15 L/kg, approximating extracellular fluid volume. Vd (volume of distribution) is 0.7 L/kg. Both vary depending on the compartment model analyzed. The $t_{1/2}$ Î± is 0.6â€“0.7 hours. The terminal elimination half-life averages 10â€“23 hours but may be 25â€–50% shorter. Baseline plasma values for L-carnitine are 40 Âµmol/L but increase to 1600 Âµmol/L following administration of 40 mg/kg of the amino acid intravenously (IV) over 10 minutes. Whereas 2 g of the amino acid administered IV produced a peak plasma concentration of 1000 Âµmol/L, oral administration of 2 g produced peaks of only 15â€“70 Âµmol/L. The time to peak concentrations following oral administration occurs at 2.5â€–7 hours, indicating slow uptake by intestinal mucosal cells. Oral absorption is already saturated following a 2-g dose, and no further absorption occurs after administration of 6 g. Following a radiolabeled dose, most L-carnitine is metabolized to trimethylamine *N*-oxide and butyrobetaine, with only approximately 4â€–8% remaining unchanged. The metabolites trimethylamine and trimethylamine *N*-oxide may accumulate after chronic high-dose oral therapy in patients with severely compromised renal function.[7] Fecal excretion of L-carnitine is < 1% of the total dose.

Carnitor (levocarnitine) tablets are bioequivalent to the Carnitor oral solution, with an absolute bioavailability of approximately

15%. After 4 days of dosing at 1980 mg (6 Ã— 330-mg tablets) twice per day or 2 g twice per day of the oral solution, the maximum plasma concentration was 80 Âµmol/L.

Valproic Acid and Hyperammonemia

Valproic acid can cause hyperammonemia (defined as plasma

ammonia concentration > 80 Âµg/dL or > 35 Âµmol/L) with or without symptoms and with or without hepatic dysfunction. Hyperammonemia and hepatic toxicity may occur either with therapeutic dosing or following an acute overdose. Approximately 35% of patients receiving valproic acid demonstrate hyperammonemia, often with corresponding reduced plasma L-carnitine concentrations.[6] In the absence of hepatic dysfunction, the postulated mechanisms for hyperammonemia are unclear but may result from interference with hepatic synthesis of urea or a small increase in ammonia production by the kidney.[18,33] Valproic acid induces both carnitine and acetyl-CoA deficiencies by combining with L-carnitine as valproylcarnitine and with acetyl CoA as valproyl-CoA. Ultimately, Î²-oxidation of all fatty acids is reduced, resulting in decreased energy production. Valproic acid stimulates glutaminase favoring glutamate uptake and ammonia release from the kidney. Reduced glutamate concentrations lead to impaired production of *N*-acetylglutamate (NAGA), a cofactor for carbamoyl phosphate synthetase I (CPS I), that is used in the liver to synthesize urea from ammonia.

In humans taking valproic acid, L-carnitine supplementation reduces ammonia concentrations.[1,,2,,4,,6,,13,,22,,24,,25] The exact time frame for normalization of ammonia concentrations is unknown, but a preliminary report suggests hastening of ammonia elimination with L-carnitine (3â€“15 h) compared to published controls (11â€“90 h).[30]

Valproic Acid and Hepatotoxicity

Valproic acid therapy is commonly associated with a transient dose-related asymptomatic rise in liver enzyme concentrations and a rare symptomatic, life-threatening, idiosyncratic Reyelike hepatotoxic syndrome.[3] Liver histology of the latter demonstrates microvesicular steatosis, similar to that described in hypoglycin-induced Jamaican vomiting sickness and Reye syndrome. This

occurrence presumably results from L-carnitine and acetyl-CoA deficiency, which inhibits mitochondrial Î²-oxidation of valproic acid and other fatty acids, causing them to accumulate in the hepatocyte.

Evidence for the benefit of L-carnitine treatment in improving survival from valproic acid-induced hepatotoxicity comes from the retrospective analysis of patients identified by the International Registry for Adverse Reactions to valproic acid.[5] When 50 patients with acute, symptomatic hepatic dysfunction who were not treated with L-carnitine were compared with 42 similar patients treated with L-carnitine, only 10% of the untreated patients but 48% of the L-carnitineâ€“treated patients survived.[5] Early diagnosis of patients, prompt discontinuance of valproic acid, and administration of IV rather than oral L-carnitine resulted in the greatest survival.[5] Most patients received 50â€“100 mg/kg/d L-carnitine, regardless of the route of administration.[5] Additionally, case reports and animal studies[29] offer both support[28,32] and lack of support for the beneficial effects of L-carnitine in the presence of valproic acid-induced hepatotoxicity.[17,21]

L-Carnitine Concentrations

In the plasma, 80% of L-carnitine is free, and the rest is acylated.[10] Normal plasma concentrations of free L-carnitine in omnivorous adults and children older than 1 year are 22â€“66 Âµmol/L and of total L-carnitine concentrations are 28â€“84 Âµmol/L. Vegetarians have L-carnitine concentrations 12% to 30% lower than omnivores.[26]

Numerous studies in patients taking valproic acid demonstrate decreases in both free and total plasma L-carnitine concentrations.[25]

Case studies demonstrate reduced plasma free L-carnitine concentrations and abnormal valproic acid metabolite profiles that

normalize with L-carnitine supplementation.[16,19,20] All of these data support the use of L-carnitine and provide a potential mechanism for its beneficial effects in valproic acid-induced hepatotoxicity.

Adverse Effects and Contraindications to L-Carnitine

L-Carnitine administration is well tolerated. Transient nausea and vomiting are the most common side effects reported, with diarrhea and a fishy body odor noted at higher doses.[7] Following chronic high doses of L-carnitine in patients with severely compromised renal function, the potentially toxic L-carnitine metabolites trimethylamine and methylamine *N*-oxide accumulate. The importance of this accumulation is unknown. Trimethylamine and its metabolite dimethylamine may contribute to cognitive abnormalities and the fishy odor.[9] In a pharmacokinetic study following intravenous administration of 6 g over 10 minutes, 2 of 6 subjects complained of transient visual blurring; 1 subject also complained of headache and light-headedness. The manufacturer of L-carnitine has received case reports of convulsive episodes following L-carnitine use by patients with or without a preexisting seizure disorder. This concern is currently included in the package insert. No reports of seizures related to L-carnitine can be found in the human literature. The only data suggesting carnitine-related seizures are found in a rat model.[12]

There are no known contraindications to the use of L-carnitine. However, only the L isomer and not the racemic mixture should be used because the DL mixture may interfere with mitochondrial utilization of L-carnitine. L-carnitine is considered pregnancy category B.

Overdose of L-carnitine

No cases of toxicity from overdose are reported, although large oral doses may cause diarrhea.[7] The LD_{50} in rats is 5.4 g/kg IV and 19.2 g/kg oral.[7]

Dosage and Administration

The optimal dosing of L-carnitine for valproic acid-induced hyperammonemia or hepatotoxicity is not established.

Recommendations for intravenous L-carnitine administration to patients with acute metabolic disorders resulting from L-carnitine deficiency range from 50â€“500 mg/kg/d.[7,8] A loading dose equal to the daily dose may be given initially, followed by the daily dose divided into every 4 hourly doses. The 500 mg/kg/d dose was intended for children[8] and did not list a maximum dose, although we

suggest a maximal daily dose of 6 g in addition to the loading dose. The oral dosing of L-carnitine usually is 50â€“100 mg/kg/d up to 3 g/d and should be reserved for patients who are not acutely ill.

For patients with end-stage renal disease undergoing hemodialysis, the package insert recommends an intravenous starting dose of 10â€“20 mg/kg dry body weight as a slow intravenous bolus over 2â€“3 minutes after completion of dialysis, followed by a dose adjustment according to L-carnitine trough (predialysis) plasma concentrations (normal 40â€“50 Âµmol/L).

For patients with an acute overdose of valproic acid and without hepatic enzyme abnormalities or symptomatic hyperammonemia, L-carnitine administration can be considered prophylactic, and enteral doses of 100 mg/kg/d divided every 6 hours up to 3 g/d is appropriate. For patients with valproic acid-induced symptomatic hepatotoxicity or symptomatic hyperammonemia, intravenous L-carnitine should be administered. We suggest a dose of 100 mg/kg

IV up to 6 g administered over 30 minutes as a loading dose, followed by 15 mg/kg every 4 hours administered over 10â€“30 minutes.

Availability

L-Carnitine is available as a sterile injection for intravenous use (Carnitor) in 1 g/5 mL single-dose vials. L-Carnitine is supplied without a preservative. Once the vial is opened, the unused portion should be discarded. Carnitor injection is compatible and stable when mixed with normal saline or lactated Ringer solution in concentrations as high as 8 mg/mL for as long as 24 hours.[7] L-Carnitine as Carnitor is also available as a 330-mg tablet and as an oral solution (with artificial cherry flavoring and methylparaben and propylparaben as preservatives) at a concentration of 100 mg/mL. The oral solution can be consumed without dilution, or it can be dissolved in other drinks to mask the taste. Slow consumption reduces gastrointestinal side effects.[7]

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Chapter 48
Antidiabetics and Hypoglycemics

George M. Bosse

MW
=
180 daltons
Normal fasting range (blood)
=
60â€“100 mg/dL
=
3.3â€“5.6 mmol/L

Glucose

An 80-year-old woman with a history of diabetes mellitus was found by family members to be unresponsive at home. Emergency medical services was called and recorded a rapid reagent glucose concentration of 39 mg/ She was given 50 mL of 50% dextrose intravenously, which resulted in ra improvement of mental status. She had a history of hypertension. Curren medications included metformin and atenolol. She denied using any other medications or ethanol, but she smoked cigarettes. Upon further questior in the emergency department (ED), she stated that she had not eaten mu

over the past several days and had â€œcoldâ€• symptoms of nonproduc cough. She denied having fever, shortness of breath, chest pain, nausea, vomiting, or diarrhea. Review of organ systems was negative.

Physical examination revealed: blood pressure, 120/67 mm Hg; pulse, 74 beats/min; respiratory rate, 26 breaths/min; temperature, 98.2Â°F (36.8Â°C). Initial pulse oximetry was 87% on room air. The patient was alert and oriented, with no focal neurologic deficits. The pupils were equa and reactive to light. Cardiopulmonary examination revealed bilateral rhonchi, expiratory wheezes, and a regular rate and rhythm without murmurs, rubs, or gallops. The abdomen was nontender to palpation.

The patient was admitted to the medicine service for monitoring and observation for recurrent hypoglycemia and for treatment of chronic obstructive pulmonary disease exacerbation. Further questioning of family members revealed that the patient was also taking glyburide. Intravenous access was maintained, her antidiabetic medications were withheld, and s was placed on a sliding-scale insulin regimen. During her hospitalization, had several episodes of altered mental status. Two episodes coincided wi rapid reagent glucose readings in the low 40 mg/dL range. Both episodes were treated with 50% dextrose intravenously. The patient was discharge to the care of her private physician 3 days later with an intact neurologic examination. Her respiratory status was improved, but she was instructed use home oxygen continuously at night and as needed during the day. At discharge, glyburide was restarted, but metformin was withheld.

Although various pharmacologic agents and medical conditions may cause hypoglycemia, this chapter focuses on the medications used for treatment diabetes mellitus. These medications include insulin and oral agents: the sulfonylureas, biguanides, Î±-glucosidase inhibitors, thiazolidinediones, a meglitinides. Some of the medications in these chemically heterogeneous groups of xenobiotics can cause unique toxic effects in addition to hypoglycemia.

Most patients with diabetes mellitus are classified as having either insulin dependent diabetes mellitus (IDDM), also known as type I diabetes, or nonâ€“insulin-dependent diabetes mellitus (NIDDM), also known as type

diabetes. This classification scheme for diabetes mellitus is not perfect. F example, some patients with type II diabetes may require insulin in addit to oral agents. Early in the course of type I diabetes, patients may enter remission period during which insulin is not required.

In diabetes mellitus, the body fails to maintain normal blood glucose concentrations. In general, neurohormonal control of glucose production healthy individuals maintains a fasting serum glucose concentration in the range from 60â€“100 mg/dL. The two glycemic complications of diabetes mellitus and its therapy are hyperglycemia and hypoglycemia.

History and Epidemiology

Insulin first became available for use in 1922 after Banting and colleague successfully treated diabetic patients with pancreatic extracts.[10] In an attempt to more closely simulate physiologic conditions, newer â€œdesignerâ€• insulins with unique kinetic properties

have been developed, including an ultrashort-acting preparation known a *lispro* .[62 , 125] Several oral delivery systems for insulin have been studied Development of a system for use in humans has not been successful beca of degradation of the oral form of insulin by digestive enzymes. Using zo occludens toxin, modulation of intestinal tight junctions in animal models has resulted in significant increases in enteral absorption of insulin.[38] An inhaled form of insulin has also been studied and appears promising.[24]

The hypoglycemic activity of a sulfonamide derivative used for typhoid fe was noted during World War II.[68] This discovery was verified later in animals. The sulfonylureas in use today are chemical modifications of tha original sulfonamide compound. In the mid-1960s, the first-generation sulfonylureas were widely used. Newer second-generation agents differ primarily in their potency.

Although insulin is widely used for treating diabetes mellitus, sulfonylurea exposures are much more commonly reported to poison centers than are insulin exposures, based on 15 years of data from 1989â€“2003 (Chap. 1

). These data likely reflect a significant percentage of intentional overdos cases. In a review of 1418 medication-related cases of hypoglycemia, sulfonylureas (especially the long-acting agents chlorpropamide and glyburide) alone or with a second agent accounted for the largest percentage of cases (63%).[115] Only 18 of the sulfonylurea cases in this series involved overdose with suicidal intent. Ethanol, propranolol, and salicylate, either alone or with another hypoglycemic drug, accounted for another 19% of cases of hypoglycemia. Quinine, quinidine, pentamidine, ritodrine, and disopyramide were the most common of the less frequently associated agents. Hypoglycemia is reported in as many as 20% of patien using sulfonylureas.[55] Besides sulfonylurea use, advanced age and fasting are identified major risk factors for hypoglycemia. Despite the lack of evidence reported in the literature, we speculate that insulin-induced hypoglycemia occurs frequently in settings other than volitional overdose

The biguanides metformin and phenformin were developed as derivatives *Galega officinalis* , the French lilac, recognized in medieval Europe as a treatment for diabetes mellitus.[7] Phenformin was used in the United Stat until 1977, when it was removed from the market because of its associat with life-threatening lactic acidosis (64 cases/100,000 patient-years). However, phenformin still is available outside the United States.[76] Travel and immigrants to the United States who continue to receive medication from their native countries may present with phenformin-induced lactic acidosis. Metformin became available in the United States in 1995. Its use also associated with lactic acidosis but to a much lesser degree than with phenformin (only 3 cases/100,000 patient-years).[28] Metformin-associated lactic acidosis is discussed in detail in Metformin-associated Lactic Acidos below.

Several newer agents for treatment of diabetes mellitus have been introduced. They include the Î±-glucosidase inhibitors acarbose and migl the thiazolidinedione derivatives troglitazone, rosiglitazone, and pioglitazone; and the meglitinides repaglinide and nateglinide. Developm of the Î±-glucosidase inhibitors began in the 1960s when an Î±-amylase inhibitor was isolated from wheat flour.[110] Acarbose was discovered more than 10 years later and approved for use in the United States in 1995.

Troglitazone and repaglinide were approved for use in the United States i 1997. The FDA subsequently directed the manufacturer of troglitazone to withdraw the product from the US market in 2000 because of associated liver toxicity.

Endocrine Disorders
- Addison disease
- Glucagon deficiency
- Panhypopituitarism (Sheehan syndrome)

Neoplasms
- Carcinomas (diverse extrapancreatic)
- Hematologic
- Insulinoma
- Mesenchymal
- Multiple endocrine adenopathy type 1 (Werner syndrome)

Reactive Hypoglycemia

Hepatic Disease
- Acute hepatic atrophy
- Alcoholism
- Cirrhosis
- Galactose or fructose intolerance
- Glycogen storage disease
- Neoplasia

Renal Disease
- Chronic hemodialysis
- Chronic renal insufficiency

Miscellaneous
- Acquired immunodeficiency syndrome (AIDS)
- Anorexia nervosa
- Autoimmune disorders
  - SLE
  - Rheumatoid arthritis
  - Graves disease
- Burns
- Diarrhea (childhood)

Leucine sensitivity
Muscular activity (excessive)
Postgastric surgery
Pregnancy
Protein calorie malnutrition
Septicemia
Shock

Exogenous

Ackee (hypoglycin)
Alloxan
Î²-Adrenergic antagonists
Disopyramide
Ethanol
Antidiabetics (insulin, sulfonylureas)
Pentamidine
Propoxyphene
Quinine
Quinidine
Ritodrine
Salicylates
Streptozocin
Sulfonamides
Vacor
Valproic acid

Artifactual

Chronic myelogenous leukemia
Polycythemia vera

TABLE 48-1. Causes of Hypoglycemia

Various xenobiotics other than the antidiabetic medications can cause hypoglycemia. Ethanol is a common cause of hypoglycemia and is discuss in depth in Chap. 75 . Other xenobiotics, including Î²-adrenergic antagon and salicylates, and a variety of medical conditions, such as sepsis and

insulin-secreting tumors, may cause hypoglycemia (Table 48-1). Certain plant xenobiotics may be implicated as well. Although not a particular problem in the United States, ingestion of the unripe fruit of the Ackee tr *Blighia sapida* , in countries where food is in short supply may result in significant hypoglycemia resulting from the compound hypoglycin contain in the unripe fruit.

Pharmacology

Insulin is synthesized as a prohormone in the Î²-islet cells of the pancrea Upon release, the prohormone is cleaved, resulting in release of both a C peptide and insulin itself, a double-chain molecule containing 51 amino a residues. Glucose concentration plays a major role in the regulation of insulin release.[102] Glucose is phosphorylated after transport into the Î²-i cell of the pancreas. Further metabolism of glucose-6-phosphate results i the formation of ATP. ATP inhibition of the K^+ channel results in cell depolarization, inward calcium flux, and insulin release. After release, ins binds to specific receptors on cell surfaces in insulin-sensitive

tissues, particularly the hepatocyte, myocyte, and fat cells. The action of insulin on these cells involves various phosphorylation and dephosphorylation reactions.

Figure 48-1 depicts the chemical structures of oral agents representing th major classes of antidiabetic and hypoglycemic agents. The sulfonylureas stimulate the Î² cells of the pancreas to release insulin; therefore, they a ineffective in type I diabetes mellitus resulting from islet cell destruction (Figure 48-2). This stimulatory effect diminishes with chronic therapy. A the sulfonylureas bind to high-affinity receptors on the pancreatic Î²-cell membrane, resulting in closure of K_{ATP} channels.[37 , 43 , 44] Inhibition of potassium ion efflux mimics the effect of naturally elevated intracellular A and results in insulin release. High-affinity sulfonylurea receptors also present within pancreatic Î² cells are postulated to be either located on granular membranes or part of a regulatory exocytosis kinase. Binding to these receptors promotes exocytosis by direct interaction with secretory

machinery not involving closure of the plasma membrane K_{ATP} channels.[3] [43, 44] Repaglinide is a new oral agent that is structurally different from t sulfonylureas. However, it also binds to ATP-sensitive potassium channels pancreatic Î² cells, resulting in increased insulin secretion.[83]

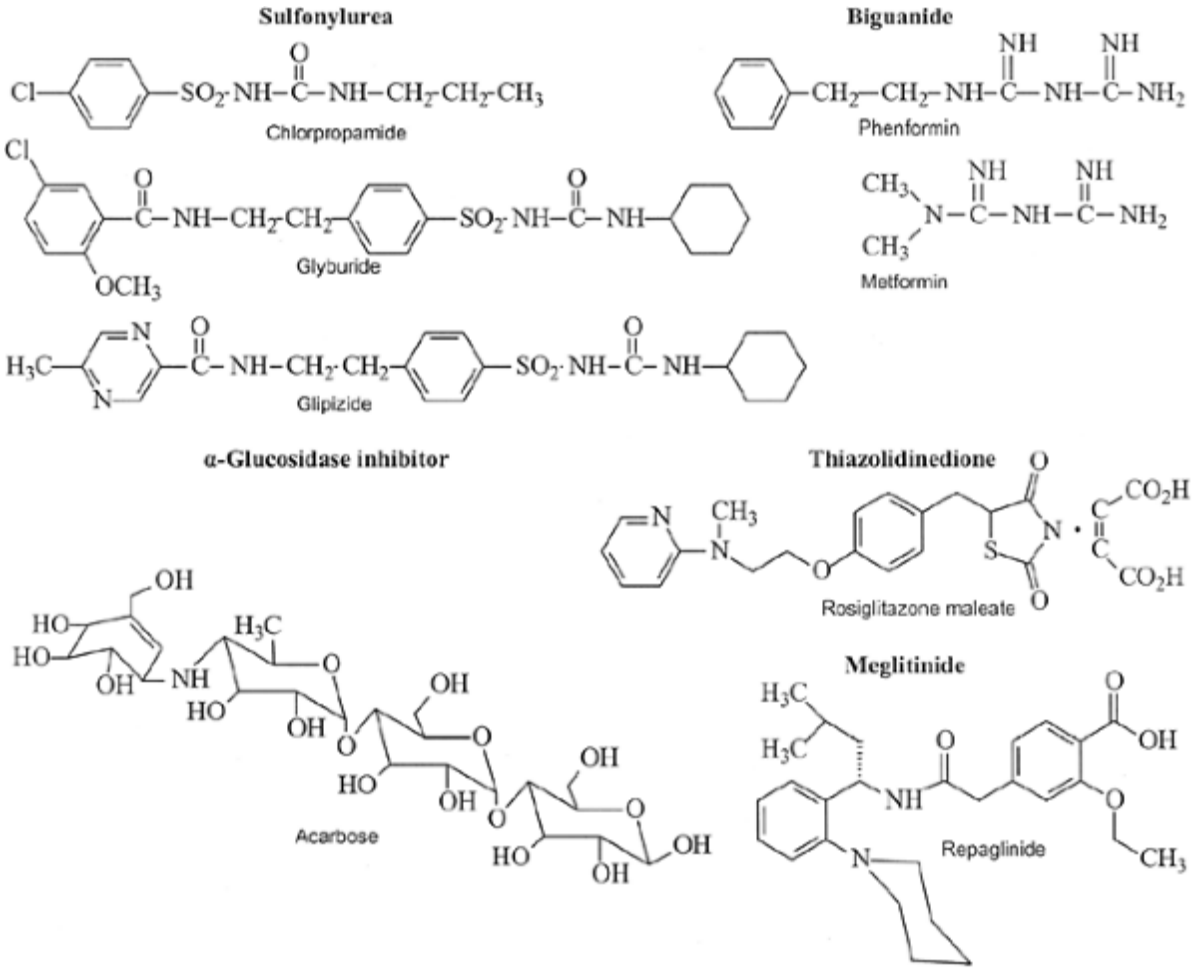

Figure 48-1. Chemical structures of representative oral antidiabetics and hypoglycemics.

The linkage of two guanidine molecules forms the biguanides. Metformin an oral compound approved for treatment of type II diabetes mellitus. Its glucose-stabilizing effect is caused by several mechanisms, the most important of which appears to involve inhibition of gluconeogenesis and subsequent decreased hepatic glucose output. Enhanced peripheral gluco uptake also plays a significant role in maintaining euglycemia. Metformin

ability to lower blood glucose concentrations also occurs as a result of decreased fatty acid oxidation and increased intestinal use of glucose.[8] In skeletal muscle and adipose cells, metformin causes enhanced activity and translocation of glucose transporters. Although the details are unclea the mechanism by which this process occurs involves an interaction betw metformin and tyrosine kinase on the intracellular portion of the insulin receptor. Figure 48-3 depicts the mechanism of action of metformin.

Insulin resistance in patients with type II diabetes mellitus may occur because of secretion of biologically defective insulin molecules, circulatin insulin antagonists, or target tissue defects in insulin action.[92] The thiazolidinedione derivatives decrease insulin resistance by potentiating insulin sensitivity in the liver, adipose tissue, and skeletal muscle. Uptake glucose into adipose tissue and skeletal muscle is enhanced, while hepati glucose production is reduced.[18, 54]

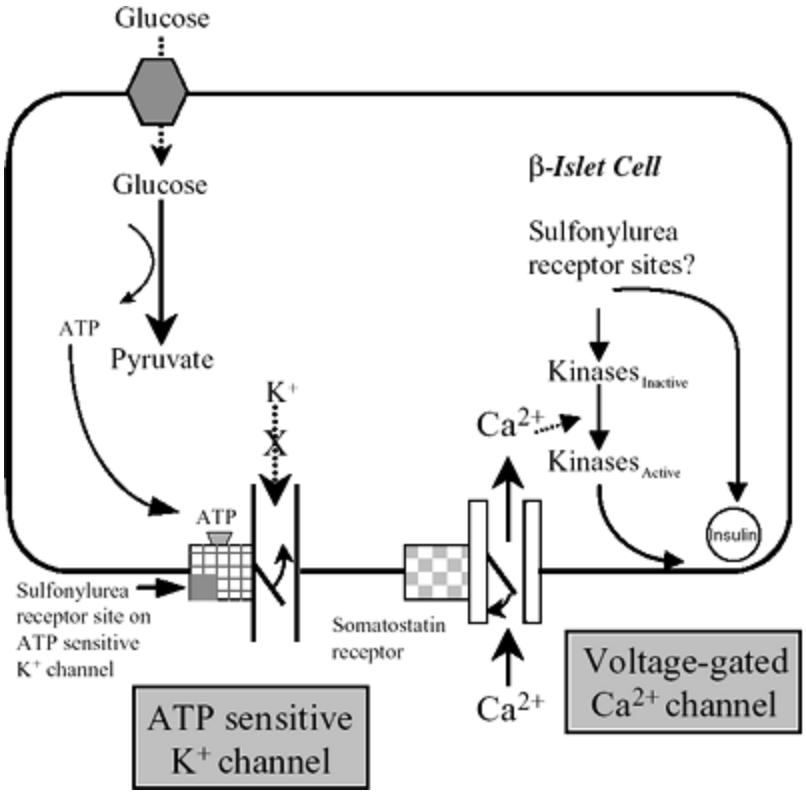

Figure 48-2. Under normal conditions, cells release insulin in response t elevation of intracellular ATP concentrations. Sulfonylureas potentiate the

effects of ATP at its â€œsensorâ€• on the ligand-gated K^+ channels and prevent efflux of K^+ . The subsequent rise in intracellular potential opens voltage-gated Ca^{2+} channels, which initiates a series of phosphorylation reactions culminating in fusion of the insulin-containing granule with the membrane and release of insulin. Release of insulin is also caused by binding of sulfonylureas to postulated receptor sites on regulatory exocytosis kinase and insulin granular membranes.

Acarbose and miglitol are oligosaccharides that inhibit Î±-glucosidase enzymes such as glucoamylase, sucrase, and maltase in the brush border the small intestine. As a result, postprandial elevations in blood glucose concentrations after carbohydrate ingestion are blunted.[134] Delayed gast emptying may be another mechanism for the antihyperglycemic effect of these oligosaccharides.[105]

Pharmacokinetics and Toxicokinetics

Pharmacokinetic parameters of the hypoglycemics are given in Tables 48- and 48-3 . Insulin is a peptide that is degraded in the gut and therefore i not active by the oral route. The onset and duration of action in therapeu doses varies considerably among preparations. Insulin overdose usually occurs after administration by the subcutaneous or intramuscular route. A might be predicted based on slow onset and prolonged duration of action some of the preparations, insulin overdose may result in delayed and prolonged hypoglycemia. However, hypoglycemia may also occur with sh acting forms because of some unusual toxicokinetic features. Some of th unpredicted responses may be caused by a depot effect following intramuscular or subcutaneous administration, and poor absorption may b further potentiated by the poor perfusion that can occur in hypoglycemia. [124] Further complicating the prediction of the clinical course is the delaye release of insulin from adipose tissue at the injection site(s). In diabetics the presence of insulin antibodies may explain a patient's recovery in spi of massive overdoses.[111] Because there is a finite number of insulin

receptors, insulin overdoses of varying extents probably are equivalent ir terms of the degree of hypoglycemia once receptor saturation occurs but in terms of its duration. A comparison can be made with the current treatment of diabetic ketoacidosis, in which lower doses of insulin are as effective as the higher doses used in the past.[61]

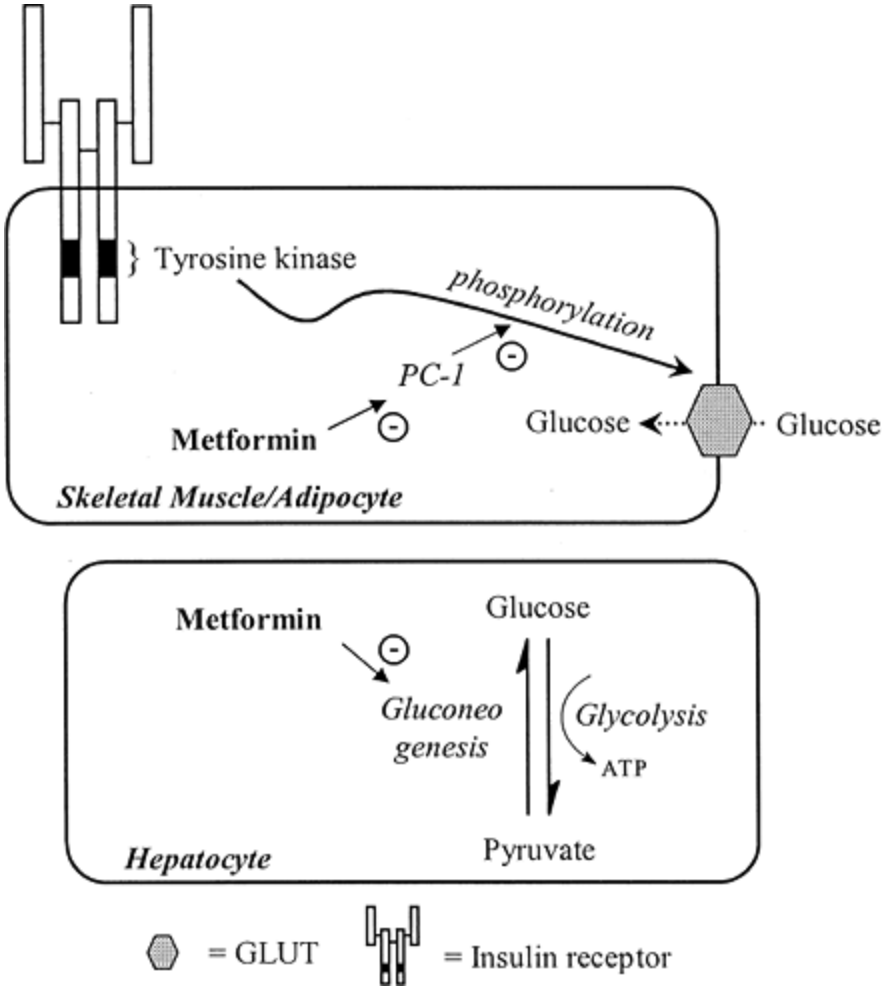

Figure 48-3. Under normal conditions, insulin binding to its receptor on myocytes and adipocytes activates tyrosine kinase, resulting in phosphorylation and activation of the membrane-bound glucose transport GLUT. Nonâ€“insulin-dependent diabetes mellitus is causally associated w an increased activity of PC-1, a glycoprotein that inhibits tyrosine kinase activity and thus reduces myocyte and adipocyte glucose uptake. Metforr reduces PC-1 activity in these cells, enhancing peripheral glucose utilizat In addition, gluconeogenesis in hepatic cells is reduced through interfere

with pyruvate carboxylase, the enzyme responsible for conversion of pyruvate to oxaloacetate.

Many of the sulfonylureas have a long duration of action, which may expl the unusually long period of hypoglycemia that can occur in both therape use and overdose. The first-generation sulfonylureas (acetohexamide, chlorpropamide, tolazamide, tolbutamide) reduce hepatic clearance of ins and produce active hepatic metabolites. These drugs are dependent on th effective urinary excretion to maintain euglycemia and prevent hypoglycemia.

Second-generation sulfonylureas (glimepiride, glipizide, glyburide) have half-lives that approach 24 hours and are characterized by substantial fe excretion of the parent drug. These agents frequently cause hypoglycemi (Table 48-2). Like insulin, the sulfonylureas may cause delayed onset of hypoglycemia following overdose.[94 , 103] The reason for the potential delayed onset of effects with sulfonylureas cannot be simply explained by known kinetic principles.

Metformin metabolism is negligible, and the majority of an absorbed dose excreted in the urine unchanged. Plasma protein binding also is negligible The kinetics of acarbose are notable for minimal systemic absorption and metabolism that occurs in the gut. As a result, serious systemic toxicity i not expected.[112] Adverse clinical effects usually are gastrointestinal. Repaglinide is a prandial glucose regulator with a short onset and short duration of action. These characteristics allow for flexible dosing in patie with irregular eating habits.[87] Despite its short half-life in therapeutic do overdose experience and toxicokinetic data for repaglinide are lacking. Whether after overdose hypoglycemia would be prolonged or delayed in onset is not clear.

I. Sulfonylureas

First generation

Acetohexamide (Dymelor)

12â€“18
Hydroxyhexamide (+++)
Hydroxyhexamide (65%)
Acetohexamide (2%)
Negligible
~1%
Chlorpropamide (Diabinese)
24â€“72
2-Hydroxychlorpropamide (+)
3-Hydroxychlorpropamide (+)
Chlorpropamide (20%)
2-Hydroxychlorpropamide (55%)
3-Hydroxychlorpropamide (2%)
Negligible
4â€“6%
Tolazamide (Tolinase)
16â€“24
Hydroxytolazamide (++)
Hydroxytolazamide (35%)
Tolazamide (7%)
Negligible
~1%
Tolbutamide (Orinase)
6â€“12
Hydroxytolbutamide (+)
Hydroxytolbutamide (30%)
Tolbutamide (2%)
Negligible
<1%
Second generation
Glimepiride (Amaryl)
24
Cyclohexylhydroxy ethyl derivative (++)
Cyclohexylhydroxy methyl derivative (63%)

15%
1â€“2%
Glipizide (Glucotrol, Glucotrol XL)
16â€“24
None
Glipizide (3%)
12%
2â€“4%
Glyburide (Micronase, Glynase, DiaBeta)
18â€“24
4-Hydroxyglyburide (++)
4-Hydroxyglyburide (36%)
Glyburide (3%)
50%
4â€“6%
II. Biguanides
Metformin (Glucophage, Glucophage XR)
Metformin/Glyburide (Glucovance)
Metformin/Rosiglitazone (Avandamet)
Metformin/Glipizide (Metaglip)
1.3â€“4.5
None
Metformin (90%)
Negligible
Rare (lactic acidosis 0.03 cases/1000 patient-years)
Phenformin
6â€“8
None
Phenformin (66%)
Negligible
Uncommon (lactic acidosis 0.64 cases/ 1000 patient-years)
III. Î±-Glucosidase Inhibitors
Acarbose (Precose)
2

None
4-Methyl pyrogallol derivative (<2%)
None
None
Miglitol (Glyset)
2
None
100%
None
None
IV. Thiazolidinedione Derivatives
Pioglitazone (Actos)
16â€“24
Hydroxy derivative
Keto derivative
?<15â€“30%
70%
None
Rosiglitazone (Avandia)
12â€“24
None
None
23%
None
V. Meglitinides
Nateglinide (Starlix)
2â€“4
Isoprene derivative (++)
Hydroxylation metabolites (+)
~16% as parent
10%
<1%
Repaglinide (Prandin)
1â€“3

None
None
90%
4â€“6%
+ = Weakly active; ++ = moderately active; +++ = more active than parent drug. The durations of action for the oral drugs are cited for therapeutic doses. These values increase for overdoses.

Drug	Duration of Action (h)	Active Hepatic Metabolite	Active Urinary Excretory Product (% of Dose)	Fecal Excretion (% of Dose)	Frequency o Severe Hypoglycem (Other Complicatior

TABLE 48-2. Characteristics of Orally Administered Hypoglycemic

Pathophysiology

With the possible exception of metformin, the thiazolidinediones, and acarbose, the other antidiabetics may all produce a nearly identical

clinical condition of hypoglycemia. The etiologies of hypoglycemia are divided into three general categories:[40] physiologic or pathophysiologic conditions (Table 48-1), direct effects of various hypoglycemic agents (Tables 48-2 and 48-3), and potentiation of hypoglycemics by interactio with other pharmacologic agents (Table 48-4).

Ultrashort-acting
Lispro
0.25â€“0.5
<5
0.5â€“2.5
Short-acting

Regular		
0.5â€“1	5â€“8	2.5â€“5
Insulin Aspart		
0.25	3â€“5	0.75â€“1.5
Intermediate-acting		
Lente		
1â€“3	18â€“24	6â€“14
NPH		
1â€“2	18â€“24	6â€“14
Long-acting		
Insulin Glargine		
1.1	24	2â€“20
Ultralente		
4â€“6	20â€“36	8â€“20

Insulin	Onset of Action (h)	Duration of Action (h)	Peak Glycemic Response (h)

TABLE 48-3. Characteristics of Routinely Used Forms of Insulin

Central nervous system (CNS) symptoms predominate in hypoglycemia because the brain relies almost entirely on glucose as an energy source.

adult brain can only use free fatty acids for ATP synthesis under aerobic conditions. However, during prolonged starvation, the brain can utilize ketones derived from free fatty acids. In contrast to the brain, other maj organs such as the heart, liver, and skeletal muscle often function during hypoglycemia because they can use various fuel sources, particularly free fatty acids.[117]

Emphasis on tighter diabetic control as a means of preventing microvascu effects carries with it an increased risk for hypoglycemia.[31, 32] Regulatio of glucose control to near-normal glucose concentrations, the characteris of each individual's awareness of hypoglycemia, and the individual counterregulatory mechanisms define the frequency and intensity of hypoglycemia.[116] The Diabetic Control and Complications Trial (DCCT) research group reported 62 episodes of blood glucose concentration < 50 mg/dL with CNS manifestations requiring assistance for every 100 patien years in patients undergoing an intensive insulin therapy regimen. This w in comparison to a conventional therapy group, which had 19 such episod per 100 patient-years.[31, 32] The intensive therapy group received â‰¥3 insulin injections per day or used a pump in an effort to achieve a glucos concentration as close to normal as possible, whereas the conventional therapy group received 1 or 2 daily insulin injections.

Angiotensin-converting enzyme (ACE) inhibitors
Allopurinol
Anabolic steroids
Î²-Adrenergic antagonists
Chloramphenicol
Clofibrate
Dicoumarol
Disopyramide
Ethanol
Fluoroquinolones
Haloperidol
Methotrexate
Monamine oxidase inhibitors

Para-aminobenzoic acid
Pentamidine
Phenylbutazone
Probenecid
Quinine
Salicylates
Sulfinpyrazone
Sulfonamide
Trimethoprim-sulfamethoxazole
See TABLE 48-1 for list of xenobiotics that cause hypoglycemia alone.

TABLE 48-4. Xenobiotics Known To React with Hypoglycemics Resulting in Hypoglycemia

The autonomic nervous system regulates glucagon and insulin secretion, glycogenolysis, lipolysis, and gluconeogenesis. Î²-Adrenergic antagonists affect all these mechanisms and can result in hypoglycemia. In the prese of chronic renal failure, Î²-adrenergic antagonist-induced hypoglycemia is particular risk[47] secondary to increased insulin half-life and reduced rena gluconeogenesis.[95] In addition, the clinical presentation of hypoglycemia may be muted when Î²-adrenergic antagonists are present because the expected autonomic responses of tachycardia, diaphoresis, and anxiety m not occur. Although this is assumed to be true, an adverse effect on hypoglycemic awareness could not be demonstrated in healthy volunteers given metoprolol, atenolol, and propranolol.[60]

The concept of hypoglycemia-associated autonomic failure in diabetes mellitus is well described.[29] Recent episodes of hypoglycemia result in autonomic failure by causing defective glucose counterregulation and hypoglycemic unawareness. As glucose concentrations fall, normal sensin mechanisms result in decreased insulin secretion and increased glucagon and epinephrine secretion. These counterregulatory defenses against hypoglycemia are defective in most people with type I diabetes mellitus a in many with type II diabetes mellitus.

Although various xenobiotics can cause hypoglycemia (Table 48-1), salicylates and ethanol are particularly notable for their unintended hypoglycemic effects. The mechanism of ethanol-induced hypoglycemia is discussed in Chap. 75 . Salicylate inhibition of prostaglandin synthesis in Î² cell of the pancreas is postulated to result in enhanced insulin secretion.[11] Salicylates may also cause hypoglycemia by poorly defined mechanisms that do not involve enhanced insulin secretion.

Besides decreasing glucose concentrations, the hypoglycemics can produce number of adverse effects, both in overdose and in therapeutic doses. The sulfonylureas, predominantly chlorpropamide, can cause a syndrome of inappropriate antidiuretic

hormone secretion.[57] Concomitant use of sulfonylureas and ethanol can cause a disulfiramâ€“ethanol reaction, as sulfonylureas inhibit aldehyde dehydrogenase.[100]

Clinical Manifestations

Hypoglycemia and its secondary effects on the CNS are the most common adverse effects related to insulin and the sulfonylureas. Clinical hypoglycemia is the failure to maintain a serum glucose concentration that prevents signs or symptoms of glucose deficiency. The glycemic threshold is the plasma glucose concentration below which clinical manifestations develop, a threshold that is host variable. In one study, the mean glycemic threshold for hypoglycemic symptoms was 78 mg/dL in poorly controlled diabetics compared to 53 mg/dL in nondiabetics.[16]

The presentations of patients with hypoglycemia are extremely variable. Hypoglycemia must be considered with any neuropsychiatric abnormality, whether persistent or transient, focal or generalized (Table 48-5). The cerebral cortex usually is most severely affected. Categorization of these findings are as follows:[99]

- Delirium with subdued, confused, or manic behavior.

- Coma with multifocal brainstem abnormalities, including posturing an respiratory abnormalities, with preservation of the oculocephalic (dol eyes), oculovestibular (cold-caloric), and pupillary responses.
- Focal neurologic deficits simulating a cerebrovascular accident (CVA) with or without the presence of coma. During a 12-month study perio 3 (2.4%) of 125 hypoglycemic patients presented with hemiplegia.[74] There are numerous reports[3, 120] and series[114, 133] of patients with focal neurologic deficits.
- Solitary or multiple seizures, with or without a significant postictal phase.

These neuropsychiatric symptoms usually are reversible if the hypoglycer is corrected promptly. The morbidity resulting from undiagnosed hypoglycemia is related partly to the etiology and partly to the duration a severity of the hypoglycemia. Because the etiologies of hypoglycemia encompass both severe diseases such as fulminant hepatic failure and benign problems such as a missed meal by an insulin-requiring diabetic, t literature with regard to outcome is confusing. Although a study of 125 E cases of symptomatic hypoglycemia reported an 11% mortality rate,[74] on 1 death (0.8%) was attributed directly to hypoglycemia. In that same stu 9 patients (7.2%) presented with seizures (focal in one case), 3 patients (2.4%) presented with hemiparesis, and 4 survivors (3.2%) suffered residual neurologic deficits. In 1 tertiary care medical center, 1.2% of all admitted patients had hypoglycemia (defined as a serum or plasma gluco concentration < 50 mg/dL). The overall mortality was 27% for this group 94 patients.[40] The longer and more profound the hypoglycemic episode, t more likely permanent CNS damage will occur.[6]

Tremor, shivering
Blurred vision
Tachycardia, palpitations
Dysesthesias, paresthesias
Diaphoresis
Inability to concentrate

Pallor	
Loss of coordination	
Piloerection	
Weakness	
Anxiety	
Somnolence, fatigue	
Hypertension	
Altered behavior pattern	
Headache	
Hypothermia	
Dry mouth	
Seizures	
Hunger	
Hemiplegia	
Nausea	
Coma	
Angina	
Death	

Caused by Catecholamine Release (Neurogenic, Autonomic)	Glucose Deprivation Caused by Cerebral (Neuroglycopenia)

TABLE 48-5. Manifestations of Hypoglycemia

No absolute criteria available from the physical examination or history distinguish one form of metabolic coma from another. Moreover, the find classically associated with hypoglycemia, such as tremor, sweating, tachycardia, confusion, coma, and seizures, frequently may not occur (Ta 48-5).[52] Patients may be unaware of hypoglycemia, particularly those w well-controlled IDDM. It appears that even in the presence of numerical hypoglycemia, diabetic individuals with near-normal glycosylated hemogl values maintain near-normal glucose uptake by the brain, thereby preserving cerebral metabolism and limiting the response of

counterregulatory hormones. The result of this limited response is unawareness of hypoglycemia.[15, 16] A threshold level likely is achieved below which the glucose concentration is inadequate, but this may be a l so close to that causing serious neuroglycopenia that patients have limite opportunity for corrective action.[15] Hypoglycemia unawareness is most li in diabetics with chronic exposure to hypoglycemics because of hypoglycemia-associated autonomic failure.[29] Acute ingestion of hypoglycemic agents in nondiabetics likely would cause classic signs and symptoms.

Hypoglycemia may not occur until 18 hours after lente insulin overdose[86] and may persist for up to 6 days after ultralente insulin overdose.[75] Deat after insulin overdose cannot be correlated directly with either the dose o preparation type. Some patients have died with doses estimated in the hundreds of units, whereas others have survived doses in the thousands units.[111] Mortality and morbidity may correlate better with delay in recognition of the problem, duration of symptoms, onset of therapy, and type of complications, as opposed to the absolute degree of hypoglycemia persistence of elevated insulin concentrations. A significant correlation exists between the amount of insulin injected and either the total amount dextrose used for treatment or the duration of dextrose infusion.[124] In th retrospective study of insulin overdose, 7 (41%) of 17 cases developed recurrent hypoglycemia between 5 and 39 hours after overdose despite o feeding and intravenous dextrose infusion ranging from 5â€“17 g dextros per hour.

In a retrospective review of 40 sulfonylurea overdose cases, the time fro ingestion to the onset of hypoglycemia, when known, was variable.[94] The longest delay was 21 hours after ingestion of glyburide and 48 hours afte ingestion of chlorpropamide. In a retrospective poison center review of 9 cases of sulfonylurea exposures in children, 25 patients (27%) developed hypoglycemia, with a time of onset ranging from 0.5â€“16 hours and a m of 4.3 hours.[103] In a prospective poison center study of sulfonylurea exposures in children, 56 (30%) of 185 patients developed hypoglycemia with a time of onset ranging from 1â€“21 hours and a mean of 5.3 hours. Single-tablet ingestions of chlorpropamide 250 mg, glipizide 5 mg, and

glyburide 2.5 mg can result in hypoglycemia in young children;[103] and th hypoglycemia may be delayed.[128]

Sinus tachycardia, atrial fibrillation, and ventricular premature contractio are the most common dysrhythmias associated with hypoglycemia.[67 , 91] outpouring of catecholamines, hypoglycemia itself, transient electrolyte abnormalities, and underlying heart disease appear to be the most likely etiologies. Based on their mechanisms of action, both insulin and the sulfonylureas are expected to promote the shift of potassium into cells, a hypokalemia after insulin overdose is well documented.[5 , 124] Other cardiovascular manifestations include angina and ischemia, which may be the sole manifestations of hypoglycemia.[36] Both are directly related to hypoglycemia.[13 , 98] Increased release of catecholamines during hypoglycemia increases myocardial oxygen demand and may decrease supply by causing coronary vasoconstriction at stenotic sites.

Hypothermia may occur in hypoglycemic patients.[41 , 59 , 126] If present, hypothermia usually is mild (90â€“95Â°F [32â€“35Â°C]), unless coexistir conditions such as environmental exposure, infection, head injury, or hypothyroidism are present. In a study comparing 2 groups of comatose stuporous patients, hypothermia was almost exclusively limited to the hypoglycemic patients; of these patients, 53% with demonstrated hypoglycemia showed hypothermia.[126] The central hypothalamic response hypoglycemia stimulated by the sympathetic nervous system may actuall â€œovershootâ€• normal temperatures, resulting in hyperthermia.[26]

Hypoglycemia is reported in 2 cases of metformin overdose.[130] In both cases, lactic acidosis was evident upon initial presentation. Hypoglycemia was present initially in one of the cases but did not develop until 7 hours later in the second case. Hypoglycemia is reported in a case of metformir associated lactic acidosis related to therapeutic use.[63] Insufficient evider supports the concept that metformin-associated hypoglycemia can develo in a patient who is not critically ill without lactic acidosis. Because many patients receiving metformin also take sulfonylureas, hypoglycemia shoul be anticipated after overdose. Phenformin ingestion alone rarely causes

hypoglycemia, both in overdose and with therapeutic use.[115]

The Î±-glucosidase inhibitors, thiazolidinediones, and meglitinides are ne agents for which overdose data are limited. Acarbose likely does not caus hypoglycemia based on its mechanism of action of inhibiting Î±-glucosida The most common adverse effects associated with its therapeutic use are gastrointestinal, including nausea, bloating, abdominal pain, flatulence, a diarrhea. Elevated aminotransferase concentrations were noted in clinical trials.[53] Most patients were asymptomatic, and the aminotransferase concentrations returned to normal after the drug was discontinued. In Sp the therapeutic use of acarbose in some cases reportedly led to hepatotoxicity that resolved after the drug was discontinued.[4 , 22] Althou hypoglycemia is unexpected after thiazolidinedione overdose, experience limited. The most serious adverse effect of troglitazone is the developme of liver toxicity with therapeutic doses, which in some cases was severe enough to require liver transplantation.[45 , 89] Liver toxicity related to therapeutic use of rosiglitazone[2 , 42] and pioglitazone is also reported.[73] Hypoglycemia should be anticipated after repaglinide and nateglinide ingestion.[83] A case of repaglinide-induced factitious hypoglycemia is reported.[51]

Diagnostic Testing

Suspicion of possible hypoglycemia is particularly important in the patien with an abnormal neurologic examination. The most frequent reasons for failure to diagnose hypoglycemia and mismanaging patients are the erroneous conclusions that the patient is not hypoglycemic but rather is psychotic, epileptic, experiencing a CVA, or intoxicated because of an â€œodor of alcoholâ€• on the breath (Chap. 75). Compounding the problem of misdiagnosis is the erroneous assumption that a single bolus 0.5â€“1 g/kg of dextrose 50% in water (D_{50} W) for an adult will always b sufficient.

Serum glucose concentrations are accurate, but treatment cannot be dela pending the results. Glucose reagent strip testing can be performed at th bedside. The sensitivity of these tests for detecting hypoglycemia is

excellent, but these tests are not perfect. In a comparison of reagent stri to serum glucose determinations, 87% of the reagent strips were within 0 mg/dL of the actual glucose concentration.[113] This determination was accurate for plasma glucose concentrations < 350 mg/dL. Remember that hypoglycemia is primarily a clinical and not a numerical disorder. Patients with poorly controlled diabetes in particular may become symptomatic at higher glucose concentrations than those without the disease.[16] The threshold reagent strip concentration that should be used as the basis for administration of hypertonic dextrose is debated, but based on the availa data[113] we suggest a cutoff of 90 mg/dL is appropriate. Note that toxic concentrations of acetaminophen and certain sugars (ex maltose) can produce false elevations of glucose concentrations noted by Glucometer I and Accu-Chek Advantage glucose meters.[23] Bedside glucose testing is discussed in more detail in Antidotes in Depth: Dextrose .

Several new glucose monitoring devices now are available. Alternate-site testing allows patients the convenience of using small amounts of blood obtained at sites other than the fingertip. Alternate-site testing results compare favorably with fingertip results when readings are obtained durir fasting and 2 hours postprandial, but not at 1 hour postprandial and immediately postexercise.[12] Continuous glucose monitoring devices also available. One such product is noninvasive and is worn like a wristwatch.[Another device requires the insertion of a subcutaneous sensor.[48] These monitoring systems appear to be useful for monitoring trends and detect unrecognized hypoglycemia, particularly at night. However, the delay in reporting results and the potential for error limit their use for rapid detection of hypoglycemia.

Diagnostic studies other than determinations of glucose concentrations m be indicated, depending on the clinical situation. In some instances, determination of serum ethanol concentration may be helpful in confirmir alcohol as a contributing or sole etiologic factor. Renal function tests may indicate the presence of renal impairment as a causative factor of hypoglycemia. This commonly occurs in diabetics taking insulin, who ofte develop renal failure after they have had the disease for several years. Insulin half-life increases as renal function declines. Measures of hepatic

function may be a clue to liver disease as a cause of hypoglycemia, altho liver disease may also be evident on physical examination. Seizures are commonly associated with hypoglycemia, but other studies, such as electrolytes, calcium, magnesium, and computed tomographic scanning o the brain, may be indicated if doubt about the etiology exists.

In the majority of overdose cases, laboratory testing for specific antidiabetics is not helpful. Exceptions might include malicious, surreptitious, or unintentional overdoses (discussed in the section on Evaluation of Malicious, Surreptitious, or Unintentional Overdose). Metformin concentrations in the setting of

overdose and metformin-associated lactic acidosis are variable and do no necessarily correlate with the clinical condition.[1 , 64 , 65]

Normal
< 6
< 0.2
< 5
â€”
Exogenous insulin
Very high
Low (suppressed)
Absent
Present[d]
Insulinoma
High
High
Present
Absent
Sulfonylurea ingestion[b]
High
High
Present
Absent

Autoimmune
Very high (artifact)
Low (or) high (artifact)
Present
Present
Decreased glucose production
Low
Low
Present
Absent
Neoplasia (nonâ€“Î²-cell)
Low
Low
Present
Absent

[a] Insulin levels are determined during fasting hypoglycemia at low concentrations, preferably <60 mg/dL of blood glucose.

[b] Sulfonylurea ingestion is diagnosed by detection of the drugs or their metabolites in plasma or urine.

[c] The antiinsulin antibodies produced spontaneously differ from those of treated (exposed to exogenous insulin) and those of untreated insulin-dependent diabetics.

[d] The presence of antiinsulin antibodies occurs less frequently in those exposed only to human insulin.

Clinical State	Insulin[a] (Plasma) (ÂµUnit/mL)	C-Peptide (Plasma) (nmol/L)	Proinsulin (pmol/L)	Antiinsuli Antibodies

TABLE 48-6. Laboratory Assessment of Fasting Hypoglycemia

For known diabetics in whom overdose is not suspected, the clinician mus search diligently for the cause of hypoglycemia. Sometimes it is as simple a missed meal or an unusually strenuous exercise routine, but in many ca

the cause is not so clear. Numerous medical conditions, as well as a varie of medications, may be involved (Table 48-1), and diagnostic testing mu be individualized episode depending on the clinical suspicion. Diagnosing etiology as â€œidiopathicâ€• is never acceptable.

Evaluation of Malicious, Surreptitious, or Unintentional Overdose

The physical examination may provide helpful clues to the evaluation of a suspected malicious, surreptitious, or unintentional insulin overdose. A meticulous search may reveal a site that is erythematous, hemorrhagic, atypically boggy in nature, or even painful if the subcutaneous (or intramuscular) injection of insulin was particularly large. Even a simple unexplained needle puncture mark in the appropriate clinical setting may suggest insulin injection.

An understanding of how the Î² cells of the pancreas secrete insulin in response to glucose concentrations in the blood is essential to understan the investigation of fasting hypoglycemia.[30] When the plasma glucose concentration is < 45 mg/dL, insulin secretion should be almost complete suppressed, so plasma insulin concentrations should be minimal or absent.[101] Moreover, insulin is secreted as proinsulin, which is cleaved in vivo to form insulin (a double-stranded peptide) and C-peptide, which are released into the blood in equimolar quantities. Insulin is biologically act whereas proinsulin has limited activity, and C-peptide has no activity. Although insulin is normally cleared during hepatic transit, C-peptide is n For this reason, C-peptide can be utilized as a quantitative marker of endogenous insulin secretion. Commercially available exogenous human insulin does not contain C-peptide fragments (Table 48-6). When plasma glucose concentration falls to hypoglycemic concentrations (usually < 60 mg/dL), insulin secretion should fall to less then 6 ÂµUnit/mL. If hypoglycemia is caused by exogenous insulin administration, plasma C-peptide concentrations should be < 0.2 nmol/L in the presence of insulin concentrations that are substantially higher than insulin concentrations resulting from an insulinoma. With insulinoma, insulin concentrations

generally are > 6 ÂµUnit/mL in the presence of hypoglycemia. Insulinoma results in elevations of both C-peptide and insulin concentrations. Sulfonylurea overdose is expected to have similar effects, but concentrat in reported cases of sulfonylurea-induced hypoglycemia vary considerably and can be within normal ranges.[34] In the face of uncertainty, sulfonylur concentrations are readily available from reference laboratories. Animal insulin can be distinguished from human insulin by high-performance liqu chromatography.[46] However, this technique has limited use because of th virtually exclusive use of human insulin at present.

In summary, patients with chronic insulin-induced factitious or surreptitio hypoglycemia will have high insulin concentrations, the presence of insuli binding antibodies,[39] and low C-peptide concentrations. Those who have taken sulfonylureas will have high insulin concentrations, absent insulin-binding antibodies, high C-peptide concentrations, and presence of urinar sulfonylurea metabolites (Table 48-6). The issues of evidence collection that are appropriate to document malicious or surreptitious use of insulin successfully have been described[71] (Chap. 135).

Management

Treatment centers on the correction of hypoglycemia and the anticipation that hypoglycemia may recur. Symptomatic patients with hypoglycemia require immediate treatment with 0.5â€“1 g/kg concentrated intravenous dextrose in the form of D_{50} W in adults, D_{25} W in children, and D_{10} W in neonates. Occasionally, patients require a larger dose to achieve an initia response. If hypoglycemia is suspected but not confirmed, as in the abse of rapid reagent strip availability or when such readings are â€œborderline,â€• dextrose should be administered. Theoretical risks ar associated with use of concentrated dextrose in the setting of cerebral ischemia, but failure to rapidly correct hypoglycemia may lead to deleter neurologic effects. Appropriate emergency and toxicologic uses of hypert dextrose are covered in detail in Antidotes in Depth: Dextrose . When concentrated dextrose is administered with potential nutritional deprivati a dose of 100 mg thiamine hydrochloride also should be given in view of

substantial association between hypoglycemia, alcoholism, and malnutriti Correction of thiamine deficiency prevents development of Wernicke-Korsakoff syndrome.

The kinetics of intravenous administration of 25 g D_{50} W have been studi in healthy euglycemic nondiabetic volunteers,[9] limiting

extrapolation to the clinical setting. At 5 minutes postinjection, glucose concentrations rise rapidly to a mean of 244 mg/dL and return to baseline 30 minutes. No mechanism reliably extrapolates back to pre-D_{50} W concentrations.

Glucagon should not be considered as an antihypoglycemic agent except the uncommon situation where intravenous access cannot be obtained. Glucagon has a delay to onset of action and may be ineffective in patient with depleted glycogen stores, as in the elderly, cancer patients, or alcoholics. Glucagon also stimulates insulin release from the pancreas, w may lead to prolonged hypoglycemia in settings such as sulfonylurea ingestion and insulinoma.[131]

Numerous articles have evaluated approaches for treating insulin reactior with carbohydrates in tablet, solution, or gel forms in a well-defined diab population.[118] None of these forms is appropriate for the undefined, poss hypoglycemic patient. Patients who have significant clinical symptoms of hypoglycemia are at risk for grave CNS complications unless they are treated quickly and adequately with glucose.

A common occurrence involves symptomatic hypoglycemic patients who receive intravenous dextrose in the prehospital setting and subsequently refuse transport to the hospital. The authors of a retrospective review of 571 paramedic runs involving hypoglycemic patients concluded that out-c hospital treatment of hypoglycemic diabetic patients is safe and effective even when transport is refused.[119] However, of the 159 patients who agr to hospital transport, 40% were admitted. The authors of a prospective study involving 132 hypoglycemic diabetic patients who refused transport after therapy concluded that most such patients have good short-term outcome, but they still encouraged transport because of the risk of recur

hypoglycemia.[82] One patient died in each of these 2 studies. A prospectiv study in 35 patients with 38 hypoglycemic events related to insulin use concluded that most patients were successfully treated.[69] Study participa were treated in the field and not transported to a healthcare facility. However, 2 patients developed recurrent hypoglycemia that they treated themselves, and 1 of these patients required placement in a long-term ca facility for hypoglycemic encephalopathy. We emphatically encourage the further education of paramedics and restructuring of their protocols, emphasizing the importance of transporting all hypoglycemic patients to EDs.

Emesis, lavage, and catharsis are of limited benefit in the management o patients who overdose on oral antidiabetic and hypoglycemic agents. The extensive affinity between chlorpropamide, tolazamide, tolbutamide, glyburide, glipizide, and activated charcoal is demonstrated in vitro.[58] Th affinities ranged from 0.45â€“0.52 g/g activated charcoal at pH 7.5 and were higher at pH 4.9. Single-dose activated charcoal should be beneficia the management of these overdoses. Although affinity studies are lacking the other oral agents, their chemical characteristics are such that single-dose activated charcoal is expected to be beneficial for these overdoses a well. Multiple-dose activated charcoal and whole-bowel irrigation may be benefit and should be considered after overdose of modified-release oral agents.

In patients who overdose on insulin, case reports describe the use of surgical excision of the injection site.[21 , 70 , 79] However, this technique not been studied in a systematic fashion, so further data are necessary before this approach can be recommended. Needle aspiration of a depot is less invasive and should be considered.

Urinary alkalinization to a pH of 7â€“8 can reduce the half-life of chlorpropamide from 49 hours to approximately 13 hours. Urinary alkalinization is not useful for other oral antidiabetics.[90]

Maintaining Euglycemia After Initial Contro

After the patient is awake and alert, further therapy depends on the xenobiotic involved and pancreatic islet cell function. Some patients, particularly those with prolonged hypoglycemia, may have persistent alte mental status despite euglycemia. Whether the event was unintentional o intentional with suicidal or homicidal intent must be determined. One problem associated with dextrose administration occurs in individuals who can produce insulin via glucose-stimulated insulin release (nondiabetics a those with type II diabetes mellitus), placing them at substantial risk for recurrent hypoglycemia. This complication can occur with insulin overdos but is particularly problematic with overdoses of sulfonylurea or meglitini because these oral agents stimulate insulin release. Treatment with hypertonic dextrose solutions can be expected to result in dramatic yet o transient increases in glucose concentrations, with a subsequent fall in serum glucose concentration possibly back to hypoglycemic levels.

For diabetic patients who unintentionally inject an excessive amount of insulin, feeding should be initiated and intravenous access maintained wh avoiding routine dextrose infusion. In the event of recurrent hypoglycemi a concentrated dextrose bolus should be used. Overdose in the setting of suicidal or homicidal intent likely involves significant quantities of insulin Nondiabetics may be particularly prone to significant hypoglycemia becau they lack insulin resistance. Feeding should be initiated and glucose concentrations maintained in the 100â€“150 mg/dL range using a concentrated dextrose infusion (D_{10} W).

Some patients may require even more concentrated dextrose infusions, s as 20% dextrose in water (D_{20} W) augmented by repeated doses of D_{50} W Central venous lines should be used when D_{20} W infusion is instituted, because concentrated dextrose solutions are substantial venous irritants. The presence of glycosuria is not an adequate indicator of euglycemia; frequent serial blood glucose or reagent strip glucose concentrations sho be obtained. The appropriate timing of glucose monitoring varies depend on the clinical situation. Mental status must be observed. As a rough guid glucose monitoring every 1â€“2 hours after initial control is reasonable, subsequent spacing of the intervals to once every 4â€“6 hours. Phosphat concentrations should be monitored because glucose loading may lead to

hypophosphatemia.[84] Potassium concentrations should be checked becau glucose administration may lead to hypokalemia in nondiabetics and hyperkalemia in patients with impaired insulin secretion.[27] The duration o sampling necessary depends on the stability of the patient, the underlyin metabolic disorders, the extent of overdose, and the rate of improvemen When the patient begins to eat an adequate diet and the initial hypoglyce is controlled, the serum glucose concentration will rise, and the concentration and rate of infusion can be tapered. Many patients may actually develop significant hyperglycemia.

The therapeutic approach differs for patients who overdose on sulfonylur or meglitinides. After initial control of hypoglycemia with concentrated dextrose, the patient should

be fed. Intravenous access is necessary, but routine dextrose infusion should be avoided. As with insulin overdose, frequent monitoring of gluco concentrations and mental status is critical. We recommend early use of octreotide in this setting because of the significant risk of glucose-stimulated insulin release.

Octreotide, a semisynthetic long-acting analog of somatostatin with an intravenous half-life of 72 minutes, inhibits glucose-stimulated Î²-cell ins release via receptors coupled to G proteins on Î²-islet cells.[14] Somatostat is present in diverse tissues such as the hypothalamus, pancreas, and GI tract. It alters the secretion of growth hormone and thyroid-stimulating hormone, gastrointestinal secretions, and the endocrine pancreas (glucag and insulin).[106 , 107] Octreotide was compared to intravenous hypertonic dextrose and to diazoxide and concomitant dextrose in normal subjects brought to hypoglycemia using glipizide.[14] Fewer episodes of recurrent hypoglycemia occurred after octreotide therapy, and overall dextrose requirements were lower than in the dextrose-alone and dextrose-plus-diazoxide groups. Several successful clinical experiences with octreotide reported with quinine-induced hypoglycemia resulting from malaria therapy,[97] insulinoma,[50] nesidioblastosis of infancy,[33] hypoglycemia rela to therapeutic use of gliclazide,[17] and tolbutamide overdose.[14] In a retrospective study of 9 patients with hypoglycemia resulting from either

glyburide or glipizide, octreotide effectively reduced the risk of recurrent hypoglycemia.[80]

Octreotide appears to be relatively free of serious side effects. The most likely adverse effects are injection-site discomfort if the agent is administered subcutaneously and gastrointestinal symptoms such as naus bloating, diarrhea, and constipation.[72] The suggested adult octreotide do is 50 Âµg subcutaneously every 6 hours (Antidotes in Depth: Octreotide) Like octreotide, diazoxide may be effective in patients with refractory sulfonylurea-induced hypoglycemia.[56 , 94] However, because of its potent to cause hypotension, diazoxide should be considered only if octreotide is ineffective or unavailable.

Admitting Patients to the Hospital

The decision to admit a patient may be complex, but several guidelines c be followed. Admission is required for hypoglycemia related to ethanol, starvation, hepatic failure, and renal failure and for hypoglycemia of unknown etiology. Patients receiving therapeutic doses of insulin require inpatient evaluation of recurrent and unexplained hypoglycemic episodes. patients with hypoglycemia after unintentional overdose with long-acting insulin should be admitted. Hospitalization is recommended after unintentional overdose with ultrashort-acting, short-acting, or intermedia acting insulin if hypoglycemia is persistent or recurrent during a 4- to 6- observation period in the ED. Many factors may be responsible for unintentional insulin overdose, such as patient error because of impaired vision, syringe structure, and prescription error, and hospital admission r be warranted. Admission is indicated for any patient, regardless of serum glucose concentration or presence or absence of symptoms, who intentionally overdoses on a sulfonylurea or any form of insulin, because delayed, profound, and protracted hypoglycemia may result. Although ins overdose by the intravenous route is expected to result in more immedia symptoms, experience with this scenario is limited. Admission in this sett is advised unless short-acting insulin is involved. Admission is not routine indicated for patients taking therapeutic doses of insulin who become

hypoglycemic after a missed meal. Hypoglycemia related to sulfonylurea in any setting requires hospitalization.[19]

Patients with possible self-induced factitious hypoglycemia should be admitted. â€œFactitiousâ€• (intentionally self-induced) hypoglycemia is most commonly recognized by members of the medical profession. Administration of insulin to a nondiabetic child is a form of child abuse or attempt at homicide.[35] Children who have been given an inappropriate do of insulin, as well as any patient who may be a victim of attempted homicide, should be admitted.

A 4- to 6-hour observation period is recommended after metformin overdose. Further observation or hospital admission is not required for patients who remain asymptomatic during this period with no evidence of metabolic acidosis or hypoglycemia. Patients who overdose on acarbose a not expected to have delayed or serious systemic toxicity, and routine medical admission is unnecessary. Although hypoglycemia is unlikely afte thiazolidinedione overdose, experience cases is limited and admission is recommended. Significant hypoglycemia is reported with repaglinide used a factitious setting.[51] Repaglinide is a new agent that is expected to beha like a sulfonylurea. For this reason alone, hospital admission after repaglinide overdose is advisable, even when the patient is asymptomatic

Children who unintentionally ingested one or more sulfonylurea tablets should be admitted. Although this recommendation may be controversial some authors suggest shorter observation periods[20] or even home monitoring in some cases,[108] we believe that delayed effects of sulfonylu ingestion in children are well documented in the literature[103 , 121 , 128] a convincing enough to support admission in all cases. Asymptomatic childr with single-tablet exposures to sulfonylureas are perhaps best managed without prophylactic intravenous glucose, which could contribute to delay onset of hypoglycemia.[20] Such patients instead are best managed by earl feeding, frequent checks of glucose concentrations, and observation of mental status.

Metformin-Associated Lactic Acidosis

The biguanides are uniquely associated with the occurrence of lactic acidosis. Phenformin causes lactic acid production by several mechanisms interference with cellular aerobic metabolism and subsequent enhanced anaerobic metabolism. Phenformin suppresses hepatic gluconeogenesis fr pyruvate and causes a decrease in hepatocellular pH, resulting in decreas lactate consumption and hepatic lactate uptake. Metformin-associated lac acidosis occurs 20 times less commonly than that occurring with phenfor In isolated perfused rat liver, metformin inhibits both hepatic lactate upt and conversion of lactate to glucose.[104] Lactic acidosis related to metfor usually occurs in the presence of an underlying condition, particularly ren impairment.[25 , 63] In this setting, increased tissue burden of metformin, which is renally eliminated, probably occurs. Other risk factors include cardiorespiratory insufficiency, septicemia, liver disease, history of lactic acidosis, advanced age, alcohol abuse, and use of radiologic contrast media.[8 , 25] Iodinated contrast material may induce acute renal failure, leading to accumulation of metformin and subsequent risk for developme of lactic acidosis. However, the risk of developing lactic acidosis after contrast administration is low in patients taking

metformin who have normal renal function and no other risk factors.[78 , 8

Severe lactic acidosis occurs after metformin overdose[65 , 81 , 93 , 130] but appears to be uncommon. In 1 case,[81] lactic acidosis was not diagnosed until 14 hours after metformin overdose. The patient had early symptoms repeated vomiting at 1 hour postingestion. In a series of 13 metformin overdose cases reported to a French pharmaceutical company, 7 patients presented with lactic acidosis.[65] The 13 cases were selected based on the overdose history and for whom arterial pH, arterial lactate, and metformi plasma concentrations were obtained. The authors do not document the number of overdose cases not included in the study. In a larger poison center series of 65 adult cases of metformin overdose, 2 patients develop significant lactic acidosis, 1 of whom died.[122] One patient developed disseminated intravascular coagulation, and hypoglycemia occurred in 7 patients with concomitant insulin or sulfonylurea overdose. The remaining cases were described as having minimal toxicity. In a poison center series

55 children exposed to metformin, lactic acidosis was not reported, and n significant adverse effects were noted.[123] The doses ingested ranged fron 250 mg to 16.5 g, with a median of 500 mg.

A systematic review from the Cochrane Library concluded that therapeuti use of metformin is not associated with an increased risk of lactic acidosi compared with other antidiabetic treatments if no contraindications are present.[109] This conclusion was based on a review of prospective comparative trials and observational cohort studies. However, the risk of metformin-associated lactic acidosis in the setting of overdose setting or renal insufficiency was not assessed. Although lactic acidosis after overdo is not common, it does occur with sufficient frequency to require vigilanc on the part of the treating physician. Case reports were not used in the Cochrane review, and a few cases of metformin-associated lactic acidosis the setting of therapeutic use with no underlying risk factors are reported , 96 , 132

Metformin-associated lactic acidosis is a potentially lethal condition. Recognition and awareness of this disorder are important. Symptoms may nonspecific and include abdominal pain, nausea, vomiting, malaise, myal and dizziness. However, gastrointestinal symptoms are common adverse effects associated with therapeutic use of metformin and do not necessar require discontinuation of the drug. More severe clinical manifestations o metformin-associated lactic acidosis include confusion, mental status depression, hypothermia, respiratory insufficiency, and hypotension. Plas metformin concentrations can be obtained as a diagnostic aid but may no correlate with the clinical state in both the acute overdose setting and in setting of therapeutic metformin use. In a series of 13 cases with metfor overdose, 6 of 7 patients with lactic acidosis had elevated metformin concentrations.[65] Of the 6 patients without lactic acidosis, 3 had markedl elevated metformin concentrations. In a series of cases of lactic acidosis related to therapeutic use, 10 of 14 patients had elevated metformin plas concentrations.[64]

Aggressive airway management and vasopressor therapy may be required Indications for use of intravenous sodium bicarbonate in critically ill patie

with lactic acidosis of various etiologies are poorly defined and controver Rather than using an arterial pH cutoff, we recommend using sodium bicarbonate given evidence of impaired buffering capacity based on a ser bicarbonate concentration of < 5 mEq/L. Based on case reports, hemodialysis using a sodium bicarbonate buffer may be effective in improving acidâ€“base status and clinical outcome in patients with significant lactic acidosis.[49 , 63 , 66] In some of these cases, metformin concentrations were measured and remained abnormally high after dialys Clinical improvement despite inadequate removal of metformin may be related to correction of acidâ€“base status.

Summary

Numerous xenobiotics and medical conditions may cause hypoglycemia. Hypoglycemia is the predominant adverse effect related to therapeutic us and overdose of the drugs used for treatment of diabetes mellitus. Variou clinical manifestations, particularly neurologic, may occur and can be confused with conditions such as ethanol intoxication, psychosis, epilepsy and cerebrovascular accidents. The potential for delayed and prolonged hypoglycemia must be recognized in overdose situations. Although severa treatment options exist, rapid intravenous administration of glucose is th most important measure. Octreotide is useful for patients with refractory hypoglycemia following sulfonylurea or meglitinide overdose.

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Antidotes in Depth

Dextrose

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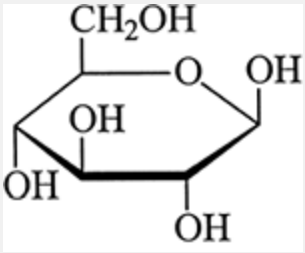

Dextrose (D-glucose)

Adenosine triphosphate (ATP) furnishes the metabolic energy that fuels critical cellular processes in all organs. In the adult human

brain, anaerobic and aerobic metabolism of glucose through glycolysis and the tricarboxylic acid cycle, respectively, are the primary sources of ATP (Chap. 48). Whereas the adult brain can utilize fatty acids, amino acids, and ketones as alternate substrates for ATP synthesis under aerobic conditions, glucose is the only substrate for ATP production in the brain of the fetus or neonate.[77,95] The onset of hypoglycemia is followed rapidly by cerebral dysfunction. Hypoglycemia causes neurologic effects that are clinically indistinguishable from those of a variety of toxic-metabolic and structural brain injuries, which can include focal stroke syndromes, seizures, confusion, delirium, and coma.[5,23,31,53,67,81,98,104] Hypoglycemia precipitates myocardial stress and is associated with angina, electrocardiographic changes, and dysrhythmias.[32,57,66,68,69] In most cases, these effects reverse following treatment of hypoglycemia. However, prolonged or severe hypoglycemia may result in permanent brain injury, myocardial infarction, and death.[33,84]

Administration of 0.5â€“1 g/kg concentrated intravenous dextrose immediately reverses the clinical effects of uncomplicated hypoglycemia if the duration of hypoglycemia is brief (Table A11-1). Because of the myriad presentations of hypoglycemia, the difficulties inherent in making the clinical diagnosis, and the serious consequences of failure to treat the condition, the empirical administration of hypertonic dextrose to all patients with altered mental status was a standard emergency department practice.[13,43,44] Previously only clinically insignificant or rare complications were attributed to this practice. The complications were readily accepted when contrasted with the risks of delayed recognition and treatment of hypoglycemia. For example, intravenous administration of dextrose causes hypophosphatemia that is clinically insignificant in healthy individuals.[3,48,63,76] Dextrose infusion may precipitate hyperkalemia in diabetic patients with type IV renal tubular acidosis.[3,38] Concern that the osmotic effects of hypertonic dextrose could precipitate pulmonary

edema in critically ill patients with fragile cardiac function has been expressed.[51] Rarely, administration of hypertonic dextrose is associated with lactic acidosis in cancer patients with large tumor burdens.[39] Concentrated dextrose solutions commonly cause phlebitis and sclerosis of veins; tissue necrosis follows soft-tissue infiltration of $D_{50}W$.[29] Tissue infarction follows inadvertent intraarterial injection of $D_{50}W$.[6] Inappropriately large boluses of $D_{50}W$ in children are associated with seizures, hyperosmolar coma, and death. Seizures and subdural hemorrhage followed administration of 100 mL hypertonic dextrose to a 20-kg child, whereas administration of 280 mL $D_{50}W$ to a 15-kg child resulted in death.[83] Anecdotal reports of precipitation of acute Wernicke encephalopathy by administration of dextrose led to the concomitant administration of thiamine as part of the â€œcoma cocktailâ€•[44] (Antidotes in Depth: Thiamine Hydrochloride). The most serious complications of administration of hypertonic dextrose are caused by medication errors, such as inadvertent substitution of a look-alike bolus of concentrated lidocaine or magnesium.[45]

Concerns Regarding Elevated Blood Glucose Concentrations in Patients with Cerebral Ischemia

An expanding body of clinical literature demonstrates that the presence of hyperglycemia upon admission is associated with poorer outcomes in patients with acute cerebrovascular accidents.[13,28,34,47,71,74,100] Complications include increased rates of hemorrhagic conversion,[14] larger infarction volumes,[9,20,34] higher incidence of cerebral edema,[90] and increased mortality.[15,20] In two studies, the magnitudes of blood glucose concentration elevation that persisted after an acute stroke were positively correlated with larger infarction volumes as measured by MRI, poor functional outcome, and increased death rate.[9,20]

The largest study to date is a retrospective evaluation of data from 624 patients reported in the National Institute of Neurological Disorders and Stroke (NINDS) study of thrombolysis in acute stroke. The study confirmed a strong association of hyperglycemia upon admission with a worse outcome in thrombotic stroke. The effect of admission blood glucose concentration on the outcome of acute stroke was closely related to the magnitude of blood pressure upon admission. The likelihood of a favorable outcome decreased with increased blood glucose and blood pressure upon admission. Hyperglycemic patients also had an increased risk for subsequent intracranial hemorrhage, whether or not they received thrombolytic therapy.[14] As in similar studies, examination of these data could not prove a cause-and-effect relationship between hyperglycemia and a poorer outcome in stroke.[14] A conundrum has been created by the difficulty of demonstrating a clear delineation of the primary effect of hyperglycemia on the ischemic brain from hyperglycemia that accompanies an intense sympathetic â€œstressâ€• response to severe brain injury. In the latter case, hyperglycemia may be an epiphenomenon related to more extensive or severe injury rather than a cause of injury.[20,70,105] A study supporting the contention that hyperglycemia is an independent predictor of increased infarction severity relied on the inability to measure elevated catecholamines in stroke patients with hyperglycemia.[94] In addition, no study has demonstrated that hyperglycemia is not simply a marker of increased cerebrovascular disease in diabetics.[14,74] In the NINDS study, 72% of patients with admission blood glucose concentrations > 200 mg/dL were known diabetics. Because hemoglobin A_{Ic} concentrations were not measured, the possibility

that other patients in this category had previously undiagnosed diabetes cannot be excluded.[14] A prospective randomized controlled study evaluating the effect of glycemic control on outcomes in stroke has not been performed, thus precluding an

assumption of a cause-and-effect relationship between hyperglycemia and increased brain injury. This situation is being evaluated in the Glucose Insulin in Stroke Trial (GIST).[79]

TABLE A-11-1. Dosing of Dextrose

Bolus	
Adult	
$D_{50}W$ (50% = 0.5 g/mL)	0.5â€“1.0-g/kg bolus
Child	
$D_{25}W$ (25% = 0.25 g/mL); 1:1 dilution of $D_{50}W$ with sterile water	0.5-g/kg bolus
Infant	
$D_{10}W$ (10% = 0.1 g/mL); 1:4 dilution of $D_{50}W$ with sterile water	0.5-g/kg bolus
Infusion	
Adults and Children	
$D_{10}W$ (10% = 0.1	Titrate Infusion as indicated

g/mL) D_5W (5% = 0.05 g/mL)	to maintain serum glucose in normal range

A deleterious effect of hyperglycemia appears to be independent of the presence of diabetes mellitus in some diabetic animal models. Whether the data on the adverse vascular effects of diabetes in animal models are comparable to those in humans is not clear.[48,97,99,101]

Clinical studies of global ischemia in patients with cardiac arrest demonstrate that admission hyperglycemia is a poor prognostic indicator. In 430 prehospital patients resuscitated from cardiac arrest, 276 patients who awakened had significantly lower blood glucose concentrations than 154 patients who did not (mean 262 mg/dL vs. 341 mg/dL, $p = 0.0005$). In 90 awake patients with persistent neurologic deficits, mean blood glucose concentration was 286 mg/dL compared with 250 mg/dL in patients who recovered fully ($p = 0.02$).[62] A poor prognosis is also demonstrated in head trauma patients with admission hyperglycemia.[35,54,107]

The cellular biochemical changes that occur in the setting of ischemia are extensively investigated. Global ischemia is associated with rapid depletion of brain glucose, ATP, and phosphocreatine, followed by a rapid rise in intracellular lactic acid, disruption of energy-dependent electrolyte gradients, increased intracellular calcium, activation of phospholipase, and generation of destructive free radicals.[7,48,87,88,91,97,100,102] Many researchers propose intracellular accumulation of lactic acid is a primary cause of cellular injury,[4,48,77,87,89,97,100] but this proposal is debated. A study suggests that lactate is a useful energy substrate in the reperfusion period and implicates corticosterone in the deleterious effects.[78] Other investigators have demonstrated postsynaptic glutamate (*N*-methyl-D-aspartate [NMDA]) receptor activation in the setting of hyperglycemia, which

is associated with programmed cell death in other models.[11,58,60] This debate likely will continue.

Hyperglycemia is associated with increased capillary permeability in ischemic tissue and delays in resolution of intracellular calcium elevation during recovery from ischemia.[7,30] Significant increases in neutrophil deposition are demonstrated in areas of focal brain injury associated with hyperglycemia, suggesting a role in injury production.[61] Hyperglycemia may interfere with membrane repair systems by suppressing the synthesis of â€œheat shockâ€• proteins in injured cells.[21,102] Administration of insulin to control hyperglycemia has been shown to decrease the extent of ischemic injury.[25,27,42,59,99,100] Because insulin promotes the synthesis of â€œheat shockâ€• protein in ischemic cells, it may have a protective effect that is independent of its effect on blood glucose.[93,96]

Controlled laboratory investigations of ischemic brain injury consistently demonstrate that higher blood glucose concentrations are associated with more extensive cerebral injury. Most of these studies consisted of animal models of global cerebral ischemia that used cardiac arrest or four-vessel ligation or models of focal ischemia that used one- or two-vessel ligation.[72] These studies showed deleterious effects of hyperglycemia on a variety of outcome end points, such as death, evidence of cerebral edema, and neurologic recovery.[22,25,26,37,46,55,75,85,86] The most severe injuries are evident when ischemia is incomplete or focal so that a small amount of blood flow is present, as when collateral circulation is present near an area of focal infarction.[24,49,73] Hyperglycemia, however, has not been shown to be detrimental in fetal and neonatal animal models of anoxia.[16,95] Hypoglycemia was associated with worse outcomes in all models in which it was studied.[25,49,86]

Physical Examination in Hypoglycemia

Neither the history nor the physical examination reliably detects patients who are hypoglycemic.[43,44] Symptoms of tachycardia, diaphoresis, pallor, hypertension, tremors, hunger, and restlessness tend to predominate when the decline in blood glucose concentration is rapid. However, the symptoms can be blunted by Î²-adrenergic antagonists. Central nervous system symptoms of glycopenia include headaches, visual disturbances, psychiatric disturbances, confusion, stupor, coma, seizures, and focal neurologic findings and are nonspecific.[65,81,82] In pediatric patients, the only symptom of neuroglycopenia may be lethargy or irritability.[106]

Clinical Implications of Studies of Hyperglycemia and Cerebral Ischemia

The clinical and laboratory studies have led to calls for reassessment of the standard practice of routine inclusion of $D_{50}W$ in the cocktail antidote for patients with altered mental status.[13,43] Although clinical studies do not prove that hyperglycemia is more than a stress-related epiphenomenon or a marker for diabetes-related cerebrovascular insufficiency, an overview of both clinical and laboratory studies offers a preponderance of evidence that hyperglycemia likely has an independent role in the extent of brain injury induced by ischemia. A thoughtful assessment recognizes the possible detriment of raising blood glucose concentrations in a patient whose altered mental status or focal neurologic symptoms are caused by ischemia. This must be weighed against the risk of failure to treat hypoglycemia and the potential resultant permanent neurologic injury. Without question the reversal of hypoglycemia is a sound clinical intervention in the patient who is hypoglycemic, and the failure to administer dextrose in a timely fashion to a patient with significant hypoglycemia can result in permanent neurologic injury. This dilemma remains particularly consequential in the

prehospital setting where reliable testing of blood glucose concentration is limited.

The new guidelines for management of patients with stroke recommend the avoidance of glucose-containing fluids and advocate for aggressive control of hyperglycemia while still avoiding hypoglycemia.[1,41]

Reliability of Bedside Blood Glucose Determinations

The bedside diagnosis of hypoglycemia is limited by the lack of availability of reagent strips that have the same reliability and accuracy of the chemistry laboratory. Sensitivities of commonly available reagent strips for detection of hypoglycemia range between 92% and 97% in various studies.[17,18,19,50,56,64,80] The accuracy of these tests is affected by the source of blood, whether venous or capillary,[8,36,52,92] and by the presence of shock.[8,92] Accuracy also can be altered by the hematocrit[10] and the presence of isopropyl alcohol in the sample.[40] A study of 66 critically ill newborns that defined critical hypoglycemia as < 30 mg/dL found a sensitivity of 100% for the detection of hypoglycemia for each of two different reagent strips.[64] False-positive capillary determinations of hypoglycemia have been demonstrated in patients in shock and cardiac arrest. A study of capillary samples in 50 patients with cardiac arrest identified 8 patients as hypoglycemic. The laboratory evaluations confirmed that 3 of these patients were hypoglycemic and that no results were false-negative. Reagent strip testing of venous blood correctly classified these 8 patients.[92] A critical care unit study that evaluated patients in shock showed that 32% were incorrectly diagnosed as hypoglycemic when capillary blood was used. Results of reagent strip tests of venous blood correlated well with laboratory results, correctly classifying all patients. No cases of hypoglycemia were

missed.[8]

Several studies have compared the accuracy of standard reagent strips for the detection of hypoglycemia from capillary and venous blood compared with the gold standard of the laboratory. As indicated, use of capillary blood from patients with cardiac arrest or shock is associated with an increased false-positive rate for detection of hypoglycemia. Two studies, one with 97 subjects[36] and one with 270 subjects,[52] evaluated the agreement between reagent strip determinations of capillary and venous blood glucose in healthy normoglycemic volunteers. Correlation in the normoglycemic range was poor (Pearson correlation 0.24 and 0.5, respectively), with a tendency for capillary measurements to correlate more closely with the laboratory measurements and to be higher than venous measurements. In the larger study, 18% of subjects had a > 15 mg/dL difference between capillary and venous reagent strip tests. In these ranges, capillary measurements were better correlated with the laboratory values. In the lower ranges of normoglycemia, the capillary sample appeared to underestimate its venous counterpart.[36,52] Whether these results have any clinical significance is not clear because none of the subjects fell out of the normoglycemic range. They suggest that the capillary blood glucose test has greater accuracy in the normoglycemic range.

The â€œsafeâ€• number at which no cases of symptomatic hypoglycemia are missed by reagent strip testing is a subject of debate because of the inherent risk of error from lack of sensitivity. In addition, poorly controlled diabetics experience hypoglycemic symptoms at blood glucose concentrations that normally are regarded as euglycemic. In one study where hypoglycemia was defined as a blood glucose concentration < 60 mg/dL, 2 of 33 hypoglycemic patients were not detected. A cutoff of 90 mg/dL would have detected 100% of numerically hypoglycemic patients.[56] An important study of diabetics demonstrated that the mean blood glucose concentration for

symptomatic hypoglycemia in poorly controlled diabetics was 78 Â± 5 mg/dL compared with 53 Â± mg/dL in normal controls.[12] Based on these studies, it can be argued that a bedside reagent measurement of 90 mg/dL is a conservative cutoff for assurance of clinical euglycemia in all patients.

Pharmacokinetics of Dextrose

Studies of the pharmacokinetics of dextrose are limited, so predicting the amount of dextrose required to effectively treat hypoglycemia is difficult. At equilibrium, 25 g dextrose distributed in total body water in a 70-kg adult is calculated to raise the serum glucose concentration by about 60 mg/dL.[44] In the few clinical studies performed, the magnitude of glucose elevation after oral or intravenous loading is highly unpredictable. In one study, administration of 25 g (50 mL) $D_{50}W$ to adults resulted in a mean blood glucose elevation of 166 mg/dL; however, the range of this elevation was 37â€“370 mg/dL above baseline.[2] In a human model of insulin-induced hypoglycemia, oral administration of 20 g dextrose raised serum blood glucose concentration 60 to 120 mg/dL over 1 hour, whereas 10 g raised the concentration from 60 to 100 mg/dL.[103]

Conclusion: A Rational Clinical Solution

An ideal clinical solution to the management of patients with altered mental status or focal neurologic symptoms misses no cases of significant symptomatic hypoglycemia but avoids the administration of dextrose to patients with brain ischemia. A realistic approach can be fashioned from our understanding of the reliability of reagent test strips and a risk-to-benefit assessment of the presenting problem.

Infants and neonates should receive dextrose when clinically indicated without concern for associated ischemia or anoxia

because the detrimental effect of hyperglycemia seems to be absent in this age group. The patient with coma or status epilepticus from hypoglycemia benefits greatly from empiric treatment with dextrose and suffers the greatest morbidity if not treated. Furthermore, a patient who is comatose from a major cerebrovascular accident has a very limited chance for recovery, and administration of dextrose likely will not impact heavily on the prognosis compared with a missed diagnosis of significant hypoglycemia. Administering $D_{50}W$ to patients in coma who do not have a measured blood glucose of at least 90 mg/dL determined by bedside reagent strip testing is rational. Similarly, although confusion and delirium without focal neurologic findings can occur as manifestations of structural brain injury, toxic-metabolic etiologies are more common. These altered patients should receive dextrose if the glucose concentration determined by bedside test is < 90 mg/dL. When a reliable bedside glucose determination is not readily available, all of these patients should receive $D_{50}W$ empirically.

Rapid reagent glucose samples of capillary blood are especially unreliable in the patient with hypotension or cardiac arrest; however, bedside reagent strip testing of venous blood appears to be more reliable.[8,80,92] Patients in shock or cardiac arrest should

undergo reagent testing using a venous blood sample (not a fingerstick sample) and should receive dextrose if results indicate they are numerically hypoglycemic (< 90 mg/dL). Administration of dextrose to a patient with a cardiac arrest who is euglycemic as determined by reagent strip testing should be considered only if the patient is diabetic.

Patients with focal neurologic deficits due to ischemia constitute a population that is reasonably expected to receive the greatest benefit from maintenance of euglycemia. Although focal presentations of hypoglycemia are not rare, they are infrequent relative to the numbers of patients with focal presentations who

have suffered cerebrovascular accidents. In one study, 3% of patients with hypoglycemia presented with focal symptoms.[65] In the patient with a history of diabetes who presents with focal symptoms, symptomatic hypoglycemia must be strongly considered when the reagent strip shows a blood glucose concentration < 90 mg/dL.

The patient with a clear history and evidence of significant head injury antedated by normal activity (eg, crossing the street, being struck by a car) should not be treated unless the bedside test indicates hypoglycemia (< 60 mg/dL). Diabetic patients may suffer unintentional injuries predisposed by hypoglycemic episodes. The treating physician must use his or her best judgment of the mechanism and evidence of injury, witness' reports, available medical history, and result of bedside glucose determination to decide whether to administer $D_{50}W$ to the traumatized patient with an altered concentration of consciousness.

In summary, dextrose should be administered to all patients with altered levels of consciousness and numerical hypoglycemia (glucose concentration < 90 mg/dL). Concerns regarding the negative effects of elevated blood glucose concentration on cerebral ischemia should not cause a physician to withhold dextrose in patients with neurologic impairment when symptomatic hypoglycemia cannot be promptly and reasonably excluded. Dextrose should be empirically administered when bedside reagent strips are not available. Studies indicated that the currently available reagent strips reliably demonstrate the absence of significant hypoglycemia at readings > 90 mg/dL. Profound neurological impairment likely is not the result of hypoglycemia when such concentrations are demonstrated, even in a diabetic patient.

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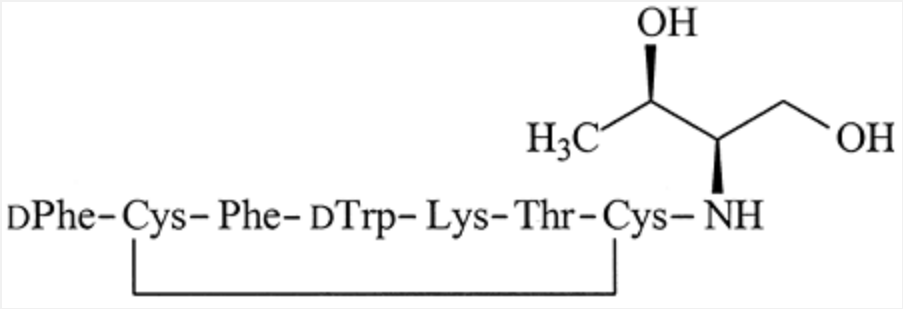
Antidotes in Depth

Octreotide

Mary Ann Howland



Octreotide is a long-acting, synthetic octapeptide analog of somatostatin that inhibits pancreatic insulin secretion. It currently is considered second only to glucose for the treatment of refractory hypoglycemia induced by overdoses of oral

hypoglycemic agents (eg, sulfonylureas) and quinine.

History

â€œSomatostatinâ€• is a collective term for shorter fragments (SRIF-28, SRIF-25, and SRIF-14) cleaved by tissue-specific enzymes from preprosomatostatin (116 amino acids) and prosomatostatin (92 amino acids).[9] Somatostatin was discovered in 1973, during the search for growth hormone releasing factor.[6] In addition to its effects on growth hormone and insulin secretion, somatostatin has far-reaching effects as a central nervous system (CNS) neurotransmitter and as a modulator of hormonal release.[26,32] Unfortunately, the role of somatostatin as a therapeutic tool is limited because somatostatin is short acting. Octreotide was purposefully synthesized in 1982 at Sandoz Labs in a quest to develop a longer-acting analog of somatostatin.[3] Octreotide currently is used therapeutically for the treatment of acromegaly, pituitary adenomas, pancreatic islet cell tumors, carcinoid tumors, portal hypertension, esophageal varices, and secretory diarrhea.[26] Octreotide is also being investigated for its inhibitory effects on tumor cell proliferation.[26,33]

Receptor Affinity

Somatostatin's effects are mediated by high-affinity binding to membrane receptors on target tissues. Five different somatostatin receptor subtypes that belong to a superfamily of G-proteinâ€“coupled receptors have been identified and assigned numbers (SSTR1â€“SSTR5) according to their order of discovery.[9] Octreotide has high binding affinity for subtypes SSTR2 and SSTR5, low affinity for subtypes SSTR1 and SSTR4, and intermediate affinity for subtype SSTR3.[26] SSTR2 is found in the pancreas, brain, pituitary, stomach, and kidney. SSTR5 is found in the brain, pituitary, heart, adrenal glands, placenta, small intestine, and skeletal muscle.[26,30,35]

Effects on Insulin Secretion and Other Hormones

Experiments using a whole-cell patch clamp technique on a hamster Î²-cell line suggest that somatostatin inhibits insulin secretion by a G-proteinâ€“mediated decrease in calcium entry through voltage-dependent Ca^{2+} channels.[20] No evidence indicates that somatostatin inhibits insulin release by promoting K^+ efflux through K^+ channels (Fig. 48-2).[27,34] However, evidence suggests that somatostatin, like epinephrine, stimulates a Gi-coupled receptor that inhibits adenylate cyclase and production of cyclic adenosine monophosphate (cAMP), thereby reducing insulin secretion.[19] Simultaneous distal reduction in protein kinase A also may be involved in reducing insulin secretion.[19] These mechanisms appear to be independent of Ca^{2+}.[19] Activation of SSTR5 on the Î²-cell of the pancreas also reduces insulin biosynthesis.[13] Experiments with somatostatin both in healthy human volunteers and in an isolated perfused canine pancreas model demonstrate the ability of somatostatin to inhibit glucose-stimulated insulin release.[1,15]

One study in human volunteers confirms the ability of somatostatin to inhibit the increased insulin response to both glucose and glucagon.[15] Intravenous (IV) infusion of 1 g tolbutamide over 2 minutes caused insulin concentrations to rise and serum glucose concentration to drop sharply. However, treatment with somatostatin blocked these changes. Similarly, in the presence of somatostatin and tolbutamide, administration of IV glucagon caused a rise in glucose concentration without the expected subsequent glucose-stimulated rise in insulin. These effects of somatostatin were short lived. Within 5 minutes of stopping the somatostatin, the insulin-releasing effects of tolbutamide continued, and within 15 minutes the serum glucose concentration fell. Peak insulin concentrations were achieved

within 25 minutes.

Studies comparing octreotide to somatostatin in rats and monkeys demonstrate that octreotide is 1.3 times as potent as somatostatin in inhibiting insulin secretion by 50%. Likewise, compared with somatostatin, octreotide was 45 times more potent in inhibiting growth hormone secretion and 11 times more potent in inhibiting glucagon release.[3] Comparable results were found using a hyperglycemic glucose clamp technique.[23] Octreotide blocks the counterregulatory response to the effects of 0.1 unit/kg IV insulin by preventing an increase in glucagon and growth hormone. In a subsequent study of the effects of octreotide on the responses of adrenocorticotropin, cortisol, prolactin, luteinizing hormone, and follicle-stimulating hormone to insulin-induced hypoglycemia, all remained intact.[27] In contrast, in this and other studies, growth hormone[12] and thyroid-stimulating hormone were significantly inhibited.[27]

Pharmacokinetics

The pharmacokinetics of IV and subcutaneous (SC) octreotide were studied in 8 healthy adult volunteers.[25] Subjects received 25, 50, 100,

and 200 Âµg IV octreotide over 3 minutes and 50, 100, 200, and 400 Âµg SC octreotide in random order. Following IV administration, the distribution half-life averaged 12 minutes, and the elimination half-life ranged from 72 Â± 22 minutes to 98 Â± 37 minutes and was linear. Vi (volume of distribution of the central compartment) was dose dependent and increased from approximately 5.7 L at 25, 50, and 100 Âµg IV to 10 L at 200-Âµg IV doses.[25] Vd (volume of distribution determined by area under the curve) was 18 Â± 6 L to 30 Â± 30 L and showed no dose dependency.[25] Renal elimination accounted for approximately 30% of the elimination and was reduced in the elderly and in those with

severe renal failure.[32]

After SC administration, bioavailability was 100%, and peak levels were achieved within 30 minutes with an absorption half-life of 5â€“12 minutes. The elimination half-life was 88â€“102 minutes. Peak plasma concentrations ranged from 2.4 ng/mL at doses of 50 Âµg to 23.5 ng/mL at doses of 400 Âµg, which represent approximately half of the intravenously administered level.[25]

The pharmacokinetics in patients with pathologic conditions may differ from the pharmacokinetics in healthy volunteers as exemplified by a lower peak concentration and a higher steady-state Vd in patients with acromegaly.[32]

The duration of action is variable. When used for tumor suppression, the duration may last up to 12 hours.[32] The duration of action for inhibition of insulin secretion is unknown.

Clinical use for Insulin Suppression

Octreotide was studied in several clinical conditions, including insulinomas and hypoglycemia of infancy.[2,16,22,37,38] In most instances, octreotide suppressed insulin concentrations, and glucose concentrations rose. However, worsening hypoglycemia is reported when glucagon suppression outlasted insulin suppression.[4,8,14,37] Octreotide currently is used for treatment of xenobiotic-induced endogenous secretion of insulin.

In controlled studies of healthy volunteers, octreotide suppressed the release of insulin associated with quinine.[36] Life-threatening hypoglycemia is a well-recognized complication of quinine treatment of *Plasmodium falciparum* malaria. In this setting, hypertonic dextrose and diazoxide therapy frequently is inadequate, with ensuing refractory hypoglycemia. In an investigation of the potential hypoglycemia-sparing effect of octreotide given for treatment of quinine-induced hypoglycemia, healthy adults were given 50 Âµg/h octreotide or placebo as a

continuous IV infusion for 4 hours, followed at the first hour by infusion of 490 mg quinine base.[36] In the control subjects, plasma insulin concentrations rose and plasma glucose concentrations fell significantly, whereas in the octreotide group, insulin concentrations fell and glucose concentrations remained constant. This effect of octreotide began within 30 minutes and persisted for 2 hours after octreotide was stopped. Octreotide was successfully used to treat refractory hypoglycemia in a woman receiving 600 mg quinine dihydrochloride IV for malaria.[36]

Several case studies and a case series of 9 patients support the efficacy of octreotide in overdoses of glipizide, glyburide, gliclazide, and tolbutamide (whether intentional or unintentional), in nonâ€“insulin-dependent diabetes or insulin-dependent diabetes, and in a pediatric patient.[5,7,10,11,17,18,21,23,28,31] In these case reports, therapeutic doses ranged considerably, and the most frequent doses were 50â€“100 Âµg subcutaneously repeated every 8â€“12 hours in the adult patients.

The efficacy of octreotide was demonstrated in a subsequent study. Eight healthy volunteers were given 1.43 mg/kg glipizide orally and randomized to receive either a variable dextrose infusion to remain euglycemic, diazoxide 300 mg IV over 30 minutes and repeated every 4 hours along with dextrose, or octreotide 30 ng/kg/min IV continuously.[5] Following administration of glipizide, hypoglycemia of 50 mg/dL was achieved within 30â€“165 minutes.[5] Insulin concentrations in the diazoxide group were comparable to those in the glipizide group, with resultant glucose concentrations slightly higher than the other groups. Four of the 8 patients in the octreotide group did not require supplemental dextrose. At the fifth hour of the protocol, an IV bolus of 50 mL 50% dextrose was given to the octreotide group to study the response to hyperglycemia. Approximately 6.5 hours was necessary for the plasma glucose concentration to drop to 85 mg/dL, whereas only 3 hours was necessary in the dextrose and diazoxide groups.[5] Diazoxide infusion was associated with higher

norepinephrine concentrations, whereas epinephrine concentrations were similar in all groups.[5] All xenobiotics were stopped at 13 hours, and plasma glucose concentrations fell to < 65 mg/dL within 1.5 hours in subjects who received the dextrose and diazoxide, whereas the plasma glucose concentrations remained > 65 mg/dL in 6 of the 8 octreotide subjects for the 4-hour observation period. Without additional octreotide, hypoglycemia continued to recur for as long as 30 hours after the initial glipizide administration.

Adverse Drug Effects

Octreotide is generally well tolerated, but experience in the toxicologic setting is limited. Adverse reactions occurring with short-term administration usually are local or gastrointestinal. Stinging at the injection site occurs in approximately 7% of patients but rarely lasts more than 15 minutes.[39] Healthy volunteers receiving octreotide noted no side effects when given IV doses of 25 or 50 Âµg or SC doses of 50 or 100 Âµg. At higher doses, early transient nausea and later-appearing but longer-lasting diarrhea and abdominal pain frequently occur.[24,25] Healthy volunteers were given IV bolus doses of octreotide as high as 1000 Âµg and infusion doses of 30,000 Âµg over 20 minutes and 120,000 Âµg over 8 hours without serious adverse effects. Single doses in healthy volunteers resulted in decreased biliary contractility and bile secretion.[32] Long-term therapy lasting weeks to months results in biliary tract abnormalities.[32,40] Product information warns of the potential for acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, and pancreatitis.[32]

Octreotide alters the balance among insulin, glucagon, and growth hormone. Glucose concentrations must be serially monitored. Hyperglycemia often occurs, but cases of hypoglycemia are reported. The most likely explanation is glucagon suppression

outlasting insulin suppression.[32]

Other adverse effects reported with long-term administration of octreotide include hypothyroidism, cardiac conduction abnormalities, worsening congestive heart failure (in at-risk patients with acromegaly), bradycardia, pancreatitis, altered fat absorption, and decreased vitamin B_{12} levels.[32] Anaphylactoid reactions are rarely reported.[32]

Drug interactions are expected with xenobiotics that affect glucose regulation. Octreotide may significantly decrease oral absorption of cyclosporine.[32]

Administration

Both SC and IV administration are acceptable, although the usual route is SC administration.[32] The SC administration sites should be rotated. For IV infusion, octreotide can be diluted in sterile 0.9% sodium chloride solution or D_5W and infused over 15â€“30 minutes or by IV bolus over 3 minutes.[32] Rapid IV bolus may be indicated for carcinoid crisis.[32] Refrigeration of octreotide is recommended for prolonged storage, although octreotide is stable at room temperature for 14 days when protected from light. Active warming of refrigerated octreotide is not recommended, although passive warming to room temperature prior to administration is suggested and may reduce the pain of SC administration.[29] Using the smallest volume possible reduces the pain with SC administration. A depot formula designed to last for 4 weeks is available (Sandostatin LAR Depot). Although the depot formula is useful for patients with insulinomas, its duration of action far exceeds that of any oral hypoglycemic agent, making it an inappropriate and unnecessary choice for management of xenobiotic-induced hypoglycemia.

Dosing

No controlled trials have evaluated the dose of octreotide for the management of sulfonylurea overdose. In adults, a 50-Âµg SC dose of octreotide given every 6 hours is suggested. In children, a dose of 4â€“5 Âµg/kg/d SC divided every 6 hours, up to the adult dose, can be used for initial therapy. This pediatric dose is derived from the literature on treatment of persistent hyperinsulinemic hypoglycemia of infancy.[16] In situations where compromised peripheral blood flow is expected, octreotide should be administered intravenously in the same dose but every 4 hours instead of every 6 hours. Further experience in the toxicologic setting should permit a better delineation of dosing recommendations. Several days of therapy may be required, depending on the duration of the offending agent. All patients must be carefully monitored for recurrent hypoglycemia during octreotide therapy and perhaps for 24 hours following termination of octreotide therapy before discharge. Octreotide is considered a category B drug (Table 30-2), and pregnant women must be carefully monitored for recurrent hypoglycemia. Use of octreotide should not diminish this vigilance.

Availability

Octreotide acetate (Sandostatin) injection is available in ampules and multidose vials ranging in concentration from 50â€“1000 Âµg/mL. The multidose vials contain phenol.

Summary

Octreotide is useful for treating refractory hypoglycemia induced by xenobiotics such as sulfonylureas and quinine that cause endogenous release of insulin. Octreotide is more effective than diazoxide in suppressing insulin and is much better tolerated.

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Chapter 49
Thyroid and Antithyroid Medications

Nicole C. Bouchard

A 3-year-old boy was found with an empty bottle of his mother's levoth 300-Âµg tablets). The mother estimated he had ingested as many as 20 were found in the nearby area or in the child's mouth. The child cried whe â€œeatenâ€• the pills. He was brought promptly to the hospital. On initi asymptomatic and had stable vital signs: blood pressure, 100/60 mm Hg; respiratory rate, 16 breaths/min; temperature 98.6Â°F (37.0Â°C). He was (1 g/kg) mixed with juice, which he drank readily. A complete blood cou electrolytes, blood urea nitrogen, serum creatinine, urinalysis, and thyroid and the child was admitted to the pediatric intensive care unit (ICU). His 5â€“12 Âµg/dL), and total triiodothyronine (T_3) was 120 ng/dL (normal other laboratory test results were within normal limits for his age. He rem days before he was transferred to a regular pediatric ward. His behavior, examination were normal at that time. After 72 hours of observation, he from the hospital. The parents were advised to monitor for signs of hyp gastrointestinal upset, and they were taught how to measure his pulse ra immediately if the child became symptomatic.

According to his parents, the child became somewhat irritable on day 5

reported that he was more disruptive than usual in day school. That ever asleep. He was awakened at night with abdominal cramps and had 2 episo morning, his parents measured his pulse rate to be 130 beats/min. The p emergency department, where the triage nurse noted the child was â€œj follows: blood pressure, 120/80 mm Hg; pulse, 153 beats/min; respirator temperature 99.5Â°F (37.5Â°C). His physical examination was remarkable reactive pupils (bilaterally), vigorous bowel sounds, warm skin, and brisk not diaphoretic or confused. His ECG showed a sinus tachycardia.

He was readmitted to the ICU and treated with 60 mg liquid propranolol d days. His pulse rate decreased to 105 beats/min, and his blood pressure after the first dose of propranolol. He remained afebrile. He had 2 more complained of mild abdominal cramping for another 24 hours. Otherwise, well hydrated, and playful throughout. He was able to tolerate a normal revealed normal serum electrolyte concentrations and a normal complete tests revealed total T_4 of 24 Âµg/dL (normal 5â€“12 Âµg/dL), total T_3 20 ng/dL), and undetectable thyroid-stimulating hormone (TSH).

The patient remained in the ICU for 2 days (postingestion day 8) before l pediatric ward. On the ward, he required no further treatment with prop asymptomatic, except for a pulse rate of 110 beats/min. He was discharge hospital day 4 (postingestion day 9). On follow-up with his pediatrician 1 asymptomatic. His parents reported no further disruptive behavior, gastr tachycardia. His TSH concentration remained suppressed until 3 weeks a

History and Epidemiology

Long before the thyroid was recognized as a functional endocrine gland, t serve a cosmetic function, especially in women. Egyptian paintings often necks of women with enlarged thyroid glands. Other early theories on the thyroid gland include lubrication of the trachea, to protect women from â€œvexationâ€• from men and from the diversion of blood flow from the defined in historical accounts, symptoms resembling hypothyroidism and sheep thyroid were described 500 years ago. In the 16th century, Parace between goiter (thyroid gland enlargement) and cretinism.[67] A syndrome and exophthalmos was first described in 1786.[79] Graves and von Basedov

and its relationship to the thyroid gland 50 years later.[32, 35, 63, 79, 10

In 1891, injection of ground sheep thyroid extract was formally described myxedema.[35] Shortly afterward, oral administration of this therapy was c Seaweed, which contains large amounts of iodine, was used to treat goit medicine as early as the 3rd century A.D. In 1863, Trousseau[100] fortuitous Graves disease when he inadvertently prescribed daily tincture of iodine i a tachycardic, thyrotoxic young woman.

Sir Charles R. Harington described the chemical structure and performed (tetraiodothyronine [T_4]) in 1926.[81] Triiodothyronine (T_3) was not isola 1950s.[35] Prior to this time, desiccated thyroid gland from animal sources hypothyroidism. Despite becoming essentially obsolete in the modern me thyroid can be easily purchased via the Internet and in health food stores Unfortunately, the misguided use of thyroid supplements, both organic ar stimulants, and weight-loss aids has become increasingly common. Two e *thyrotoxicosis* that occurred in the United States in the mid 1980s secon beef contaminated with bovine thyroid gland demonstrated the potential sequelae following unknown thyroid hormone ingestion by a community.[4]

Today, hypothyroidism and hyperthyroidism are relatively common endoc incidence of neonatal hypothyroidism is 1 per 3000â€“4500 births. It is affects 1â€“7% of adults.[89] According to 2003 US retail pharmaceutical s prescriptions, Synthroid (T_4) was ranked second overall for total prescri 47,000â€“49,000 prescriptions written in 2003.[46, 73] Many cases of inte overdoses with thyroid hormone are reported in both adults and children. thyroid hormones on physiologic homeostasis and the widespread use and hormone, morbidity and mortality from overdose are very low overall.

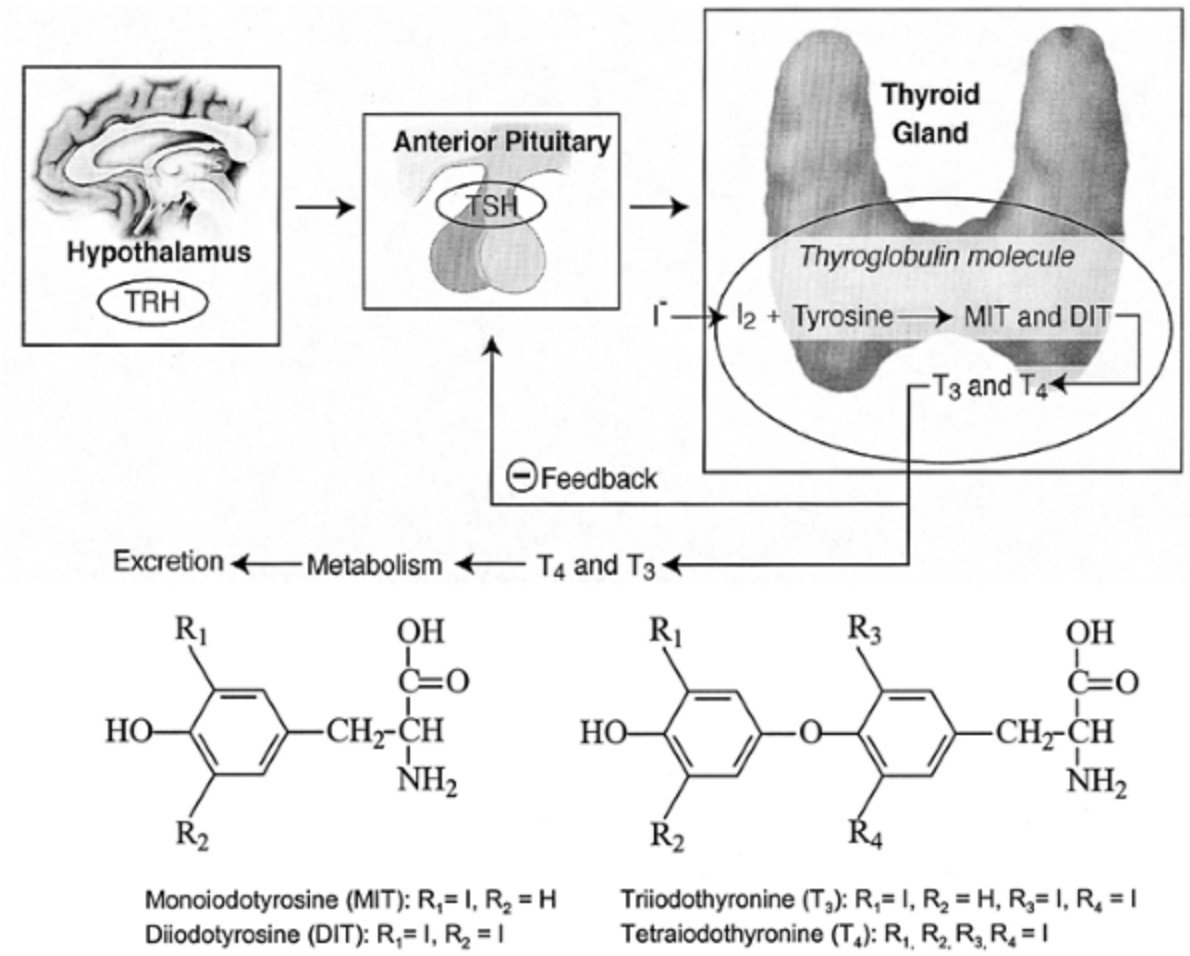

Figure 49-1. Thyroid hormone synthesis: its control, metabolism, and r
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Physiology

To properly understand the impact of thyroid supplements and antithyroid human body, an understanding of thyroid physiology is required. Thyroid following: (1) the hypothalamus, (2) the pituitary gland, (3) the thyroid g for the thyroid hormones (Figure 49-1).

The hypothalamus is an intermediate between cerebral centers and the p hypothalamus receives specific neurotransmitter stimulation, thyroid-releas produced. TRH is transported through the venous sinusoids to the pituita thyroid-stimulating hormone (TSH). TSH enters the circulation and stimul

of the thyroid hormones T_3 and T_4 by the thyroid gland. Thyroid physiolo autoregulation or â€œfeedback controlâ€• of hormonal function. When a released, they exert an inhibitory effect on the pituitary gland, leading to (Figure 49-1). Suppression or upregulation of TSH production is a freque the evaluation of the hyperthyroid and the hypothyroid state, respectivel

Thyroid hormones are tyrosine molecules with iodine substitutions. Two fo physiologically active: T_3 and T_4 (Table 49-1). Synthesis of these thyroid process. The amino acid tyrosine is concentrated in the follicles of the thy epithelial layer surrounding a proteinaceous colloidal substance called t contains a large amount of tyrosine. After iodide (I^-) is absorbed from t in thyroid cells by an active transport process called *iodide trapping* , wh by thyroid (iodide) peroxidase. Iodine rapidly iodinates tyrosine residues and diiodotyrosine (DIT). These substituted tyrosine molecules then combi ratio of T_3 to T_4 in thyroglobulin is 1:5. T_3 and T_4 (thyroxine) ultimately from the thyroglobulin matrix inside the follicles of thyroid gland.

Iodide trapping can be inhibited pharmacologically by monovalent anions pertechnetate (TcO_4^-), and perchlorate (ClO_4^-). Thyroid peroxidase is of intrathyroidal iodide and by thioamide drugs. High intrathyroidal iodide the release of thyroid hormone into circulation (Table 49-2).

Approximately 95% of circulating or peripheral thyroid hormone is T_4 ; th the peripheral T_3 is secreted directly by the thyroid; the balance results of T_4 to T_3 . When circulating T_4 enters the cell, it is deiodinated to T_3 . occurs by monodeiodination of either the outer ring or the inner ring by deiodinase, yielding 3,5,3â€²-T_3 and 3,3â€²,5â€²- triiodothyronine (rever approximately 3 times greater hormonal activity than T_4 . rT_3 is metaboli effects by binding to thyroid hormone receptors inside the nucleus. This receptors regulates gene transcription and protein synthesis, which ultim consumption and underlies the thermogenic effects of thyroid hormones.

Î²-Adrenergic antagonism, corticosteroids, ipodate, starvation, and severe deiodinase, which results in decreased production of metabolically active monodeiodination to metabolically inactive rT_3 (Table 49-2). This energ attenuation of the thermogenic effects of thyroid hormones in times of p

Pharmacology

T_4 and T_3

Thyroid supplementation for treatment of hypothyroidism is widespread in medicine. Thyroid hormones historically were derived from animal origin b synthetically produced. Desiccated thyroid (Armour) still is derived from both T_3 and T_4 . Because it is less pharmacologically stable and carries a thyrotoxicity from T_3 , its use has largely been supplanted by safer syn is the preparation of choice because of its low immunogenicity, 7- day ha regimen. Synthroid is the commercial name of the most commonly prescri (Cytomel or Triostat, available PO and IV) and liotrix (Thyrolar, available are seldom used secondary to their short half-lives, high cost, rare thera risk of thyrotoxicosis. The typical levothyroxine dose in adults is 1.7 Âµg patients are started on lower doses (range 12.5â€“Âµg/d [0.0125â€“0.025 sensitivity to thyroxine excess. Infants with congenital or acquired hypoth doses of 8â€“10 Âµg/kg/d (~25â€“50 Âµg/d). Older infants and children a kilogram: age > 12 years: 2â€“3 Âµg/kg once daily until the adult daily d reached; 6â€“12 years: 4â€“5 Âµg/kg/d or 100â€–150 Âµg once daily; 1â 75â€–100 Âµg once daily; 6â€–12 months: 6â€–8 Âµg/kg/d or 50â€–75 Âµ regard to suppression of TSH and elevation of T_4 is reached approximatel therapy. Doses usually are titrated in increments of 12.5 or 25 Âµg/d afte measurements. Different sources suggest that bioequivalence of Synthroi may and may not be equivalent.[17] Thyroid hormone concentrations and th should be followed when transitioning between levothyroxine formulations present an opportunity for an adverse drug reaction.

Pharmacokinetics and Toxicodynamics

In circulation, T_3 and T_4 both are highly and reversibly bound to plasma and 99.97%, respectively, in the nonpregnant adult. Thyroxine-binding gl approximately two thirds of the circulating thyroid hormones; albumin and remainder. It is estimated that only 0.4% of T_3 and 0.04% of T_4 exist in derived thyroid hormones exhibit similar binding characteristics when dosi

The amount of thyroid hormone bound to proteins varies greatly with dif pharmacologic conditions, for example, increasing in pregnancy and levo decreasing in chronic disease. Such changes in protein binding must be thyroid hormone concentrations in the blood (see Diagnostic Testing). T thyroid hormones is very large: 40 L/kg for T_3 and 10 L/kg for T_4 . Table pharmacokinetic properties of thyroid hormones.

The oral bioavailabilities of exogenous thyroid hormones are high: 80% fo Gastrointestinal absorption is thought to occur primarily in the duodenum absorption can be decreased by variations in intestinal flora and binding b containing antacids, calcium preparations, carbonate salts, sucralfate, iron cholestyramine resins, colestipol hydrochloride), and infant soy formula (

Oral bioavailability (exogenous drug)
95%
80%
Volume of distribution (L/kg)
40
10
Half-life (days)
1
7
Protein binding (normal adult)
99.96%
99.6%
Relative potency
4
1

Pharmacokinetic Property T_3 T_4

TABLE 49-1. Pharmacokinetic Properties of Thyroid Hormones

Thyroid hormones undergo their ultimate metabolism peripherally. Intra

accounts for approximately two thirds of inactivation. Most of the remain metabolism by glucuronidation or sulfation. Xenobiotics that induce hepa as rifampin, phenobarbital, phenytoin, and carbamazepine, increase the n (Table 49-2).

Inhibit TRH and TSH synthesis
Dopamine, levodopa, corticosteroids, somatostatin
No hypothyroidism
Inhibit thyroid hormone synthesis or release
Iodides (including amiodarone), lithium, aminoglutethimide
Hypothyroidism
Inhibit iodide uptake to thyroid gland
Monovalent anions (SCN^- , TcO_4^- , ClO_4^-)
Treatment for iodide-induced hyperthyroidism
Increase TBG
Estrogens, tamoxifen, heroin, methadone, mitotane
Altered thyroid hormone transport in serum
â†‘ Total measured thyroid hormone (vs. *free* hormone)
Decreased TBG
Androgens, glucocorticoids
Altered thyroid hormone transport in serum
â†“ Total measured thyroid hormone (vs. *free* hormone)
Displace T_3 or T_4 from TBG
Salicylates, mefenamic acid, furosemide
Transient hyperthyroxinemia
Inhibit thyroid peroxidase
Thioamides (methimazole, propylthiouracil)
Decrease thyroid hormone synthesis
Induction of hepatic enzymes
Phenytoin, carbamazepine, phenobarbital, rifampin, rifabutin
â†“ Total thyroid hormone measurements
Inhibition of 5â€²-deiodinase
Iopanoic acid, ipodate, amiodarone, Î²-adrenergic antagonists, corticost
Decrease peripheral conversion of T_4 (â†“T_3 , â†‘rT_3)
Interfere with GI absorption of T_4

Cholestyramine, colestipol, aluminum hydroxide, sucralfate, ferrous sulfat infant soy formula
Decreased oral bioavailability of T_4
Induction of autoimmune thyroid disease
Interleukin-Î±, interleukin-2
Hyperthyroidism or hypothyroidism
TRH = thyroid-releasing hormone; TSH = thyroid-stimulating hormone; T GI = gastrointestinal.

Interaction Xenobiotic Effect

TABLE 49-2. Xenobiotic Interactions: Effects on Thyroid Hormone

Pathophysiology

Thyroid hormones are critical for optimal physiologic growth and function. important determinant of basal metabolic rate (BMR). In addition, the th effect on many hormones, notably catecholamines and insulin.

Hyperthyroidism is a condition characterized by excess active thyroid hor carbohydrate and protein metabolism are increased in the presence of th metabolism and cholesterol synthesis are increased. The clinical picture c increased metabolism, along with tachycardia, tremor, anxiety, other beh tachydysrhythmias such as atrial fibrillation.[24, 54, 87] This constellation *thyrotoxicosis*, may result from overproduction of the hormone, increase excess exogenous hormone. Graves disease, an autoimmune disorder, is t excess thyroid hormone secretion. It accounts for approximately two thirds accompanied by exophthalmos. Severe thyrotoxicosis accompanied by dec *thyroid storm* or *thyrotoxic crisis.* Mortality in thyroid storm, even with t [24]

An increased in sensitivity to catecholamines is suggested to underscore inotropy and chronotropy produced by thyroid hormones. Plasma catecho established to be normal or decreased in hyperthyroid states.[14, 84] Altho thyroid hormones can cause decreased systemic vascular resistance leadin

cardiac output, two general mechanisms are proposed for the direct card
although their relative contributions are uncertain.[3,16,54,99] (1) T_3 in
adrenergic receptors in various tissues, including cardiac cells.[16] This pro
Î²-adrenergic receptor synthesis at the level of the Î²-adrenergic gene.[4]
intracellular signaling mechanisms that lead to increased catecholamine e
intracellular signaling activity involving protein kinase A, cyclic adenosine
and increased phosphorylation of thyroid hormone receptor proteins all a
degrees.[23,54,82,83,86,93,101] Enhancement of myocardial transmer
reticulum ion channel function, L-type voltage-gated Ca^{2+} channels, and
sarcoplasmic reticulum also are suggested.[50,51,72,92] Whether these
signaling represents a direct T_3 effect on intracellular signaling mediators
the individual Î²-adrenergic receptor response to catecholamines with a s
postreceptor signaling is unclear.[3]

In addition to these two mechanisms, T_3 upregulates synthesis of cardiac
TRÎ± and TRÎ² genes). Comprehensive reviews on this topic explore the
thyroid hormones and their effects on the cardiovascular system.[15,54,

Hypothyroidism, a condition characterized by decreased BMR and decreas
common disorder, especially in women and the elderly. It often is autoin
function diminishes significantly with age in many patients. In infants, u
deficiency and severe dietary iodine deficiency (goitrous hypothyroidism)
mental retardation and dwarfism (also referred to as cretinism). In devel
salt has essentially eliminated dietary iodine deficiency as a cause of hyp
the world, particularly mountainous regions such as the Andes, Alps, and
hypothyroidism still is endemic. Myxedema and myxedema coma

are potentially life-threatening emergencies that represent extremes of
is not discussed in this chapter, except to note that treatment of hypoth
with T_3 , can result in thyrotoxic symptoms. Comprehensive reviews of

Clinical Manifestation

The widespread availability and use of thyroid supplements make thyroid
in acute intentional and unintentional overdoses. In addition, chronic exc
is a relatively frequent occurrence. Symptoms of toxicity from exogenous

those of catecholamine excess. Pronounced catecholamine effects occur i especially tachycardia, tachydysrhythmias (usually atrial fibrillation or flu cardiac failure.[24, 54, 87] Interestingly, although hyperthyroid patients typ agitated, patients with thyroid storm may present with a decreased level coma.[8, 45, 57, 85, 91] Hyperthermia can occur secondary to the thermog hormones and psychomotor agitation. Hyperthermia can be extreme (ie, > tachycardia associated with thyrotoxicosis often is disproportionate to th

Acute Toxicity

Acute overdoses with thyroid hormone preparations most commonly occu Significant ingestions of levothyroxine usually do not manifest clinically u but are rarely reported to manifest as early as 2â€“3 days postingestion. peripheral conversion of T_4 to the metabolically active T_3 and the time t protein synthesis account for this clinical latency of hours to days follow administration. Acute overdoses involving preparations containing T_3 can hours days after exposure.[62]

In children, acute thyroxine overdoses almost universally are benign beca unintentional nature and lower doses ingested. Most pediatric patients re only mild symptoms. No deaths have been reported.[21, 28, 48, 58, 60, 6 with unintentional overdose, only 3 children developed mild symptoms 1 Similarly, large case series that involved 41 children (ages 1â€“5 years) thyroxine (estimated doses ranged from 40â€“800 Âµg) found mild symp tachycardia, fever, vomiting, diarrhea, diaphoresis, and flushing) in only 2 clinical outcomes. The degree of symptoms did not correlate with the am serum thyroxine concentrations (measured 1â€“5 hours postingestion) for Diagnostic Testing).[28] Two other series involving 78 and 92 cases of ur found that mild symptoms developed in only 4 and 8 patients, respective severe toxicity in children are reported: 1 child without a history of a seiz days after a levothyroxine ingestion (18,000 Âµg),[56] and another child be 12-hour period (blood pressure, 120/68 mm Hg; pulse, 200 beats/min; t hours after ingesting a large amount (3.2 g, or â€œ50 grainsâ€•) of a containing both T_3 and T_4 .[61]

Ingestions in adults have a wide range of toxicity. Many patients are asy

symptomatic.[30 , 64 , 76] Severe sequelae occur more frequently in adults resemble thyrotoxicosis and, in extreme cases, thyroid storm. Hyperther [58 , 91] and severe agitation[34] are well described. Hemiparesis,[8] muscle w respiratory failure,[26] sudden death,[7] myocardial infarction,[7] cardiac failu rhabdomyolysis with muscle necrosis,[8] delayed palmar desquamation (> and hematuria[34] are also described. Because patients are expected to be ingestion and laboratory tests correlate poorly with the degree of sympto findings early in the course of the ingestion are not reliable indicators of (see Diagnostic Testing).

Chronic Toxicity

Following chronic excessive thyroid hormone ingestions, patients may pre have a more subtle and insidious presentation. Classically, chronic ingesti occurs in patients with hypothyroidism, psychiatric disorders, and eating thyroid hormones chronically may develop significant weight loss, anxiety osteoporosis.[75] More severe manifestations, such as cardiac dysrhythmia and psychosis, also occur. As in patients with hyperthyroidism, intercurre stressors can trigger thyroid storm in these patients.

Numerous miniepidemics of hyperthyroidism and thyrotoxicosis have resul ground meat containing neck muscle contaminated with thyroid gland.[19] , these epidemics had 3 volunteers consume a single large portion of â€c implicated ground beef that previously had been frozen. Although all vo the mean serum peak T_4 (8â€“12 hours postingestion) was elevated ~15 undetectable for 4â€“17 days.[41] The practice of gullet trimming (using lar to these outbreaks has since been prohibited in US slaughter houses. The exists, especially when laryngeal muscles are used or when farmers and meat.[78] Until an exogenous source of thyroid hormone is suspected or id misdiagnosed with painless thyroiditis or thyrotoxicosis factitia.

Thyrotoxicosis factitia is a symptomatic disorder that mimics physiologic intentional chronic ingestion of exogenous thyroid hormone. The pattern surreptitious and maladaptive. Patients frequently have comorbid psychiat Munchausen syndrome or eating disorders, or are taking thyroid hormone with thyrotoxicosis factitia disorder often have access to thyroid medicatic

friends, or they can obtain the medications at their place of employment.

In recent years, thyroid hormones have gained popularity among dieters a hormones as weight-loss aids and as stimulants. Severe consequences car reported in 3 patients suspected of chronic ingestion of thyroid hormone enhancement.[7] In 2002, the heavily promoted Singaporean diet pill Slim and hyperthyroidism in numerous

patients.[39] Investigators found the proprietary herbal preparation was a amounts of the undeclared ingredients T_4 , T_3 (from thyroid gland extract banned drug). The medication was promptly withdrawn and the manufact Singapore Poisons Act.[39 , 40] Unfortunately, supplements containing thyro remain highly promoted and are readily available to the general public w Internet and in stores selling nutritional supplements (Chap. 44).[90]

Diagnostic Testing

Traditionally, thyroid testing was undertaken using combinations of measu measurement of hormone binding (T_3 uptake). Free T_4 and T_3 also can b dialysis (*free* T_4), analogue assays (ie, competitive analogs of either fre competitively bind for spaces on the serum-binding proteins), and antibo sequential assays that capture a representative portion of the free fractio Assessment of pituitary production of TSH has improved greatly in recent assays can readily detect suppression of TSH production. TSH is now relie thyroid function screening. Suppressed or elevated concentrations of TSH with a free T_4 assay and, if necessary, a free T_3 assay (Table 49-3).

The clinical manifestations of thyrotoxicosis and thyroid storm are well kn moderate, and high concentrations of T_3 and T_4 .[10] This lack of correlatio serum concentrations is also true for exogenous thyroid hormone ingestio [76 , 105] In a large case series of children with unintentional estimated in 40 and 800 Âµg), serum T_4 concentrations were drawn in 11 patients (1 Serum T_4 concentrations were normal in 5 of these children and were slig (mean 16 Âµg/dL). In this series, one infant who was estimated to have i significantly higher concentration (55 Âµg/dL at 4.5 hours) and developed diaphoresis and a â€œstaring spellâ€• 7 days postingestion. Another chil

4200 Âµg had a concentration of 12 Âµg/dL and developed significant ta
In a pediatric case associated with severe toxicity and seizures (see Acute
(estimated ingestion 18,000 Âµg levothyroxine) had a serum T_4 concentra
postingestion and 38 Âµg/dL on day 7, when he was symptomatic.[56] In a
of levothyroxine (720,000 Âµg), serum T_4 concentrations were > 30 Âµg/
(normal 0.7â€“1.86 ng/dL). In this case, TSH remained undetectable unti
Overall, the observed symptoms following thyroid hormone ingestion corre
ingested or with measured serum T_4 concentrations. Prolonged suppressior
ingestion of excess thyroid hormone.

TSH
0.5â€“5.0 ÂµIU/mL
Available assays with respective detection limits:
First generation = 1.0 ÂµIU/L
Second generation = 0.1 ÂµIU/L
Third generation = 0.01 ÂµIU/L
Total T_4 by RIA
5â€“12 Âµg/dL (64â€“153 nmol/L)
â†‘ In pregnancy, estrogens, oral contraceptives
Total T_3 by RIA
40â€“132 ng/dL (1.1â€“2.0 nmol/L)
â†‘ In pregnancy, estrogens, oral contraceptives
Free T_4
0.7â€“1.86 ng/dL (9â€“ 24 pmol/L)
â†‘ In hyperthyroidism, exogenous thyroxine ingestion
Free T_3
0.2â€“0.52 ng/dL (3â€“8 pmol/L)
â†‘ In hyperthyroidism, exogenous thyroid hormone (T_3 or T_4)
[a] Interlaboratory and interassay variations may occur.
RIA = radioimmunoassay; TSH = thyroid-stimulating hormone.

Diagnostic Test	Normal Values[a]	Comments

TABLE 49-3. Diagnostic Tests for Thyroid Hormone and Thyroid F

Routine analysis of laboratory thyroid function tests in the setting of acu likely will not affect management. Analysis of thyroid hormone concentrat confirmation of a suspected ingestion is desired and in massive ingestions symptoms may occur. Suppression of TSH and elevated thyroid hormone serum thyroglobulin concentration may help to differentiate between thyr disease.[68]

Management

General

Based on the existing literature, conservative management is adequate in unintentional thyroxine ingestions in both adults and children. Most childr managed with home observation and follow-up appointments. In cases wh estimated to be > 4000 Âµg, patient follow-up by regular telephone conta Historically, most children with unintentional ingestions have been treated activated charcoal and/or syrup of ipecac or by gastric lavage,[28 , 48 , 56] procedures probably are unnecessary. Based on 2 large series of uninten which no toxicity was observed in the vast majority of cases, clinically si with estimated ingestions < 5000 Âµg.[78 , 102] Because children almost un minor symptoms, activated charcoal administration should be considered o Âµg thyroxine. Aspiration risks are minimal in awake, alert children who a and take activated charcoal orally, without nasogastric tube placement.[58] acute ingestions > 5000 Âµg thyroxine also should be treated with activa presentations with massive thyroxine ingestions (> 10,000â€“50,000 Âµg) ingestions of preparations containing large amounts of T_3 , gastric empty emesis and orogastric lavage are unwarranted.[8 , 34] Similarly, patients w 10,000â€“50,000 Âµg) or ingestion of T_3 -containing products should be anticipation of development of significant symptoms.[8 , 34 , 56 , 61]

Treatment should be based on the development of symptoms and should protection, and control of sympathomimetic symptoms, mental status alt Adrenergic antagonism with propranolol has been used for sympathomime cases.[28 , 48 , 56 , 60 , 76 , 95]

Empirical treatment with Î²-adrenergic antagonists is not recommended. T
for significant tachycardia, dysrhythmias, and other symptoms of catecho

Agitation

When sedation is required, parenteral benzodiazepines and barbiturates
benzodiazepines such as midazolam or diazepam should be used to contr
symptomatic patients. Phenobarbital should be considered as a sole agent
adjunct in patients requiring sedation because it offers the added theoret
enhanced hepatic elimination of thyroxine (Table 49-2). Because of the
the lack of evidence regarding the clinical use of enhanced hepatic elimi
sedation with phenobarbital for the sole purpose of enhanced elimination
antipsychotic agents such as haloperidol and droperidol should be avoide
anticholinergic properties can exacerbate thyrotoxic symptoms. In addition
drugs to prolong the QTc interval and predispose to malignant dysrhythmi
catecholaminergic patient. Antipsychotic agents should be reserved for m
strong psychiatric behavioral manifestations.

Catecholamine Excess and Cardiovascular

The principal mechanism of action of Î²-adrenergic antagonists in hyperth
receptorâ€“mediated effects.[75] In addition to their sympatholytic effects
inhibit 5â€²-deiodinase, thereby decreasing peripheral conversion of T_4 t
electrocardiographic and blood pressure monitoring are indicated when Î
used. The clinical significance of decreased peripheral conversion in the s
Propranolol is the most frequently used Î²-adrenergic antagonist in thyro
[63 , 76 , 95] Parenteral Î²-adrenergic antagonists should be used when sym
rapid control of heart rate is required. Starting doses of 1â€“2 mg IV pr
are recommended. High doses have been reported in massive thyroxine o
received 23 mg propranolol IV over 1 hour on initial presentation, then re
mg/day IV for 5 more days.[34] Oral propranolol can be used for persistent
both hemodynamically and medically stable and are not acutely agitated.
20â€“120 mg every 6 hours may be required. Other Î²-adrenergic antago
provided they do not have intrinsic sympathomimetic activity (ie, partial
receptors), such as acebutolol, oxprenolol, penbutolol, and pindolol (Chap

When Î²-adrenergic antagonists are contraindicated, as in patients with a heart failure, calcium channel blockers can be used. Among calcium chan most studied for the management of thyrotoxicosis.[71, 88] A double-blind, propranolol to diltiazem for thyrotoxic symptoms found that diltiazem was as effective as propranolol.[71] Another study successfully used diltiazem as of cardiovascular symptoms in 11 thyrotoxic patients.[88] Doses of 60â€“12 daily or 5â€“10 mg/hour parenterally have been used.[71, 88] A possible e calcium channel blockers in thyrotoxicosis is that thyroid hormone enhanc voltage-gated Ca^{2+} channels, accelerates Ca^{2+} entry into the sarcoplasm cellular Ca^{2+} storage capacity.[50, 51, 72, 92] The net effect of these chan chronotropy. Calcium channel blockers, particularly diltiazem and verapam of parenteral Î²-adrenergic antagonists in combination with parenteral cal contraindicated because of the risk for profound hypotension and cardiov

Hyperthermia

Antipyretics are recommended for hyperpyrexia, with acetaminophen being particularly high doses (1.5â€“3 g/d), should be avoided because it carrie thyrotoxicity from displacement of T_3 and T_4 from TBG (Table 49-2). No especially extreme hyperthermia (> 106Â°F [> 41Â°C]), most likely is se agitation and excess heat production from the hypermetabolic, catechola Extreme hyperthermia should be considered a medical emergency and sh treated with active external cooling with ice baths and with Î²-adrenergic benzodiazepines and/or barbiturates, and intubation with paralysis if nece

Other Therapies

Bile acid sequestrants, such as cholestyramine and colestipol, and alumir sucralfate bind to exogenous T_4 and decrease GI absorption (Table 49-2 supporting their effectiveness is poor, they are not routinely recommende overdose.[58]

Oral iodine contrast media is known to decrease peripheral conversion of PO daily are routinely used for thyroid storm. Thioamides, such as propy methimazole, and the corticosteroids are thyroid gland inhibitors that are

nonâ€“drug-related hyperthyroidism. In addition, thioamides inhibit periph Evidence from limited case reports suggests poor efficacy of both thioam overdose[8 , 26 , 58] (see Thioamides).

Although use of antithyroid drugs such as PTU, corticosteroids, and iodine overdose has theoretical benefits, these drugs are unvalidated, potentially additional benefit, or be superior, to conventional therapy with activated antagonism, and sedation. These treatments are not recommended as ac of exogenous thyroxine overdose.

Extracorporeal Drug Removal

Extracorporeal drug removal procedures, such as plasma exchange or pl transfusion (in children), and charcoal hemoperfusion, have been used in hormone overdose and thyroid storm.[1 , 8 , 9 , 26 , 42 , 58 , 62 , 69 , 74 , 97] regarding improvement of clinical condition and plasma clearances of thyr methods are

conflicting. The largest series of acute ingestions involved 6 patients who massive thyroxine ingestions of prescribed capsules containing a 1000-fol thyroxine (dose range 50,000â€“125,000 Âµg/d for 2â€“12 days). Charco plasmapheresis were used in all patients. Plasmapheresis was found to be hemoperfusion in the extraction of thyroxine. The authors suggest this in duration of thyrotoxicosis. Rebound elevations in plasma concentrations oc patients, suggesting redistribution between extravascular and intravascu redistribution is expected given the large volume of distribution for thyroi There may be a role for early plasmapheresis in the exceptional situation of thyroid hormone. Because the outcomes from most ingestions of thyroi with good supportive care, sedation, and Î²-adrenergic antagonism, the r be evaluated on case-by-case basis after consultation with a medical tox

Xenobiotics with Antithyroid Effects

Thioamides

Antithyroid drugs are used to decrease the amount of thyroid hormone ir commonly in Graves disease. Thioamides are a group of chemicals with tl Methimazole and PTU are the two principal thioamides used for treatmen Carbimazole, which is bioactivated methimazole, is available in Europe an both inhibit the activity of thyroid peroxidase in the thyroid gland.[98] PTU inactivating 5â€²-deiodinase, which decreases the peripheral conversion o active T_3 .[20 , 59] Because thioamides act primarily by decreasing thyroid release), a lag time of 3â€“4 weeks may occur before T_4 is depleted. The 50â€“80%. It is rapidly absorbed from the GI tract and may undergo first Although its plasma half-life is only 1.5 hours, its effects are long-lasting thyroid gland. PTU is inactivated by glucuronidation and is renally elimin absorbed, is concentrated in the thyroid, and is more slowly eliminated th Doses of PTU are in the range of 100 mg orally every 6â€“8 hours. Methir daily. Although PTU is 10 times less potent than methimazole, it is more for its use are mild-to-moderate hyperthyroidism.

The two thioamides traverse the placenta (methimazole more than PTU) a during pregnancy. However, they are minimally secreted in breast milk. A 3â€“12% of patients taking thioamides. The most common adverse effect rash. Methimazole, PTU, and, to a lesser extent, carbimazole can cause and age-related agranulocytosis and neutrophil dyscrasias.[61 , 70 , 80] This adverse effect can be treated by administration of granulocyte colony-sti withdrawal of thioamides can lead to rebound symptoms and thyrotoxic s

Little data exist regarding overdose with thioamides. A 12-year-old girl w who was estimated to have ingested 5000â€“13,000 mg PTU, developed c concentration and elevated alkaline phosphatase concentration (7350 mU functioning thyroid gland may have contributed to the benign course in th sequelae have been associated with acute overdose of thioamides.

Iodides

Prior to the development of thioamides, iodide salts were the principal t Iodides decrease thyroid hormone concentrations by inhibiting formation a high-dose iodides (> 2g/d) decrease thyroid hormone release and produc 2â€“7 days. Common sources of iodides include calcium iodide, sodium io

pharmaceutical preparations, oral drops commonly referred to as SSKI [s
methyl iodide (industrial preparations).

The adverse reaction to chronic ingestion of small or excessive amounts
is characterized by cutaneous rash, laryngitis, bronchitis, esophagitis, co
taste, salivation, headache, and bleeding diathesis. Immune-mediated h
consisting of urticaria, angioedema, eosinophilia, vasculitis, arthralgia, ly
anaphylactoid reactions may occur. Chronic iodide therapy has produced
rarely hyperthyroidism. As much as 10 g sodium iodide has been adminis
signs or symptoms of toxicity.

Iodide (I^-), unlike iodine (I_2) (Chap. 98), is not a caustic. KI is added
for prevention of goiter. It also is used as a prophylactic agent after expo
nuclear fallout to prevent uptake of radioactive iodine into the thyroid gla
most commonly used iodide for thyroid suppression in hyperthyroidism. Io
described but rare disorder characterized by severe sialadenitis (or paro
conjunctivitis following administration of ionic and nonionic iodine-containi
iodide salts (Table 49-4).[12, 13, 49] Although the mechanism remains unc
idiosyncratic or secondary to iodide accumulation and subsequent inflamm
the salivary gland. Symptoms tend to occur within 12 hours and resolve
hours.[12]

Iodides should be avoided in pregnancy because they readily cross the p
complications, such as cretinism and death from respiratory failure secon
reported.[22, 43, 66] Iodide salts adsorb to activated charcoal.

Methyl iodide is a methylating agent used in the chemical and pharmaceu
microscopy, as a catalyst in production of organic lead compounds, as an
in fire extinguishers, and formerly as a soil fumigant. Methyl iodide toxic
with early pulmonary congestion, lethargy, and renal failure. It also is a
degeneration, multifocal neuropathies (cranial nerve and spinal), Parkinso
persistent psychiatric symptoms (months to years).[2, 44] Chronic repeated
misdiagnoses such as multiple sclerosis. The toxicity is similar to that of
112).

Lithium

Goiter (in 37% of patients)

Hypothyroidism (in 5â€“15% of patients)
Mechanism unclear
Amiodarone (37% iodine by weight)
1. Hypothyroidism (in 25% of patients)
â†‘ Peripheral conversion of T_4 to T_3
1. Inhibition of 5â€²-deiodinase
2. Hyperthyroidism, type 1: in patients with preexisting goiters from low
2. Type 1: iodine excess stimulates thyroid hormone production
3. Hyperthyroidism, type 2: in patients with previously normal thyroid fu
3. Type 2: causes thyroid inflammation
Î²-Adrenergic antagonists
â†“ Peripheral conversion of T_4 to T_3
Inhibition of 5â€²-deiodinase
PTU
Decreased thyroid hormone synthesis
â†“ Peripheral conversion of T_4 to T_3
Inhibition of thyroid peroxidase
Inhibition of 5â€²-deiodinase
Corticosteroids
â†“ Peripheral conversion of T_4 to T_3
Inhibition of 5â€²-deiodinase
Iodine

1. Low dose: transient or no effect
2. High doses (>10 g/d): â†“ thyroid hormone secretion
3. Transient thyrotoxicosis (ie, Jod-Basedow effect)
    A. With rapid correction of hypothyroidism from iodine deficiency
    B. From topical iodine
4. Delirium
5. Caustic injury

1. Transiently stimulates thyroid hormone secretion
2. Inhibition of thyroid hormone synthesis
3. Increases thyroid hormone synthesis
4. Mechanism unclear

5. Direct cytotoxic injury to cells

Iodinated contrast material
1. Rapid â†“ peripheral conversion of T_4 to T_3 (adjunctive treatment in tl
1. Inhibition of 5â€²-deiodinase
2. Prolonged suppression of T_4 to T_3
2. Mechanism unclear
3. Causes thyrotoxicosis and thyroid storm
3. Mechanism unclear
4. Iodide mumps
4. Idiopathic, toxic accumulation of iodide
Radioactive iodine
Treatment of hyperthyroidism, causes hypothyroidism
Uptake into thyroid follicles causes local destruction
Anion inhibitors[a]
â†“ Iodine uptake into thyroid follicle, used in iodide-induced hyperthyro
Blocks uptake of iodide into the thyroid gland by competitive inhibition
[a] Also referred to as monovalent anions, ie, thiocyanate (SCN^-), pertech
perchlorate (ClO_4^-).

Xenobiotic Effect Mechanism

TABLE 49-4. Common Xenobiotics That Alter Thyroid Function an
Effects[6,11,27,33,37,38,53,54,106,

Summary

Despite the high prevalence of thyroid disorders in the general population levothyroxine, remarkably little morbidity and mortality associated with c is reported. Most unintentional ingestions in children are benign, and they outpatients for 5â€“10 days. Intentional ingestions in adults may result ir ICU management. Supportive care with sedation, cooling measures, and adequate in most cases. Chronic ingestions may produce more severe syn more insidiously or are complicated by thyroid storm. Unregulated dietar

thyroid hormone used for weight loss and athletic enhancement are becc consumers via the Internet and in health food or supplement stores. Clir thyroid hormone exposure in patients with thyrotoxicosis and suppressed

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Chapter 50
Antihistamines and Decongestants

Anthony J. Tomassoni

Richard S. Weisman

A 17-year-old man was brought to the emergency department by friends who noted progressive onset of drowsiness and confusion. The friends indicated the patient became progressively more disoriented and made statements that were out of context. The patient repeatedly told his friends that he was thirsty. Shortly thereafter, his friends reported he seemed to be responding to internal stimuli. Upon questioning by his friends while en route to the emergency department, the patient admitted taking â€œa bottlefulâ€• of diphenhydramine capsules in a suicide attempt between 1 and 2 hours earlier. The bottle was not located. Past medical history obtained from friends and family was negative. Family history was negative for epilepsy. Social history was positive for smoking and occasional ethanol and marijuana use. Upon initial evaluation, the patient was lethargic, he had no verbal response to questions, and when aroused with vigorous stimulation he became agitated and muttered unintelligible sounds. His initial vital signs were: blood pressure, 175/90 mm Hg; pulse, 135 beats/min;

respiratory rate, 18 breaths/min; temperature 100.0Â°F (37.8Â°C). His skin was warm, dry, and pink. Examination of the head, eyes, ears, nose, and throat was notable for 7-mm pupils that were sluggishly reactive to light and for dry mucous membranes. His neck showed no evidence of meningismus. Chest and heart examinations were normal except for tachycardia. Abdominal examination was remarkable only for absent bowel sounds. The patient's neurologic status was notable for periods of lethargy alternating with agitation upon stimulation and lack of spontaneous verbal output. During his agitation, the patient sometimes appeared to be picking at the bed sheets or the clothing of caregivers. Occasional myoclonic jerks were present. Deep tendon reflexes were symmetric and plantar reflexes were downgoing.

Oxygen was administered via nasal cannula at 2 L/min. Cardiac monitoring was instituted. Intravenous 0.9% sodium chloride solution was administered at a rate of 150 mL/h. Blood was sent to the laboratory for a complete blood count, electrolytes, glucose, toxicology screen, and acetaminophen concentration. A nasogastric tube was inserted, gastric fluid was aspirated to minimize potential for aspiration, and 50 g activated charcoal was administered. A Foley catheter was inserted, and nearly 1 L of clear urine was immediately drained. The patient's agitation improved immediately after this procedure. ECG revealed sinus tachycardia with a normal QRS duration of 0.08 seconds and normal QTc interval. Ethanol concentration was 55 mg/dL. No acetaminophen was detected, and immunoassay-based toxicology screen was negative for cyclic antidepressants and common drugs of abuse.

Approximately 3â€“4 hours after his ingestion, the patient had a grand mal, tonicâ€“clonic seizure that lasted approximately 2 minutes. As the seizure appeared to be subsiding, diazepam 5 mg was administered. Following the seizure, the patient had a brief postictal period. He then remained somnolent but arousable for 4 hours, after which he progressively became alert and oriented over the next 8 hours. His vital signs gradually returned to normal over

the same time period, and bowel sounds returned. The Foley catheter was removed, and the patient was able to void spontaneously. No significant rhabdomyolysis occurred. The patient was transferred for psychiatric assessment.

Antihistamines

History and Epidemiology

H_1 receptor antagonists were introduced into clinical use in the early 1940s. The class continues to find widespread application in the treatment of anaphylaxis, allergic rhinitis, urticaria, and other histamine-mediated disorders. The numerous functions of histamine and its receptors in the nervous system, immune system, and other organ systems have been further elucidated in recent years.

Antihistamines are available worldwide, and many do not require a prescription. They often are used for symptomatic relief of allergy symptoms and are included in many combination cold preparations. They also are found in nonprescription sleeping aids. Antihistamines are frequently ingested in suicide attempts, probably because of their ready availability. Poison center and clinical experience suggests that recreational use of antihistamines is increasing, but whether the increased use results simply from inclusion of antihistamines in cold preparations containing the widely abused cough suppressant dextromethorphan is unclear (Chap. 38). Terfenadine and astemizole were associated with cardiac dysrhythmias and are no longer approved for use in the United States[47] (Chap. 133).

Unintentional exposures to antihistamine-containing preparations are common, with > 14,000 cases involving children younger than 6 years reported annually.[32] Liquid formulations attractive to children are available, and children occasionally are administered diphenhydramine or another antihistamine as a sedative by parents and daycare workers.[3] Although ingestion is the usual route of

exposure, toxicity can also result from exposure to topical preparations containing antihistamines.[43]

Physiology of the Histamine Receptor System

Four types of histamine receptors are recognized and designated H_1 , H_2 , H_3 , and H_4 . All are helical transmembrane molecules that transduce extracellular signals via G proteins to intracellular second-messenger systems. H_1 receptors are located in the CNS, heart and vasculature, airways, sensory nerves, gastrointestinal smooth muscle cells, immune cells, and adrenal medulla. The many functions of histamine and the H_1 receptor include control of the sleepâ€“wake cycle, cognition, memory, and endocrine homeostasis. The H_1 receptor also causes vasodilation, increases vascular permeability and bronchoconstriction, and decreases atrioventricular nodal conduction when histamine is present. H_2 receptors are located in cells of the gastric mucosa, heart, lung, CNS, uterus, and immune cells. The action of histamine on H_2 receptor results in increased gastric acid secretion, increased vascular permeability, and other effects. Endogenous histamine is one of the triggers for gastric acid secretion through interaction with the H_2 receptor located on gastric parietal cells. This process results in increased adenyl cyclase and cyclic adenosine monophosphate (cAMP), with activation of the H^+ - K^+ -ATPase pump and ultimately release of H^+ into the gastric lumen.

H_3 receptors are found in neurons of the central and peripheral nervous systems, airways, and GI tract. The action of histamine on H_3 receptors of the CNS decreases further release of histamine, acetylcholine, dopamine, norepinephrine and serotonin.[64] H_3 receptors partly act to prevent excessive bronchoconstriction. H_3 receptors also are implicated in control of neurogenic inflammation and proinflammatory activity.[37] The recently identified H_4 receptor is located in leukocytes, bone marrow, spleen, lung, liver, colon, and

hippocampus. It apparently has roles in the differentiation of myeloblasts and promyelocytes and eosinophil chemotaxis. This chapter focuses on H_1 and H_2 antihistamines, as no H_3 or H_4 receptor active pharmaceuticals are currently in clinical use.

Pharmacology

Histamine Antagonists

All known H_1 histamine antagonists function as inverse agonists and not simply competitive antagonists.[54] For consistency with the medical literature and the current clinical use of these drugs, we use the terms *H_1 antihistamine* and *histamine antagonist* rather than inverse agonist to describe agents of this class.

Agonists and antagonists that act at each of the four histamine-modulated receptor sites have been identified. Through these receptors, histamine interacts with G proteins in the plasma membranes. Stimulation of H_1 receptors results in increased synthesis of inositol-1,4,5-triphosphate and several diacylglycerols (DAGs) from phospholipids located in cell membranes. Inositol-1,4,5-triphosphate causes release of calcium, which then activates calciumâ€“calmodulin-dependent myosin light-chain kinase, resulting in enhanced cross-bridging and smooth muscle contraction. The reaction at the H_1 receptors is mediated by phospholipase C. H_2 receptor stimulation is mediated by adenyl cyclase activation of cyclic AMP-dependent protein kinase in smooth muscle and in parietal cells of the stomach and results in increased gastric acidity through stimulation of the H^+ -K^+ -ATPase pump.

Six major classes of â€œfirst-generationâ€• antihistamines are traditionally recognized. They are first-generation derivatives of ethylenediamine, ethanolamine, alkylamines, phenothiazines, piperazines, and piperidines. Many of the classic antihistamines are substituted ethylamine structures with a tertiary amino group linked by a 2- or 3-carbon chain with two aromatic groups.[20] This structure

differs from histamine by the absence of a primary amino group and the presence of a single aromatic moiety. Figure 50-1 shows the structures of the pharmacologic classes of the antihistamines.

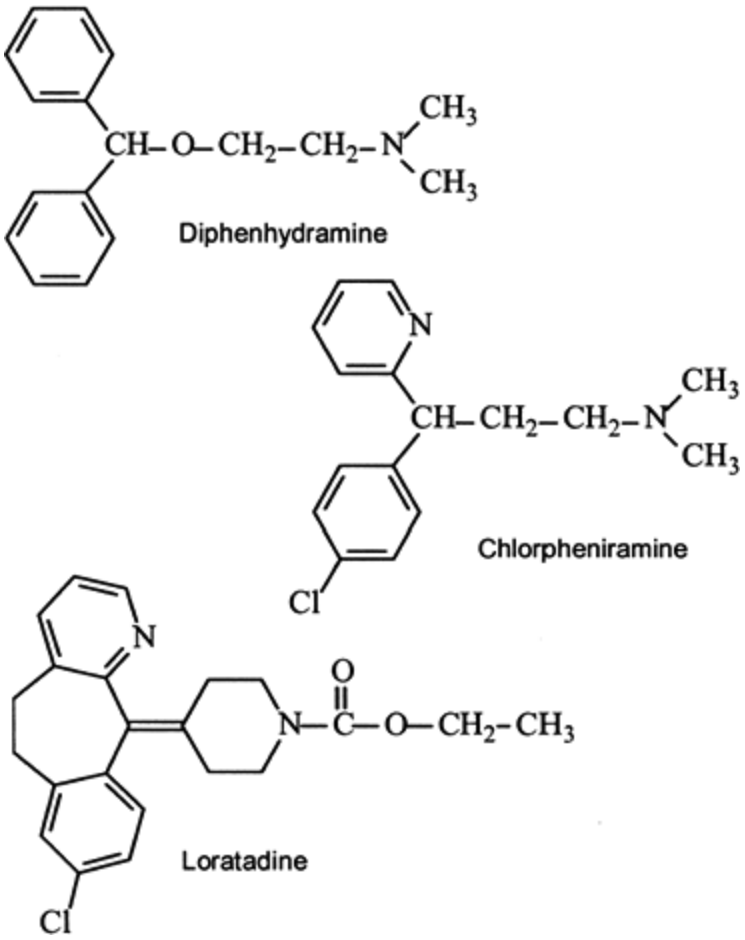


Figure 50-1. Structures of diverse H_1 receptor antagonists.

Currently, the more clinically useful classification may distinguish between the older â€œfirst-generationâ€• agents, which readily penetrate the bloodâ€“brain barrier and produce CNS effects, and the peripherally selective or â€œsecond-generationâ€• H_1 antihistamines, which have a higher therapeutic index. Central effects of the first-generation H_1 antihistamines likely result from their interference with histamine function as a neurotransmitter. The first-generation H_1 antihistamines also bind to muscarinic and

perhaps adrenergic receptors. In addition, some first-generation antihistamines are not recognized by the P-glycoprotein efflux pump on the luminal surfaces of vascular endothelial cells in the CNS. Second-generation H_1 receptor antagonists are highly specific for peripheral rather than central H_1 receptors receptors.[45] They do not penetrate the CNS well because of their hydrophilicity, their relatively high molecular weight, and recognition by the P-glycoprotein efflux pump on the luminal surfaces of vascular endothelial cells in the CNS. Cetirizine, fexofenadine, loratadine, azelastine (nasal spray), and ebastine have lower binding affinities for the cholinergic, Î±-adrenergic, and Î²-adrenergic receptor sites than do the first-generation antihistamines. Some second-generation H_1 receptor antagonists, such as azelastine, a phthalazinone derivative, do not easily fit the standard classification scheme. Of note, using recommended doses of antihistamines, PET scanning shows that first-generation agents occupy > 70% of the H_1 receptors in the frontal cortex, temporal cortex, hippocampus, and pons. In contrast, the second-generation agents occupy < 20â€“30% of the available CNS H_1 receptors.[60, 61]

Given the absence of anticholinergic effects of the second-generation antihistamines, antihistamine therapy for patients with seasonal asthma has been reintroduced and has proved efficacious.[19] The relative incidence of anticholinergic and CNS adverse effects caused by second-generation H_1 antihistamines is similar to that produced by placebo.[2, 8] However, some patients report sedation, especially if higher-than-recommended dosages are taken.[8] Table 50-1 lists the peripheral selectivity of the antihistamine that is principally defined by the relative absence of anticholinergic and sedative properties of the H_1 antagonists.

Acrivastine
Alkylamine
+

6â€“8
8 mg tid
Azatadine
Piperidine
+
12
1â€“2 mg bid
Brompheniramine
Alkylamine
++
4â€“6
4 mg qid
Buclizine
Piperazine
++
4â€“6
50 mg bid
Carbinoxamine
Ethanolamine
++++
3â€“6
4â€“8 mg qid
Cetirizine
Piperazine
+
12
5â€“10 mg qid
Chlorpheniramine
Alkylamine
++
4â€“6
4 mg qid
Clemastine
Ethanolamine

++++
12â€“24
2 mg bid
Desloratadine
Piperidine
0
24
5 mg qd
Dexbrompheniramine
Alkylamine
++
12
3â€“12 mg bid
Dexchlorpheniramine
Alkylamine
++
3â€“6
4â€“6 mg tid
Dimenhydrinate
Ethanolamine
++++
4â€“6
50â€“100 mg qid
Dimethindene
Alkylamine
++
8
1â€“2 mg tid
Diphenhydramine
Ethanolamine
++++
4â€“6
25â€“50 mg qid
Doxylamine

Ethanolamine
++++
6
7.5â€“12.5 mg qid
Fexofenadine
Piperidine
+
12
60 mg bid
Hydroxyzine
Piperazine
++
6â€“8
25 mg qid
Levocetirizine
Piperazine
0
24
5 mg qd
Loratadine
Piperidine
+
8â€“12
10 mg qd
Meclizine
Piperazine
++
6â€“8
25 mg tid
Pheniramine
Alkylamine
++
4â€“6
5â€“15 mg q4h

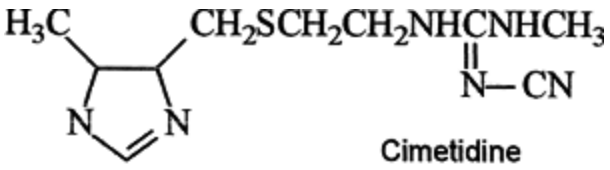
Phenyltoloxamine
Ethanolamine
+ + + +
4â€“8
7.5â€“25 mg tid
Promethazine
Phenothiazine
+ + + +
4â€“6
12.5â€“25 mg qid
Trimeprazine
Phenothiazine
+ + + +
4â€“6
2.5 mg qid
Tripelennamine
Ethylenediamine
+ + +
4â€“6
25â€“50 mg qid
Triprolidine
Alkylamine
+ +
4â€“6
2.5 mg qid

Antihistamine	Anticholinergic Class	Sedation	Duration of Action (h)	Typical Adult Dose

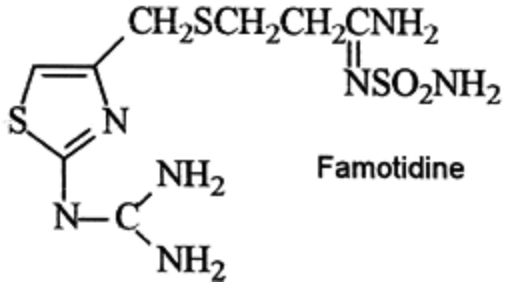
TABLE 50-1. The Pharmacologic Characteristics of Antihistamine

H_2 Receptor Antagonists

These histamine congeners are highly selective and competitively inhibit the H_2 receptor site. The original compound in this class, which retains the imidazole ring of histamine, is cimetidine (Figure 50-2). Although newer compounds, such as ranitidine and famotidine, have replaced this ring with a furan or thiazole group, respectively, they retain significant similarity to the histamine structure.[56]



Cimetidine



Famotidine

Figure 50-2. Structures of H_2 receptor antagonists.

The effectiveness of H_2 receptor antagonists in the treatment of gastroesophageal reflux disease is improved further by their concomitant alteration in the response of parietal cells to acetylcholine and gastrin, two other stimulants for gastric acid secretion (Figure 50-3). Of note, H_2 receptor antagonists have little effect elsewhere in the body, and they have weak CNS penetration secondary to their hydrophilic properties.

Reports on the effect of H_2 antihistamines on ethanol metabolism yield conflicting results. Definitive studies have not been performed, but at this time any effect at clinically relevant doses of alcohol appears insignificant. Questions regarding the effect of accelerated

gastric emptying time caused by H_2 antagonists on ethanol absorption, metabolic enzyme polymorphisms, interindividual variability of the effects of H_2 blockers on ethanol metabolism, and magnitude of the effect (if any) caused by different H_2 blockers remain to be answered.[22 , 59]

Pharmacokinetics and Toxicokinetics

H_1 Receptor Antagonists

The antihistamines are generally well absorbed following oral administration, and most achieve peak plasma concentrations within 2â€“3 hours. Although less well studied, dermal absorption appears to be consequential, especially with extensive or prolonged application to abnormal skin.[43] The maximum antihistaminic effect occurs several hours after peak serum concentrations. The durations of action range from 3 hours to > 24 hours, which is much longer than predicted from the extremely variable serum elimination half-life values of the antihistamines.

Hepatic metabolism is the primary route of metabolism for antihistamines.[48] Many Asian patients can acetylate therapeutic concentrations of diphenhydramine to a nontoxic metabolite twice as rapidly as white patients, making Asians much less sensitive to both the psychomotor and sedative effects.[58] Alterations in usual dosages may be required for patients taking other medications, those with hepatic or renal dysfunction, the young, and the elderly. Such modifications often must be made empirically because formal studies and recommendations for many agents are lacking. Drugâ€“drug interactions may be caused by modulation of CYP450 metabolism or interference with active transport mechanism (eg, P-glycoprotein).[54]

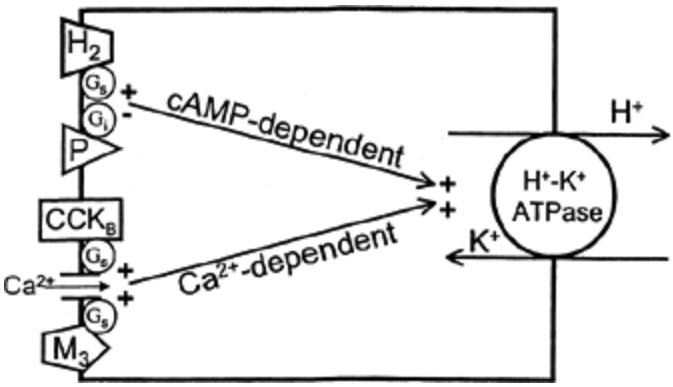


Figure 50-3. Schematic representation of a gastric parietal cell demonstrating the mechanism of hydrogen ion secretion into the lumen. Gastric acid is modulated by both calcium-dependent and cyclic adenosine monophosphate (cAMP)-dependent pathways. Histamine binding to the H_2 receptor increases gastric acidity by increasing cAMP through the stimulatory G protein G_S . Prostaglandins (P) decrease gastric acidity by decreasing cAMP through the inhibitory G protein G_i . Both acetylcholine and gastrin increase gastric acidity by increasing the influx of calcium through G_S interactions. Acetylcholine binds at the muscarinic$_3$ (M_3) receptor, whereas gastrin binds at the cholecystokinin B (CCK_B) receptor.

H_2 Receptor Antagonists

Cimetidine is the prototypical H_2 receptor antagonist. Cimetidine is rapidly and completely absorbed following oral administration. Cimetidine has a volume of distribution of approximately 2 L/kg, with 13â€“25% protein binding.[1] Up to 75% of cimetidine is eliminated unchanged in the urine, 15% is metabolized by the liver, and 10% is eliminated unchanged in the stool. The elimination half-life in patients with normal renal function is approximately 2 hours, but the half-life is substantially prolonged with impaired renal function.[1] Cimetidine is responsible for numerous drugâ€“drug interactions because it can inhibit cytochrome P450 activity, thereby impairing hepatic drug metabolism. It can reduce hepatic blood flow, resulting

in decreased clearance of drugs highly extracted by the liver. None of the other currently available H_2 receptor antagonists inhibit the cytochrome P450 oxidase system.[42] Additionally, by altering gastric pH, cimetidine and all the other H_2 antagonists may alter the absorption of acid-labile xenobiotics. Finally, cimetidine is associated with enhanced myelosuppression if it is administered with xenobiotics capable of causing bone marrow suppression.[51] Table 50-2 lists the pharmacologic properties of H_2 receptor antagonists.

Cimetidine
800
1.0
19
2.0
62
Ranitidine
300
1.3
15
2.1
69
Nizatidine
300
1.2
28
1.3
61
Famotidine
40
1.3
17
2.6
67

Drug	Typical Adult Dose (mg)	Volume of Distribution (L/kg)	Protein Binding (%)	Half-Life (hours)	Urinary Elimination (%)

TABLE 50-2. Pharmacology of Histamine H_2 Receptor Antagonists

Clinical Manifestations

H_1 Receptor Antagonists

Although dry mouth and mydriasis are common adverse therapeutic effects, sedation is of the greatest concern. Therapeutic antihistamine use may be as incapacitating as ethanol intoxication with regard to operating motor vehicles.[23] Compared with adults, children may more commonly present with excitation and irritability and may be more prone to hallucinations and seizures.

The clinical manifestations of H_1 receptor antagonist overdose are largely extensions of the adverse effects noted with therapeutic use of these agents. Following overdose with a first-generation H_1 antihistamine, patients typically present with CNS depression and an anticholinergic syndrome. Findings typically include mydriasis, tachycardia, fever, dry mucous membranes, urinary retention, diminished bowel sounds, and disorientation (Table 50-3). The patient's skin may appear flushed, warm, and dry. Hyperthermia correlates with the extent of agitation, ambient temperature and humidity, and length of time during which the patient cannot dissipate heat because of anticholinergic-mediated reduction in sweating. Ingestion of second-generation antihistamines usually does not result in significant CNS depression or anticholinergic effects. Some patients with therapeutic dosing or following overdose develop the central anticholinergic syndrome, in which CNS anticholinergic

effects, such as delirium or hallucinations, outlast peripheral anticholinergic effects. The lack of tachycardia, skin changes, or other peripheral anticholinergic manifestations complicates obtaining the correct diagnosis for antihistamine-poisoned patients who arrive late to healthcare and have a clear exposure history.[18, 65]

In a review of 136 patients with diphenhydramine overdose, somnolence, lethargy, or coma occurred in approximately 55% of patients, whereas 15% experienced a catatonic stupor.[34] Several reports suggest that young children experience more respiratory complications, CNS stimulation, anticholinergic effects, and seizures than do adult patients. In a placebo-controlled study comparing the CNS effects of first- and second-generation H_1 receptor antihistamines, the second-generation agents caused less cognitive

dysfunction and somnolence.[8, 26] This finding was corroborated in the simulated driving model, in which loratadine produced significantly less impairment than diphenhydramine.[23] Use of diphenhydramine compared with loratadine in a work setting results in significantly higher injury rates.[14]

Agitation
Hypertension
Hallucinations
Tachycardia
Confusion
Hyperthermia
Sedation
Mydriasis
Coma
Dry, flushed skin
Seizures
Urinary retention

Central Peripheral

TABLE 50-3. Anticholinergic Signs and Symptoms

Sinus tachycardia is a consistent finding following an antihistamine overdose with anticholinergic effects. Both hypotension and hypertension may occur.[39] These findings probably relate more to the patient's age, volume status, and vascular tone than to a specific class of antihistamines. As a result of sodium channel blockade following a large diphenhydramine overdose, prolongation of both the QRS complexes and QT intervals may occur.[31, 50, 52, 62] Of note, postmortem findings are generally limited to pulmonary and visceral edema, suggesting cardiogenic death.[33]

Mydriasis develops at both therapeutic and toxic doses, with most patients describing blurred vision and/or diplopia. Both vertical and horizontal nystagmus occur in patients with diphenhydramine overdose. Other CNS effects include seizures, hallucinations, acute extrapyramidal movement disorders, and psychoses.[13, 30]

Rhabdomyolysis can occur in patients with extreme agitation or seizures following an H_1 antihistamine overdose. Rhabdomyolysis is commonly noted in patients who overdose with doxylamine, even in the absence of trauma or any of the other common, etiologies such as seizures, shock, or crush injuries.[16, 35, 38] The mechanism is undefined. Rhabdomyolysis is reported as a rare adverse event following diphenhydramine overdose.[11]

Topical application of some antihistamines, particularly to children with skin lesions such as chickenpox, may produce classic systemic anticholinergic toxicity.[43] Promethazine and other H_1 antihistamines are associated with sudden infant death syndrome, although causality is not proven.[49] Cetirizine, a second-generation H_1 antihistamine, is suggested as safer for infant use, but further study is warranted.[55] Other adverse effects include pancytopenia and jaundice.

Elderly patients are more susceptible to adverse events because renal and hepatic dysfunction, which are more common in the elderly,

delays antihistamine metabolism.[26] Several infants who died of diphenhydramine overdose had serum concentrations lower than expected for adults; the implications are unclear.[3] All H_1 antihistamines cross the placenta, and some are teratogenic in animals. Because of their antimuscarinic effects, first-generation antihistamines are generally contraindicated in patients with glaucoma or prostatic hypertrophy.

H_2 Receptor Antagonists

Acute toxic effects appear to be extremely rare, even after large (20 g) oral ingestions of H_2 receptor antagonists.[28] Patients may develop tachycardia, dilated and sluggishly reactive pupils, slurred speech, and confusion.[57, 63] Bradycardia, hypotension, and cardiac arrest have followed rapid intravenous administration of cimetidine in seriously ill patients.[53] Famotidine and ranitidine produce even fewer dose-related toxicities in overdose. In addition, they are less likely than cimetidine to induce or inhibit the cytochrome P450 enzyme system, thereby producing fewer drugâ€“drug interactions.[27, 44]

Management

Patients who will develop severe complications may be indistinguishable from those who will have a benign course. The patient's vital signs and mental status must be monitored. The individual should be attached to on a cardiac monitor and observed for signs of sodium channel blockade (increased QRS duration and prolonged QT_c interval), development of seizures, and dysrhythmias. Assessment of the serum acetaminophen concentration is important because many analgesics and cough and cold products contain acetaminophen. Other laboratory studies should be obtained as indicated by history or physical signs and symptoms, such as creatine kinase in patients with seizures or doxylamine overdose. Measurement of antihistamine concentrations in body fluid is not readily available and is generally unnecessary for clinical assessment

and management. A serum pregnancy test should be obtained in women of childbearing age with ingestions.

Gastrointestinal decontamination using oral activated charcoal should be considered.[21] Orogastric lavage may be indicated in patients with massive overdose of a first-generation H_1 antihistamine. Serial assessments of the patient's vital signs, particularly temperature, and mental status should be made. The potential for clinical deterioration necessitates management of symptomatic patients in a monitored environment.

Specific Therapy

H_1 Receptor Antagonists

Hypotension generally responds to isotonic fluids (0.9% sodium chloride solution or lactated Ringer solution). If the desired increase in blood pressure is not attained, dopamine or norepinephrine can be titrated to achieve an acceptable blood pressure. In one instance, cardiogenic shock and myocardial depression resulting from a 10-g ingestion of pyrilamine maleate could be reversed only with an intraaortic balloon counterpulsation device.[17] This approach is a rarely needed but potentially useful intervention. Agitation, psychosis, or seizure generally responds readily to titration of a benzodiazepine such as diazepam or lorazepam. Cooling via evaporative methods (tepid mist via spray bottle or similar device; fan) is generally sufficient, but patients with severe hyperthermia should receive more rapid cooling using an ice bath. Hyperthermic patients should be monitored for development of disseminated intravascular coagulation and other complications. Seizures should be treated with an intravenous benzodiazepine such as diazepam 10 mg (0.1â€“0.2 mg/kg in children) or lorazepam with repeated dosing as necessary. Recurrent seizures refractory to the benzodiazepine should be treated with phenobarbital, propofol, or general anesthesia. In addition, proper fluid management and urinary

alkalinization are necessary to prevent myoglobin-induced nephrotoxicity.

The sodium channel-blocking (type IA antidysrhythmic) properties of diphenhydramine may lead to wide-complex dysrhythmias that resemble cyclic antidepressant overdose (Chaps. 61 and 71). Hypertonic sodium bicarbonate can reverse diphenhydramine-associated conduction abnormalities.[52] Cardioversion or pacing may be required for dysrhythmias. Type IA (quinidine, procainamide, disopyramide), IC (flecainide), and III (amiodarone, sotalol) antiarrhythmic drugs are contraindicated because of their capacity to prolong the QT_c interval.

Physostigmine can effectively reverse the peripheral or central anticholinergic syndrome if clinically indicated.[41] In a retrospective comparison of physostigmine and benzodiazepines, physostigmine was found to be safer and more effective for treating anticholinergic agitation and delirium.[5] Physostigmine can reverse both peripheral and central anticholinergic effects (Table 50-3). Contraindications to physostigmine use include a wide QRS complex or bradycardia noted by electrocardiography, asthma, and pulmonary disease.

The primary benefits of physostigmine use in patients with antihistamine overdose include restoration of gastrointestinal motility, elimination of agitation, and possible obviation of the need for CT scan or lumbar puncture if the patient regains a normal mental status and can provide a clear history. The anticipated benefits of physostigmine must outweigh the potential risks prior to its use.

For physostigmine administration, the patient should be attached to a cardiac monitor, and secure intravenous access should be established. Physostigmine (1â€“2 mg in adults; 0.5 mg in children) should be administered by *slow* intravenous push with continuous monitoring of vital signs, breath sounds, and oxygen saturation by pulse oximetry. The initial dose of physostigmine can be repeated at 5- to 10-minute intervals if anticholinergic symptoms are not

reversed and cholinergic symptoms such as salivation, diaphoresis, bradycardia, lacrimation, urination, or defecation do not develop. When improvement occurs as a result of physostigmine, readministration of physostigmine at 30- to 60-minute intervals may be necessary. Alternatively, sedation with benzodiazepines may be appropriate once the diagnosis is confirmed. A dose of intravenous atropine that is half the dose of physostigmine should be available at the patient's bedside to treat cholinergic toxicity if it occurs (Antidotes in Depth: Physostigmine).

H_2 Receptor Antagonists

Patients who overdose on an H_2 antihistamine should receive 1 g oral activated charcoal per kilogram body weight at most if indicated. H_2 antihistamine antagonists rarely result in significant toxicity and therefore do not warrant exposure to the risks of complications from orogastric lavage or emesis. Monitoring for uncommon complications and assessment of coingestants should be performed as clinically indicated.

Decongestants

History and Epidemiology

Decongestants are sympathomimetic agents that act on Î±-adrenergic receptors, producing vasoconstriction, shrinking swollen mucous membranes, and improving bronchiolar air movement. Ephedrine, the first agent of this class to be used pharmaceutically, is derived from *Ephedra* spp plants. Ephedrine was used in China for at least 2000 years before it was introduced into Western medicine in 1924. Phenylephrine was introduced into clinical medicine in the 1930s. Several topical imidazoline decongestants (see Figure 50-4) have since been developed for clinical use.

Recreational use of ephedrine-containing stimulants is common, and

combinations of these compounds with caffeine or other herbs may be marketed as â€œherbal ecstasyâ€• (Chap. 39). The sale of dietary supplements containing Ephedra (ephedrine alkaloids) was banned by the FDA in 2004 because of concerns over their cardiovascular effects, including increased blood pressure and irregular heart rhythm. Xenobiotics that contain chemically synthesized ephedrine, traditional Chinese herbal remedies, and herbal teas are not covered by the rule.[15]

Pharmacology and Pharmacokinetics

Decongestants are pharmacologically active following topical or oral administration. Absorption from the gastrointestinal tract is rapid, with peak blood concentrations occurring within 2â€“4 hours of ingestion. Oral decongestants can affect the cardiovascular, urinary, central nervous, and endocrine systems.[4] The decongestants phenylephrine, pseudoephedrine, ephedrine, and phenylpropanolamine reduce nasal congestion by stimulating the Î±-adrenergic receptor sites on vascular smooth muscle.[29] This process constricts dilated arterioles and reduces blood flow to engorged nasal vascular beds. The $\hat{I}\pm_1$ -mediated decrease in volume ultimately lowers resistance to airflow. Prolonged topical administration may produce rebound congestion upon discontinuation; possible mechanisms include desensitization of receptors and mucosal damage. This damage is thought to be caused by $\hat{I}\pm_2$ -mediated arteriolar constriction resulting in decreased nutritional supply to the mucosa. Therefore, selective $\hat{I}\pm_1$ agonists may cause less mucosal damage.

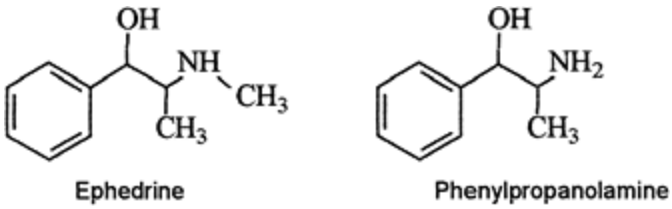


Figure 50-4. Structures of ephedrine and phenylpropanolamine.

Phenylephrine is a powerful Î±$_{1,2}$ -adrenergic receptor agonist with very little Î²-adrenergic agonist activity. Pseudoephedrine and ephedrine are direct-acting nonspecific Î±$_{1,2}$ - and Î²$_{1,2}$ -adrenergic receptor stimulants. Pseudoephedrine is the D-isomer of ephedrine and has only 25% of the adrenergic receptor activity of ephedrine.[9] Phenylpropanolamine is an Î±$_{1,2}$ -adrenergic receptor stimulant devoid of Î²-adrenergic receptor activity. Phenylpropanolamine can directly stimulate Î±$_{1,2}$ receptors and can indirectly stimulate these receptors by causing norepinephrine release (Table 50-4).

The imidazoline (I) category of sympathomimetics are generally reserved for topical application and are used for their local effects in the nasal passages and the eye. The more common medications include oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, and naphazoline hydrochloride (Figure 50-5). The imidazolines are rapidly absorbed from the gastrointestinal tract and mucous membranes. The elimination half-lives of these agents range from 2â€“4 hours. Their vasoconstrictor effects are mediated by their actions as Î±-adrenergic agonists, with binding to Î±$_{1,2}$ receptors on blood vessels. The Î±$_1$ -mediated vasoconstriction is complemented by an additive effect of preferential binding to Î±$_2$ receptors located on resistance vessels regulating blood flow. In

addition, these compounds show high affinity for imidazoline receptors, which are located in the ventrolateral medulla and some peripheral tissues. Stimulation of imidazoline receptors produces a sympatholytic effect that results in bradycardia and hypotension. All imidazoline preparations have a relatively rapid onset of action, with 60% of maximum effectiveness after only 20 minutes. Oxymetazoline is the only compound with a duration of action > 8 hours. The other preparations have an average duration of action of approximately 4 hours.[25]

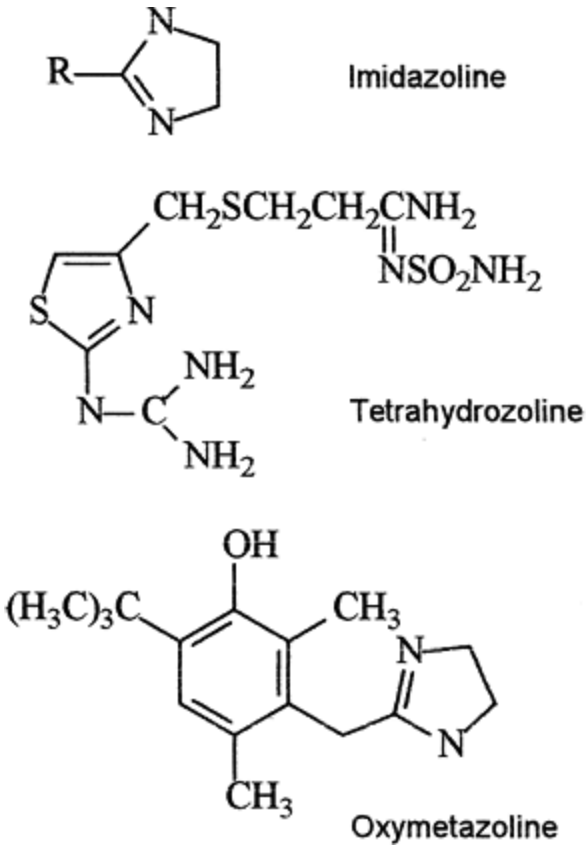


Figure 50-5. Structures of the imidazoline decongestants, tetrahydrozoline, and oxymetazoline.

Ephedrine
Sympathomimetic
3â€“5 h
Î ±1,2 and Î²1,2
Naphazoline
Imidazoline
8 h
Î ±2 , I
Oxymetazoline
Imidazoline
6â€“7 h
Î ±2 , I
Phenylephrine

Sympathomimetic
1 h
Î±1,2
Phenylpropanolamine
Sympathomimetic
12 h (sustained release)
Î±1,2
Pseudoephedrine
Sympathomimetic
3â€“4 h
Î±1,2 and Î²1,2
Tetrahydrozoline
Imidazoline
4â€“8 h
Î±2 , I
Xylometazoline
Imidazoline
5â€“6 h
Î±2 , I

Decongestant Class Duration of Action Receptor Activity

TABLE 50-4. The Pharmacologic Characteristics of Decongestants

The imidazoline decongestants such as oxymetazoline and naphazoline are pure central and peripheral α_2 -adrenergic receptor agonists; tetrahydrozoline stimulates α_2 receptors and H_2 receptors. These medications are primarily used as nasal decongestants. Tetrahydrozoline is available without prescription as an ophthalmic preparation to decrease eye irritation and redness.

Clinical Manifestations

Following a decongestant overdose, most patients present with CNS

stimulation, hypertension, tachycardia, or reflex bradycardia (in response to pure Î±-adrenergic agonist-induced hypertension only). Approximately 4â€“5 times the recommended dose of pseudoephedrine[9] but less phenylpropanolamine may be required to cause hypertension.[10] An increase in sinus dysrhythmias is reported in adults with ingestion of 120 mg pseudoephedrine and moderate exercise.[4] Headache was the most common initial symptom (39%) reported by patients who later developed severe toxicity.[36] In 45 patients who developed hypertensive encephalopathy from phenylpropanolamine ingestion, 24 patients developed intracranial hemorrhages, 15 developed seizures, and 6 died.[36] In more severe exposures, seizures, myocardial infarction, bradycardia, atrial and ventricular dysrhythmias, ischemic bowel infarction, and cerebral hemorrhages are reported.[6, 12] In a review of 500 reports of adverse reactions from patients who had ingested ephedrine and associated stimulants as dietary supplements, 8 fatalities from myocardial infarction and cerebral hemorrhage were reported.[7] Symptoms of toxicity from decongestants usually resolve within 8â€“16 hours. However, symptoms may persist for > 24 hours if a sustained-release product is ingested. Acute myocardial infarction is reported with therapeutic dosing of pseudoephedrine.[40]

When ingested, the imidazoline decongestants naphazoline, oxymetazoline, tetrahydrozoline, and xylometazoline are potent central and peripheral $\hat{I}\pm_2$ -adrenergic and imidazoline receptor stimulants. In overdose, they can cause CNS depression, hypotension, bradycardia, and respiratory depression.[24, 46] Children are particularly sensitive to the effects of the imidazoline decongestants.

Management

Extreme agitation, seizures, tachycardia, hypertension, and psychosis should initially be treated with administration of oxygen and intravenous benzodiazepines, expeditiously titrated upward to effect.

A patient who remains hypertensive or is believed to have chest pain of ischemic origin (ECG indicated) may be treated with phentolamine, an Î±-adrenergic antagonist, or nitroprusside, a venous and arterial vasodilator.

A patient with a focal neurologic deficit or an abnormal neuropsychiatric examination following decongestant ingestion should be evaluated for cerebral hemorrhage by noncontrast head CT scan and, if indicated, subsequent lumbar puncture to exclude subarrachnoid hemorrhage.[36]

Patients who have overdosed on a decongestant generally should receive 1 g activated charcoal per kilogram body weight as a single dose. Activated charcoal administration may be beneficial several hours after ingestion of sustained-release decongestant preparations, and serial doses of activated charcoal may be considered in this context. Syrup of ipecac has no role, and orogastric lavage should be reserved only for life-threatening ingestions within the previous hour.

Ventricular dysrhythmias from decongestant ingestions should be treated with standard doses of lidocaine or amiodarone.[66] Refractory dysrhythmias may require antiadrenergic therapy with propranolol, but only after pretreatment with phentolamine, if possible, or with strict expectant management of the patient's blood pressure. Patients who develop hypertension following propranolol should immediately receive phentolamine. Phenylpropanolamine ingestions may cause hypertension with a reflex bradycardia and atrioventricular block that is responsive to standard doses of atropine.[68] Atropine must be used with caution because it can cause a dangerous increase in blood pressure as the reflex bradycardia reverses. Therefore, a direct-acting vasodilator such as phentolamine or nitroprusside is preferred because the stimulus for the bradycardia is corrected with reversal of the hypertension. Imidazoline-induced hypertension rarely requires therapy, but in the setting of symptomatic hypertension a short-acting Î±-adrenergic antagonist such as phentolamine may be administered.[67] However, the hypertension is generally transient and

followed by hypotension that raises the risk of antihypertensive therapy.

Summary

The popularity and availability of antihistamines and decongestants make them readily accessible for deliberate or unintentional ingestions in both adults and children. Recreational use of these agents may lead to exposure to substantial doses of these medications. Fortunately, nearly all patients exposed to excessive doses of members of these classes of medications that are currently available in the United States do well if they receive treatment early in

the course of ingestion. Patients treated with activated charcoal, continuous assessment, supportive care, management of abnormal vital signs, electrocardiography, cardiac monitoring, and mental status have an excellent outcome with little risk of adverse sequelae. Familiarity with the more severe complications of antihistamine and decongestant overdoses results in early and appropriate interventions to reduce both morbidity and mortality from these exposures.

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Antidotes in Depth

Physostigmine Salicylate

Mary Ann Howland

Physostigmine is a carbamate that reversibly inhibits cholinesterases in both the peripheral nervous system and the central nervous system (CNS).[44] The tertiary amine structure of physostigmine permits CNS penetration and differentiates it from neostigmine and pyridostigmine, which are quaternary amines and thereby have limited ability to enter the CNS. This action inhibits the metabolism of acetylcholine, thereby allowing acetylcholine to accumulate and antagonize the anticholinergic effects of xenobiotics such as atropine, scopolamine,[51] and diphenhydramine. Although physostigmine previously was used as an antagonist to the anticholinergic effects of the tricyclic antidepressants and the phenothiazines, its use is no longer recommended because of a poor risk-to-benefit ratio given the potential for exacerbation of life-threatening cardiotoxicity. A review of 30 years of the literature reassessed and questioned the contraindication to physostigmine use for cyclic antidepressant ingestions. The review concluded that the safety of physostigmine use for seizures or cardiotoxicity was difficult to predict, but the

author still did not recommend physostigmine use in the setting of cyclic antidepressant toxicity.[43] Similarly, physostigmine likely will have a poor risk-to-benefit ratio in the management of presumed Î³-hydroxybutyrate (GHB) toxicity. A study in rats revealed that physostigmine did not effect arousal but increased the risk of physostigmine-induced toxicities of fasciculations and seizures.[4] Atypical antipsychotics have complex pharmacologic effects. Although some atypical antipsychotics (eg, olanzapine) have significant antimuscarinic side effects, the benefit of treating these anticholinergic effects with physostigmine in the often confusing overdose setting must be weighed against the potential risks of exacerbating cardiotoxicity.[45]

History

The history of physostigmine dates to antiquity and the Efik people of Old Calabar in Nigeria.[17,20,23,44] The chiefs in those areas used a poisonous concoction made from the beans of an aquatic leguminous perennial plant found in the area to deliver the *esere ordeal*. Esere was the word used to represent both the bean and the ritual used to test the innocence or guilt of an accused person. They also believed that the esere had the power to detect and kill those persons practicing witchcraft. Supposedly, innocent persons quickly swallowed the poison, which caused immediate emesis.[23] Vomiting allowed them to survive on their own or to be given an antidote of excrement in water. The guilty, however, hesitated swallowing, leading to speculation that sublingual absorption led to severe systemic symptoms without the benefit of vomiting. These persons were noted to develop mouth fasciculations and died foaming at the mouth. Daniell, a British medical officer stationed in Calabar, brought samples of the bean and the plant back to England in 1840.[23] John Balfour, a professor of medicine and botany at the Edinburgh Medical School, is credited with characterizing the plant, which became known as *Physostigma venenosum Balfour* (family *Leguminoseae*) in 1857. The active

alkaloid isolated from the Old Calabar, or ordeal bean, by Jobst and Hesse in 1864 was named physostigmine. Independently, 1 year later Vee and Leven also isolated the active alkaloid and named it eserine.

Christison performed the first toxicologic studies, including self-experimentation with increasing doses of the seed. Fraser, Christison's student and later successor, originated the concept of antagonism from his experiments with physostigmine and atropine. Fraser plotted the dose relationships between the effects of atropine versus physostigmine on various organs such as the eye and the heart. He demonstrated, that up to a certain dose, atropine acted as an antidote to the lethal effects of physostigmine.[17] Experiments with physostigmine paved the way for Anderson, to propose the existence of a transmitter as the mechanism of action of physostigmine in 1906. In the 1920s, Loewi proposed and then proved the theory of neurohumoral transmission. Stedman and Burger established the chemical structure of physostigmine in 1925. Julian and Pikl synthesized physostigmine in 1935. By this time, physostigmine was already used as a miotic agent for patients with glaucoma, as a treatment for patients with myasthenia gravis, as a reversal agent to the paralytic effects of curare, as an antidote to atropine, and as a prototypical insecticide. In summary, physostigmine, a prototypical carbamate insecticide, was instrumental in the development of a bioassay for acetylcholine, concepts of neurohumoral transmission, mapping of cholinergic nerves, the concept of antagonism, the kinetics of enzyme inhibition, and improved understanding of the bloodâ€“brain barrier.[20]

Chemistry and Affinity for Cholinesterase

Figure 50-6A shows the general formula for carbamate inhibitors. Figures 50-6B and C show the chemical structures of

physostigmine ($C_{15}H_{21}O_2N_3$), a tertiary amine, and neostigmine, a quaternary amine. Like acetylcholine, physostigmine is a substrate for the cholinesterases (choline ester hydrolases) erythrocyte acetylcholinesterase and plasma cholinesterase. Both acetylcholine and physostigmine bind to the cholinesterase enzymes to form a complex. Then a part of the substrate known as the *leaving group* (ie, choline for acetylcholine) is removed, and the remaining acetylated (for acetylcholine) or carbamoylated (for physostigmine) enzyme is hydrolyzed, regenerating the enzyme and freeing the acetate or carbamate groups, respectively (Figures 109-2, 109-3, 109-4). For acetylcholine, the process is extremely quick, with a turnover time of 150 ms. In contrast, the half-life for hydrolysis of the carbamoylated enzyme is 15â€“30 minutes.[44] The I_{50} (molar concentration that inhibits 50% of the enzyme) of physostigmine is 2.3 Ã— 10^{-7} M for acetylcholinesterase, which is much weaker than for other carbamates at 1 Ã— 10^{-10} M or many organic phosphorus compounds at 1 Ã— 10^{-11} M.[21] Only the S-isomer inhibits cholinesterases, with plasma cholinesterase just a little more sensitive than acetylcholinesterase.[3] Newer xenobiotics used in patients with Alzheimer

disease[11] show selectivity for the CNS and for acetylcholinesterase. They include tacrine, donepezil, and galantamine, which are reversible cholinesterase inhibitors; metrifonate, an irreversible inhibitor; and rivastigmine, a pseudo-irreversible or slowly reversible inhibitor. These xenobiotics and neostigmine[22] have undergone limited study for reversal of anticholinergic poisoning.[11,22,26,38]

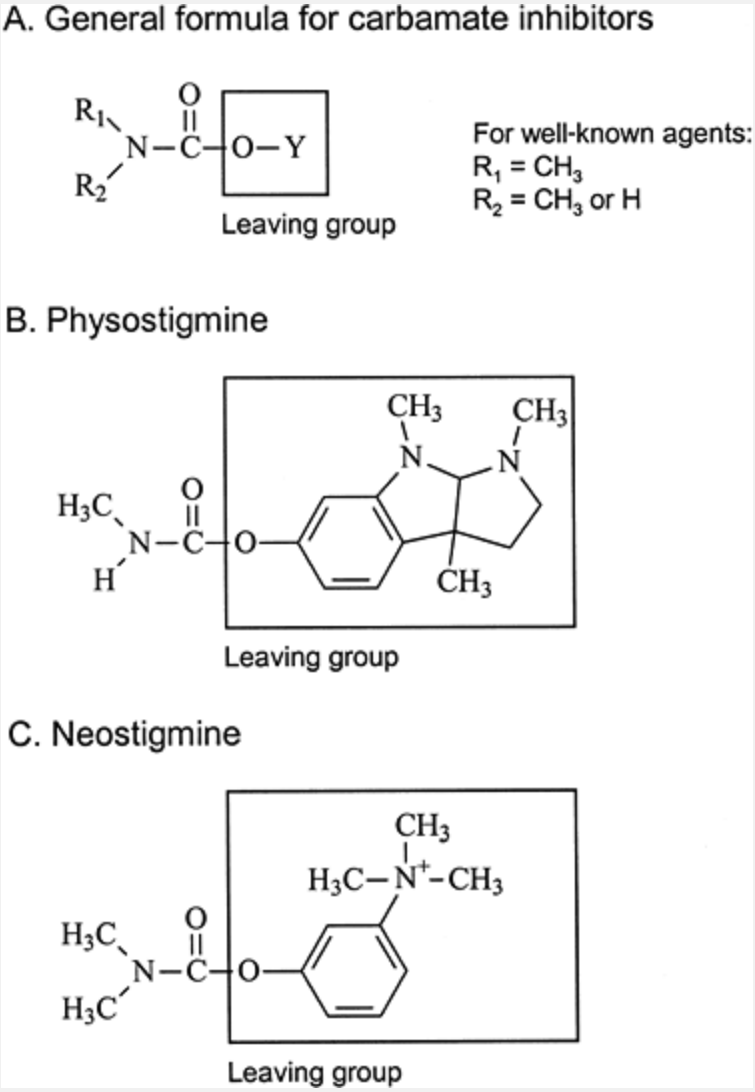

Figure A13-1. A: General formula for carbamate inhibitors. B: Structure of physostigmine. C: Structure of neostigmine.

Pharmacokinetics

Physostigmine is poorly absorbed orally, with a bioavailability of <5â€“12%.[1,31] Cholinesterases cleave the ester linkage, and very little xenobiotic is eliminated unchanged in the urine.

Pharmacokinetic parameters following IV administration of 1.5 mg over 60 minutes in 9 patients with Alzheimer disease demonstrated the following: Vd 2.4 Â± 0.6 L/kg; $t_{1/2}$ 16.4 Â± 3.2 minutes; peak plasma concentration 3 Â± 0.5 ng/mL; clearance 0.1 L/min/kg (7.7 L/min). There was a 3-fold interindividual variability in plasma physostigmine concentrations. Plasma cholinesterase concentrations demonstrated inhibition within 2 minutes of initiating the physostigmine infusion. The half-life of plasma cholinesterase inhibition was 83.7 Â± 5.2 minutes, with full recovery within 3 hours of termination of physostigmine infusion. The effects on plasma cholinesterase inhibition last approximately 5 times longer than the half-life of physostigmine.[25] All patients experienced varying degrees of diaphoresis, nausea, vomiting, headache, and generalized fatigue despite pretreatment with 2.5 mg methscopolamine.[2]

Clinical Use

Physostigmine was first used as an antidote in 1864 to counteract severe atropine poisoning.[33] Today its role is primarily in the treatment of antimuscarinic xenobiotics. More than 600 of these xenobiotics respond to physostigmine.[12] Anticholinergics fall into the categories of antimuscarinic (atropine, scopolamine, propantheline, benztropine, trihexyphenidyl), neuromuscular blockers (exemplified by curare), and ganglionic blockers (eg, trimethaphan). Other xenobiotics (eg, antihistamines, antipsychotics, and antidepressants) have anticholinergic properties that are not their primary therapeutic actions and are often considered adverse drug effects.

Clinical use of physostigmine has varied over time.[40] Enamored with its ability to cause CNS arousal, physostigmine was used in the 1970s to reverse the CNS effects of a large number of anticholinergics. It also was used inappropriately to treat toxicity from nonanticholinergics.[18,30,32,34,36] The success with regard to

anticholinergics is directly antidotal by virtue of its inhibition of cholinesterase. Effects of xenobiotics such as the benzodiazepines, opioids,[27,37,49] and GHB[4,46] result from either acetylcholine's direct action on the reticular activating system or interdependence of central neurotransmitters.[34] Few serious adverse effects are reported.[48] However, asystole followed administration of physostigmine in 2 patients with tricyclic antidepressant overdose.[35] This occurrence led to the realization that toxicity from tricyclic antidepressants is complex and consists of more than just anticholinergic effects.[35] Tricyclic antidepressant-induced sodium channel blockade causes myocardial depression, QRS and QTc interval prolongation, and ventricular dysrhythmias. Physostigmine probably augments vagal effects, thus contributing to decreased cardiac output and cardiac conduction defects. A reevaluation must conclude that the risks of physostigmine use for xenobiotics that are not primarily antimuscarinic often outweighs any benefit.

This analysis appears to hold true for reversing the effects of GHB (Chap. 78) as well.[46] GHB is rarely used alone, and its effects are highly variable. Recovery occurs spontaneously in approximately 2 hours (16 minutesâ€“6 hours).[7,8,14,28,47] Three patients in whom a presumptive diagnosis of GHB toxicity was made were treated with physostigmine.[7] The 3 patients had an improved mental status within 5â€“15 minutes. One of these patient relapsed and then fully awakened 40 minutes later. This patient was incontinent of feces, an adverse effect likely caused by the physostigmine.[7] A closer look at the patient descriptions reveals that all 3 improved with stimulation prior to physostigmine. Justification for use based upon a study performed in the 1970s in the operating room at a time when GHB was first being evaluated as an anesthetic appears illogical when caring for those who illicitly use GHB.[19]

However, in cases of anticholinergic overdose, physostigmine use clearly is beneficial. A study of 52 patients showed that physostigmine controlled agitation and reversed delirium in 96%

and 87% of patients, respectively,[6] whereas benzodiazepines controlled agitation in 24% of patients but were ineffective in reversing delirium. A shorter time to recovery following agitation was observed in those treated with physostigmine. No significant differences between these groups with regard to side effects and length of stay were noted.[6]

Indications

Indications for physostigmine use include the presence of peripheral or central anticholinergic manifestations without evidence of QRS or QTc prolongation. Peripheral manifestations include dry mucosa, dry skin, flushed face, mydriasis, hyperthermia, decreased bowel sounds, urinary retention, and tachycardia. Central manifestations include agitation, delirium, hallucinations, seizures, and coma.[16,29] The peripheral and central findings usually occur simultaneously. In the early phases of overdose, finding only central manifestations is uncommon, although they often are more remarkable.[1,5,9,13,15,21,39,42] The central findings may persist longer than the peripheral findings, particularly when a patient is recovering from an overdose of an antimuscarinic xenobiotic.

Adverse Effects

An excess of physostigmine results in accumulation of acetylcholine at peripheral muscarinic receptors, nicotinic receptors (skeletal muscle, autonomic ganglia, adrenal glands), and CNS sites.[24] Muscarinic effects produce stimulation of smooth muscle and glandular secretions in the respiratory, gastrointestinal, and genitourinary tracts and inhibition of contraction of most vascular smooth musculature. Nicotinic effects are stimulatory at low doses and depressant at high doses. For example, acetylcholine excess at the neuromuscular junction

produces fasciculations followed by weakness and paralysis. Its effect on the CNS results in anxiety, dizziness, tremors, confusion, ataxia, coma, and seizures.[24] Electroencephalograms (EEGs) demonstrate desynchronous discharges followed by higher-voltage discharges and a pattern similar to tonicâ€“clonic seizures.[24] The cardiovascular effects are dose dependent and directly related to the presence of the diverse muscarinic and nicotinic effects.[24] In addition to its inhibition of cholinesterase, physostigmine has a direct action on the nicotinic acetylcholine receptor ionic channel on the neuromuscular junction, resulting in decreased Î³-aminobutyric acid in the striatum.[41]

Physostigmine toxicity results when physostigmine is used in the absence of antimuscarinic toxicity or when an excess in relation to the antimuscarinic xenobiotic is administered. Patients overdosed with physostigmine should be managed with intensive supportive care, including mechanical ventilation if needed, intravenous atropine[50] titrated to reverse bronchial secretions, and, rarely, pralidoxime to reverse skeletal muscle effects.[10]

Relative contraindications to physostigmine use include reversible airway disease, peripheral vascular disease, intestinal or bladder obstruction, intraventricular conduction defects, and atrioventricular block. Little information is available regarding the effects of physostigmine in pregnancy. Transient muscular weakness occurred in 10â€“20% of neonates whose mothers received anticholinesterases for treatment of their myasthenia gravis.[31]

Drug interactions with cholinergic agonists (eg, ophthalmic pilocarpine), depolarizing neuromuscular blocking agents, or other anticholinesterase agents (eg, carbamates, organic phosphorous compounds, and pyridostigmine) are expected to be at least additive when these agents are taken concomitantly with physostigmine. The actions of drugs metabolized by plasma cholinesterases (eg, cocaine, succinylcholine, or mivacurium) are

expected to be prolonged.

Dosing

The dose of physostigmine is 1â€“2 mg in adults and 0.02 mg/kg (maximum 0.5 mg) in children intravenously infused over at least 5 minutes. The onset of action usually is within minutes.[21] The dose can be repeated in 10â€“15 minutes if an adequate response is not achieved and muscarinic effects are not noted. Rapid administration may cause bradycardia, hypersalivation leading to respiratory difficulty, and seizures. Although the half-life of physostigmine is approximately 16 minutes, its duration of action usually is much longer (often >1 hour) and is directly related to the duration of cholinesterase inhibition.[2] After reversal of anticholinergic symptoms is achieved, additional doses may be required if clinical relapse occurs. The effective dose depends upon the ingested dose and duration of action of the antimuscarinic xenobiotic. Although a total of 4 mg in divided doses usually is sufficient in most clinical situations,[16] significant interindividual variability exists. Atropine should be available at the bedside and titrated to effect should excessive cholinergic toxicity develop. A dose of atropine administered at half the physostigmine dose is often recommended.

Physostigmine is available as an ophthalmic ointment that can be applied topically to the conjunctival sac, where it causes miosis for treatment of acute angle-closure glaucoma. Miosis occurs within 10â€“30 minutes and persists for 12â€“48 hours.[31]

Availability

Physostigmine is available as Antilirium in 2-mL ampules, with 1 mL containing 1 mg physostigmine salicylate. The vehicle contains sodium bisulfite and benzyl alcohol.

Summary

Physostigmine has been used extensively in the fields of anesthesiology and emergency medicine. The only use of physostigmine with sound scientific support is for the management of patients with an anticholinergic syndrome, particularly those without cardiovascular compromise who have an agitated delirium. In this population, physostigmine has an excellent risk-to-benefit profile.

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Chapter 51
Antimigraine Medications

Jason Chu

Neal A. Lewin

Cluster headaches were recently diagnosed in a 57-year-old man with a controlled with valsartan and hydrochlorothiazide. Indomethacin, prednis acetaminophen-caffeine, and hydrocodone were prescribed, but the patier Subsequently, his neurologist prescribed 2 therapeutic doses of 10 mg riz 2 days prior to his presentation to the emergency department (ED). Upon patient complained of nausea, vomiting, and crampy abdominal pain. His pressure, 156/93 mm Hg; pulse, 94 beats/min; respiratory rate, 22 bre 98.2Â°F (36.8Â°C); pulse oximetry, 99% on room air. Physical examinatic right-sided abdominal tenderness to palpation. A 12-lead electrocardiogra and laboratory evaluation revealed blood urea nitrogen, 23 mg/dL; creat urinalysis; and normal prothrombin and partial thromboplastin times. Cor both oral and intravenous contrast of the abdomen and pelvis revealed a of the right kidney, which was confirmed by magnetic resonance angiogra arteriogram of the renal arteries showed no evidence of renal artery dis dysplasia. He was treated with intravenous hydration and pain manageme resolved.

When the patient was examined 1 month following discharge from the ho
further episodes of cluster headaches or abdominal discomfort, and his r
normal.

A migraine headache is a neurovascular disorder often initiated by a trigg
characterized by a headache that may be associated with an aura and po
variety of multiple organ system complaints, such as visual disturbances,
urinary frequency. For an extensive review, see the diagnostic criteria for
migraine established by the International Headache Society.[32] The initiati
fully understood, but likely involves genetic abnormalities in central nervo
channels predisposing sufferers to migraine triggers. Patients with familia
which is an autosomal dominant disorder, have missense mutations in the
specific P/Q voltage-gated calcium channels, which mediate serotonin and
wave of cortical spreading electrical depression.[24] Dysfunction of the P/Q
channels, which impairs serotonin release, is theorized to trigger this spr
depression. Once triggered, an electrical wave of cortical neuronal depol
the cortex in a caudal to rostral direction, followed by a spreading wave
an aura in some migraineurs. Current theories suggest these spreading w
patients without aura. Studies have demonstrated that migraineurs have
magnesium, which is needed for proper calcium channel activity, thus len
theory of migraine as a channelopathy.

Cephalagia begins with rebound cerebral vasodilation and antidromic activ
neurons of the ophthalmic division of the trigeminal nerve and branches o
(first-order neurons), located on dural arteries at the base of the brain. I
orthodromically to the trigeminal nucleus caudalis (second-order neurons)
and upper cervical spinal cord, then to the thalamus (third-order neurons)
cortical areas (fourth-order neurons) via the quintothalamic tract.[18 , 24 -
complex also produces retrograde parasympathetic impulses from the su
in the pons, through the pterygopalatine, otic, and carotid ganglia, to the
Vasoactive neuropeptides, including serotonin, vasoactive intestinal peptic
substance P, neurokinin A, and calcitonin-gene-related peptide (CGRP), ar
process, which exacerbates vasodilation and irritates the meninges at the
causing further pain. CGRP from trigeminal AÎ´-fibers produces dural va
substance P and neurokinin A, from trigeminal C-fibers, increase dural v
Abortive therapy and prophylactic therapy ideally target these processes

Toxicity of many of these medications are discussed in depth elsewhere ir formerly the mainstay of therapy for treatment of migraines, but the trip has essentially replaced the ergots.

Ergot Alkaloids

History and Epidemiology

Ergot is the product of *Claviceps purpurea* , a fungus that contaminates r spores of the fungus are both wind-borne and transported by insects to y germinate into hyphal filaments. When a spore germinates, it destroys th a curved body called the *sclerotium* , which is a major commercial source This fungus can elaborate diverse substances, including

ergotamine, histamine, tyramine, isomylamine, acetylcholine, and acetal

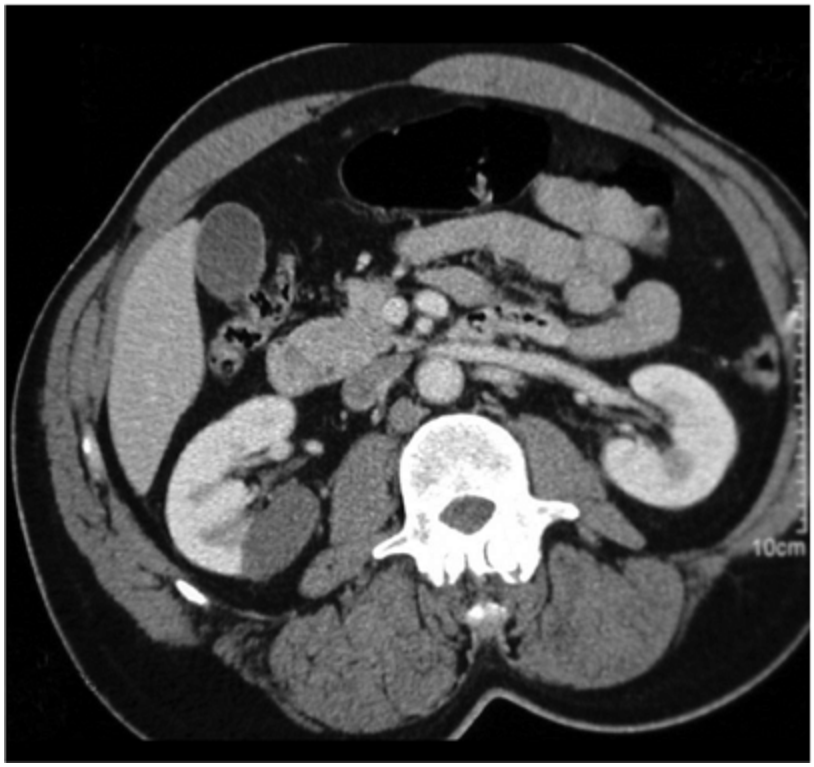


Figure 51-1. Infarction of right kidney after rizatriptan use.

In 600 B.C., an Assyrian tablet mentioned contamination of grain believed *purpurea* . In approximately 400 B.C., a contaminated grass that killed p described. In the Middle Ages, epidemics causing gangrene of the extrer of limbs, were depicted in the literature. The disease was called *holy fire* because of the blackened limbs resembling the charring from fire and the expressed by its victims. Any improvement that reportedly occurred when shrine of St. Anthony probably was the result of a diet free of contamina the journey.[27] Abortion and seizures also were reported to result with th early as 1582, midwives used ergot to assist in the childbirth process. De physician to use ergot for obstetric care in 1818. In 1822, Hosack reporte used for control of postpartum hemorrhage, but that its routine use during avoided because of the drug's toxicity.[65] Since 1950, clinical use of ergot limited almost entirely to treatment of vascular headaches. Ergonovine, is used in obstetric care for its stimulant effect on uterine smooth muscl used for postpartum uterine atony and hemorrhage. Ergot derivatives have â€œcognition enhancers,â€• [67] to help manage orthostatic hypotension,[6] secretion of prolactin.[56]

Angiotensin II receptor blockers
Acetaminophen
Î²-adrenergic antagonists
Antiemetics
Botulinum toxin A (Botox A)
Aspirin
Butterbur root
Butalbital
Calcium channel blockers
Caffeine
Coenzyme Q10
Corticosteroids
Feverfew
Ergots
Flunarizine
Lidocaine (intranasal)

Gabapentin
Magnesium (IV)
Lamotrigine
Midrin (isometheptene/dichloralphenazone/acetaminophen)
Levetiracetam
Magnesium (oral)
NSAIDs
Monoamine oxidase inhibitors
Opioids
Pizotifen
Oxygen
Riboflavin
Sedative-hypnotics
Selective serotonin reuptake inhibitors
Triptans
Valproic acid (intravenous)
Topiramate
Tricyclic antidepressants
Valproic acid

Prophylactic xenobiotics usually are taken to prevent triggering of migrai
xenobiotics usually are taken to stop the clinical manifestations of migrai
triggered. However, the separation between the two groups is not strict,
used in both roles.

Prophylactic Abortive

TABLE 51-1. Xenobiotics Used for Migraine Treatment

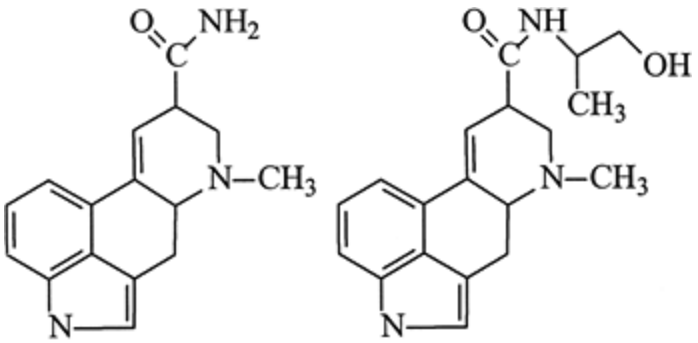
Presently in the United States, epidemics of ergotism are prevented by g
grain fields. A grain field that contains more than 0.3% infected grain is
sale. In some years as much as 36% of the grain is rejected.[56] Ergot toxi
animals, remains a problem elsewhere in the world.[5,36]

Pharmacology and Pharmacokinetics

The ergot alkaloids can be divided into three groups: amino acid alkaloic acid alkaloids, and amine alkaloids. All ergot alkaloids are derivatives of 6-methylergoline (Figure 51-2).

The pharmacokinetics of the ergot alkaloids are well defined from control studies, whereas the toxicokinetics are

essentially unknown (Table 51-2). Almost all of the ergots are poorly ab considerable first-pass hepatic metabolism occurs, resulting in highly va Intramuscular absorption is unpredictable, and actions often are delayed. dose is approximately 10 times the intramuscular dose.[48] Ergotamine sup bioavailability 20 times compared to orally administered doses by avoidin metabolism in oral dosing.[31 , 55] Peak plasma concentrations with oral er 45â€“60 minutes.[48] The volume of distribution is approximately 2 L/kg, a from 1.4â€“6.2 hours. Ergot alkaloids are metabolized in the liver by CYP are excreted in the bile.[4 , 56]



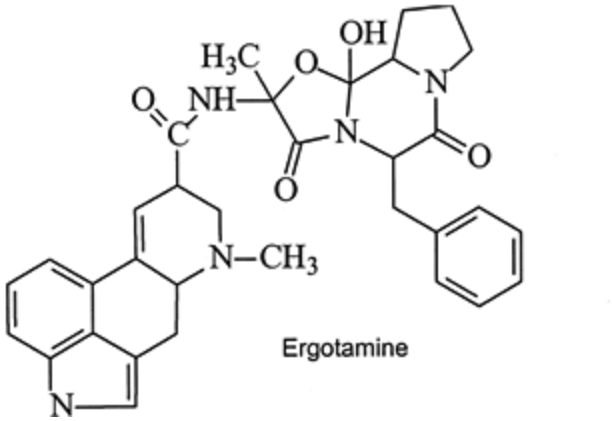


Figure 51-2. Structures of representative ergot derivatives.

Ergotamine
2 (1.4â€“6.2)
22 (IV)
100 (IV)
47 (IM)
<5 (PO)
Liver
Bile excretion
Dihydroergotamine
2.4
3â€“4 (IM)
100 (IM)
Liver

40 (nasal)
<5 (PO)
%Bile excretion
Ergonovine
1.9
3
â€”
Liver
Methylergonovine
1.4â€“2
3
78 (IM)
60 (PO)
Liver
Methysergide
1 (PO)
â€”
13 (PO)

Liver (metabolized to methylergonovine)

Medication	tÂ½ (hours)	Duration of action (hours)	Bioavailability (%)	M

TABLE 51-2. Pharmacokinetics of Ergot Derivatives

The pharmacologic effects of the ergot alkaloids are complex and can be These actions can be subdivided into central and peripheral effects (Table ergotamine stimulates serotonergic (tryptaminergic) receptors, potentiate blocks neuronal serotonin reuptake, and has central sympatholytic action alkaloids interact with all known 5-hydroxytryptamine $(5\text{-HT})_1$ and 5-HT_2 is increased intrasynaptic serotonin activity in the median raphe neurons Because serotonin is an inhibitory CNS neurotransmitter in the brainstem dihydroergotamine are thought to decrease the neuronal firing rate and s cerebrovascular smooth musculature. This stabilization of the cerebrovascu alkaloids makes them useful drugs for both acute and prophylactic treatm headaches, which are characterized by cerebrovascular hyperreactivity as

Ergotamine (amino acid alkaloid)
Vasculature: Partial agonist Smooth muscles: Nonselective antagonist
CNS: Emetic (potent)
Vasculature: Partial agonist/antagonist Smooth muscles: Partial agonist/

CNS: Poor agonist/antagonist

CNS: Antagonist
PNS: Antagonist
Bromocriptine (amino acid alkaloid)
Weak antagonist
CNS: Partial agonist/antagonist; inhibits prolactin secretion; emetic (mild
Vasculature: Antagonist
Dihydroergotamine (dihydrogenated group)
Smooth muscles: Partial agonist/antagonist
CNS: Emetic (mild)

Vasculature: Partial agonist (veins); antagonist (arteries)

CNS: Agonist lateral geniculate nucleus
Sympathetic ganglia: Antagonism
Smooth muscles: Antagonist
CNS/PNS: Antagonist
Ergonovine and methyl ergonovine (amine alkaloid)
Smooth muscles: Potent antagonist
CNS: Emetic (mild); inhibits prolactin (weak); partial agonist/antagonist
Vasculature: Partial agonist

Vasculature: Agonist in umbilical and placental vessels
CNS: Partial antagonist/agonist
Vasculature: Weak antagonist

Methysergide (amine alkaloid)
Vasculature: Partial agonist
CNS: Potent antagonist
None
None
Adapted with permission from Peroutka SJ: Drugs effective in the therapy Hardman JG, Limbird LE, Molinoff PB, et al, eds: Goodman and Gilman's Basis of Therapeutics, 9th ed. New York. McGraw-Hill, 1996, pp. 491â€“4

Compound	Interactions with Tryptaminergic (Serotonergic) Receptors	Interactions with Dopaminergic Receptors

TABLE 51-3. Pharmacology of Ergot Derivatives

Peripherally, ergotamine acts as a partial Î±-adrenergic agonist or as an dopaminergic, and serotonergic (tryptaminergic) receptors.[56] The ergopep ergot alkaloids (ergotamine, ergotoxine) exhibit Î±-adrenergic agonism, (dihydroergotamine) of the lysergic acid

nucleus increases Î±-adrenergic agonism.[56] However, their peripheral va predominate over the Î±-adrenergic antagonist effects. An additional vas be caused by direct action of ergotamine on the media of the arterioles.[5 at therapeutic doses is vasoconstriction. Table 51-3 summarizes the phar selected ergot alkaloids currently used in clinical medicine. The spectrum dosage, host response, and physiologic conditions.

The difference between therapeutic and toxic doses in peripheral vessels of ergotamine produce only mild vasoconstriction, and this effect is direct doses, extreme vasoconstriction produces the characteristic ischemic chan ergotism.

The cerebrovascular effects of ergot alkaloids are not clearly understood. for example, therapeutic doses of ergotamine produce mild vasoconstrict agonism, especially in intracranial vessels that already are dilated during vasoconstriction is one mechanism by which ergot terminates a migraine little definitive information is available regarding the effects of toxic doses on the cerebral vasculature. Cephalic vasodilation may occur, but the mec unknown. One hypothesis is that toxic doses of the drug initially produce and ischemia, just as they do in the periphery. However, because the ce tolerate hypoxia and hypercapnia, rapid vasodilation ensues and improves addition, Î±-adrenergic receptors in the CNS function differently from thos possibly CNS vascular tone cannot be maintained in the setting of local t

Clinical Manifestations

Ergotism, a toxicologic syndrome resulting from excessive use of ergot a by intense burning of the extremities, hemorrhagic vesiculations, pruritus vomiting, and gangrene (Table 51-4). Headache, fixed miosis, hallucinat cerebrovascular ischemia, and convulsions also are associated with this c called â€œ*convulsive* â€• ergotism.[27] Chronic ergotism usually presents of the lower extremities, although ischemia of cerebral, mesenteric, coron beds is well documented.[2 , 19 , 20 , 53 , 54] Ergotism also can result from with cytochrome CYP3A4 inhibitors, such as macrolide antibiotics and pro increase the area under the curve of ergots.[3 , 4]

Ergotaminism is a syndrome caused specifically by ergotamine use. Symp insufficiency, such as cold extremities, extremity pain at rest, numbness, intermittent claudication, are most commonly reported.[27] CNS manifestati ergotaminism. However, the adverse effects reported may not result from many published cases describe ingestions of combination therapeutic pre ergot alkaloid and caffeine. Restlessness, nausea, vomiting, or agitation d an acute overdose, but peripheral vasospasm may not be obvious for 24

Agitation
Bradycardia
Cerebrovascular ischemia
Hypertension
Hallucinations
Ischemic Effects
Headaches
Angina
Miosis (fixed)
Gangrene
Nausea
Hemorrhagic vesiculations and skin bullae
Seizures
Mesenteric infarction
Twitching (facial)
Myocardial infarction
Vomiting
Renal infarctio

Central Effects Peripheral Effects

TABLE 51-4. Clinical Manifestations of Ergotism

The vascular effects ascribed to ergot alkaloids are complex and sometim 3). Subintimal and medial fibrosis, vasospasm, and arteriolar and venou stasis related) are all reported.[41] Angiography can demonstrate distal, se with increased collateralization in patients with chronic ergotism. The co

ophthalmic, and mesenteric vasculature,[54] as well as the vessels of the c affected.[58] Neuropathic changes may be secondary to ischemia of the va

Bradycardia is a characteristic effect of the ergot alkaloids. Bradycardia is baroreceptor-mediated phenomenon associated with vasoconstriction, but sympathetic tone, direct myocardial depression, and increased vagal activ

One finding is particularly striking, especially considering attention to a s a recently withdrawn group of dietary aids. Myocardial valvular abnormali ergot alkaloids. Ergotamine and methysergide both cause mitral and aort and immobility resulting in valvular regurgitation.[21 , 53]

Methysergide use is limited because of its well-described adverse effects pleuropericardial, endocardial, and endovascular fibrosis.[47 , 53]

Treatment

The treatment for a patient with ergot alkaloid toxicity depends on the na findings. Gastric emptying should be used rarely, if at all, because vomitir occurrence, and the ingestion may be complicated by seizures. Shortly aft overdose, if the patient is not vomiting, activated charcoal should be adm management. If emesis is present, metoclopramide or a 5-HT_3 antagonist can be used as an antiemetic to facilitate administration of activated char characterized by minimal pain of the extremities, supportive measures su analgesia are all that is needed. With more serious cases, severe periph produce ischemic changes, including angina, myocardial infarction, cereb claudication, and mesenteric ischemia. Intravenous vasodilators, such as [7 , 46] nitroglycerin,[30] and phentolamine, are indicated to reverse the isch captopril,[69] and nifedipine[11] also have been used to achieve peripheral v with mild signs and symptoms of vasospasm, such as dysesthesias and m the digits.

Although sympathetic block, epidural block, or sympathectomyâ€”all of wh pastâ€”may relieve vasoconstriction mediated via the CNS, these modalitie antagonize the direct action of the ergot alkaloids on arteriolar smooth m corticosteroids, or low-molecular-weight dextran[57] can be used to prever subsequent clot formation. Use of thrombolytic agents in this setting has

been evaluated but may have some theoretical utility. Arteriotomy may b large clots. Hyperbaric oxygen may correct local tissue hypoxia.[17] Benzod used to treat seizures or hallucinations.

Triptans

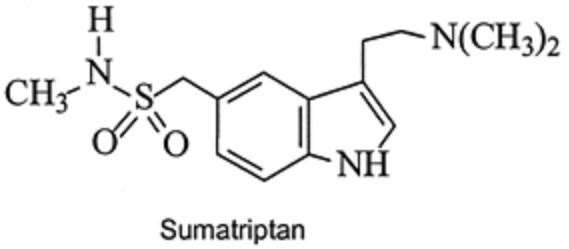
In 1974, investigations began on new compounds that produced vasocons receptors. The first compound successfully used in this context was 5-ca CT). When applied to an isolated dog saphenous vein, 5-CT caused poter induced significant hypotension in vivo. The next compound developed, A aminoethyl)-*N* -methyl-1-H-indole-5-acetamide], also constricted dog saph more 5-HT receptor selectivity. AH25086 was effective against acute migr volunteers, but further research was stopped because the compound was development in humans.[28] Sumatriptan was synthesized in 1984, and its the rapid development of other triptans, which currently include naratrip rizatriptan, eletriptan, almotriptan, and frovatriptan (Figure 51-3 and Tab

Pharmacology

The triptans are all primarily 5-HT_{1B} and 5-HT_{1D} receptor agonists and ha HT_{1A} and 5-HT_{1F} receptors[22] (Chap. 14). In the CNS, 5-HT_{1B} receptors a vessels.[25] Stimulation of these receptors results in cerebral vasospasm[12] cerebral vasodilation. In contrast, the 5-HT_{1D} receptors are located pres neurons and act as â€œautoreceptors,â€• decreasing neurotransmitter r trigeminal nerve terminals.[34] The triptans also inhibit dural neurogenic in preventing the release of vasodilating neuropeptides from peripheral trig Peripherally, triptans cause vasospasm systemically through the 5-HT_{1B}

The available triptans are pharmacodynamically similar but have differen 51-5). Sumatriptan has an oral bioavailability of only 14% (range 10â€“ extensive first-pass hepatic metabolism. Peak plasma concentrations are a (range 0.5â€“4.5 hours).[22] An intranasal formulation is available, but the 17%.[55] Subcutaneous administration results in a much higher bioavailabil peak plasma concentrations at 10 minutes; therefore, sumatriptan is pref

subcutaneous route. The volume of distribution is 2.4â€“3.3 L/kg, and the approximately 2 hours. The newer triptans differ substantially from sumat oral bioavailability, plasma half-life, time to maximum effect, and recurre (Table 51-5).



Sumatriptan

Figure 51-3. Structure of a representative triptan, sumatriptan.

Sumatriptan
2â€“2.5
4
Low
14 (PO);
96 (SQ)
MAO-A
Almotriptan
3â€“3.7
24
Unknown
70â€“80
CYP3A4, CYP2D6 (PO), MAO-A (minor)
Eletriptan
3.6â€“6.9
14â€“16
High
50
CYP3A4
Frovatriptan
25

24
Low
24â€“30
CYP1A2 Renal elimination
Naratriptan
4.5â€“6.6
Unknown
High
63â€“74
Renal (major) CYP
Rizatriptan
1.8â€“3
25
Moderate
40â€“45
MAO-A
Zolmitriptan
1.5â€“3.6
18
Moderate
40â€“49
CYP1A2, MAO-A (minor)

Medication	tÂ ½ (hours)	Lipophilicity	Duration of action (hours)	Bioavailability (%)	M

TABLE 51-5. Pharmacokinetics of Triptans

Clinical Manifestations

With appropriate therapeutic use, the adverse effects associated with the include nausea, vomiting, dyspepsia, flushing, and paresthesias.[13,56] Hc

consequential adverse effects are related to vasospasm. Chest pressure is of sumatriptan users.[6, 50] Although triptans reduce coronary artery diam chest pressure usually is not believed to be secondary to cardiac ischem for chest pressure sensations include a generalized vasospastic disorder esophageal spasm, bronchospasm, alterations of skeletal muscle energy sensitization of pain pathways.[15] Therapeutic sumatriptan use is also ass infarction, dysrhythmias, renal infarctions, and ischemic colitis.[1, 10, 35] Although the triptans result in some degree of coronary artery constrictio hence recommendations state that routine stress tests are not necessary to therapy with triptans.[16, 38, 64]

Cephalic vasospasm is the desired effect of sumatriptan, but adverse neu from transient ischemic attacks to cerebral vascular events, hemorrhages, reported.[8, 33, 37, 41, 42] Spinal cord infarction is reported after therap and renal infarction is reported after therapeutic rizatriptan use.[23] These been reported with the other triptans, possibly because the other triptans become available.

Animal studies showed a wide margin of safety with oral sumatriptan. Su administration of 2 g/kg sumatriptan to rats was lethal. Death was prece inactivity, and tremor.[29] Dogs survived 20 mg/kg and 100 mg/kg subcuta developed hind limb paralysis, erythema, tremor, salivation, and loss of in other animals

include seizures, inactivity, reduced respiratory rate, cyanosis, ptosis, at salivation, and lacrimation.[29, 61] Dogs given oral sumatriptan 2 mg/kg/d opacities and corneal epithelial defects after 1 month of treatment.[61]

Two cases of excessive sumatriptan taken for treatment of headaches are old man took 66 doses of sumatriptan 6 mg subcutaneously over 4 weeks headaches and had no adverse effects.[62] A 43-year-old man who took 23 25 mg and 32 tablets of Midrin (a combination medication with isomethep dichloralphenazone 100 mg, acetaminophen 325 mg) over 7 days for hea occipital infarction with a right hemianopsia. Digital subtraction angiogra narrowing in multiple cerebral vessels. The hemianopsia and vessel findir cessation of the sumatriptan and Midrin and treatment with nicardipine.[42]

drugâ€“drug interactions with the triptans and other medications, such as inhibitors (MAOIs), are reported, although the potential exists because of MAO-A or P450 enzymes.

Treatment

Treatment of triptan-induced vasospasm is dependent on the route of exp system affected. Decontamination is not feasible after subcutaneous expos effective in overdoses of oral preparations. Most triptans are oral prepara rizatriptan and zolmitriptan are formulated to dissolve orally on the tongu decontamination with activated charcoal should only be performed for ing preparation of other triptans. Because vomiting is not as prominent with exposure to the ergot alkaloids, gastric emptying procedures such as orog considered early, but only after massive and early exposure.

Calcium channel blockers have been used successfully in the setting of ischemia.[42] Patients with sumatriptan-associated myocardial infarction we heparin, and intravenous nitroglycerin.[49] Thrombolytic therapy has not b setting but, rationally, should be instituted if clinically warranted after i vasoconstriction and ischemia should be reversed with a calcium channel vasodilator (eg, sodium nitroprusside or nitroglycerin), or the Î±-adrener phentolamine.

Isometheptene

Isometheptene is a mild vasoconstrictor marketed as a combination prep includes dichloralphenazone, a muscle relaxant, and acetaminophen. It has adrenergic agonist effects and minor direct Î±-adrenergic agonist effects vasculature.[63] When administered early during a migraine exacerbation, effective as sumatriptan in relieving migraine headache. Cerebral vasoco after excessive isometheptene and sumatriptan use and after therapeutic [51] Autonomic dysreflexia was reported in a man with spinal cord injury w for treatment of a migraine headache.[68] Treatment of isometheptene-ind should include discontinuation of the medication and reversal of the vaso channel blockers or vasodilators, such as sodium nitroprusside, nitroglyc

Summary

Although epidemic ergotism no longer is a common concern because of g poisoning by both unintentional and intentional ingestions continues to be the complex pharmacologic and physiologic actions of these agents and u pharmacologic antidotes enables the clinician to minimize the morbidity a associated with ergot alkaloids. The introduction of the triptans has decre alkaloids for treatment of migraine. Triptan toxicity is infrequent but, whe consequential complications. Clinicians should be aware of the pharmacolo agents, in order to anticipate and minimize the adverse effects of exposu

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Chapter 52 Antineoplastics

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A 70-year-old woman was brought to the emergency department (ED) from an extended-care facility because of the sudden onset of epistaxis. Her vital signs were: blood pressure, 120/70 mm Hg; pulse, 100 beats/min; respiratory rate, 18 breaths/min; and temperature, 98.6Â°F (37Â°C). The patient stated that for the last 2 days she had dysphagia, progressive weakness, and intermittent shaking. She had a past medical history of rheumatoid arthritis and pulmonary emboli. Her medications include methotrexate (MTX) and Coumadin, which were both started within the last month for her underlying medical disorders. An anterior nasal packing was placed to stop the bleeding. Further examination of the oropharynx demonstrated several ulcers. The skin showed ecchymoses. Chest and abdominal findings were unremarkable. A large-bore IV line was established, and blood was drawn for a complete blood cell count (CBC) with platelets, international normalized ratio (INR), partial thromboplastin time (PTT), electrolytes, blood urea nitrogen (BUN), and creatinine. Blood was also sent for a serum MTX concentration and a type and cross-

match. The CBC showed hemoglobin, 8 g/dL; white cell count, 2000/mm^3 (81% neutrophils, 13% lymphocytes, 1% monocytes, 5% eosinophils); platelet count, 3000/mm^3 ; and INR, 2.0. PTT and renal function were normal. The extended-care facility was contacted, and it was discovered that the patient was inadvertently given methotrexate 2.5 mg daily for 1 month instead of once a week for 1 month.

The patient was transfused with packed red blood cells, platelets, and fresh-frozen plasma. Prophylactic broad-spectrum antibiotics were initiated. Leucovorin 10 mg/m^2 was started and administered every 4 hours IV. The serum MTX concentration was later determined to be zero and leucovorin therapy was discontinued. The white blood cell count (WBC) was lowest on day 3 of hospitalization and rose thereafter.

Although overdoses of antineoplastic medications are infrequent, these events are of greater consequence than overdoses of many other medications because of their narrow therapeutic margin. From 1988 to 2003, the annual number of people exposed to antineoplastic agents reported to US poison control centers was about 1000 (Chap. 130). This figure represents about 1 per 1000 cases of pharmaceutical exposures, or 1 per 2000 cases of all exposures annually reported to US poison control centers. Two-thirds of the people exposed to antineoplastic agents in these reports were adults, one-fourth were young children, and the remainder were adolescents. Between 1999 and 2003 there was an observable change in the annual trend of the proportion of exposures between adults and young children: From 1999 to 2002, the annual percent of exposures for adults increased to approximately 50â€“70%, and for children younger than 6 years old, this figure decreased from 30% to 20%. Children and adolescents between the ages of 6 and 19 years accounted for approximately 7% of the population annually exposed, and this frequency did not change between these years. The reasons for these observations are not apparent and further analysis is

warranted to define the causes of these trends. Approximately 10% of the annual exposures in this setting resulted in morbidity defined as moderate or major in severity. This was higher than expected because unintentional exposures occurred 8 times more frequently than intentional exposures. The mortality was about 1 per 1000 exposures.

A review of the 2819 orders for cytotoxic agents at a pharmacy satellite showed that 93 orders (3%) contained at least 1 error in the dosage regimen and 442 (16%) contained at least 1 error in the instructions for drug preparation.[89] Three of the errors in dosage regimen were classified as potentially lethal, 13 as serious, 5 as significant, and 72 as minor. Two of the potentially lethal overdoses of cisplatin were a result of errors in duration of administration (100 mg/m^2 for 3â€“4 consecutive days instead of for 1 day). Lack of healthcare provider familiarity with the agent and its dosing was a major cause of these events. In another study evaluating drug errors, 49% occurred at the ordering/prescribing stage. This was most commonly caused by physicians who lacked knowledge of the drug and of the intended patient.[162] Other areas in which errors occurred were during transcription and nurse administration. As more antineoplastics become available and their indications broaden, unintentional exposures and unintended dosing regimens (Chap. 134) will increase in number and frequency.

Aside from unintentional exposures, additional factors leading to increased toxicity associated with antineoplastics include age, gender, comorbidities/compromised host state, and diminished renal and hepatic function. Diminished hepatic clearance caused by altered enzyme expression can be accounted for by age, gender, smoking status, and the concurrent use of other medications. Differences in gender can contribute to varying pharmacokinetic parameters, including bioavailability, distribution, metabolism, and elimination. In a study, women treated with 5-fluorouracil (5-FU) for colon cancer were found to have a 2-fold higher frequency of

drug-related toxicity than men.[266] The manifestations included leukopenia, diarrhea, and stomatitis, which also was observed in other reports.[211, 251] Although the basis for this difference in toxicity between genders is not known, it may be

because of a decreased 5-FU clearance from diminished dihydropyrimidine dehydrogenase activity in women.[187, 211] Dihydropyrimidine dehydrogenase inactivates more than 80% of fluorouracil by metabolizing it to 5-fluorodihydrouracil, and low activity of this enzyme can result in hematologic and gastrointestinal toxicity.

Alkylating

Busulphan

Hyperpigmentation, pulmonary fibrosis, hyperuricemia

Dacarbazine

Hypotension, hepatocellular toxicity, influenzalike syndrome

Melphalan

Pulmonary fibrosis

Mustards

Chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine

Hemorrhagic cystitis, encephalopathy, pulmonary fibrosis

Seizures, myocardial necrosis, hyponatremia

MESNA; sodium bicarbonate; methylene blue(?)

Nitrosourea

Carmustine, lomustine, semustine

Pulmonary fibrosis, hepatocellular toxicity, renal insufficiency

Platinoids
Cisplatin
Renal failure, peripheral neuropathy, hypomagnesemia, hypocalcemia, hyponatremia, ototoxicity
Seizures, encephalopathy, ototoxicity, retinal toxicity
Amifostine (nephrotoxicity); thiosulfate
Carboplatin, iproplatin
Myelosuppression, hypomagnesemia, hypocalcemia, hyponatremia

Procarbazine
MAOI activity

Antimetabolite
Methotrexate
Mucositis, nausea, diarrhea, hepatocellular toxicity
Mucositis, myelosuppression, renal failure
Folinic acid (leucovorin); carboxypeptidase; thymidine
Purine analogs
Fludarabine Mercaptopurine
Encephalopathy, muscle weakness Hyperuricemia, pancreatitis, cholestasis

Pentostatin
Hepatocellular toxicity

Thioguanine
Hyperuricemia

Pyrimidine analogs

Cytarabine
Acute lung injury, neuropathy, cerebellar ataxia

Fluorouracil
Cardiogenic shock, cardiomyopathy, neuropathy, cerebellar ataxia

Antimitotic
Epipodophyllotoxin
Etoposide, teniposide
CHF, hypotension

Paclitaxel
GI perforation, peripheral neuropathy, dysrhythmias

Vinca alkaloids
Vinblastine, vincristine, vindesine
Peripheral neuropathy, hyponatremia
Encephalopathy, seizures, autonomic instability, paralytic ileus, myelosuppression

Antibiotics
Anthracycline
Daunorubicin, doxorubicin, epirubicin, idarubicin
Congestive cardiomyopathy
Dysrhythmias, CHF
Dexrazoxane
Bleomycin
Pulmonary fibrosis

Dactinomycin
Hepatocellular toxicity

Mithramycin
Flush

Mitomycin C
Hemolytic uremic syndrome

Mitoxantrone
Congestive cardiomyopathy

Enzyme
L-Asparaginase
Hypersensitivity, pancreatitis

Class	Antineoplastic	Adverse Effects	Overdose	Antidotes

TABLE 52-1. Classification of Antineoplastics and Their Effects

At an individual level, genetic polymorphisms can contribute to differences in xenobiotic response with resultant toxicity by altering targets, transporters, and enzyme complexes. Such variations have been characterized for several enzymes that are involved in the metabolism of antineoplastic agents. Irinotecan and amonafide are two examples that are associated with toxicity.

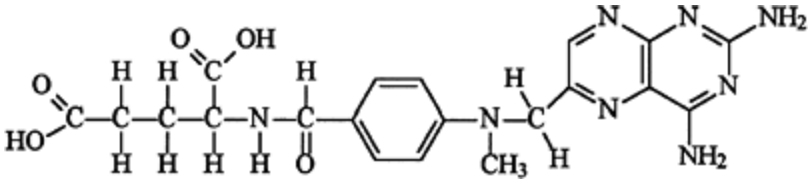
Irinotecan is a topoisomerase I inhibitor that works through its active metabolite, SN-38, which can cause diarrhea and neutropenia at elevated levels.[279] A genetic variant of uridine diphosphate glucuronosyltransferase (UGT1A1) containing the T7 allele glucuronidates SN-38 at a slower rate than other variants, resulting in increased SN-38 levels and toxicity.[12 , 125] Another example is amonafide, which is a topoisomerase II inhibitor; and its active

metabolite, *N* -acetyl amonafide is formed by *N* -acetyltransferase 2 (NAT2). People capable of â€œrapid acetylationâ€• have a genetic variation of NAT2 and are more likely to develop myelotoxicity than are people with a slower rate of acetylation activity.[215] There are additional polymorphisms in metabolism associated with antineoplastic agents; however, further work is necessary to define their clinical significance. Because of the narrow therapeutic index of the antineoplastic agents, the significance of such findings demonstrates the benefit of individual drug monitoring to maximize the therapeutic efficacy of the these agents while limiting host toxicity.

Most antineoplastic agents can be grouped into one of these four categories: alkylating agents, antimetabolites, antimitotics, and antibiotics (Table 52-1). The antimetabolites are grouped by the substrates with which they interfere. Methotrexate is a folate antagonist; other drugs with similar but lesser toxicity include trimethoprim and pyrimethamine. The antimitotics are plant alkaloids and they exert toxic effects by interrupting microtubule assembly. Other naturally derived agents include the antibiotics and the enzyme L-asparaginase, which can be isolated from bacteria. The alkylating agents are more commonly used than other antineoplastic agents and cause covalent binding to nucleic acids, which inhibits DNA activity. These xenobiotics include the nitrogen mustards, platinoids, and nitrosoureas. The antimetabolites and the alkylating agents are cell-cycle active,

meaning that they only affect cells undergoing cell division. Some agents are phase specific; that is, they affect the cell only at a period during cell division. The cell cycle consists of the S phase (DNA replication) and the M phase (mitosis). DNA regulation and chromosomal separation occur during the mitosis. Vincristine is M-phase specific and cytarabine is S-phase specific, in their sites of action. A new class of antineoplastics inhibits topoisomerase I, which is necessary for DNA replication because it allows for reversible DNA single-strand breaks. Because the majority of the cases of antineoplastic overdoses involve the methotrexate, vincristine, mitoxantrone (related to the anthracyclines), mustards, and cisplatin, this discussion focuses on these xenobiotics. Other sources for information regarding these agents are the American Cancer Society (http://www.cancer.org/docroot/home/index.asp) and the American Society of Health-System Pharmacists (http://www.ashp.org/).

Methotrexate



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Pharmacology

Methotrexate (MTX) is an important therapeutic agent for a variety of cancers, such as non-Hodgkin lymphoma, lymphocytic leukemia, breast cancer, and small-cell lung carcinoma. Its immunosuppressive activity allows it to also be used for rheumatoid arthritis, organ transplantation, psoriasis,

trophoblastic diseases, and therapeutic abortion.[52, 133] Its therapeutic and toxic effects are based on its ability to limit DNA and RNA synthesis by inhibiting dihydrofolate reductase (DHFR) and thymidylate synthetase (Fig. 52-1). Thymidylate synthesis is inhibited by polyglutamic derivatives of methotrexate. DHFR reduces folic acid to tetrahydrofolate (FH_4), which serves as an essential cofactor in the synthesis of purine nucleotides. These reduced folates are also required by thymidylate synthetase to serve as methyl donors in the formation of thymidylate. Thymidylate is then used for DNA synthesis. MTX is a structural analog of folate and competitively inhibits DHFR by binding to this enzyme's site of action. This stops reduced folate production, which is necessary for nucleotide formation and DNA/RNA synthesis.

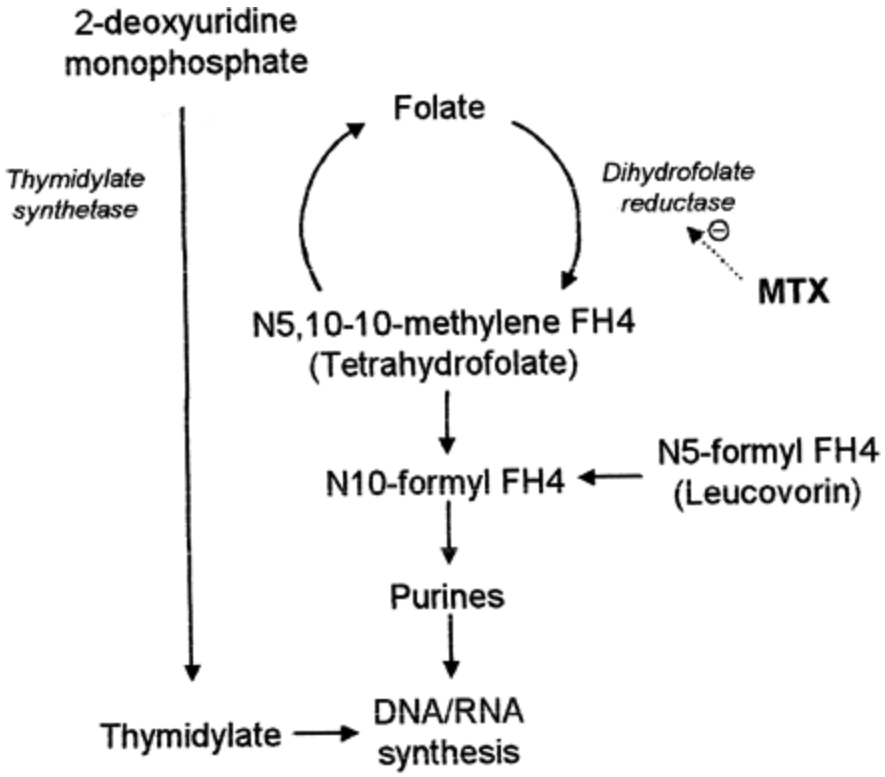


Figure 52-1. Mechanism of methotrexate (MTX) toxicity. MTX inhibits DHFR activity, which is necessary for DNA and RNA synthesis. Leucovorin bypasses blockade to allow for continued

synthesis.

The bioavailability of methotrexate appears to be limited by a saturable intestinal absorption mechanism. At oral doses less than 30 mg/m^2 , the absorption is 90%; at doses greater than 80 mg/m^2 , the absorption is less than 10â€“20%.[36] The weekly adult dose used for the treatment of psoriasis and rheumatoid arthritis is low and can be administered orally. However, the dose used to induce abortion is higher (50 mg/m^2) and must be administered parenterally to achieve effective drug concentrations. MTX dosing regimens for chemotherapy are variable, but can be generally classified as low, moderate, and high doses. Conventional intravenous doses of up to 100 mg/m^2 can be administered without leucovorin rescue. Doses of 1000 mg/m^2 are considered potentially lethal. Much higher doses (2â€“3 g/m^2) can be given when MTX is followed by leucovorin in order to prevent life-threatening toxicity. Mortality from high-dose MTX is approximately 6%, and occurs primarily when patients' MTX levels are not monitored.[86 , 255 , 275]

MTX has a triphasic plasma clearance. The initial plasma distribution half-life is shortâ€”0.75 hours. The second half-life is 2â€“3.4 hours and represents renal clearance of the drug. The third phase has a half-life of about 8â€“10.4 hours and represents tissue redistribution into the plasma. This third phase can be prolonged in the setting of renal failure and is associated with bone marrow and gastrointestinal (GI) toxicity. The kidneys eliminate 50â€“80% of MTX unchanged within 48 hours of administration. At high doses, drug and insoluble drug metabolites 7-hydroxy methotrexate and 2,4-diamino-10-methyl pteroic acid accumulate and may precipitate in the renal tubules, causing reversible acute tubular necrosis. MTX is one-tenth as soluble at a pH of 5.5 as it is at a pH of 7.5.[36 , 231] The serum concentration threshold for nephrotoxicity is 2.2 mmol/L at a urine pH of 5.5, and 22 mmol/L at a urine pH of

6.9. Patients who are either inadequately hydrated or not alkalinized are at risk for acute renal failure from high dose MTX treatment.[3,92,135] MTX is excreted unchanged in the urine by both glomerular filtration and active tubular secretion. Folic acid blocks MTX renal reabsorption and can enhance elimination during leucovorin rescue.[118] A small amount of MTX is metabolized intracellularly to polyglutamate derivatives, which inhibit DHFR and thymidylate synthetase and are believed to be responsible for the persistent cytotoxic effect of MTX.

Toxicity of MTX depends more on the duration of exposure than the dose itself. Thus, greater toxicity is expected from a 7-g (approximately 4 g/m^2 , adult) IV dose administered over 48 hours than from a 20 g (approximately 12 g/m^2 , adult) IV dose administered over 24 hours.[99] Patients with a plasma MTX concentration greater than 1.0 Âµmol/L at 48 hours posttreatment are considered at risk for bone marrow and gastrointestinal mucosal toxicity.[255] Risk factors for MTX toxicity are impaired renal function (primary route of drug elimination), third compartment spacing, ascites, and pleural effusions, use of nonsteroidal antiinflammatory drugs (NSAIDs), age, folate deficiency, and concurrent infection.[255] The contribution of NSAID use to MTX toxicity may be a result of diminished renal clearance of the drug.[153]

Clinical Manifestations

In the course of MTX therapy, a variety of disorders can occur, resulting from either increased patient susceptibility to toxicity or excessive administration. The clinical manifestations of MTX toxicity include stomatitis, esophagitis, renal failure, myelosuppression, hepatitis, and central neurologic system dysfunction. In a group of 23 patients who received 45 courses of high-dose MTX therapy with leucovorin rescue, the commonly

observed signs included increased aspartate aminotransferase (AST)/alanine aminotransferase (ALT) (81%), nausea and vomiting (66%), mucositis (33%), dermatitis (18%), leukopenia (11%), thrombocytopenia (9%), and creatinine elevation (7%).[216]

Nausea and vomiting, considered rare after low-dose cancer therapy (<40 mg/m^2), typically begin 2â€“4 hours after high-dose therapy (>1000 mg/m^2) and last for about 6â€“12 hours. Mucositis, characterized by mouth soreness, stomatitis, or diarrhea, usually occurs 1â€“2 weeks after therapy and can last for 4â€“7 days. Other gastrointestinal symptoms resulting from MTX therapy include pharyngitis, anorexia, gastrointestinal hemorrhage, and toxic megacolon.[16] Hepatocellular toxicity, as described by increased AST (>1000), ALT (>1000), and hyperbilirubinemia, can be observed with both acute and chronic therapy.[180 , 194] It is usually associated with high-dosage regimens. Laboratory abnormalities improve within 1â€“2 weeks of discontinuation of MTX. The mechanism is incompletely understood, but toxicity is attributed to reduced liver folate stores.[19] Factors associated with hepatotoxicity are sustained high plasma levels, increased cumulative dosages, chronic therapy, and host factors such as increase in age, obesity, diabetes, and alcoholism.[280]

Pancytopenia usually occurs within the first 2 weeks after an acute exposure. There are several reports demonstrating the occurrence of pancytopenia in individuals receiving chronic MTX therapy for rheumatoid arthritis and psoriasis.[74 , 147 , 180 , 222]

When used in small IV doses of 40â€“60 mg/m^2 , MTX is not associated with appreciable nephrotoxicity. However, at doses greater than 5000 mg/m^2 (approximately 130 mg/kg for an adult), several investigators report severe kidney damage, with oliguria, azotemia, and renal failure.[25] The renal function can normalize over time. Patients at risk for nephrotoxicity include the elderly, those with underlying renal disease defined as a glomerular

filtration rate of less than 50 mL/min, and those who receive concurrent drug therapy that can delay MTX excretion, which includes agents that reduce renal blood flow such as NSAIDs, the nephrotoxic agents cisplatin and the aminoglycosides, or weak organic acids such as salicylates and piperacillin.[127 , 255]

The neurologic complications associated with either high-dose systemic MTX therapy or intrathecal administration are the most consequential manifestations. The incidence of neurologic toxicity from high-dose MTX therapy is approximately 5â€“15%.[136] The manifestations usually occur from hours to days after the initiation of therapy and include hemiparesis, paraparesis, quadraparesis, seizures, and dysreflexia.[84 , 179 , 277] These events are reversible to varying degrees. The mechanisms remain unclear, but may be the result of direct toxicity to neuronal glial and endothelial cells and decreased neurotransmitter synthesis.[2] Clinical findings occurring within several hours (usually within 12 hours) of therapy are attributed to chemical arachnoiditis, and they include acute onset of fever, meningismus, pleocytosis, and increased cerebrospinal fluid (CSF) protein concentration.[119] Leukoencephalopathy is associated with the onset of behavioral disorders and progressive dementia from months to years after treatment and is irreversible.[7] CSF analysis and computerized tomography of the brain may be normal or show demyelination of white matter (especially in the anterior and frontal lobes).[7]

Management

In the event of an oral overdose of methotrexate, the initial concern should be gastrointestinal decontamination. Activated charcoal adsorbs methotrexate and should be administered as soon as possible to limit absorption.[94] The administration of multiple-dose activated charcoal and cholestyramine[84 , 242] can significantly decrease the elimination half-life of methotrexate by interrupting the enterohepatic circulation.[94 , 105] This can increase

MTX clearance when it is administered parenterally, but is of most benefit to patients with diminished renal creatinine clearance.

Adequate hydration with 0.9% sodium chloride solution as well as urinary alkalinization with IV sodium bicarbonate (to urine pH 7â€“8) (Antidotes in Depth: Sodium Bicarbonate) is also important to prevent renal failure in patients who receive inadvertent high doses. The CBC should be monitored on days 7, 10, and 14 because life-threatening complications, such as bleeding disorders and overwhelming sepsis, can occur.[159]

Patients presenting with meningismus or altered mental status following MTX therapy require an initial computed tomography (CT) scan of the brain and then CSF analysis for infection.[145] Although not considered standard, the CSF may be assayed for MTX if excessive exposure to this compartment is suspected. The CSF MTX concentration is about 0.1 Âµmol/L and lasts for 48 hours after an IV MTX dose of 1500 mg/m^2 , and 100 Âµmol/L for the peak therapeutic concentration after a 12-mg intrathecal MTX dose.[198] Magnetic resonance imaging (MRI) of the brain may demonstrate a high signal throughout the pachymeningeal (dura mater) region, which is consistent with a chemical meningitis.[93] MRI scans of the brain of patients with leukoencephalopathy shows hyperintense lesions in the white matter area.[93] This is a finding similar to that in patients presenting with subacute neurologic symptoms following MTX therapy.[179]

Antidotes

Folinic acid (leucovorin, *N* -5-formyl-tetrahydrofolate) rescue therapy allows higher doses of methotrexate to be administered therapeutically, as leucovorin limits bone marrow and gastrointestinal toxicity. The effectiveness of leucovorin depends on both the timing of administration and the dose. Leucovorin is most beneficial when administered within 1 hour of exposure, but

should still be given to patients who present in a delayed manner after an excessive exposure. The only complications associated with leucovorin administration are the possible drug interaction with anticonvulsants (phenobarbital, phenytoin, primidone) to lower seizure threshold at high leucovorin dosages[219] and hypersensitivity reactions.[120]

The initial leucovorin dose to be administered should achieve a plasma concentration equal to or greater than that of the MTX. In this manner, the reduced folate antidote can successfully compete with MTX for active transport sites on the cell membrane, displace MTX from its intracellular binding site, and, most importantly, restore reduced folate stores to allow for continued purine and subsequent DNA/RNA synthesis.[134 , 210] The lower doses of leucovorin used during MTX therapy are an attempt to protect normal body cells but not tumor cells. Under therapeutic circumstances delay leucovorin rescue as long as possible, administer the minimal effective dose, and discontinue therapy as soon as it is no longer necessary.[25] It is important to adjust the leucovorin dose according to the actual plasma MTX level for an overdose situation, and not to continue at the original rescue dose for routine therapy (Antidotes in Depth: Folic Acid and Leucovorin [Folinic Acid]).[146]

Serum MTX levels should be monitored at 12, 24, and 48 hours postexposure so that leucovorin therapy can be adjusted accordingly. Generally, leucovorin therapy is continued in patients undergoing chemotherapy if the plasma MTX level is above 1.0 Âµmol/L (1 Ã— 10^{+6} M) at 48 hours postexposure,[255] and maintained until the level is below 0.1 Âµmol/L.[264] However, for patients without cancer, the leucovorin therapy should be continued until the MTX level is less than 0.01 Âµmol/L, because DNA synthesis is impaired above this value.[53] In patients with marrow toxicity, leucovorin therapy should be considered until marrow recovery occurs, even if serum MTX is no longer detectable,[173] because intracellular MTX activity may still be

ongoing. It should be noted that trimethoprim, a folate antagonist, can cause false elevations with certain MTX assays (competitive protein binding technique, enzyme inhibition).[22] Spectrophotofluorimetric analysis may misinterpret folinic acid for MTX and should not be used as the analytic method during leucovorin therapy.[149]

Thymidine is also used to rescue cells from the cytotoxic effects of MTX by what is called *thymidylate salvage*.[82, 259] Thymidine can be converted to thymidine triphosphate by thymidine kinase, which is not inhibited by MTX, thus allowing for DNA synthesis. Thymidine rescue is not as effective as leucovorin.[185, 259] It is currently available under an investigational protocol (NCI 92-C-0134) for use by patients with high serum MTX concentration, severe manifestations of toxicity (ie, mucositis, thrombocytopenia, neutropenia, and hepatic insufficiency), and renal insufficiency from the National Cancer Institute (e-mail: ncicssc@mail.nih.gov ; tel: 888â€“624â€“1937 or 301â€–496â€–5725; fax: 301â€–881â€–8239). The investigational dose for thymidine is 8 g/m^2 /d IV, and this treatment is used in conjunction with leucovorin and carboxypeptidase.

Carboxypeptidase G_2 ($CPDG_2$) is a rescue agent that inactivates MTX by cleaving its terminal glutamate group.[292] It is a recombinant bacterial (*Pseudomonas*) enzyme that is well tolerated by patients undergoing high-dose MTX therapy.[68, 283, 284, 292] On its administration, serum MTX concentration decreases within 1 hour. Hypersensitivity reactions may occur because of this agent's bacterial origin. $CPDG_2$ is available for compassionate (protocol No. NCI 92-C-0134) use by patients with high serum MTX concentration (at least 10 Âµmol/L more than 42 hours after initiation of MTX therapy) or under investigational protocol (NCI 92-C-0137) for intrathecal (IT) overdoses (â‰¥100 mg IT MTX) from the National Cancer Institute (e-mail: ncicssc@mail.nih.gov ; tel: 888â€“624â€“1937 or 301â€–496â€–5725; fax: 301â€–881â€–8239). Leucovorin and thymidine treatments are

continued during $CPDG_2$ use because this enzyme does not enter the cell. The investigational dose for $CPDG_2$ is 50 U/kg IV and repeat administration may be necessary if the MTX concentration remains greater than 1 Âµmol/L. It is essential that the high-performance liquid chromatography (HPLC) technique be used to assay for MTX concentration after $CPDG_2$ therapy, because the enzymatic byproducts of MTX yield falsely elevated values with the routine enzyme immunosorbent assay method.[292]

Extracorporeal Elimination

There are several reports of the use of hemodialysis and/or hemo-perfusion for patients with MTX toxicity. Although the volume of distribution (0.6â€“0.9 L/kg) and protein binding (50%) suggest that methotrexate is dialyzable, clinical evidence suggests otherwise.[250] In one report, less than 10% of an initial 0.7 g dose of methotrexate was cleared in 12 sessions of hemodialysis.[261] The measured clearance was only 38 mL/min, which can be compared to 5 mL/min for peritoneal dialysis,[111] 0.28â€“24 mL/min for continuous venovenous hemodiafiltration,[137, 146] and 180 mL/min for normal renal clearance.[167] Using plasma exchange transfusion to remove MTX is not recommended because of the drug's low degree of protein binding, which limits the efficacy of this procedure.[25, 146, 261]

Acute intermittent hemodialysis with a high-flux dialyzer membrane yielded an effective mean plasma MTX clearance of 92 mL/min in 6 patients with renal failure that was a result of either chronic disease or high-dose MTX therapy.[278] These patients received high-dose MTX therapy and had a predialysis plasma MTX concentration ranging from 1.45 to 1813 Âµmol/L. The time of dialysis initiation after MTX treatment was from 1 hour to 6 days in this patient population. A plasma MTX concentration of 0.3 Âµmol/L was used as an end point for dialysis. The reported plasma MTX clearance by this technique closely approximates

normal renal MTX clearance and should be considered if it is available.

Charcoal hemoperfusion removed more than 50% of methotrexate in 4 patients with impaired renal MTX clearance during high-dose MTX therapy.[73] This was thought to have prevented severe skin and mucosal toxicity. Sequential hemodialysis and hemoperfusion were used for a patient with substantial MTX toxicity.[105] These procedures decreased the half-life of elimination from 45 hours to 7.6 hours. In experimental animals, hemoperfusion significantly reduced the terminal half-life of methotrexate. In surgically anephric dogs, hemoperfusion decreased the half-life from more than 20 hours to 1.3 hours.[126] Consequently, hemoperfusion is recommended over hemodialysis.

In vitro studies indicate that the toxic effects of 100 Âµmol/L of MTX cannot be reversed by 1000 Âµmol/L of leucovorin.[210] This suggests the need for hemoperfusion to lower persistent MTX

plasma concentrations of greater than 100 Âµmol/L.[217] It is important to perform hemoperfusion early, prior to distribution into tissues. Rebound of MTX levels from tissues may be expected after hemodialysis, which can begin at 2 hours postdialysis and plateau at 16 hours.[98, 111, 278] If hemoperfusion is not available, and the patient is in renal failure and has a plasma MTX concentration greater than 8 Âµmol/L, hemodialysis may be considered until more definitive treatment, such as enzymatic cleavage, is available.[73]

Patients who are at the greatest risk for developing MTX toxicity despite leucovorin treatment should be considered for extracorporeal elimination because they are most likely to benefit from this procedure. This includes patients with progressively diminishing renal clearance.[255] Although hemoperfusion is preferred over hemodialysis, hemodialysis can be used if it is the only choice available. Hemodialysis can offer the additional benefit

of correcting fluid and electrolyte disorders resulting from renal failure. Other treatment options, including leucovorin and urinary alkalinization, should be continued during extracorporeal MTX removal. Folic acid is water soluble and can be removed by hemodialysis.[64 , 217 , 241 , 245] This is probably also applicable for leucovorin, and replacement doses of leucovorin postdialysis should be considered.

Granulocyte Colony-Stimulating Factor

The decision to use myeloid growth factors in patients with agranulocytosis depends on the severity and nature of the neutropenia, and the anticipated speed of recovery. Granulocyte-macrophage colony-stimulating factor (GM-CSF) was used in a patient with a chronic MTX overdose and pancytopenia.[250] The patient had a serum MTX concentration of 1.25 Âµmol/L on admission and was in renal failure. Bone marrow biopsy showed promyelocytes, but no mature white cells, and a marked reduction of megakaryocytes. Because of deteriorating conditions, GM-CSF (125 Âµg/m^2 /d) was administered when the MTX level fell below the reference limit for toxicity. Seven days after the initiation of GM-CSF, the WBC count rose and reached normal values within 10 days. Typically, if promyelocytes and myelocytes are present in the bone marrow, neutrophil recovery will occur spontaneously in 4â€“7 days, following the withdrawal of the offending agent.[91] However, when granulopoiesis is completely absent, neutrophil recovery cannot be expected for at least 14 days. Using granulocyte colony-stimulating factor (G-CSF) or GM-CSF can accelerate neutrophil recovery during cytotoxic antineoplastic therapy. When myeloid precursors are present in the bone marrow, G-CSF can accelerate neutrophil recovery in 1â€“4 days. If myeloid precursors are absent, neutrophil recovery with G-CSF may take longer, but can be expected to occur sooner than without G-CSF therapy. GM-CSF is indicated for use in neutropenic patients following induction antineoplastic therapy for acute myelogenous

leukemia because this agent enhances the response of macrophages, neutrophils, and eosinophils. Serum levels of the antineoplastic should be below detection before institution of G-CSF to gain maximal response; typically, G-CSF is initiated 24 hours upon the completion of the treatment cycle. The initial dose is 5 Âµg/kg/d IV or subcutaneously (SC), and it is continued beyond the expected WBC nadir. This is usually a 2-week course; however, it can be prolonged with lomustine overdoses.[1,263] The dose may be adjusted, depending on the patient's WBC response. Therapy can be discontinued when the post nadir absolute neutrophil count is greater than 10 Ã— 10^3 cells/mm^3 . Bone pain can be anticipated from the use of these agents, presumably because of the increase in cellularity in the marrow space. Additional side effects can be expected from GM-CSF therapy, including myalgia, fevers, and pericarditis.

GM-CSF might produce a transient beneficial response in the WBC in patients with aplastic anemia.[55] However, when the anemia was severe, the GM-CSF therapy was not effective. Another hematopoietic growth factor is erythropoietin (EPO), which is approved for use in patients with anemia associated with cancer chemotherapy treatment.[100]

Vincristine and Vinblastine

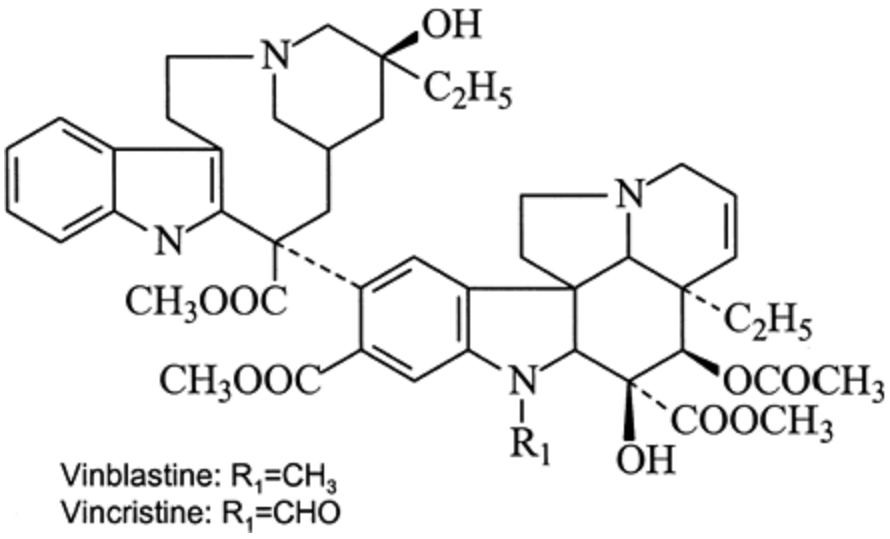


Figure. No Caption Available.

Pharmacology

Vincristine and vinblastine are derived from the periwinkle plant (*Catharanthus roseus*) and used for the treatment of leukemias, lymphomas, and certain solid tumors. Their mechanism of activity is similar to that of colchicine, podophyllotoxin, and the taxoids (eg, paclitaxel, docetaxel).[69 , 78] These xenobiotics disrupt microtubule assembly from tubulin subunits by either preventing their formation or depolymerization, both of which are necessary for routine cell maintenance. Microtubules are responsible for several basic cellular functions including cell division, axonal transport of nutrients and organelles, and cellular movement. Mitotic metaphase arrest is commonly observed because of the inability to form spindle fibers from the microtubules. Cell death quickly ensues as a result of the interruption of these homeostatic functions, accounting for the clinical manifestations.

The vinca alkaloids are primarily eliminated through the liver and have a terminal plasma half-life of about 24 hours.[193] Patients with hepatic dysfunction are susceptible to toxicity. The capacity of vincristine to be bound by plasma proteins ranges from 50% to

80%.[208]

Vincristine overdose is the most frequently reported antineoplastic overdose in the literature. This is because there are at least 4 different ways to misdose this agent, including confusing it with vinblastine, misinterpreting the dose, administering it by the wrong route, and confusing two different-strength vials. The normal dose of vincristine is 0.06 mg/kg, and a single dose is not to exceed 2.0 mg for either an adult or child.

Clinical Manifestations

Despite their similarity in structure, vincristine and vinblastine differ in clinical toxicity. Vincristine produces less bone marrow suppression and more neurotoxicity than does vinblastine. During the therapeutic use of vincristine, myelosuppression occurs in only

5â€“10% of patients.[115] However, this effect is common in the overdose setting and when it occurs the need for replacement blood products and concern for overwhelming infection is apparent.[172] The fall in cell counts begins within the first week and may last for up to 3 weeks. Other manifestations of acute vincristine toxicity are mucositis, CNS disorders, and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

Central nervous system disorders are varied and unusual during therapeutic vincristine therapy because of the agent's poor penetrance of the bloodâ€“brain barrier.[131] They are, however, more common when there is delayed elimination, damage to the blood brainâ€“barrier, overdose, or inadvertent intrathecal administration. Generalized seizures from toxicity or secondary effects may occur from 1 to 7 days after exposure.[121 , 141 , 144 , 256] Treatment with benzodiazepines or phenobarbital is usually successful, and phenytoin was used successfully in a patient with barbiturate hypersensitivity.[144] Other manifestations are depression, agitation, insomnia, and hallucinations. Vincristine

stimulation of the hypothalamus may be responsible for the fevers and SIADH noted in overdosed patients.[223] The fevers begin 24 hours after exposure and last 6â€“96 hours. Serum electrolytes need to be monitored, typically for 10 days.

Autonomic dysfunction is observed, and it commonly includes ileus, constipation, and abdominal pain. Atony of the bladder, hypertension, and hypotension also can occur.[144]

Ascending peripheral neuropathies occur during vincristine therapy and can be limited by keeping the total for a single dose below 2 mg.[246] Neuropathy may appear after an overdose, starting at about 2 weeks and lasting for 6â€“7 weeks. Paresthesias, neuritic pain, ataxia, bone pain, wrist drop, foot drop, involvement of cranial nerves IIIâ€“VII and X, and diminished reflexes can be observed.[281] The incidence of paresthesia increases with dose and is reported to be 56% in patients treated at doses between 12.5 and 25 Âµg/kg.[115] At a dose of 75 Âµg/kg, the incidence of patients with a sensory disorder increased by 6-fold. The loss of reflexes, the earliest and most consistent sign of vincristine neuropathy, is maximal at 17 days after a single massive dose. Muscular weakness is a limiting point in therapy, and typically involves the distal dorsiflexors of the extremities, although laryngeal involvement is also reported.[165 , 230] These severe neurologic symptoms may be reversed by either withholding therapy or reducing dosage upon manifestation of these findings.[165] The mechanism of toxicity is not well understood, but appears to be related to inhibition of microtubular synthesis, which leads to axonal degeneration.[103 , 196] A brain biopsy of a patient suffering a vincristine-related death showed neurotubular dissociation, which is characteristic of vincristine damage in experimental animals.[40 , 57] Unlike the vinca alkaloids, Taxol-induced peripheral neuropathy is predominantly sensory and resolves faster with discontinuation of the offending agent.[170] This is because of the different effects on microtubule assembly by these agents. Nerve conduction studies and the Achilles tendon

reflex are useful in monitoring patients for toxicity after exposure.

Vincristine-induced myocardial infarctions are reported but their cause is not understood.[175 , 247 , 257 , 289] It may be related to vinca alkaloid-induced platelet aggregation, coronary artery spasm, or increased sensitivity of myocardium to hypoxia.

Management

Patients receiving an inadvertent amount of an IV dose of vincristine should be admitted to a cardiac-monitored bed and observed for 24â€“72 hours.[174] Seizures, dysrhythmias, and alterations in blood pressure can be expectantly managed, although prophylactic phenobarbital and benzodiazepine were used to prevent seizures in two patients.[54 , 152] Calcium channel-blockers (nifedipine and amlodipine) were used to control hypertension in a patient with vincristine overdose.[54] Blood counts must be monitored daily, and G-CSF may be used to treat neutropenia.[54 , 172 , 256] However, the red cell response from the use of erythropoietin may be limited because of the induction of metaphase arrest in the erythroblasts by these particular xenobiotics.[177]

If patients remain asymptomatic during the observation period, they can be discharged with followup for bone marrow suppression and SIADH; otherwise, depending upon the patients' clinical condition, continual observation for progression of neurologic symptoms is warranted.[27] The symptoms of acute toxicity usually last for 3â€“7 days, and the neurologic sequelae may last for months before some resolution is observed.

In a controlled clinical trial, for vincristine-induced peripheral neuropathy glutamic acid therapy had limited efficacy. Patients receiving vincristine therapy were given glutamic acid as 500 mg orally 3 times a day.[132] It was observed that there was a decreased incidence in loss of Achilles tendon reflex and delayed

onset of paresthesias in the glutamic acid-treated group. No reported adverse effects with glutamic acid were observed in this investigation. Animal studies involving the administration of glutamic and aspartic acid to mice poisoned with either vinblastine or vincristine demonstrate increased survival and decreased sensorimotor peripheral neuropathy.[39, 66, 130] The mechanisms of these observed effects with glutamic acid remain unclear, but several have been suggested, including glutamic acid's ability to competitively inhibit a common cellular transport mechanism for vincristine,[37, 63] its ability to assist in the stabilization of tubulin and promote its polymerization into microtubules,[41, 110] and the ability of glutamic acid to improve cellular metabolism by overcoming the inhibition by these agents in the Krebs cycle.[77, 220] Although the role of glutamic acid in acute toxicity needs further study, it is not harmful and should be considered. Glutamic acid may be initiated as 500 mg orally 3 times a day and continued until the serum drug concentration is below toxicity.[132] L-Glutamic acid is the preferred stereoisomer because it is biologically active and this product is available as a powder from various distributors in the United States.

Leucovorin may shorten the course of vincristine-induced peripheral neuropathy[107] and myelosuppression.[152] The mechanism is attributed to leucovorin's ability to overcome a vincristine-mediated block of dihydrofolate reductase and thymidine synthetase.[107] However, neither leucovorin[24, 128, 262] nor pyridoxine[129] has been shown definitely to be effective. An initial experimental investigation evaluating the efficacy of antibody therapy to limit vinca alkaloid toxicity shows promise.[108]

Enhanced Elimination

Vincristine is rapidly distributed to tissue stores and highly bound to proteins and red cells.[48] Although elimination of vincristine is via the hepatobiliary system,[48] there is no evidence demonstrating

the efficacy of multiple-dose activated charcoal in enhancing the elimination in the overdose setting. In more than 50% of children given vincristine IV, plasma concentrations were not detected 4 hours after administration.[190] Such characteristics favor early intervention and methods other than hemodialysis. Double-volume exchange transfusion was performed at 6 hours postexposure in

3 children who were overdosed with 7.5 mg/m^2 of vincristine IV.[152] This procedure replaced approximately 90% of the circulating blood volume by exchanging twice the patient's blood volume. Of the 2 survivors, their respective postexchange serum vincristine concentrations were 57% and 71% lower than their preexchange concentrations. The amount of vincristine removed was not determined. Although these patients developed peripheral neuropathies, myelosuppression, and autonomic instability, the author noted that the duration of illness was shorter than previously reported. Thus, based on the pharmacokinetic profile of vincristine and these two reports, exchange transfusion in the child is the preferred method of enhanced elimination when the patient presents soon after the administration of the drug, and plasmapheresis is the preferred method in the adult.

Plasmapheresis was attempted with vinca alkaloid overdoses.[172, 208] In an 18-year-old patient who received two 8-mg IV doses of vincristine at 12-hour intervals, the procedure was performed 6 hours after the second dose and 1.5 times the plasma volume was plasmapheresed.[208] Postplasmapheresis serum vincristine concentration was 23% lower than the starting concentration. The patient survived with myelosuppression, neurotoxicity, and SIADH.

Anthracyclines

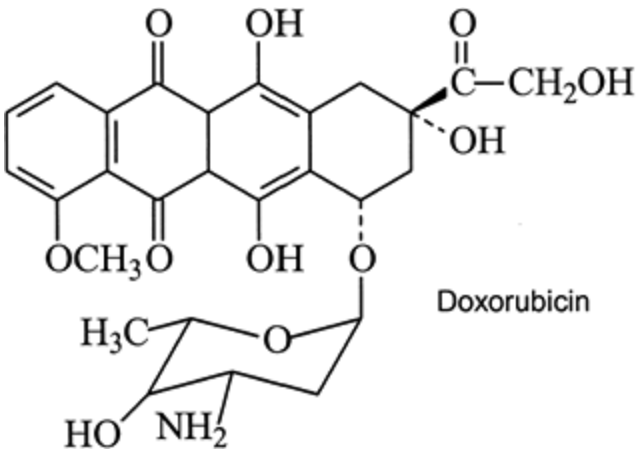


Figure. No Caption Available.

Pharmacology

The antineoplastics derived from the bacterium *Streptomyces* are dactinomycin, daunorubicin, doxorubicin, bleomycin, mitomycin, and plicamycin. Only plicamycin crosses the bloodâ€“brain barrier. The terminal elimination half-life for doxorubicin is about 30 hours.[104] Doxorubicin and daunorubicin are both eliminated by the liver and patients with hepatic dysfunction should have their dosage decreased. Delayed drug elimination contributes to increased drug area under the plasma drug concentration versus time curve (AUC) and peak serum concentration, which are associated with myelosuppression and cardiac toxicity, respectively.[166] The mechanism of therapeutic action of the anthracyclines is attributed to DNA intercalation[228] and activation of topoisomerase II.[260] These xenobiotics are metabolized to active metabolites, which have lesser degrees of activity than their parent compounds. A typical dose schedule for daunorubicin is 30â€“60 mg/m^2 daily for 3 days; for doxorubicin, 45â€“60 mg/m^2 every 18â€“21 days. Daunorubicin and doxorubicin share many common indications for cancer therapy, but they differ in that doxorubicin is used in solid tumors such as breast carcinoma.

The red anthracycline antibioticsâ€”dactinomycin and

doxorubicinâ€”are associated with cardiotoxicity, which limits their therapeutic use. The mechanism responsible for their therapeutic effects is different from that which causes cardiotoxicity.[260] The mechanism of cardiac toxicity is believed to result from the formation of free radicals.[191] Doxorubicin and dactinomycin are quinone derivatives and can be reduced to free radicals. These metabolites are extremely cytotoxic through the promotion of lipid peroxidation. Paraquat and bleomycin have similar mechanisms of toxicity. The limited efficacy of free radical scavengers (Î±-tocopherol, *N* -acetylcysteine) for anthracycline cardiotoxicity led to an understanding of the importance of iron as a cofactor for these radical-producing reactions.[192] The anthracyclines have a high affinity for metal ions. Doxorubicin has an iron (Fe^{3+})-binding constant of 10,[41] which is comparable to deferoxamine.[96] The heart's increased susceptibility to free radicals is attributed to its lack of sufficient enzyme activity responsible for free radical scavenging.[75]

Clinical Manifestations

The cardiotoxic manifestations can be divided into acute and chronic categories. The various findings described with acute toxicity include dysrhythmias, ST and T-wave changes on the ECG, diminished ejection fraction that usually resolves over 24 hours, and sudden death.[42 , 252 , 288] Abnormal findings on the ECG are present in 41% of patients receiving doxorubicin.[14 , 112 , 164 , 252 , 276 , 291 , 294] These are neither dose related nor associated with the development of cardiomyopathy. Acute pericarditis and myocarditis resulting in conduction defects and congestive heart failure are also reported.[42] Animal studies with doxorubicin demonstrate beneficial effects of adrenergic antagonists for toxicity because of elevated levels of catecholamines,[43] although the use of Î²-adrenergic antagonists in the potential setting of diminished cardiac output needs to be considered.

Significant cardiotoxicity results from elevated peak serum levels and accounts for the continuous and periodic infusions practiced in therapy. In cumulative doses, the anthracycline antibiotics cause a cardiomyopathy that results in congestive heart failure. The condition is irreversible and is associated with a 48% mortality.[212] This drug-induced congestive heart failure is associated with pathognomonic changes on electron microscopy that can distinguish it from infectious and ischemic etiologies. These histologic changes include reduced number of myocardial fibrils, and mitochondrial and cellular degeneration.[33] The potential mechanisms for cardiac failure include free radical damage and impaired intracellular calcium homeostasis.[206] The incidence of chronic cardiotoxicity for doxorubicin is between 1 and 10% when the cumulative dose is less than 450 mg/m^2 , and becomes greater than 20% when more than 550 mg/m^2 (comparable to dactinomycin, 950 mg/m^2) is administered.[274] At a cumulative dose of 720 mg/m^2 for epirubicin, the incidence of cardiac dysfunction is reported to be 19%.[186]

The best way of monitoring cardiac function during therapy is to use radionuclide cineradiography to measure the left ventricular ejection fraction.[6] Therapy should be discontinued when the ejection fraction falls below 50%. Two-dimensional echocardiography can demonstrate left ventricular wall thickening and fractional shortening from anthracycline overexposure. Newer techniques used to assess subclinical cardiac muscle pathology from these agents include cardiac-specific contractile protein troponin T and troponin I,[168] and radionuclide-tagged monoclonal antibody imaging.[49] In a small clinical trial of patients treated with doxorubicin,

serum cardiac troponin T levels did not correlate with echocardiographic findings.[150] In 21 of 24 patients, the serum troponin T level was below detection and 9 patients had abnormal echocardiographic findings. Further studies are necessary to

determine the role of these new laboratory studies in clinical management.

Factors associated with an increased risk for cardiotoxicity include mediastinal irradiation, preexisting cardiac disease in children, age more than 70 years, and the concomitant use of cyclophosphamide, paclitaxel, and other anthracycline agents.[42] Children are at risk for developing increased left ventricular afterload from doxorubicin toxicity because of the drug's ability to inhibit myocardial growth, which can lead to a disproportionate ratio of left ventricular wall thickness to left ventricular chamber size.[169] Fatalities are reported with minimum doses of 150â€“333 mg/m^2 , and occur within 1â€“16 days after exposure.[65]

Myelosuppression and mucositis are other effects associated with the use of the anthracycline agents. They typically occur in 1â€“2 weeks, and patients recover.[26] The white cells are affected more than either the red cells or platelets. Patients with diminished drug clearance (eg, liver failure) are at risk for the development of these findings.

Mitoxantrone is recognized to be less toxic than doxorubicin and daunorubicin. Major organs of toxicity remain the heart, bone marrow, and gut. Gastrointestinal effects are less severe and less frequent with mitoxantrone than with doxorubicin.[244] Four cases of mitoxantrone overdose are reported in the literature.[109 , 244] Common to these events is a 10-fold error in dosing (100 mg/m^2 instead of 10 mg/m^2), early onset of nausea with vomiting, and myelosuppression with fever. Acute decreased cardiac contractility was observed by echocardiography in 1 patient who was asymptomatic.[109] Otherwise, no patient developed dysrhythmias, congestive failure, ECG changes, or elevated creatine phosphokinase levels early after exposure. Three patients developed fatal congestive heart failure (CHF) from 1â€“4 months later.[244]

Management

There are no specific antidotes for this class of agents except for dexrazoxane; thus, management is largely supportive. Monitoring for cardiotoxicity and pancytopenia is necessary. A baseline chest radiograph, electrocardiogram, and echocardiogram to determine left ventricular ejection fraction (at rest and/or with stress) are required. Endomyocardial biopsy and cardiac catheterization can assist in distinguishing other causes of cardiac dysfunction. Left ventricular function is the best predictor for cardiomyopathy.[88, 235] A 10% absolute decrease in the left ventricular ejection fraction (LVEF) or a drop in LVEF of 50% from baseline is a significant finding for the discontinuation of further anthracycline therapy.[235] Although digoxin and furosemide should be used to manage acute CHF, a variable response can be expected.[244] Digoxin and low-dose verapamil benefit patients treated with doxorubicin; however, this benefit may be limited by the severity of the disorder.[95, 282] At higher doses of verapamil, hypotension and heart block were observed, which limited further use.[202, 254]

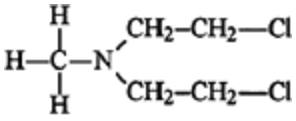
Dexrazoxane is a cardioprotectant that limits the effects of doxorubicin by chelating intracellular iron, which mediates the formation of free radical cellular damage. In clinical trials, patients receiving dexrazoxane had smaller decreases in LVEF per dose of doxorubicin, fewer histologic changes on cardiac biopsy, were better able to tolerate doxorubicin doses greater than 600 mg/m^2, and had a lower occurrence of serum cardiac troponin T elevations than did patients who were not pretreated with dexrazoxane.[169, 248] The current role of this chelator is to limit cardiotoxicity in patients receiving more than 300 mg/m^2 of doxorubicin.[238] It is administered 30 minutes before doxorubicin in a 10:1 ratio. Dexrazoxane increases the systemic clearance of epirubicin in a clinical trial, which may be an added benefit to patients with increased exposure.[23] Further investigations are required to determine the use of dexrazoxane in overdose exposures and with

other anthracycline agents.[5, 186] Other cardioprotectants under investigation include amifostine[50] and monohydroxyethylrutoside. Monohydroxyethylrutoside is a semisynthetic flavonoid that can chelate iron and scavenge free radicals. In experimental models, monohydroxyethylrutoside decreased doxorubicin-induced cardiotoxicity as measured by ST segment elevation on the ECG[268] and left ventricular function.[122] Clinical trials are lacking with this agent.

Enhanced Elimination

The anthracycline agents are highly protein bound and have a large volume of distribution, which make them unlikely candidates for hemodialysis. However, the early institution of hemoperfusion may enhance elimination. In an animal model, plasma doxorubicin clearance could be enhanced up to 20-fold with hemoperfusion.[286] Factors determining this were duration of therapy, rate of flow, and the use of a 2% acrylic hydrogel-coated cartridge. Three patients with a doxorubicin overdose were treated with hemoperfusion, 1 with an Amberlite cartridge, and all had a rapid reduction in their serum levels.[65] One survived a 10-fold error in dosing. In a patient with a mitoxantrone overdose of 98 mg IV, hemoperfusion was begun within hours, but in two trials, only 0.287 and 0.236 mg of drug were removed.[109]

Nitrogen Mustards



Mechlorethamine

Pharmacology

The nitrogen mustard agents are cyclophosphamide, ifosfamide, chlorambucil, mechlorethamine, and melphalan. Their indicated uses include immunosuppression (eg, controlling graft-versus-host rejection, collagen vascular diseases) and chemotherapy. The tumoricidal activity of these xenobiotics is the result of the formation of reactive intermediates that bind to nucleophilic moieties on the DNA chain, which inactivates DNA synthesis. Unlike the other xenobiotics, cyclophosphamide and ifosfamide require mixed function oxidation to achieve their alkylating properties. Mechlorethamine is the original compound from which all of the others were derived. It is highly reactive when it comes in contact with water and undergoes rapid chemical transformation. Local reactions caused by mechlorethamine spillage (eg, extravasation) include tissue injury and thrombophlebitis (see Extravasational Injury below). Nonenzymatic hydrolysis is the major route by which these agents are metabolized, thus accounting for their relatively short elimination half-lives (ie, less than 3 hours).[31] Cyclophosphamide,

ifosfamide, and chlorambucil have active metabolites, which prolongs their alkylating activity after administration.[142]

Clinical Manifestations

Chlorambucil and ifosfamide can produce altered mental status and seizures from therapeutic use or from an overdose.[46] Both compounds undergo *N* -dechloroethylation to produce chloroacetaldehyde, which is purported to be a nervous system toxin.[102] Encephalopathy occurs in 9% of patients receiving 5 g/m^2 of ifosfamide, and is more frequent with oral than with IV administration because of the first-pass effect and increased chloroacetaldehyde production.[181] Seizures are more commonly associated with chlorambucil. Acute overdoses reported in the literature are all from the oral route, and range in dosing from 1.5â€“6.8 mg/kg (therapeutic is 0.1â€“0.2 mg/kg).[10 , 47] The

seizures occur within 6 hours, may appear as generalized tonicâ€“clonic activity or staring spells, and can last for 24 hours. However, in one instance in which therapeutic dosing was increased, seizures occurred 17 hours later. This delay may be attributed to a lower serum concentration or a slower time to peak than in the overdose setting. A similar reasoning would explain why a patient with a chronic overdose of 4.1 mg/kg over 5 days did not sustain CNS toxicity.[81] Patients with increased likelihood to seize are those with underlying seizure disorders or with nephrotic syndrome, which can alter pharmacokinetics.[229] Electroencephalograms (EEGs) demonstrated multiple paroxysms of bilaterally symmetric 2â€“3-Hz spikes and slow high-voltage rhythmic slowing that progressed to slower bursts of rhythmic spike and wave discharge in a child with an acute overdose.[47] Myelosuppression occurs in patients with both acute and chronic overdoses, and can present as late as 41 days postexposure. Recovery is expected within 1 week of the nadir, and G-CSF treatment may be necessary.[140]

Cyclophosphamide and its analog ifosfamide induce hemorrhagic cystitis from their irritating metabolite acrolein. This occurs in approximately 5â€“10% of patients who receive therapy.[45 , 62] The incidence of cystitis does not appear to be related to the total dose and administration route, age, or gender. The course is usually self-limiting, although blood transfusions may be required. Free water retention is observed in patients receiving more than 50 mg/kg of cyclophosphamide.[70] This effect is attributed to the activity of the alkylating metabolite on the renal tubule and is observed at 6â€“8 hours after drug administration. The patient experiences decreased urinary output, increased urine osmolality, and decreased serum osmolality. This is self-limiting, lasting for about 12â€“16 hours.

In the overdose setting, cyclophosphamide can cause dysrhythmias, myocardial necrosis, and death. ECG changes are noted at doses of 120 mg/kg and heart failure and myocarditis at

doses greater than 150 mg/kg.[13 , 188] An ordering error led to the death of 1 patient and to irreversible cardiac damage in another patient from cyclophosphamide overdose. These 2 patients received 6520 mg of the agent daily for 4 consecutive days, when the amount was to be divided over 4 days.[225] The onset of heart failure can be sudden, and patients older than 50 years of age, and those with prior treatment with anthracyclines, are at greatest risk for cardiac toxicity.[253]

Management

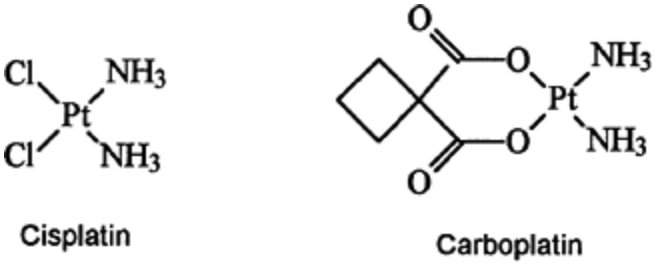
Recommendations for patients with an acute chlorambucil exposure include routine gastrointestinal decontamination, a 6-hour observation, a baseline CBC and hepatic enzymes, and a followup CBC weekly for 4 weeks.[269] Ifosfamide-induced encephalopathy can be managed with methylene blue (50 mg IV as a 1% solution), although the mechanism by which methylene blue acts is unknown.[155 , 293] Seizures are reported to be more effectively managed with benzodiazepines and barbiturates than with phenytoin.[10 , 34 , 287]

When gross hematuria from cyclophosphamide or ifosfamide therapy persists, treatments reported to be effective in the literature can be considered. These treatments include electrocauterization, systemic vasopressin,[213] intravesical administration of silver nitrate,[154] formalin,[90 , 239] prostaglandin F-î± ,[243] and hydrostatic pressure.[116] Some of the preventive therapies that seem to reduce this occurrence include adequate hydration for dilution effect, frequent bladder emptying, IV administration of 2-mercaptoethane sulfonate sodium (MESNA), and intravesical *N* -acetylcysteine.[45] The thiol group of *N* -acetylcysteine is believed to directly interact with acrolein to limit its irritating effect on the bladder epithelium. MESNA is believed to work by inactivating acrolein to an inert thioether.[117] The IV dose of MESNA is 20% of the cyclophosphamide or ifosfamide amount

(wt/wt) and administered during therapy and again at 4 and 8 hours. MESNA is used during standard-dose therapy for ifosfamide and high-dose therapy for cyclophosphamide.

Patients with large exposures to cyclophosphamide require baseline ECGs and echocardiograms. Intravenous fluid restriction, digoxin, and furosemide were successfully used to treat a patient with cyclophosphamide-induced congestive cardiomyopathy.[273]

Platinoids



Cisplatin Carboplatin

Figure. No Caption Available.

Pharmacology

The cytotoxic effects of the platinum-containing compounds were first recognized in 1965; since then, many types have been derived. The ones of clinical significance are cisplatin, carboplatin, and oxaliplatin.[189] These xenobiotics were designed to reduce the incidence of nephrotoxicity and to counter drug resistance. Differences in chemical structure exist. Most notably, cisplatin is an inorganic and carboplatin an organic compound. Similarities exist in their mechanism of toxicity, which is the binding of platinum to DNA to form inter- and intrastrand bonds, which lead to DNA dysfunction and strand breakage. These xenobiotics are eliminated from the body primarily in the urine and at varying rates. The amount eliminated at 24 hours is 25% for cisplatin and 90% for carboplatin. Patients with decreased creatinine clearance

(<30 mg/m^2) will have prolonged elimination half-lives of platinoids.[83]

Clinical Manifestations

The more common manifestations of toxicity with cisplatin during therapy are renal dysfunction, auditory impairment, and peripheral sensory neuropathy. The other antineoplastics recognized to cause

a peripheral neuropathy are the vinca alkaloids and the taxoids. Oxaliplatin-induced neuropathy is triggered or enhanced by exposure to cold and can subside over several months.[87] Myelosuppression is a dose-limiting factor for carboplatin and iproplatin, which does not occur with cisplatin. At a carboplatin dose of 800 mg/m^2 , 25% of patients develop marrow toxicity.[203] The marrow effects are delayed, with nadir occurring 3â€“5 weeks after the start of therapy. Patients developing an anemia within the first week of cisplatin therapy should be evaluated for hemolytic anemia.[59]

The sources of error associated with cisplatin are frequency of administration (total dose versus over a period of time), mistaking it for carboplatin, and writing the wrong dose.[60 , 209] Manifestations in the overdose setting involve neurologic, visual, hearing, bone marrow, pancreatic, and renal disorders.[242] The most common renal disorder is renal failure, which is dose-related and begins at 50 mg/m^2 . The result is irreversible distal tubular necrosis.[224 , 232] Cell death may be from intracellular glutathione depletion.[67 , 72 , 101] The presence of urinary alanine aminopeptidase and *N* -acetyl-Î²-D-glucosaminidase may be used as early indicators of renal tubular damage.[67 , 72 , 101] Saline diuresis can limit renal toxicity. Hyponatremia is an uncommon finding with cisplatin exposure and is attributed to either sodium-wasting nephropathy from renal tubular dysfunction or SIADH. At doses greater than 200 mg/m^2 , the development of seizures,

encephalopathy, and irreversible peripheral sensory neuropathy is of concern.[28 , 61 , 114 , 203 , 204] Pathologic evaluation demonstrates axonal degeneration and damage to the dorsal root ganglion. At this dose, visual impairment may occur within the first week of exposure.[58 , 178 , 285] This can include temporary visual loss, with permanent loss of color discrimination. Physical examination of the anterior chamber and fundus of the eye will be normal; however, an electroretinogram will demonstrate a disorder with the postphotoreceptor neural function. Some other ocular disorders are papilledema and retrobulbar neuritis. High-frequency (>2000 Hz) hearing loss is evident 2â€“3 days after exposure to doses greater than 500 mg/m^2 .[56]

Management

Renal protection and enhanced elimination of platinum are the two primary goals in the management of a cisplatin overdose. Expectant management for myelosuppression and neurotoxicity can follow. Sodium chloride diuresis both promotes the inactive anionic state of cisplatin and decreases the urine platinum concentration to limit nephrotoxicity during therapy.[8 , 272] Hydration with 0.9% NaCl solution and an osmotic diuretic (eg, mannitol) should be administered to achieve a high urine output (eg, 1â€“3 mL/kg/h) for 6â€“24 hours postexposure. In the setting of nonoliguric renal failure, careful hydration is recommended to maintain urinary output, because platinum renal excretion is directly related to urinary flow, and independent of creatinine clearance.[58] Aside from evaluating the BUN and creatinine, assessment of renal function can include the glomerular filtration, filtration fraction, and renal plasma flow.[106 , 183 , 184 , 197]

Amifostine and sodium thiosulfate are effective nephroprotectants. Amifostine's role is more preventative and is approved by the FDA for use to protect against cisplatin-induced nephrotoxicity. Unlike thiosulfate, amifostine is activated intracellularly by alkaline

phosphatase to scavenge free radicals, prevent cisplatin-DNA adduct formation, and facilitate DNA repair.[151] The patient requires adequate hydration during amifostine infusion because hypotension can occur. Sodium thiosulfate is effective postexposure. Thiosulfate remains in the extracellular space to bind free platinum and limit cellular damage at the renal tubules. Little or no renal toxicity occurred in patients receiving as much as 270 mg/m^2 of cisplatin when thiosulfate was given as an IV bolus of 4 g/m^2 followed by infusion of 12 g/m^2 over 6 hours.[113 , 207] Thiosulfate may offer the additional benefit of limiting neurotoxicity and should be administered to all patients after an overdose.[176 , 270] The use of thiosulfate is limited by the time in which it needs to be administered after exposure (ie, 1â€“2 hours). *N* -acetylcysteine and BNP7787 are being investigated as alternative rescue agents for cisplatin toxicity.[242]

Hemodialysis is ineffective in patients with cisplatin overdoses, likely as a result of this agent's high protein binding.[44] However, in patients with renal failure, hemodialysis may be beneficial. Plasmapheresis was performed in 2 adults and there was a fall in blood serum platinum concentrations with clinical improvement. The first patient received an overdose of 280 mg/m^2 and was plasmapheresed on day 12 of exposure.[58] After 3 daily treatments, the serum platinum concentration decreased from 2900 to 200 ng/mL and the patient had noticeable improvement in gastrointestinal and visual symptoms. On day 20, the serum platinum concentration rebounded to 700 ng/mL and the symptoms worsened. Further plasmapheresis lowered the concentration to 290 ng/mL by day 27 and symptoms improved. The other patient received 300 mg/m^2 of cisplatin and received 4 daily treatments of plasmapheresis starting on day 6 postexposure.[143] The plasma serum platinum concentration declined from 2979 to 430 ng/mL and the patient became more awake and less nauseous. On day 11, platinum concentrations rebounded to 834 ng/mL and fell to 279 ng/mL on reinstitution of

plasmapheresis. The amount of platinum removed by 3 trials was 4622 Âµg. The author of the paper contends that plasmapheresis prevented the need for hemodialysis in renal failure. Thus, plasmapheresis appears to be effective in cisplatin overdose and should be instituted immediately after exposure. Patients who remain symptomatic days later also may benefit.

Intrathecal Overdose

Intrathecal overdoses with vincristine, methotrexate, doxorubicin, daunorubicin, and cytarabine are reported in the literature.[156] Common sources of error are confusing the IV for the intrathecal agent and misidentifying the strength of the solution vial in the preparation of the medication. These events are distressing because of the disastrous consequences they bring and the immediacy with which the agent must be removed from the intrathecal space. Removal of as much of the agent as possible is the patient's only chance of having an acceptable prognosis (see Chap. 19).

Upon recognition of the occurrence, the patient needs to be placed in a gravity-dependent position to prevent upward flow of the agent towards the cisterna magnum. The upright position significantly delays the flow of an intralumbar administered agent to the cerebral ventricles, when compared with the flow in a patient lying flat or in the Trendelenburg position.[80] The lumbar puncture site needs to be maintained or reestablished so that as much of the CSF can be drained as possible. With an intrathecal MTX model, if 20 mL of CSF is removed within 30 minutes of administration, then 94% of the agent given is retrieved.[4] However, by removing the same volume at 3 hours, only 10% of the agent is recovered. CSF drainage can be accomplished in short time intervals, considering that CSF production is 30 mL/h. CSF exchange should be accomplished by lavaging the intrathecal space with lactated

Ringer solution. An equal volume of the CSF space should be used in each pass of the lavage, and 2â€“3 passes should be performed to complete the procedure. The volume of CSF in a child older than age 3 years approaches that of an adult (ie, 120 mL). For large exposures, CSF perfusion must follow. This is performed by passing solution through a ventriculostomy and out a lumbar drainage catheter. Lactated Ringer solution with 15â€“25 mL of fresh-frozen plasma added per liter of crystalloid is infused at 150 mL/h for 18â€“24 hours.[79, 290] The ventriculostomy and lumbar drain can then be removed. The thecal effluent can be collected to determine the amount of drug recovered. Depending on the antineoplastic involved, additional measures may be necessary.

Intrathecal vincristine overdoses are devastating. Only 2 of 13 patients reported in the literature survived, and their survival was attributed to the CSF evacuation of this agent within minutes of exposure as described above.[79, 290] There is no indication for the intrathecal administration of vincristine or vinblastine. This mishap is usually the result of confusing vincristine with the other medications (eg, cytarabine, MTX) that are commonly dispensed for intrathecal use. Death follows a characteristic course, consisting of back pain, meningismus, lower-limb weakness, urinary difficulty, loss of deep tendon reflexes, encephalopathy, and respiratory failure. Alteration in mental status appeared earlier when vincristine was administered intraventricularly.[182] Pathologic changes are most notable in the cerebellum, the brainstem, and the anterior horns of the spinal cord.[18] There are only 2 reported survivors from intrathecal vincristine, and the amount of vincristine recovered in one case was 95% of the 2 mg of vincristine that had been administered.[79] Additional therapies provided in these cases were glutamic acid (10 g IV over 24 hours, then 500 mg orally 3 times a day),[132] folinic acid (25 mg IV every 6 hours), and pyridoxine (50 mg IV every 8 hours). These therapies were continued for 1 week or until the neurologic

symptoms stabilized. Dexamethasone (4 mg/m^2 IV every 6 hours) may be given for meningeal inflammation. The roles of these agents are unclear, but because of the seriousness of the situation, aggressive therapy should be offered.

Intrathecal overdoses of MTX commonly occur because a more concentrated solution vial is mistaken for one that is less concentrated.[249, 163] Overdoses reported in the literature range as high as 650 mg and death is associated with amounts greater than 500 mg.[249] The therapeutic intrathecal MTX dose, according to age, is 6 mg for a patient younger than 1 year old; 8 mg for a patient between the ages of 1 and 2 years; 10 mg for a patient between the ages of 2 and 3 years; and 12 mg for a patient older than 3 years of age.[36] The neurotoxicity associated with these events includes chemical arachnoiditis, ascending neuropathy, encephalopathy, and seizures. The seizures can be treated with phenobarbital and benzodiazepines.[163, 221]

Unlike intrathecal vincristine overdoses, the prognosis for an intrathecal MTX exposure is more favorable because of the different mechanism of action and the availability of rescue therapy. Two deaths are reported with intrathecal MTX overdose after the patients received amounts greater than 500 mg.[85, 249] CSF removal of MTX is still crucial, and for amounts less than 100 mg, CSF drainage may be adequate if performed within 30â€“60 minutes of administration.[138, 198] When a longer period of time has elapsed, or a larger amount is involved, CSF exchange is necessary, and possibly CSF perfusion as well. At amounts greater than 500 mg, CSF perfusion must follow because drainage and exchange cannot remove enough MTX to prevent significant toxicity. CSF decontamination should continue until the final CSF MTX concentration is about 100 Âµmol/L, which is a peak therapeutic level for a 12-mg intrathecal MTX dose.[198] Large amounts of MTX administered intrathecally pass into the systemic circulation, which poses a threat to the bone marrow. Although there are no reports of myelosuppression resulting from such an

event, IV leucovorin is indicated. High-dose leucovorin rescue should be started upon recognition of the overdose. The following IV leucovorin regimen was used in a patient who received 600 mg of intrathecal MTX and survived: 1000 mg/m^2 , followed by 100 mg/m^2 every 3 hours until the plasma MTX concentration was less than 0.1 Âµmol/L.[198] Leucovorin is not to be administered intrathecally because seizures with resultant death can occur, and the etiology of MTX-induced neurotoxicity is chemical irritation, not folate inhibition.[138] Additional therapies are hydration and urinary alkalinization to prevent renal toxicity, and IV dexamethasone to lessen meningeal inflammation. Enzymatic agents that inactivate MTX are a new and promising form of rescue therapy for intrathecal overdoses. $CPDG_2$ dramatically shortened the MTX CSF half-life in a patient with a 600-mg intrathecal overdose.[198] The patient received the carboxypeptidase agent intrathecally, following CSF decontamination, and survived. Enzymatic cleavage may obviate the future need for CSF perfusion in large overdoses.

Extravasational Injury

Extravasational injuries are among the most consequential local toxic events. When an antineoplastic leaks into the perivascular space, significant necrosis of skin, muscles, and tendons can occur with resultant loss of function. The initial manifestations may include swelling, pain, and a burning sensation that can last for hours. Days later, the area becomes erythematous and indurated and can either resolve or proceed to ulceration and necrosis.[226] Sometimes, these early findings may be difficult to distinguish from other forms of local drug toxicity, such as irritation and hypersensitivity. Either the drug or its vehicle (ethanol, propylene glycol) can cause local irritation. The drugs associated with local irritation include fluorouracil, carmustine, bisantrene, cisplatin, and dacarbazine. The local irritation and hypersensitivity manifestations are self-limiting and typified by an immediate onset

of a burning sensation, pruritus, erythema, and a flare reaction of the vein in which the agent is being infused. Pretreatment with an antihistamine usually prevents some of the hypersensitivity manifestations upon subsequent administrations.[271] Drugs reported to cause hypersensitivity reactions include daunorubicin, doxorubicin, idarubicin, and mitoxantrone. This event is typified by the presence of pruritus. Nevertheless, when local reactions cannot be differentiated, it is always best to presume extravasation and manage the situation accordingly.

The occurrence of these inadvertent events appears to be about 50 times more frequent in the hands of the inexperienced clinician.[123] Several factors are associated with extravasational injuries from peripheral intravenous lines, including (a) patients with poor vessel integrity and blood flow, such as the elderly, those who undergo numerous venipunctures, and radiation therapy to the site; (b) limited venous and lymphatic drainage caused by either obstruction or surgical resection; and (c) use of sites over joints, which increases the risk of dislodgments because of movement.[124, 226] Extravasational injuries from implanted ports in central venous vessels can occur from inadequate placement of the needle, needle dislodgment, fibrin sheath formation around the

catheter, perforation of the superior vena cava, and fracture of the catheter.[234] When extravasation from a port is suspected and radiographic studies are not diagnostic, a CT scan of the chest with a contrast dye study is necessary for evaluation.[11]

General

Stop infusion and maintain intravenous cannula at the site.

Aspirate extravsate from the site by accessing the original intravenous cannula.

Irrigation of subcutaneous tissue at the site with normal saline by accessing the original intravenous cannula.

Minimizes amount of antineoplastic localized at the site.
Apply dry cool compresses for 1 hour, every 8 hours for 3 days.
Localizes area of involvement and diminishes cellular uptake of the antineoplastic.
Elevate extremity and administer analgesia.
Promotes drainage, prevent dependent edema, and for comfort.
Specific
Anthracyclines
Dimethyl sulfoxide (DMSO)â€”55â€“99%.
Applied topically and allowed to dry.
Every 6â€“8 hours for 3â€“10 days.
Free radical scavenger.
Dexrazoxane 1000 mg/m^2 , daily, on days 1 and 2, and then 500 mg/m^2 on day 3: IV.
Limits free radical formation.
Mechlorethamine
Sodium thiosulfateâ€”Prepare a sterile 0.17 Msolution by mixing 4 mL thiosulfate 10% weight/volume with 6 mL water for injection.
Infiltrate the site of extravasation.
Prevents tissue alkylation.
Mitomycin
DMSO applied topically.
Free radical scavenger.
Vinca alkaloids and epipodophyllotoxins
Hyaluronidaseâ€”Inject, intradermally or subcutaneously, 150â€“900 U into the site.
Degrades hyaluronic acid to enhance systemic absorption.

Dry warm compresses.
Promotes systemic absorption.

Therapy Purpose/Mechanism

TABLE 52-2. Management of Extravasational Injuries [29]

The factors associated with a poor outcome from extravasational injuries include (a) areas of the body with little subcutaneous tissue, such as the dorsum of the hand, volar surface of the wrist, and antecubital fossa, where healing is poor and vital structures are more likely to be involved; (b) concentration of extravasate; (c) increased volume and duration of contact with tissue; and (d) the type of agent.[226, 227] Vesicant agents, such as doxorubicin, daunorubicin, dactinomycin, epirubicin, idarubicin, mechlorethamine, mitomycin, and the vinca alkaloids, appear to result in more significant local tissue destruction. Mitomycin infusions can cause dermal ulcerations at venipuncture sites remote from the location of administration.[205] The anthracycline antibiotics are associated with a higher incidence of significant injuries and delayed healing, which may be a result of their slow release from bound tissue into surrounding viable tissue. Doxorubicin extravasation is associated with local tissue necrosis in approximately 25% of cases. The extravasational injuries from taxanes appear similar to the vesicant agents, but are milder in response and longer in days to presentation.[17, 214] Prevention is the best form of therapy for these injuries. Specialized nursing care and the use of indwelling central venous catheters have limited the extent of these injuries.

Management

The treatment for extravasational injuries is somewhat controversial, varying from conservative care to early surgical debridement and the use of selective antidotes.[236] This uncertainty is a result of the limited number of clinical cases available for study and the discordance between animal studies and clinical findings. However, general management guidelines for an extravasation and their theoretical foundations exist (Table 52-2).[29, 38]

Once extravasation is suspected, the infusion should be

immediately halted. A physician should be notified and the xenobiotic, its concentration, and the approximate amount infused should be noted. The venous access should be maintained so that aspiration of as much of the infusate as possible can be performed and antidote can be administered, if indicated. Injection of normal saline into the catheter to dilute the extravasate may be beneficial.[148 , 236] The intermittent local application of ice and elevation of the extremity should be done for 48â€“72 hours so as to limit further progression of the agent and the development of dependent edema. Cooling the area is believed to prevent cell injury by reducing the amount of xenobiotic absorbed by the tissue and lowering the cellular metabolic rate. It was demonstrated that, with just cold application and strict elevation, only 13 (11%) of 119 patients with mild extravasations required surgical intervention for their injuries.[160] In the past, heat was recommended to disperse the agent, but investigations with mice treated with intradermal doxorubicin demonstrated that this practice increases the area of skin ulceration.[76 , 160] However, dry, warm compresses are still recommended for the vinca alkaloids and etoposide to promote systemic uptake.[29] This is combined with the local infiltration with hyaluronidase to enhance absorption (Table 52-2). The amount of hyaluronidase administered at the site ranges from 150â€“900 U, and the working concentration of the solution depends on the area to be treated. For extravasational injuries involving a small area, the initial solution of 150 U/mL may be adequate. Otherwise, the solution may be

diluted by 10-fold with normal saline to increase the amount of volume that would be needed to treat a larger surface area. If the intravenous cannula is still accessible, 1 mL of hyaluronidase can be administered through the catheter. Wounds that are either cancerous or infected should not be treated with hyaluronidase.

The wound should be observed closely for the first 7 days, and a

surgeon consulted if either pain persists or evidence of ulceration appears.[226] However, in severe extravasationsâ€”where there is a high incidence of necrosis because of the type of drug (doxorubicin), the volume or concentration, and any area in which there may be significant long-term morbidity (over joints)â€”early surgical consultation is warranted. If tissue ulceration occurs, initial management can be with sterile dressings to prevent secondary infections. After the area of necrotic skin has evolved to the point where it can be clearly delineated from surviving tissue, surgical debridement may be beneficial to limit secondary infection. The use of intravenous fluorescein or other dye indicators can aid in identifying viable tissue.[15] The patient may require surgical reconstruction or skin grafts depending on the extent of the injury.

Antidotal therapy should be considered when the extravasate is known to respond poorly to conservative care. The vesicant-type agents are associated with a significantly worse outcome, and when the exposure is large, a more aggressive approach should be initiated. Otherwise, conservative supportive management may be adequate. The specific antidotal treatments can be divided into several categories based upon their mechanism of action, one of which is the reduction of the inflammatory response through the application of steroids. Hydrocortisone has been used in varying concentrations (50â€“200 mg) as either subcutaneous or intradermal injections for doxorubicin and the vinca alkaloids,[20 , 123 , 161 , 267] and as a topical cream.[148] Steroids may have only a limited role in doxorubicin-induced lesions because inflammatory cells are not found in predominance at the wound site.[32] The addition of steroids to doxorubicin infusions, so as to limit morbidity if extravasation should occur, is not recommended because the drugs are chemically incompatible.[265] A prophylactic approach is to inactivate the drug by affecting the pH of the environment. The administration of 5 mL of 8.4% sodium bicarbonate through the same IV line to decrease the DNA binding

of doxorubicin has been advocated.[21] The use of sodium bicarbonate should be cautious and not be considered as routine treatment because its hyperosmolarity can cause tissue necrosis.[97] Sodium thiosulfate is recommended for mechlorethamine extravasations, and is believed to work by inactivating the agent by reacting with the active ethylenimmonium ring.[124 , 199] The site is infiltrated with sterile sodium thiosulfate solution and then ice compresses are applied intermittently for 48â€“72 hours.[29] Finally, there are agents, such as dimethyl sulfoxide (DMSO), that scavenge the free radicals that are believed to cause tissue damage from doxorubicin. Dimethyl sulfoxide is beneficial for anthracycline extravasations in both animal and human clinical trials.[30 , 71 , 161 , 199 , 258] The concentration of DMSO used ranged from 55â€“99% and was applied topically with intermittent cool compresses.[29 , 161 , 198] Some of the other beneficial properties of DMSO are its antiinflammatory, analgesic, and vasodilatory effects, and its ability to promote systemic absorption of drug at local sites.[171] The systemic administration of dexrazoxane was demonstrated to limit anthracycline-induced skin lesions in a murine model[158] and used successfully in patients with doxorubicin[157] and epirubicin[139 , 157] extravasations. Dexrazoxane was given to these patients over 3 days and by the intravenous route at a starting dose of 1000 mg/m^2 . Additional clinical evidence needs to be gathered to better define the dosing regimen for this type of therapy. Although the overall incidence of extravasations with antineoplastic agents is small, the associated morbidity from any one event may be significant. Prevention is the best form of therapy.

Antineoplastics in the Workplace

A variety of workers are at risk for increased exposure to antineoplastics, including pharmacists, nurses, physicians, and others involved in the preparation and dispensation of these agents, and who may be exposed to the body fluids of patients

treated with these agents. Several studies demonstrate that these agents can be detected in the work environment and measured in workers,[233] and there is concern about the possible genotoxic effects from these exposures.[237] The worker may absorb these xenobiotics by either the dermal, inhalational, or gastrointestinal route. The factors determining the amount of worker exposure include the nature of the work, the amount of drug used, the frequency and duration of exposure, the physical and chemical nature of the drug, and the use of ventilated cabinets and personal protection equipment during the handling of these agents. The workplace guidelines for antineoplastics fall under the broader category of hazardous agents. A sample list of drugs considered as hazardous agents by National Institute for Occupational Safety and Health (NIOSH) is available for further information.[51] NIOSH defines a drug as a hazardous agent if it is either carcinogenic, teratogenic, genotoxic, associated with developmental or reproductive toxicity, or toxic to organs at low dose.

Regulatory and workplace recommendations for exposure levels and the waste management of these agents are available from various agencies and organizations. These recommendations are limited in scope because only a small number of xenobiotics or adverse health effects have been adequately studied, and many agents do not meet the current definition for inclusion. US Environmental Protection Agency (Resource Conservation and Recovery Act, 40 CFR Â§Â§260â€“279) regulates 9 antineoplastics (arsenic trioxide chlorambucil, cyclophosphamide, daunomycin, melphalan, mitomycin C, naphthylamine mustard, streptozocin, and uracil mustard) and the equipment and devices associated with their preparation or delivery, as well as their disposal, as hazardous waste.[218] The current recommendations for worker safety with these agents in the workplace includes the proper management of the work environment (eg, storage, handling, preparation, administration, use of personal protection equipment, decontamination, waste disposal) and the institution of a medical

surveillance program with approved laboratory testing.[9, 195]

Summary

The antineoplastics are a unique therapeutic class because their cytotoxicity is a direct effect. Medicine is challenged to carefully balance this measure so that there is limited damage to native cells, and thus the patient. Over the years, the number of antineoplastic exposures reported to the American Association of Poison Control Centers Toxic Exposure Surveillance System has remained small; however, the consequences of toxicity to the patient in these reports were great. The majority of these occurrences were iatrogenic, involving misreading of the product label, and

errors in dosing and transcription of orders (Chap. 134). A key element was the lack of familiarity of the healthcare provider with the use of these select xenobiotics. The number of antineoplastics and their indicated use have increased over the years and will continue in this fashion into the future, increasing the chance for medical error and patient toxicity. The clinical manifestations of toxicity can develop in various organ systems and are primarily determined by the mechanism of action, route of administration, and duration of exposure. The gut epithelium and bone marrow are extremely susceptible to toxicity because of their high mitotic activity. They are important because their failure will lead to overwhelming sepsis and death. Treatment remains primarily supportive in nature. New additions in this area include carboxypeptidase, the antidote for MTX, and G-CSF to limit the severity of neutropenia. Further work is necessary to define the role of erythropoietin in exposures resulting in anemia. Although cytoprotectants will continue to be developed, they cannot be relied on to rescue patients from exposures because their number will be few in comparison to the quantity of available antineoplastics and their effectiveness limited to pretreatment.

Thus, prevention is the best treatment, which can be accomplished by maintaining a heightened awareness when working with these agents, educating the patient and healthcare provider regarding their use, and providing increased skilled care.

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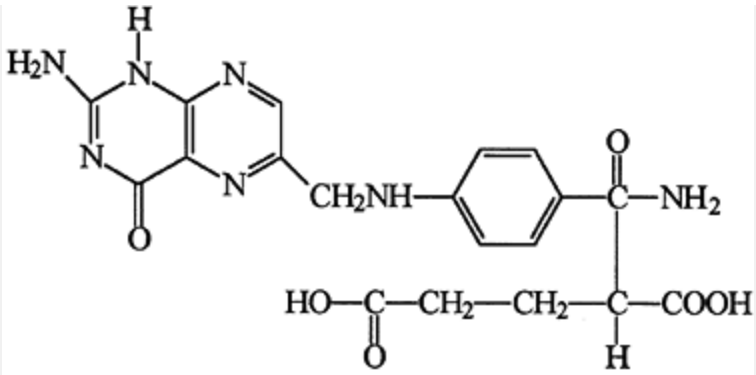
Antidotes in Depth

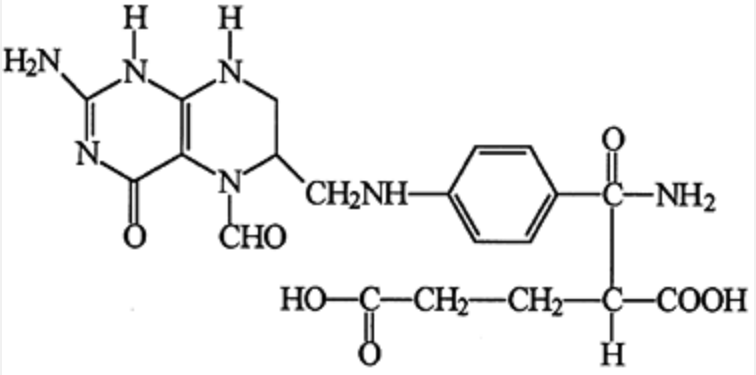
Leucovorin (Folinic Acid) and Folic Acid

Mary Ann Howland

Pharmacology



Folic Acid



Folinic Acid

Folinic Acid

Folic acid, an essential water-soluble vitamin, consists of a pteridine ring joined to PABA (*para*-aminobenzoic acid) and glutamic acid.[6] Folic acid is the most common pharmaceutical preparation of the many folate congeners that exist in nature and perform essential cellular metabolic functions. After absorption, folic acid is reduced by dihydrofolic acid reductase (DHFR) to tetrahydrofolic acid, which accepts 1-carbon groups.

Tetrahydrofolic acid serves as the precursor for several biologically active forms of folic acid, including 5-formyltetrahydrofolic acid, which is best known as folinic acid, leucovorin, and citrovorum factor. These biologically active forms of folate are enzymatically interconvertible and function as cofactors, providing the 1-carbon groups necessary for many intracellular metabolic reactions, including the synthesis of thymidylate and purine nucleotides, which are essential precursors of DNA.[21,23,27,28,32] The minimum daily requirement of folate is normally 50 Âµg, but in pregnant women and nutritionally deprived, acutely ill patients, 100 to 200 Âµg may be required.[6,7]

Role in Methotrexate Toxicity

Methotrexate, an antimetabolite, is a structural analog of folic acid, differing only in the substitution of an amino group for a hydroxyl group at the number 4 position of the pteridine ring (see Fig. 52-1). Methotrexate binds to the active site of DHFR, rendering it incapable of reducing folic acid to its biologically active forms, and incapable of regenerating the necessary active forms required for the synthesis of purine nucleotides and thymidylate. At physiologic pH the binding between methotrexate and DHFR is competitive, with an inhibition constant of about 1 Âµmol/L.[25] Leucovorin is a reduced, active form of folate. As such, it does not require DHFR for enzymatic interconversion to the form required for purine nucleotide and thymidylate formation. *Leucovorin rescue* is the term used to describe the practice of limiting the toxic effects of high-dose methotrexate therapy. Folic acid would be ineffective to counteract methotrexate toxicity because DHFR would be unavailable to convert folic acid to the necessary reduced and active forms.

Role in Methanol Toxicity

Administering folic acid to monkeys accelerates formate

metabolism.[17] Pretreatment with folic acid or leucovorin decreased formate levels and the accompanying metabolic acidosis, without affecting the rate of methanol elimination.[19] Leucovorin was still effective in hastening the elimination of formate when given 10 hours after methanol administration. Other studies demonstrate that rats and monkeys experimentally made folate-deficient develop methanol toxicity at lower methanol levels.[11]

Total folate, leucovorin, and folate dehydrogenase (which increases leucovorin levels) are all diminished in the livers of methanol-poisoned humans.[11] In an analysis[8] of a single methanol-poisoned patient who was given folate and ethanol and hemodialyzed, the half-life of formate was 1.1 hours.[20] In another methanol-poisoned patient treated without folate, the formate half-life was 2.8 hours.[8] This comparative data is inadequate to draw definitive conclusions, but may support the therapeutic role of folate, in addition to that of fomepizole and hemodialysis.

Leucovorin Pharmacokinetics

Leucovorin is naturally formed in the body as the active (*l* or â€“) isomer, whereas the commercial preparation consists of equal amounts of the inactive (*d* or +) and active (*l* or â€“) isomers. The pharmacokinetics of the racemic mixture of leucovorin and its active metabolite were studied after IV infusion, and as a constant infusion in normal human volunteers.[15,29] During constant infusion, the steady-state concentration for the active isomer was 2.33 Âµmol, the half-life was 35 minutes, and the volume of distribution was 13.6 L. The active isomer is metabolized to an active metabolite (L-5-CH3-THF). A more recent study detected no adverse effects of the inactive isomer on the intracellular uptake of the active isomer and concluded that giving the active isomer provided no pharmacokinetic advantage over the racemic mixture.[26]

The pharmacokinetics of orally administered leucovorin was studied in healthy, fasted, male volunteers in single doses ranging from 20â€“100 mg, and 200 mg IV over 5 minutes as compared to 200 mg orally.[16,22] Bioavailability decreased from 100% for the 20-mg dose to 78% for the 40-mg dose, and ultimately to 31% for the 200-mg dose. A microbiologic assay was used to measure total tetrahydrofolates (reduced and active folates). Normal plasma folate levels are approximately 0.05 Âµmol/L.[9] The 200-mg oral dose produced a peak plasma concentration of 1.82 Âµmol/L, compared to 0.66 Âµmol/L for the 20-mg oral dose and 27.1 Âµmol/L for the 200-mg IV dose.[16,22]

Leucovorin Dosing for Methotrexate Overdoses

When a patient overdoses on methotrexate, a dose of leucovorin estimated to produce the same plasma concentration as the methotrexate dose should be given as soon as possible and, preferably, within 1 hour. One mole of methotrexate weighs 455 daltons and 1 mole of leucovorin calcium weighs 511 daltons. Because of the safety of leucovorin and because of the toxicity of methotrexate, underdosing leucovorin should be avoided. Although plasma concentrations are often closely followed in patients on diverse oncologic regimens,[2,3] it is inappropriate to wait for a methotrexate plasma concentration before initiating treatment with leucovorin in the overdose setting, or in the treatment of tubal pregnancies.[1] The toxic threshold for methotrexate is reported to be 1 Ã— 10^{-8} mol/L (0.01 Âµmol/L or 10 nmol/L).[4] Normal plasma folate levels are in the range of 13â€“43 nmol/L. In a patient who is not receiving methotrexate therapeutically, there is no need to permit any methotrexate to remain unantagonized by leucovorin.

For example, if a child unintentionally ingests one hundred 2.5-mg methotrexate tablets for a total dose of 250 mg, only part of this

dose is absorbed because methotrexate absorption is saturable.[5] The bioavailability of methotrexate decreases from 100% with doses less than 30 mg/m^2 to approximately 10â€“20% with doses greater than 80 mg/m^2. In this case, it is safe to assume that a bioavailability of 50% would result in an absorbed dose of methotrexate of 125 mg. For this substantial exposure an intravenous dose of 125 mg of leucovorin could be given over 15â€“30 minutes. This dose of IV leucovorin should be repeated every 3â€“6 hours until the methotrexate concentration is less than 1 Ã— 10^8 mol/L, and preferably zero. The methotrexate half-life may vary from 5â€“45 hours, depending on the dose and the patient's renal function. For this reason, leucovorin therapy should be continued for 12â€“24 doses (3 days) or longer if methotrexate concentrations are unavailable. Patients who may develop third-space storage in ascites or pleural effusions may also require leucovorin dosing for an extended period of time. Patients with bone marrow toxicity require more prolonged dosing because plasma half-lives of methotrexate do not reflect persistent intracellular concentrations.

Unintentional overdose with intrathecal methotrexate is potentially quite serious and is dose dependent. In these cases, intravenous leucovorin should be administered. Intrathecal leucovorin was considered a major factor in the death of a child given a slightly higher dose of intrathecal methotrexate than was prescribed.[10,14] Not all intrathecal methotrexate overdoses require aggressive intervention, but consultation with experienced hematologists/oncologists and medical toxicologists is warranted.[12]

An intravenous leucovorin dose of 100 mg/m^2 every 3â€“6 hours should be effective, in all but the most severe overdoses. A constant intravenous infusion of 21 mg/m^2/h has been safely administered for 5 days. A transition to the oral administration of leucovorin depends on the plasma concentration of the methotrexate and whether adequate plasma concentrations of

leucovorin can be achieved by that route. In adults, a 200-mg oral dose produces a peak plasma concentration of 1.82 Âµmol/L as compared to 27.1 Âµmol/L with a 200-mg IV dose.

Administration of activated charcoal precludes the subsequent administration of oral leucovorin. In addition to leucovorin, other modalities to treat methotrexate overdoses should be used (activated charcoal, urinary alkalinization), or considered (carboxypeptidase G, extracorporeal removal, and thymidine) (Chap. 52).

Adverse Effects and Safety Issues

Reports of adverse reactions to parenteral injections of folic acid or leucovorin are uncommon; however, adverse reactions may include allergic or anaphylactoid reactions.[6] Seizures are rarely associated with leucovorin administration.[18] The calcium content of leucovorin warrants a slow intravenous infusion at a rate not faster than 160 mg/min in adults. Leucovorin should never be administered intrathecally.[10,13,24,31]

Dosing

The routine dose of leucovorin for â€œleucovorin rescueâ€• ranges from 10â€“25 mg/m^2 IM or IV every 6 hours for 72 hours to 100 mg/m^2 every 3 hours in patients with renal compromise. If administration to neonates is necessary, a benzyl alcohol-free preparation must be used because of the toxicity of benzyl alcohol in neonates (Chap. 53).[30] For methotrexate overdoses, a dose of leucovorin equal to that of the ingested methotrexate dose should be administered IV as soon as possible over 15â€“30 minutes, but not faster than 160 mg/min in adults.

An intravenous leucovorin dose of 100 mg/m^2 every 3â€“6 hours should be effective, in all but the most severe overdoses. This dose should be continued for several days, or until the MTX serum

concentration falls below 1 Ã— 10^{-8} mol/L and no bone marrow toxicity is evident.

Either folic acid or leucovorin (folinic acid) should be administered parenterally at the first suspicion of methanol poisoning. No complications are reported with the use of 50â€“70 mg of IV folic acid every 4 hours for the first 24 hours, in the treatment of methanol-poisoned patients.[20] The precise dose necessary is unknown, but 1â€“2 mg/kg every 4â€“6 hours is probably reasonable. The folic acid should be continued until the methanol and formate are eliminated. As the first dose is usually administered prior to hemodialysis, a second dose should be administered at the completion of hemodialysis, because hemodialysis will probably remove this highly water-soluble vitamin.

Availability

Folic acid is available parenterally in 10-mL multidose vials with 1.5% benzyl alcohol in concentrations of 5 or 10 mg/mL, from a

variety of manufacturers. Once opened, this vial must be kept refrigerated.

Leucovorin (folinic acid) powder for injection is available in 50-, 100-, and 350-mg vials. Reconstitution with sterile water for injectionâ€”5 mL to the 50-mg vial, or 10 mL to the 100-mg vialâ€”results in a final concentration of 10 mg/mL. Adding 17 mL of sterile water for injection to the 350-mg vial results in a final concentration of 20 mg/mL. Because of the calcium content, the rate of intravenous administration should not be faster than 160 mg/min in adults. Leucovorin is also available orally in a variety of strengths, including 5-, 10-, 15-, and 25-mg tablets.

Summary

Leucovorin (folinic acid) is the primary antidote for a patient who receives an overdose of methotrexate. Leucovorin is the biologically active, reduced form of folic acid, the synthesis of which is prevented by methotrexate. Only leucovorin (folinic acid) is an acceptable antidote for a patient with methotrexate toxicity, but either folic acid or leucovorin is acceptable for a patient poisoned by methanol. Following a methanol overdose, folic acid enhances the elimination of formate.

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Chapter 53
Pharmaceutical Additives

Sean P. Nordt

Lisa E. Vivero

A 32-year-old man was brought to the emergency department (ED) after confused and inarticulate at a motel by paramedics. The patient's tongue and he had urinary incontinence. In the ED, the patient had a blood press mm Hg, a pulse of 101 beats/min, respirations of 20 breaths/min, and a 97.4Â°F (36.3Â°C). Physical examination revealed abrasions on the left si his pupils were 6 mm, equal, and reactive to light; his lungs were clear and his abdomen was soft and nontender. A 12-lead electrocardiogram sh tachycardia, a rate of 102 beats/min, a PR interval of 200 msec, a QRS c msec, and a QTc interval of 450 msec. An old ED chart revealed that the suffered a gunshot wound to the head and subsequently had developed a disorder.

A loading dose of 1 g phenytoin equivalents of fosphenytoin was given i over 5 minutes. Immediately following the fosphenytoin, the patient beca hypotensive with a blood pressure of 85/50 mm Hg. His heart rate decrea beats/min, and his QRS interval widened to 140 msec. Atropine 1 mg was intravenously, resulting in an increase in heart rate to 82 beats/min. Int

sodium chloride solution at 1 L over 15 minutes was administered, which blood pressure to 140/60 mm Hg. Several minutes later the patient's QRS 100 msec without other intervention. Subsequently, it was realized that t unintentionally given phenytoin instead of fosphenytoin. The patient had reaction to the rapid infusion of phenytoin, which contains 400 mg/mL of glycol.

History and Epidemiology

During the last century there were several US outbreaks of toxicity assoc pharmaceutical additives (Chap. 1). The 1937 Massengill sulfanilamide d most notorious of these epidemics. Diethylene glycol, an excellent solvent nephrotoxin, was substituted for the additives propylene glycol and glycer formulation of a new sulfanilamide antibiotic because of a lower cost.[25] , result, more than 100 people died from acute renal failure.[25] More recent of acute renal failure occurred when diethylene glycol was used to solubi acetaminophen in South Africa, Bangladesh, Nigeria, and Haiti.[18] , [47] , [67]

In December 1983, E-Ferol, a new parenteral vitamin E formulation, was contained 25 U/mL of Î±-tocopherol acetate, 9% polysorbate 80, 1% pol and water for injection. At the time, no premarketing testing was required formulations of an already-approved xenobiotic. Several months after its syndrome in low-birth-weight infants, characterized by thrombocytopenia, dysfunction, cholestasis, hepatomegaly, and ascites, was described.[1] , [95] deaths and 43 cases of severe symptoms were attributed to E-Ferol. Vitar thought to be the cause and E-Ferol was recalled from the market 4 mon release. It is now believed that the polysorbate emulsifiers were respons

More recently there has been concern over potential mercury toxicity fror preservative thimerosal, a mercury derivative that has been used in pare for 70 years. Although there are a few reports of toxicity from large oral thimerosal dosages, no evidence has yet shown toxicity to result from ro vaccination. Potential concerns of toxicity, particularly autism, have spur efforts to eliminate thimerosal from vaccines, wherever possible.

Although these additive-related occurrences are rare, relative to the freq

pharmaceutical additive use, they illustrate the potential of pharmaceutic toxicity.

Pharmaceuticals are labeled specifically to focus attention on the active i a product, thus giving the misimpression that additive ingredients are ine unimportant. Additives, or excipients, as they are more properly termed, to act as vehicles, add color, improve taste, provide consistency, enhance solubility, and to impart antimicrobial properties to medicinal formulations is true that most cases of excipient toxicity involve exposure to large qua prolonged or improper use, these adverse events are nonetheless related toxicologic properties of the excipient.

Prior to selecting the specific additives and quantity necessary for a drug the drug manufacturer must consider several factors, including the active physical form, its solubility and stability, the desired final dosage form an administration, and compatibility with the dispensing container materials. active ingredient may require different excipients to impart appropriate characteristics to different dosage forms, such as in long-acting and imı formulations. Similarly, multiple-dose injection vials containing the same ingredients as single-dose vials specifically require the addition of a bact not necessary for single-dose vials.

Unlike requirements for active ingredients, there is no specific FDA appro pharmaceutical excipients. As such, the FDA determines the amount and t necessary to support the use of a specific excipient on a case-by-case ba current practice, only excipients that were previously permitted for use in pharmaceuticals are defined as *generally recognized as safe* (GRAS), or a listed.â€• All components of a pharmaceutical product, including excipien produced in accordance with current good manufacturing practice standar purity. Recently, the Safety Committee of the International Pharmaceutic Council developed guidelines for the toxicologic testing of new excipients patent protection laws, it was not until very recently that manufacturers to provide a list of inactive ingredients contained in all pharmaceutical p Although it is becoming easier to identify pharmaceutical additives in pro information on their effects and the mechanisms by which they cause ad

are often unknown or difficult to obtain.

Cardiovascular
- Chlorobutanol
- Propylene glycol

Fluid and electrolyte
- Polyethylene glycol
- Propylene glycol
- Sorbitol

Gastrointestinal
- Sorbitol

Neurologic
- Benzyl alcohol
- Chlorobutanol
- Polyethylene glycol
- Propylene glycol
- Thimerosal

Ophthalmic
- Benzalkonium chloride
- Chlorobutanol

Renal
- Polyethylene glycol
- Propylene glycol

TABLE 53-1. Potential Toxicity by Organ System of Various Pha Excipients

This chapter summarizes the available literature on commonly used addi with direct toxicities. Data on pharmacokinetics and mechanism of toxicit where data are available. Although many additives are associated with l reactions, including anaphylaxis, these are not discussed because of their nonpharmacologic basis. However, excipients should always be considered causative agents in patients developing hypersensitivity reactions (Table

Benzalkonium Chloride

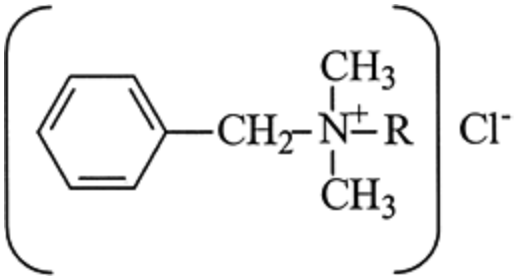


Figure. No Caption Available.

Benzalkonium chloride (BAC) or alkyldimethyl (phenylmethyl) ammonium quaternary ammonium cationic surfactant composed of a mixture of alkyl dimethyl ammonium chlorides. Although it is the most widely used ophth preservative in the United States, it is also considered the most cytotoxic).[79 , 85] Benzalkonium chloride is also used in otic and nasal formulations, small-volume parenterals. The antimicrobial activity of BAC includes Grar Gram-negative bacteria, and some viruses, fungi, and protozoa. Because onset of action, good tissue penetration, and long duration of action, BAC over other preservatives. The concentration of BAC in ophthalmic medica ranges from 0.004 to 0.01%.[85] Ingestion of strong BAC solutions (greater can be caustic (Chap. 98).

Ophthalmic Toxicity

Corneal epithelial cells harvested from human cadavers within 12 hours o exposed to a medium containing 0.01% BAC.[134] The surfactant properties resulted in intracellular matrix dissolution and loss of epithelial superficia Following exposure to the medium, mitotic activity ceased, and degenera corneal epithelium were noted. During a 24-hour observation period, epit cytokinetic or mitotic activity did not occur. Patients with a compromised epithelium may be at increased risk for the adverse corneal effects of BA

Two case reports demonstrate the potential toxicity of BAC and the difficu recognizing it. A 36-year-old woman complained of decreased vision wher inadvertently switched from Lensrins, a contact lens cleaning solution, to

isotonic boric acid solution, preserved with BAC. After 3 days, she had i pain, and decreased visual acuity. Examination of the cornea revealed m punctate erosions of the epithelium. An in vitro experiment identified sig of BAC to soft contact lenses.[53] In the second case, a 56-year-old man c keratoconjunctivitis sicca was treated with topical antibiotics and artificial containing BAC. Following 1 year of

continual use, the patient developed intractable pain, photophobia, and breakdown of the corneal epithelium. Not suspecting the BAC-containing patient continued to use the artificial tears solution for another 9 years c continued pain and decreasing visual acuity. Replacement with a preserv solution resulted in resolution of pain, photophobia, and corneal changes.

Artificial tears (various)
0.005â€“0.01
Acular (ketorolac)
0.01
Betagan (levobunolol)
0.004
Betoptic (betaxolol)
0.01
Ciloxan (ciprofloxacin)
0.006
Cyclogyl (cyclopentolate)
0.01
Decadron (dexamethasone)
0.02
Garamycin (gentamicin)
0.01
Glaucon (epinephrine)
0.01
Isopto Carpine (pilocarpine)
0.01
Murocoll-2 (scopolamine/phenylephrine)
0.01

Mydriacyl (tropicamide)
0.01
Phenylephrine (various)
0.005â€“0.01
Ocuflox (ofloxacin)
0.005
Ocupress (carteolol)
0.005
Polytrim (polymyxin B sulfate/trimethoprim)
0.004
Timoptic (timolol)
0.01
Tobrex (tobramycin)
0.01
Visine (tetrahydrozoline)
0.01

Medication Percent (%)

TABLE 53-2. Benzalkonium Chloride Concentrations of Common Medications

Nasopharyngeal and Oropharyngeal Toxicit

Human adenoidal tissue was exposed to oxymetazoline nasal spray preser at concentrations ranging from 0.005â€“0.15 mg/mL for 1â€“30 minutes. and broken epithelial cells were seen with all concentrations, however, it earlier and more frequently with the higher concentrations. The number c ciliary bodies also decreased as the duration and the concentrations incr Benzalkonium chloride may decrease the viscosity of the normal protectiv lining of the naso- and oropharynx, resulting in cytotoxicity.

Giving rats 1 of 3 nasal steroid sprays preserved with either 0.031% or 0 their right nostril twice daily for 21 days caused squamous cell metaplasia decrease in the number of goblet cells, cilia, and mucus.[14] No histologic

occurred in rats receiving the preservative-free steroid or in tissue expose sodium chloride solution administered into the left nostril as the control. another study, epithelial desquamation, inflammation, and edema occurre and 0.10% BAC was applied hourly to the nasal cavities of rats for 8 hou developed in the nasal cavities of rats receiving 0.01% BAC.

Benzyl Alcohol

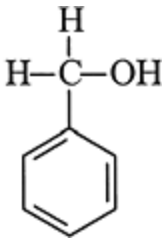


Figure. No Caption Available.

Benzyl alcohol (benzene methanol) is a colorless, oily liquid with a faint that is most commonly added to pharmaceuticals as a bacteriostatic agent In 1982, a â€œgaspingâ€• syndrome, which included hypotension, brad respirations, hypotonia, progressive metabolic acidosis, seizures, cardiov collapse, and death, was first described in low-birth-weight neonates in i units.[20 , 60 , 90] All the infants had received either bacteriostatic water or chloride solution containing 0.9% benzyl alcohol to flush intravenous cath parenteral medications reconstituted with bacteriostatic water or saline.[2 syndrome occurred in infants who had received greater than 99 mg/kg of (range, 99â€“234 mg/kg).[60] The World Health Organization (WHO) curre the acceptable daily intake of benzyl alcohol to be not more than 5 mg/kg weight.[22]

Pharmacokinetics

In adults, benzyl alcohol is oxidized to benzoic acid, conjugated in the liv and excreted in the urine as hippuric acid. The immature metabolic capac diminish their ability to metabolize and excrete benzyl alcohol.[60] Preterm greater ability to metabolize benzyl alcohol to benzoic acid than do term

unable to convert benzoic acid to hippuric acid, possibly because of glyci This results in the accumulation of benzoic acid (Fig. 53-1).[82] A fatal cas acidosis was reported in a 5-year-old girl who had received 2.4 mg/kg/h preserved with benzyl alcohol for 36 hours to control status epilepticus. benzoic acid levels were identified in serum and urine samples. The estim dosage of benzyl alcohol was 180 mg/kg.[60 , 86]

Ativan (lorazepam)
2.0
0.02
Bacteriostatic water for injection
1.5
â€”
Bacteriostatic saline for injection
1.5
â€”
Bactrim, Septra (trimethoprim-sulfamethoxazole)
1.0
0.61[b]
Bumex (bumetanide)
1.0
0.03
Compazine (prochlorperazine)
0.75
0.01
Cordarone (amiodarone)
2.0
0.42[b]
Lasix (furosemide)
0.9
0.04
Librium (chlordiazepoxide)
1.5
0.03
Methotrexate

0.9
0.01
Norcuron (vecuronium)
0.9
0.01
Tracrium (atracurium)
0.9
0.03
Valium (diazepam)
1.5
0.03
Vasotec (enalapril)
0.9
0.01
VePesid (etoposide)
3.0
0.14
Versed (midazolam)
1.0
0.01
Vistaril (hydroxyzine)
0.9
0.01
[a] Based on dosage for a 70-kg person.
[b] Based on 24-hour dosage.

Medication Percent (%) mL/Average Dose[a]

TABLE 53-3. Benzyl Alcohol Concentration of Common Medication

Neurologic Toxicity

Benzyl alcohol is believed to have a role in the increased frequency of ce intraventricular hemorrhages and mortality reported in very-low-birth-we

infants (weight <1000 g) who received flush solutions preserved with be
An increased incidence of developmental delay and cerebral palsy is also
same VLBW patient population, suggesting a secondary damaging effect c
alcohol.[11]

There are several case reports of transient paraplegia following the intrat
epidural administration of antineoplastics

or analgesics containing benzyl alcohol as a preservative.[8, 36, 66, 120] T
anesthetic effects are most likely responsible for the immediate parapares
duration of effects, rather than actual demyelination of nerve roots. In a
lumbosacral dorsal root action potential amplitudes were measured after
0.9% or 1.5% benzyl alcohol solutions in either 0.9% sodium chloride sol
distilled water.[66] Rats exposed to all benzyl alcohol solutions for less thar
inhibited dorsal root action potentials. This was attributed to the local ar
of benzyl alcohol. Nerve function was 50â€“90% restored after rinsing the
0.9% sodium chloride solution. Chronic intrathecal exposure to benzyl alc
7 days showed scattered areas of demyelinization and early remyelinizatic
benzyl alcohol solution-exposed dorsal nerve roots showed greater chang
widespread areas of demyelinization and fatty degeneration of nerve fibe

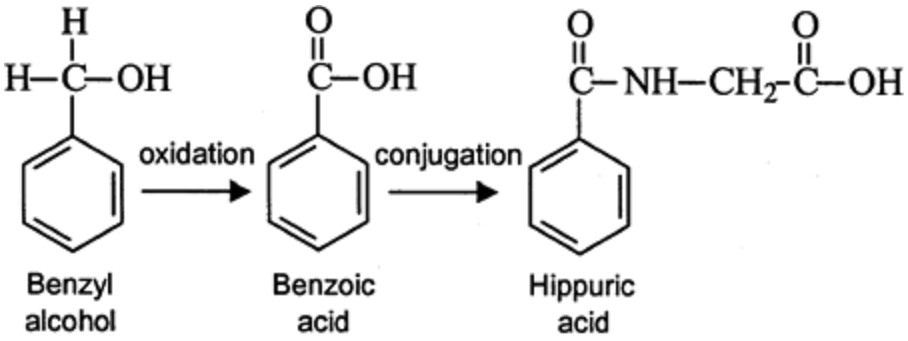


Figure 53-1. The oxidative metabolism of benzyl alcohol.

Chlorobutanol

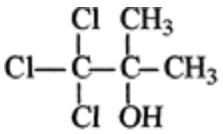


Figure. No Caption Available.

Chlorobutanol or chlorbutol (1,1,1-trichloro-2-methyl-2-propanol) is availa volatile, white crystals with an odor of camphor. Chlorobutanol has antib antifungal properties and is widely used as a preservative in injectable, and cosmetic preparations at concentrations up to 0.5% (Table 53-4). C also has mild sedative and local anesthetic properties and was formerly u therapeutically as a sedative-hypnotic.[17] Because chlorobutanol is a halo hydrocarbon, theoretically it can sensitize the myocardium to catecholam no cases of ventricular dysrhythmias are described in the literature to da human chlorobutanol dose is estimated to be 50â€“500 mg/kg.[104]

Central Nervous System Depression

Chlorobutanol has a chemical structure similar to trichloroethanol (Fig. 7 active metabolite of chloral hydrate, and is believed to exhibit similar ph properties. Central nervous system depression was reported in a 40-year male who chronically abused Seducaps, formerly available in Australia an countries, a nonprescription hypnotic containing chlorobutanol as the act ingredient.[17] On admission to the ED he had drowsiness, dysarthria, slur occasional episodes of myoclonic movements. His peak plasma chlorobuta concentration was 100 Âµg/mL, decreasing to 48 Âµg/mL over 2 weeks, v of 13 days. His speech abnormality resolved over 4 weeks. Only chlorobu detected in the patient's urine or plasma. In a second case, a possible ce system depressant effect from chlorobutanol was suggested in a 19-year- treated with high doses of intravenous morphine preserved with chlorobu received approximately 90 mg/h of chlorobutanol for several days. Her pe chlorobutanol concentration was 83 Âµg/mL, a level similar to that in the report;[17] however, the coadministration of morphine precludes the effects attributed to chlorobutanol alone.

Adrenalin chloride (epinephrine) injection
0.5
5
Chloroptic (chloramphenicol) ophthalmic solution
0.5
â€”
Dolophine (methadone) injection
0.5
10
Epinephrine ophthalmic solution
0.5
â€”
Novocain (procaine) injection
0.25
87
Phospholine iodide (echothiophate iodide) ophthalmic solution
0.55
â€”
Rhinall (phenylephrine) nasal spray
0.14
â€”
Tobrex (tobramycin) ophthalmic ointment
0.5
â€”

Medication Percent (%) mg/Dose

TABLE 53-4. Chlorobutanol Concentrations of Common Medicatior

Ophthalmic Toxicity

Chlorobutanol is a commonly used preservative in ophthalmic preparations shown to be less toxic to the eye than benzalkonium chloride.[107] Chlorob increases the permeability of cells by impairing cell membrane structure.[

experiment, using corneal epithelial cells harvested from human cadaver arrested mitotic activity following chlorobutanol exposure.[134]

Lipids

In general, there are three types of commercial intravenous lipid drug-de available: lipid emulsion, liposomal, and lipid complex (Table 53-5). Lipi immiscible lipid droplets dispersed in an aqueous phase stabilized by an egg or soy lecithin). Liposomes differ from emulsion lipid droplets in that vesicles comprised of one or more concentric phospholipid bilayers surrou aqueous core. Lipophilic drugs can be formulated for intravenous adminis partitioning them into the lipid phase of either an emulsion or liposome. capable of encapsulating hydrophilic therapeutic agents within their aqueo exploit lipid pharmacokinetic properties.[130] Attaching a therapeutic agent form a lipid complex is another way to take advantage of lipid pharmaco

Lipid carriers are biocompatible because of their similarity to endogenous membranes. They can be used to stabilize labile drugs against hydrolysis to decrease toxicity, and to enhance therapeutic efficacy by altering drug pharmacokinetic and pharmacodynamic parameters. The biodistribution, ar release and metabolism of a drug incorporated in a lipid formulation can the type and concentration of oil and emulsifier used; pH; drug concentr in the medium; the size of the lipid particle; and the manufacturing proce Intravenous formulations are usually isotonic and have a pH of 7â€“8.[130]

Propofol (Diprivan)
Emulsion
Cytarabine (DepoCyt)
Liposome
Daunorubicin (DaunoXome)
Liposome
Doxorubicin (Doxil)
Liposome (stealth)
Amphotericin B (AmBisome)
Liposome

Amphotericin B (Abelcet)
Lipid complex
Amphotericin B (Amphotec)
Cholesteryl complex

Medication Lipid Carrier

TABLE 53-5. Lipid Carrier Formulations of Common Medications

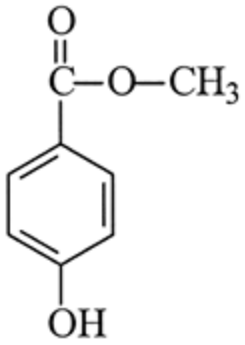
The rate of clearance of a lipid carrier from the blood depends on its phy properties, and the molecular weight of the emulsifier. Electrically charge are removed faster than neutral particles.[24,109] Smaller lipid particle siz molecular-weight emulsifiers decrease clearance. Stealth liposome formul Doxil) incorporate a polyethylene glycol coating that prevents rapid detec clearance of liposomes by the reticuloendothelial system prolonging circu Active drug targeting can be achieved by conjugating antibodies or vector chains on the emulsifier.[24,109] For a therapeutic agent available in more lipid-carrier formulation (eg, amphotericin B in AmBisome, Abelcet, and A important to note that any change in the lipid formulation can alter its p pharmacodynamic, and safety parameters; consequently, they are not ec formulations.

The physiochemical properties of lipid emulsions not only effect the thera carried by them, but the lipids themselves may also have direct pharmac on the central nervous[144] and immune systems.[84] Lipid fatty acid mediato the membrane receptor channels of *N* -methyl-D-aspartate (NMDA) recep potentiating synaptic transmission. This is supported by 1 animal[96] and s vitro[97,110,133] studies. Dogs given a medium-chain triglyceride emulsi infusion were reported to have dose-related central nervous system meta neurologic effects, accompanied by electroencephalographic changes cons encephalopathy observed when plasma octanoate concentration reached mM.[96] In an in vitro model, 3 of 9 lipid emulsions tested (Abbolipid, 20% safflower oil; Intralipid, 20% soya oil; and Structolipid, 20% structured demonstrated a dose-related activation of cortical neuronal NMDA recept

The lipid source for all but one (Omegaven, 10% fish oil) of the emulsion made up solely or partially by soya oil. The authors could not explain why lipid emulsions did not induce membrane currents. Adequate control for t constituent contribution of these emulsions is lacking. In a more recent ir the same authors found that NMDA-induced neuronal currents are reduced unknown factor in the aqueous portion of Abbolipid.[145] They suggest that may pharmacologically enhance the anesthetic effect of hypnotic agents s Propofol. The clinical relevance of these studies remains to be assessed.

Triglycerides in parenteral nutrition emulsions are implicated in altering t system, leading to an increased susceptibility to infection,[52, 142] and alt function and hemodynamics in patients with acute respiratory distress sy (ARDS).[84] Phospholipid activation of phospholipase A_2 may be an initiatir [142] however, it is not clear if these immunologic effects are a consequer other than the lipid in the emulsion.

Parabens



Methylparaben

The parabens, or parahydroxybenzoic acids, are a group of compounds w as preservatives in cosmetics, food and pharmaceuticals because of thei fungistatic, and antioxidant properties (Table 53-6).[121] A survey conduct and Drug Administration identified the parabens as the second most com in cosmetic formulations, with water being the most common.[87] Parabens in combination, because the presence of 2 or more parabens results in s action.[87] Methylparaben and propylparaben are most commonly used.[121]

paraben concentrations usually range from 0.1â€“0.3%.[115]

Aldomet (methyldopa) injection
0.17
8
Brofed (pseudoephedrine/brompheniramine) elixir
0.2
20
Haldol (haloperidol) injection
0.2
2
Inapsine (droperidol) injection
0.2
2
Isopto Cetamide (sulfacetamide) ophthalmic solution
0.06
â€”
Narcan (naloxone) injection
0.2
2
Oncovin (vincristine) injection
0.15
4
Prolixin HCl (fluphenazine) injection
0.11
1
Prostigmin (neostigmine) injection
0.2
2
Romazicon (flumazenil) injection
0.2
4
Trandate (labetalol) injection
0.09
4

Xylocaine (lidocaine) injection
0.1
â€”
Zofran (ondansetron) injection
0.14
3

Medication Percent (%) mg/Dose

TABLE 53-6. Paraben Concentrations of Common Medications

Widespread usage of parabens since the 1920s has shown that they have low order of toxicity;[87] however, because of their allergenic potential the considered less suit-able for injectable and ophthalmic preparations.[115] B term animal studies, the WHO has set the total acceptable daily intake of and propyl parabens to 10 mg/kg body weight.[115]

In addition to allergic reactions, parabens have the potential to cause otl effects. Bilirubin displacement from albumin binding sites occurred with of methyl and propyl paraben preserved gentamicin when serum paraber were 3â€“15 Âµg/mL.[39] Gentamicin alone has no effect on bilirubin displ Spermicidal activity was demonstrated in an in vitro study of human sem exposed to local paraben concentrations of 1â€“8 mg/mL.[127] Possible inte conception and potential adverse effects on fertility were not investigated

Phenol

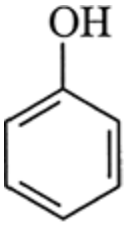


Figure. No Caption Available.

Phenol (carbolic acid, hydroxybenzene, phenylic acid, phenylic alcohol) is used preservative in injectable medications (Table 53-7). Phenol is a co pink, caustic liquid, with a characteristic odor. When exposed to air and l turns a red or brown color.[35] Phenol exerts antimicrobial activity

against a wide variety of microorganisms, such as Gram-negative and G bacteria, mycobacteria, and some fungi and viruses.[35] Phenol is well absc gastrointestinal tract, skin, and mucous membranes, and is excreted in th phenyl glucuronide and phenyl sulfate metabolites.[35] Although there are reports of phenol toxicity following intentional ingestions or unintentional exposures (Chap. 98), adverse reactions to its use as a pharmaceutical uncommon, most likely because of the small quantities used.[35]

Antivenom (Crotaline)
0.25
25 (per vial)
Antivenom (*Micrurus fulvius*)
0.25
25 (per vial)
Pneumovax 23 (pneumococcal) vaccine
0.25
1.25
Prostigmin (neostigmine) injection
0.45
4.5
Quinidine gluconate injection
0.25
18.75

Medication	Percent (%)	mg/Dose

TABLE 53-7. Phenol Concentration of Common Medications

Commercially available glucagon is a lyophilized powder that is packaged a 1-mL diluent that formerly contained phenol. According to the manufactu

used to prolong the shelf life of the glucagon solution (Lilly Pharmaceutic communication, May 2005). Reconstitution of glucagon with the sterile w preserved with 0.2% phenol and 1.6% glycerin would subsequently contai phenol. Glucagon in doses of 0.5â€“1 mg is employed in the treatment o However high doses of glucagon are used in the treatment of severe Î²-a antagonist and calcium channel-blockade poisonings. Since the total reco intravenous phenol dosage in humans should not exceed 50 mg in a 10-h because of the concerns for systemic phenol toxicity,[19 , 35 , 98] it was re that glucagon be reconstituted with either 0.9% sodium chloride solution, in water, or sterile water for injection when the dosage exceeded 10 mg.[3 Glucagon diluent no longer contains phenol.[23]

Cutaneous Absorption

Systemic toxicity from cutaneous absorption of phenol is reported. Ventr tachycardia was observed in a 11-year-old boy following administration of peel solution containing 88% phenol in water and liquid soap. The solutio to 15% of his body surface area for the treatment of xeroderma pigment Immediately following the onset of the ventricular tachycardia, the phen were irrigated with saline, an infusion of 0.9% sodium chloride solution w 2 intravenous lidocaine boluses were given followed by a lidocaine infusio dysrhythmia persisted for 3 hours. The urinary phenol concentration the was 58.9 mg/dL.[137] In a similar case, multifocal premature ventricular c (PVCs) were observed in a 10-year-old boy after application of a chemica solution of 40% phenol, 0.8% croton oil in hexachlorophene soap, and wa treatment of a giant hairy nevus.[143] The PVCs were refractory to intrave but resolved with intravenous bretylium. No phenol levels were obtained systemic absorption.

Drowsiness, respiratory depression, and blue-colored urine were noted in infant 12 hours after topical application of magenta paint over most of th seborrheic eczema.[117] Magenta paint (also known as Castellani paint) was for seborrheic eczema and contains 4% phenol, magenta, boric acid, res and methylated spirit. Further investigation found that phenol was detecte samples of 4 of 16 other infants with seborrheic eczema who had approx

11â€“15% of their body surface area painted with magenta paint for 2 da

Polyethylene Glycol

Polyethylene glycols (PEGs, Carbowax, Macrogol) include several compoun varying molecular weights (MWs) (200â€“40,000 MW).[114] They are typica mixtures designated by a number denoting their average molecular weig glycols are stable, hydrophilic substances, making them useful excipients and pharmaceuticals of all routes of administration (Table 53-8). Pegyla that modifies the pharmacokinetics of therapeutic liposomes and proteins peginterferon-Î±), is the most recent application of PEG. At room temper with molecular weights less than 600 are clear, viscous liquids with a slig characteristic odor and bitter taste. Those PEGs with molecular weights g 1000 are soluble solids and range in consistency from pastes and waxy fl powders.[114] Commercially available products such as GoLYTELY and Colyt of PEG 3350 combined with electrolytes (PEG-ELS).

The solid, high-molecular-weight PEGs are essentially nontoxic. Converse molecular-weight PEG exposures have caused adverse effects similar to t related toxic alcohols ethylene and diethylene glycol.

Pharmacokinetics

High-molecular-weight PEGs (>1000) are not significantly absorbed from gastrointestinal tract, but low-molecular-weight PEGs may be absorbed w orally.[43 , 124 , 125] Topical absorption can occur when PEGs are applied t skin.[21 , 131] The pharmacokinetics of intravenously administered PEG 3350 studied; however, it did not appear to have any systemic effects when u given by this route.[116] Once in the systemic circulation, PEGs are mainly unchanged in the urine;[43] however, low-molecular-weight PEGs are metal alcohol dehydrogenase to hydroxyacid and diacid metabolites. PEG may a broken down to ethylene glycol although the clinical consequence of this [132]

Nephrotoxicity

In rats fed various PEGs (200, 300, and 400) in their drinking water for 9 solution of 8% PEG 200 produced renal tubular

necrosis in all the animals, followed by death within 15 days; however, a solution resulted in only 2 of 9 rats dying within 80 days. A 16% PEG 40 all animals within 13 days; however, both 8% and 4% PEG 400 solutions observable effect except for a decrease in kidney weight when compared animals.[126]

Chloroptic (chloramphenicol) ointment
300
Furacin (Nitrofurazone) ointment
300
VePesid (etoposide) injection
300
Ativan (lorazepam) injection
400
Decadron (dexamethasone) ophthalmic ointment
400
Depo-Provera (medroxyprogesterone)
3350
Polyethylene glycol electrolyte solution
3350
Peginterferon alfa-2a (PEGASYS)
40,000

Medication PEG Molecular Weight (Daltons)

TABLE 53-8. Common Medications Containing Polyethylene Glycol

Acute tubular necrosis with oliguria, azotemia and high anion gap metabo been reported after oral and topical exposures to low-molecular-weight PE 300). Acute renal failure occurred in a 65-year-old male with a history of and seizure disorder, after ingestion of the contents of a lava lamp conta 200.[44] Forty-eight hours after admission (approximately 50â€“72 hours

the patient became oliguric with an anion gap metabolic acidosis and acu Blood sample analysis confirmed traces of the lava lamp fluid; no traces in the urine. After clinical complications from ethanol withdrawal and asp pneumonitis, the patient was discharged 3 months later with residual kid attributed to the PEG component of the lamp contents. Acute tubular nec on autopsy of 6 burn patients treated with a topical antibiotic cream in a base.[21 , 131] Mass spectrometry detected hydroxyacid and diacid metaboli and urine samples. Oxalate crystals were seen in 2 cases. These effects v reproduced with the topical application of PEG for 7 days to rabbits with skin defects.[131]

Neurotoxicity

There are reports of neurologic complications, such as paraplegia and tra paralysis, following intrathecal steroidal injections containing 3% PEG as [16] In an in vitro experiment, rabbit vagus nerves were exposed to concer 3350 ranging from 3â€“40% for 1 hour.[12] Three percent and 10% PEG ha nerve action potential amplitude or conduction velocity. Twenty percent a significantly slowed nerve conduction and had varying effects on the amp action potentials. Forty percent PEG completely abolished action potential changes were reversible and thought to be related to PEG-induced osmot

Fluid, Electrolyte, and Acidâ€“Base Disturl

Hyperosmolality was reported in 3 patients with burn surface areas rangi 20â€“56%, following repeated applications of Furacin, a topical antibiotic containing 63% PEG 300, 32% PEG 4000, and 5% 1000.[21] Polyethylene g an osmotic effect that is greater than expected for its molecular weight.[1 theorized that PEG increases osmolality by sequestering water through h binding, reducing the availability of water to interact with solutes, thus i chemical and osmotic activity of the solute. Hyperosmolality following th of a PEG-containing substance may suggest systemic PEG absorption.

Two cases of metabolic acidosis were reported following administration o dosages of an intravenous nitrofurantoin solution containing PEG 300.[132]

otherwise unexplained increased anion gap was reported in 3 patients bei a topical PEG-based burn cream.[21] Metabolism of PEG by alcohol dehydro hydroxyacid and diacid metabolites can explain the metabolic acidosis.[70]

Propylene Glycol

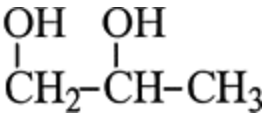


Figure. No Caption Available.

Propylene glycol (PG), or 1,2-propanediol, is a clear, colorless, odorless, liquid employed in numerous pharmaceuticals (Table 53-9), foods, and Propylene glycol is used as a solvent and preservative with antiseptic pr to ethanol. The WHO has set the daily allowable intake of PG at a maximu mg/kg,[146] or 1.8 g/d for a 70-kg person.

Pharmacokinetics

Propylene glycol is rapidly absorbed from the gastrointestinal (GI) tract f administration and has a volume of distribution of approximately 0.6 L/kg applied to intact epidermis, the absorption of PG is minimal. Percutaneou may occur following application to damaged skin (eg, extensive burn surf Approximately 12â€“45% of PG is excreted unchanged in the urine;[42] the hepatically metabolized sequentially by alcohol dehydrogenase and aldeh dehydrogenase to lactic acid. Lactic acid may be additionally oxidized to and then to carbon dioxide and water.[102] The terminal half-life of propyle reported to be between 1.4 and 5.6 hours in adults, and as long as 16.9 neonates.[42 , 128]

Cardiovascular Toxicity

Intravenous preparations of phenytoin contain 40% PG to facilitate the s phenytoin. Nine years after intravenous phenytoin became available, sev were attributed to the rapid administration of phenytoin used for the trea

cardiac dysrhythmias.[59, 135, 153]

Cardiovascular effects reported in these cases include hypotension, brad widening of the QRS interval, increased amplitude of T waves with occas and transient ST elevations. Studies in cats[89] and calves[63] confirmed PG cardiotoxin. Bradycardia and depression of atrial conduction were not

observed in cats pretreated with atropine, or in those with vagotomy foll intravenous infusion of PG, suggesting that these effects are vagally mec Amplification of the QRS complex was noted in these same pretreated cat suggesting a direct cardiotoxic effect of PG. Similar results were reported pretreated with atropine that received oxytetracycline in a PG vehicle.[63]

Agenerase (amprenavir) oral solution
55
57.75
Amidate (etomidate)
35
3.60
Ativan (lorazepam) injection
80
0.64
Bactrim, Septra (trimethoprim-sulfamethoxazole) injection
40
10.00[b]
Brevibloc (esmolol) injection
25
2.50[b]
Dilantin (phenytoin) injection
40
4.80
Lanoxin (digoxin) injection
40
0.40
Librium (chlordiazepoxide) injection

20
0.08
Luminal (phenobarbital sodium) injection
67.8
0.70
MVI-12 (multivitamins) injection
30
0.45
Nembutal (pentobarbital)
40
1.2
Tridil (nitroglycerin) injection
30
0.30[b]
Valium (diazepam) injection
40
0.4

[a] Based on dosage for 70-kg person.

[b] Based on 24-hour dosage.

Medication Percent (%) g/Average Dose[a]

TABLE 53-9. Propylene Glycol Concentration of Common Medicati

Neurotoxicity

Smaller infants appear to have a decreased ability to clear PG when comp children and adults.[90] An increased frequency of seizures was reported ir weight infants who received PG 3 g daily in a parenteral multivitamin pr Seizures developed in an 11-year-old boy receiving long-term oral therap D dissolved in PG.[6] Serum calcium, magnesium, electrolytes, and blood g normal. Seizures abated after the product was discontinued. Propylene g inebriating properties similar to ethanol. Central nervous system depressi reported following an intentional oral ingestion of a PG-containing produc

A black-boxed warning was added to the product information for amprena (Agenerase), an oral protease inhibitor solution, because of concerns over (550 mg/mL) vehicle content.[119] The recommended daily dosage of amp 1650 mg/kg/d of PG. A 61-year-old man experienced visual hallucinations disorientation, tinnitus, and vertigo after receiving a 750-mg dose (474 m amprenavir solution.[76]

Ototoxicity

Otic preparations can contain up to 94% PG in solutions and 10% in susp of their vehicles.[48] In animal studies, application of high concentrations o to the middle ear can produce hearing impairment[100 , 101 , 140] and mor changes, including tympanic membrane perforation, middle ear adhesions cholesteatoma.[100 , 139 , 150] Although the effects of PG in the human mic not been studied, all medications applied to the external ear canal are c patients with perforated tympanic membranes.

Fluid, Electrolyte, and Acidâ€“Base Disturl

Patients receiving continuous or large intermittent quantities of medicati PG can develop high PG concentrations, particularly those with renal or h insufficiency.[27 , 42] Propylene glycol electrolyte and metabolic disturbance evidenced by hyperosmolality, and an elevated osmolar gap attributed to active properties of PG. In most cases, an elevated anion gap, with an o unexplained metabolic lactic acidosis, is also present. Metabolic acidosis r lactic acid produced from PG metabolism.[26] These adverse effects have b with intravenous preparations such as lorazepam,[5 , 151] diazepam,[147] eto nitroglycerin,[42] pediatric multivitamins,[61] and topical silver sulfadiazine.[1

Systemic absorption of PG from topical application of silver sulfadiazine c resulted in hyperosmolality in patients with burn surface areas greater tha body.[10 , 49 , 80] In one study, 9 of 15 burn patients had osmolar gaps (> application of the cream.[80]

Hyperosmolarity occurred in 5 infants receiving a parenteral multivitamin a daily PG dose of 3 g.[61] After 12 days, 1 premature infant had a PG con

930 mg/dL and an osmolar gap of 136. Anion gap and lactic acid concent normal. In a study of 11 intubated pediatric patients, ages 1 to 15 month receiving continuous lorazepam infusions over 3â€“14 days, accumulated concentrations of 17â€“226 mg/dL did not result in significant increases i or serum lactic acid concentrations from baseline.[31] This was attributed t function and the low cumulative PG doses received (mean 60 g).

Two small studies found a strong correlation between PG serum concentra osmolar gap in critically ill patients receiving lorazepam infusions.[5 , 151] patients on lorazepam high-dose infusions received a mean cumulative PG mg/kg/d.[5] At 48 hours the mean serum PG concentration was 200 mg/dL mg/dL), and all patients had elevated osmolar gaps (mean, 48; range, 2 patients had elevated anion gaps, although it is questionable whether this of PG because lactic acid concentrations were either not reported or were for 8 of the 9 patients. In the second study,[151] laboratory values were re patients at the time of peak serum creatinine concentrations (median, 9 receiving lorazepam infusions of 2â€“28 mg/h. Mean PG serum concentrat mg/dL (18.6â€“345 mg/dL). Elevated osmolar gaps (mean, 32; range, 1 occurred in 7 patients, and 4 of these 7 patients had high anion gaps. La concentrations were not reported for 1 patient and were high in the other

Using an elevated osmolar gap as a surrogate marker for PG accumulatio receiving lorazepam infusions, has been suggested.[5 , 151] An osmolar gap corresponds to a PG serum concentration of approximately 48 mg/dL.[5] Th should be used cautiously, as larger, more comprehensive studies are ne it. In addition, there are rare cases where PG accumulation did not result gap.[62 , 151] Anion gap and lactic acid concentration should be obtained, as concentration to eliminate other potential causes for an elevated osmolar

Nephrotoxicity

Human proximal tubular cells exposed in vitro to PG concentrations of 5(mg/dL exhibited significant cellular injury and membrane damage within 1 exposure.[102] Repeated exposure for up to 6 days produced dose-depende at lower concentrations (76, 190, and 380 mg/dL).[103]

The chronic administration of PG may contribute to proximal tubular cell subsequent decreased renal function. In a retrospective study of 8 patien developed elevations in serum creatinine while receiving continuous lora infusions, serum creatinine rose within 3â€“60 days (median, 9 days).[151] of serum creatinine rise was found to correlate with the PG serum concer duration of infusion. Serum creatinine decreased within 3 days of discont infusion. Patients with renal dysfunction are at greater risk for accumulat 45% of PG is eliminated unchanged by the kidneys;[42] the remainder is m the liver. Caution should be used when prolonged administration of a PG medication is necessary in the presence of renal or hepatic dysfunction.[10

Propylene glycol-induced renal tubular necrosis has been reported in sev Daily PG-vehicle dosages of 11â€“90 g/d over 14 days was associated wi creatinine concentrations (from 0.7 mg/dL to 2.1 mg/dL), elevated serum

concentrations, osmolar and anion gaps, and a serum PG concentration of Urine sediment analysis revealed numerous granular, muddy-brown-colore eosinophils, suggesting an acute renal tubular necrosis. A renal biopsy ar microscopy showed extensive dilation of the proximal renal tubules, with epithelial cells and mitochondria. Numerous vacuoles containing debris we A renal biopsy of another case with a serum PG concentration of 30 mg/c disrupted brush borders of the proximal renal tubules after a sudden rise creatinine (3.1 mg/dL), nonoliguric renal failure, and metabolic acidosis. attributed to an average daily PG dose of 70 g for 17 days.[68]

Sorbitol

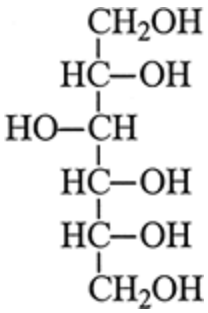


Figure. No Caption Available.

Sorbitol (D-glucitol) is widely used in the pharmaceutical industry as a s agent, moistening agent, and a diluent (Table 53-10). Sorbitol occurs na ripe berries of many fruits, trees, and plants, and was first isolated in 18 berries of the European mountain ash (*Sorbus aucuparia*).[105] It is partic chewable tablets because of its pleasant taste. In addition, it is widely us industry in chewing gums, dietetic candies, foods, and enteral nutrition Sorbitol is approximately 50â€“60% as sweet as sucrose.[105]

Pharmacokinetics

Unlike sucrose, sorbitol is not readily fermented by oral microorganisms a absorbed from the gastrointestinal tract. Any absorbed sorbitol is metabol liver to fructose and glucose.[105] Sorbitol has a caloric value of 4 kcal/g a tolerated by diabetics than sucrose; however, because some of it is meta glucose, it is not unconditionally safe for diabetics.[105]

There is a concern of potentially fatal toxicity for individuals with heredit intolerance (HFI) receiving sorbitol-containing agents.[50] HFI is an autosc disorder caused by a deficiency of fructose-1,6-bisphosphonate aldolase i kidney, cortex, and small intestine.[77] This results in the accumulation of phosphate, which causes hypoglycemia by preventing glycogen breakdowr synthesis. The prevalence of HFI is most commonly reported to be 1 in 2 but can range between 1 in 11,000 and 1 in 100,000.[2 , 75 , 77]

Brofed elixir (brompheniramine and pseudoephedrine)
20
2
Calcium carbonate suspension
28
1.4
Fer-In-Sol drops (ferrous sulfate)
31
0.2
Symmetrel syrup (amantadine HCl)

64
6.4
Triaminic syrup (chlorpheniramine and pseudoephedrine)
7
0.7

Medication Percent (%) g/Dose

TABLE 53-10. Common Medications Containing Sorbitol

In individuals with HFI, the prolonged administration of sorbitol, fructose, result in death from liver or renal failure.[34,123] Dietary exclusion of fru and sorbitol prevents the adverse effects. This condition should not be co more common disorder of dietary fructose intolerance (DFI), which is caus in the glucose-transport protein 5 (GLUT5) system. This leads to the brea fructose to carbon dioxide, hydrogen, and short-chain fatty acids by colo resulting in abdominal pain and bloating.[83] Dietary fructose intolerance s minimized by limiting sorbitol, fructose, and sucrose in the diet.

Gastrointestinal Toxicity

In large dosages, sorbitol can cause abdominal cramping, bloating, flatul and diarrhea. Sorbitol exerts its cathartic effects by its osmotic properties fluid shifts within the gastrointestinal tract. In a human volunteer study, adults ingested 10 g of a sorbitol solution. Sorbitol intolerance was detect 55% of subjects.[74] One theoretical explanation for why all subjects did n the gastrointestinal adverse effects is unrecognized DFI. Diarrhea resultin sorbitol-containing medications is common and often overlooked as a pos etiology.[30,69] Ingestion of large quantities of sorbitol (>20 g/d in adults recommended (Antidotes in Depth: Whole-Bowel Irrigation and Other Int Evacuants).[105]

Thimerosal

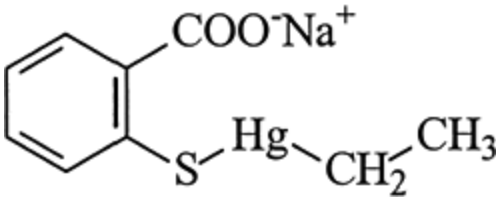


Figure. No Caption Available.

Thimerosal (Merthiolate, Mercurothiolate) or sodium ethylmercurithiosalicy organic mercury compound that is approximately 49% elemental mercury weight.[118 , 141] It is metabolized to ethylmercury and thiosalicylate. Thim wide spectrum of antibacterial activity at concentrations ranging from 0. however, higher concentrations are sometimes also used.[78 , 99] Thimerosa widely used as a preservative since the 1930s in contact lens solutions, l vaccines, particularly those in multidose containers (Table 53-11). The u thimerosal necessary for the production process of some vaccines (eg, p influenza) may leave trace amounts in the final product.[9] High-dose thim has resulted in neurotoxicity and nephrotoxicity. Over the last several ye have arisen about infant exposure to low-dose thimerosal through vaccina effects on neurodevelopment, including possible links to causes of autism

Because specific guidelines for ethylmercury exposure have not been dev regulatory guidelines for dietary methylmercury exposure have been used ethylmercury exposure from injected thimerosal-containing vaccines. Meth similar, but more toxic, organic mercury compound (Chap. 92).

Maximum daily recommended methylmercury exposures range from 0.1 Â Environmental Protection Agency [EPA]) to 0.47 Âµg Hg/kg (WHO).[3 , 29 ,

Injectable

Antivenom (Crotalidae [Equine])	
0.005	
0.5 (per vial)	
Antivenom (Crotalidae Fab [Ovine])	

0.001
0.11 (per vial)
Antivenom (*Lactrodectus mactans*)
0.01
0.25 (per vial)
Antivenom (*Micrurus fulvius*)
0.005
0.5 (per vial)
Diphtheria and tetanus toxoids[a]
0.01
0.05
DTwP (all products)
0.01
0.05
Fluzone[a] (influenza virus vaccine)
0.01
0.05
Menomune-A/C/Y/W-135[a] (meningococcal vaccine)
0.01
0.05
Rabies vaccine (adsorbed)
0.01
0.1
Tetanus toxoid (adsorbed)
0.01
0.05
Topical

Mersol (thimerosal tincture)
0.1
â€”
Neosporin (triple antibiotic) ophthalmic solution
0.001

â€”
Ocufen (flurbiprofen) ophthalmic solution
0.005
â€”
Sulf-10 (sulfacetamide) ophthalmic solution
0.01
â€”
[a] Multidose.

Medication	Percent (%)	mg/Dose

TABLE 53-11. Thimerosal Concentration of Common Medications

A 1997 FDA review of thimerosal-containing vaccines revealed that some depending on the immunization schedule, vaccine formulations, and infar might be exceeding the EPA exposure limit of 0.1 Âµg Hg/kg/d for methy the first 6 months of life, a total cumulative dose of up to 187.5 Âµg Hg thimerosal-containing vaccines was possible. The US Public Health Service the American Academy of Pediatrics (AAP) responded jointly by recommer preemptive reduction or removal of thimerosal from vaccines wherever p The WHO and European regulatory bodies have made similar recommend date, thimerosal has been removed from most US-licensed immunoglobuli vaccines routinely recommended for children younger than 7 years of age thimerosal free or contain only trace amounts (<0.5 Âµg Hg/dose), with some inactivated influenza vaccines. Multidose vials requiring thimerosal remain important for immunization programs in developing countries. Alt continue to eliminate all sources of mercury exposure, complete eliminati thimerosal from all vaccines is unlikely in the near future.[9] When a thime containing vaccine is the only alternative, the benefits of vaccination far theoretical risk of mercury toxicity.[106]

Prior to thimerosal use in pharmaceuticals, evidence for its safety and ef provided in several animal species and in 22 humans.[113] Only limited data infant mercury exposure from thimerosal-containing vaccines. Clinical stu assess the effects of thimerosal exposure on neurodevelopment and renal

immunologic function are lacking. Based on a comprehensive review of e data from the United States,[54 , 55 , 56 , 57 , 141] Denmark,[73 , 91] Sweden, United Kingdom,[4 , 71] the Institute of Medicine's (IOM) Immunization Saf Committee,[106] the Global Advisory Committee on Vaccine Safety (GACVS European Agency for the Evaluation of Medicinal Products (EMEA),[45] have that there is no causal relationship between thimerosal-containing vaccine Continued surveillance of autistic spectrum disorders as thimerosal use de conducted to evaluate any associated trends.

Pharmacokinetics

Limited pharmacokinetic data exists for thimerosal and ethylmercury. On thimerosal breaks down to form ethylmercury and thiosalicylate. Some e further decomposes into inorganic mercury in the blood, and the remainc into kidney and, to a lesser extent, brain tissue.[92 , 93] Because of its lon chain, ethylmercury is less stable and decomposes more rapidly than me leaving less ethylmercury available to enter kidney and brain tissue.[93] Et crosses the bloodâ€“brain barrier by passive diffusion.[92] Intracellular et decomposes to inorganic mercury which accumulates in kidney and brain half-life of thimerosal is estimated to be about 18 days.[93] Thimerosal is e the feces as inorganic mercury.[112]

Mercurial Toxicity

Oral Administration

A case report described a 44-year-old man who ingested 5 g (83 mg/kg) a suicide attempt; within 15 minutes he began vomiting spontaneously. G was performed and chelation therapy begun with dimercaptopropane sulf Gastroscopy revealed a hemorrhagic gastritis. Polyuric acute renal failure the day of admission and persisted for 40 days. Four days after admissior developed a fever and a maculopapular exanthem attributed to thimerosa also developed an autonomic and ascending peripheral polyneuropathy th 13 days. Chelation therapy was continued for a total of 50 days with DMF succimer. Elevated blood and urine mercury levels persisted for more thar

The patient was discharged 148 days following the ingestion with only se his toes. No other neurologic sequelae were noted.[111]

Oral absorption of thimerosal resulted in the fatal poisoning of an 18-mo from the intraotic instillation of a solution containing 0.1% thimerosal an sodium borate. Tympanostomy tubes placed 1 year earlier allowed the ir to flow through the auditory tube into the nasopharynx, and subsequently swallowed and absorbed through the oral mucosa and gastrointestinal trac 1.2 L of solution (500 mg Hg) was instilled over a 4-week period, resultin mercury poisoning. Four days after admission, the plasma mercury conce 163 Âµg/dL. The patient also received 1.7 g of boric acid. It is unclear wl contribution, if any, the boric acid made to the plasma mercury concentr therapy with *N* -acetyl-D-penicillamine was initiated on day 51. Despite i urinary mercury concentrations following administration of the *N* -acetyl- penicillamine, her neurologic function and blood mercury concentrations unchanged. The child died 3 months after admission. An autopsy was not

Intramuscular Administration

Urine mercury levels of 26 patients with hypogammaglobulinemia, who r intramuscular IgG replacement therapy preserved with 0.01% thimerosal The dosages of IgG ranged from 25â€“50 mg/kg, containing 0.6â€“1.2 mg per dose.[64] The total estimated dose of mercury administered ranged fron over a period of 6 months to 17 years. Urine mercury levels were elevate

in 19 patients ranging from 31â€“75 Âµg/L; however, no patients had cli of chronic mercury toxicity.[64]

Six cases of severe mercury poisoning resulting in 4 deaths were reporte intramuscular administration of chloramphenicol preserved with thimerosa manufacturing error produced vials containing 510 mg of thimerosal (250 instead of 0.51 mg per vial. Two adults received 4 and 5.5 g of mercury e children received 0.2â€“1.8 g each. All 6 patients had extensive tissue ne site of injection. Fever, altered mental status, slurred speech, and ataxia Autopsy identified widespread degeneration and necrosis of the renal tub creatine kinase concentrations were not reported so pigment-induced ne

cannot be ruled out. Elevated mercury concentrations were found in the tissues, and in the kidneys, livers, and brains.[7]

Topical Administration

Thirteen infants were exposed to 9â€“48 topical applications of a 0.1% t tincture for the treatment of exomphalos. Analysis for elevated mercury was performed in 10 of 13 infants who unexpectedly died. Mercury conce determined in various tissues from 6 of the infants. Mean tissue concentr samples of liver, kidney, spleen, and heart ranged from 5152 to 11,330 percutaneous absorption from these repeated topical applications.[46]

Ophthalmic Administration

Nine patients undergoing keratoplasty were exposed to a contact lens stor solution containing 0.002% thimerosal.[148] After 4 hours, the lens was re mercury concentrations of the aqueous humor and excised corneal tissues determined. Mercury concentrations were elevated in both aqueous humo 20â€“46 ng/mL higher) and corneal tissues (range, 0.6â€“14 ng higher) a eyes that had not been fitted with contact lenses. Only residual amounts remained on the contact lenses after 4 hours of wear. The authors noted the aqueous humor concentrations were in the same range as those meas patients with vision loss from systemic mercury poisoning (11â€“104 ng/ effects did not occur.

A possible drug interaction between orally administered tetracyclines and reported to result in acute, varying degrees of eye irritation in contact le using thimerosal-containing contact lens solutions who started treatment tetracycline.[38]

Summary

The benefits of pharmaceutical excipients include improved drug solubility palatability, the availability of various dosage forms, the provision of proc term storage, and the availability of multiple-dose packaging. Excipients termed â€œinert,â€• implying that they possess no pharmacologic or to

properties of their own. While excipients are essential and efficacious, the responsible for severe, and sometimes fatal, adverse effects.

The toxicity of pharmaceutical excipients should be considered for patien high dosages or prolonged administration of any medication containing e particularly those additives known to have toxicities. Individuals with dec hepatic functions or patients at the extremes of age may be at an increas accumulating excipients. Under circumstances in which there is no option continue treating a patient with a particular therapeutic agent, switching t preservative-free product, or to another brand without the offending exci obviate the need for discontinuation of an effective agent. In addition to toxicities, many excipients may also be responsible for allergic reactions. prevalence in numerous pharmaceuticals, cosmetics, and foods may allow sensitization. However, in the majority of cases, pharmaceutical excipients effective, and their benefits far exceed their potential for adverse effects administered properly.

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Chapter 54

Antibiotics, Antifungals, and Antivirals

Christine M. Stork

A 56-year-old man with a past medical history significant for lumbar spinal stenosis and a recent laminectomy for chronic back pain was admitted to the hospital for a trial of intrathecal morphine. Because of a medication error, the postoperative order for intravenous cefazolin was administered into the intrathecal catheter. The error was detected when the patient complained of back pain 13 hours after initiation of the infusion; an estimated total dose of 350 mg (2.5 mL/h Ã— 13.5 h at 10 mg/mL) was infused. Soon thereafter, the patient developed generalized seizures, was intubated for airway support, and was treated using intravenous benzodiazepines, phenytoin, and phenobarbital (30 mg). Seizure activity resolved and the patient was extubated 5 days later.

History and Epidemiology

The majority of the adverse effects related to antibiotics occur as

a result of iatrogenic complications rather than intentional overdose. The origins of these complications are diverse and include dosing and decision errors, allergic reactions, adverse drug effects, and drug interactions. Prevention in the form of process improvements and information regarding population risk for adverse drug effects is required to minimize these untoward events. As dosing errors are commonly noted in neonates and infants treated with intravenous antibiotics, careful and constant diligence on the part of all healthcare providers is required to minimize such errors.

Antibiotics are more commonly associated with anaphylactic reactions than are other medications. The reason for this is unclear, but it may be a result of their high frequency of use, repeated interrupted exposures caused by intermittent prescriptive use, or because of environmental contamination. A complete and clear allergy history is essential to minimize these reactions in patients being considered for antibiotic therapy.

Many adverse effects attributed to antibiotics are difficult to predict even when given patient- and population-specific parameters. In some cases, a diluent or ancillary chemical constituent of the drug is responsible for the adverse effect, as recognized with the use of procaine penicillin G in patients with procaine allergy. Antibiotics are involved in many of the common and severe drug interactions, primarily through the inhibition of metabolic enzymes. Patients being considered for antibiotic therapy should be carefully assessed for the use of concomitant drug therapy that may be pharmacokinetically or pharmacodynamically affected by the chosen antibiotic.

Pharmacology and Toxicology

Antibiotic pharmacology is aimed at the destruction of microorganisms through the inhibition of cell-cycle reproduction or by directly altering a critical function within a microorganism.

Table 54-1 lists antibiotics and their associated mechanisms of antimicrobial activity. Often the mechanisms for toxicologic effects following acute overdose differ from the therapeutic mechanisms. Table 54-1 also lists the toxicologic effects and related mechanisms. Table 54-2 lists the pharmacokinetics of each class of drugs.

Antibacterials

Aminoglycosides

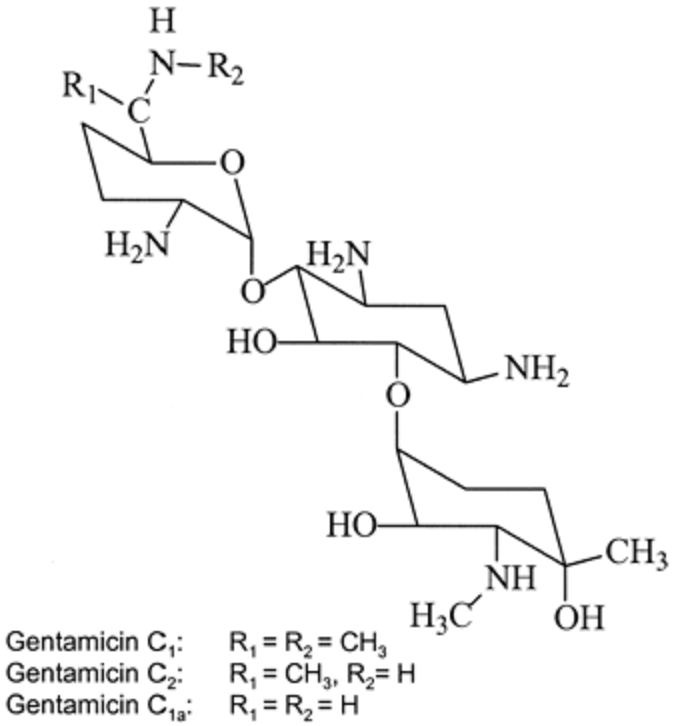


Figure. No Caption Available.

Aminoglycoside antibiotics that are in current use include amikacin, gentamicin, kanamycin, neomycin, netilmicin, streptomycin, and tobramycin.

Antibiotic
Aminoglycosides
Inhibit 30s ribosomal subunit
Neuromuscular blockade â€”inhibits the release of acetylcholine from presynaptic nerve terminals and antagonist at acetylcholine receptors
Renal toxicity/ototoxicity â€”forms an iron complex that inhibits mitochondrial respiration and causes lipid peroxidation
Penicillins, cephalosporins, and other Î²-lactams
Inhibit cell wall mucopeptide synthesis
Seizures â€”agonist at picrotoxin binding site causing GABA antagonism
Hypersensitivity â€”immune *Other* â€”see text
Chloramphenicol
Inhibits 50s ribosomal subunit and inhibits protein synthesis in rapidly dividing cells
Cardiovascular collapse
â€œGray baby syndromeâ€•
Same as mechanism of action
Fluoroquinolones
Inhibit DNA topoisomerase and DNA gyrase
Same as mechanism of action; binds to cations, particularly, magnesium, seizures
Not entirely known; binds to cations, particularly, magnesium; tendon rupture, hyper- and hypoglycemia
Linezolid
Inhibits bacterial protein synthesis through inhibition of N-formylmethionyl-t RNA
None clinically relevant
MAOI activity: pressor response to tyramine; and serotonin syndrome with SSRI and possibly meperidine
Macrolides and ketolides
Inhibit 50s ribosomal subunit in multiplying cells
Wide QTc â€”block delayed rectifier potassium channel

Not entirely known; cytotoxic effect; exacerbation of myasthenia gravis

Sulfonamides

Inhibit *para* -aminobenzoic acid and/or *para* -amino glutamic acid in the synthesis of folic acid

None clinically relevant

Hypersensitivity â€”metabolite is hapten leading to *hemolysis/methemoglobinemia* â€”exposure to UVB causes free radical formation, which results in an oxidant stress

Tetracycline

Inhibits 30s and 50s ribosomal subunits; binds to aminoacyl transfer RNA

None clinically relevant

Unknown

Vancomycin

Inhibits glycopeptidase polymerase in cell wall synthesis

â€œRed-man syndromeâ€• â€”anaphylactoid

Unknown

Antifungal

Amphotericin B

Binds with ergosterol on cytoplasmic membrane to cause pores to facilitate organelle leak

Same as mechanism of action

Nephrotoxicity â€”vehicle deoxycholate may be involved; nephrocalcinosis

Triazoles and imidazoles

Increase permeability of cell membranes

None clinically relevant

None clinically relevant

?CYP inhibition

TABLE 54-1. Antibiotic and Antifungal Pharmacology

Drug	Pharmacology of Antibiotic Effect	Acute Overdose Adverse Effect and Related Pharmacology	Chronic Administration Adverse Effect and Related Pharmacology
Antibiotic			
Aminoglycosides			
Parenteral			
0.25			
Renal			
2â€“3			
Penicillins, cephalosporins, and other Î²-lactams			
Oral, parenteral			
Variable			
Renal (predominant)			
Variable			
Chloramphenicol			
Oral, parenteral, otic			
0.5â€“1.0			
90% Hepatic, 10% renal			
1.6â€“3.3			
Fluoroquinolones			
Oral, parenteral			
Variable			
Renal			
3â€“5			
Ketolides			
Oral			
2.9 L/kg			
63% Renal, 37% hepatic (50% of which is CYP3A4)			

10â€“13
Macrolides
Oral, parenteral
Variable
Hepatic
Variable
Sulfonamides
Oral, parenteral
Variable
Hepatic
Variable
Tetracyclines
Oral
Variable
Hepatic
6â€“26
Vancomycin
Parenteral
0.2â€“1.25
Renal
4â€“6
Antifungal

Amphotericin B
Parenteral
4.0
Hepatic
360
Triazoles and imidazoles
Oral
Variable

Hepatic
Variable

Drug	Absorption	Volume of Distribution (L/kg)	Elimination Route	Half-life (h)

TABLE 54-2. Antibiotic and Antifungal Pharmacokinetics

Kanamycin
Neomycin
Amikacin
Gentamicin
Tobramycin
Streptomycin
Amikacin
Gentamicin
Kanamycin
Neomycin
Streptomycin
Tobramycin

Cochlear Cochlear and Vestibular Vestibular Renal

TABLE 54-3. Predominant Aminoglycoside Toxicity

As aminoglycosides are only available in parenteral and ophthalmic forms, overdoses of aminoglycoside antibiotics are almost exclusively the result of dosing errors. Fortunately, overdoses are rarely life-threatening, and most patients can be safely managed with minimal intervention.[24 , 92 , 122 , 147] The adverse effects of aminoglycosides are generally class based, although subtle differences may exist in the potency with which the adverse effects occur (Table 54-3).

Large intravenous doses of aminoglycosides are both sufficiently effective and safe for use in single daily doses.[5] Rarely, acute aminoglycoside overdose results in nephrotoxicity, ototoxicity, or vestibular toxicity.[140, 168] In one reported case, postmortem analysis confirmed complete loss of hair cells in the inner and outer cochlear.

Aminoglycosides may infrequently exacerbate neuromuscular blockade, particularly at times corresponding to high-peak serum aminoglycoside concentrations (Chap. 66).[200, 274] These effects relate to the ability of aminoglycosides to inhibit the release of acetylcholine from presynaptic nerve terminals. This effect is mediated by antagonism by the aminoglycoside of the presynaptic calcium channel, and may be a result of the ability of aminoglycosides to block postsynaptic acetylcholine receptors.[2, 111] Risk factors for enhanced neuromuscular blockade include patients with abnormal neuromuscular junction function, such as those with myasthenia gravis and botulism, and patients receiving concomitant neuromuscular blocking drugs.[2]

Adverse Effects Associated with Therapeutic Use

Adverse effects, including nephrotoxicity and ototoxicity, correlate more closely with elevated trough serum concentrations of aminoglycosides than with elevated peak concentrations.[2, 88, 129, 177, 181] Less-common adverse effects associated with chronic aminoglycoside use include electrolyte abnormalities, allergic reactions, hepatotoxicity, anemia, granulocytopenia, thrombocytopenia, eosinophilia, retinal toxicity, reproductive dysfunction, tetany, and psychosis.[61, 65, 134, 153, 247, 262] When aminoglycosides are administered at high doses or during once-daily dosing, sepsislike reactions, including chills and malaise, can occur.[48] This is likely a result of contaminants that are delivered to the patient during the infusion.

Nephrotoxicity

The mechanism of nephrotoxicity and ototoxicity is inconclusive, but appears to include the ability of the aminoglycoside to form reactive oxygen species in the presence of iron. Mitochondrial respiration is inhibited, lipid peroxidation occurs, and stimulation of glutamate activated *N* -methyl-D-aspartate (NMDA) receptors may play a role.[113 , 232 , 241 , 269] The incidence of nephrotoxicity with aminoglycoside therapy is estimated at 5â€“10%.[10] Although the aminoglycosides are almost completely excreted prior to biotransformation in the kidney, a small fraction of filtered aminoglycoside is transported by absorptive endocytosis across the apical membrane of proximal tubular cells where it becomes sequestered within lysosomes. The aminoglycoside binds to and destroys phospholipids contained on brush border membranes in the proximal renal tubule.[10]

Clinically, acute tubular necrosis occurs after 7â€“10 days of standard-dose therapy. Laboratory abnormalities include granular casts, proteinuria, elevated urinary sodium, and increased fractional excretion of sodium. Usually the renal dysfunction is reversible; however, irreversible toxicity is reported.[9] Functional renal injury occurs days prior to elevations in serum creatinine, and for this reason, a delay in diagnosis is common.[233] Risk factors for the development of nephrotoxicity include increasing age, renal dysfunction, female sex, previous aminoglycoside therapy, liver dysfunction, large total dose, long duration of therapy, frequent doses, high trough levels, presence of other nephrotoxic drugs, and the presence of shock.[10 , 183 , 209] Because the uptake of aminoglycosides into organs causing toxicity is saturable, appropriate once-daily high-dose regimens are less problematic than several lesser doses given in a single day.

Ototoxicity

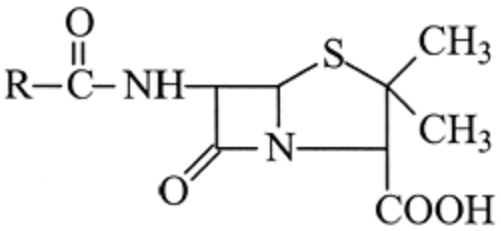
Ototoxicity can occur after acute or prolonged exposure to aminoglycosides. Both cochlear and vestibular dysfunction are correlated with high aminoglycoside trough concentrations.[41, 182] Because aminoglycosides bioaccumulate in the endolymph and perilymph spaces, they have prolonged contact time with sensory hair cells.[146] Vestibular toxicity, caused by destruction of sensory receptor portions of the inner ear or destruction of hair cells in the utricle and saccule, occurs in 0.4â€“10% of patients.[159, 182] Symptoms include vertigo or tinnitus. Table 54-3 details the relative characteristic toxicity of various aminoglycosides.

Full-tone audiometric testing may first show high-frequency hearing loss, which may subsequently progress. Given the inability of cochlear hair cells to regenerate, all hearing loss that develops is permanent. Electronystagmography is the diagnostic tool of choice for vestibular dysfunction, and up to 63% of patients with early findings of vestibular dysfunction may have improvement after discontinuation of the drug.[133] Simultaneous administration of other xenobiotics capable of causing ototoxicity enhances ototoxicity of aminoglycoside antibiotics (Chap. 21).[36, 146, 254]

Withdrawal of the offending xenobiotic is indicated in patients with either nephrotoxicity or ototoxicity caused by an aminoglycoside antibiotic. Supportive care is the mainstay of therapy. Experimental treatments in animal models include the use of deferoxamine, glutathione, and NMDA receptor antagonists in an attempt to chelate and/or detoxify a reactive intermediate.[195, 251] The antibiotic ticarcillin forms a renally eliminated complex with aminoglycosides in the blood to provide protection against tobramycin-induced renal toxicity. In humans, ticarcillin removes 50% more aminoglycoside in 48 hours than do 2 hemodialysis sessions.[80] However, ticarcillin therapy is generally of limited value because in most instances the serum concentration of the aminoglycoside has decreased before any therapeutic measures

can be employed. The use of ticarcillin should be considered only early after large overdose in patients with either demonstrated toxicity or renal failure where the risks of toxicity are significant.

Penicillins



Penicillins nucleus

Penicillin is derived from the fungus *Penicillium* and many semisynthetic derivatives have clinical utility. Penicillins, as a class, contain a 6-aminopenicillanic acid nucleus, composed of a Î²-lactam ring fused to a 5-member thiazolidine ring. Classic available penicillins include penicillin G, penicillin V, and the antistaphylococcal penicillins (nafcillin, oxacillin, cloxacillin, and dicloxacillin). Penicillins developed to enhance the spectrum of antibiotic efficacy, particularly against Gram-negative bacilli, include the second-generation penicillins (ampicillin, amoxicillin, bacampicillin, and mezlocillin), third-generation penicillins (carbenicillin and ticarcillin), and fourth-generation penicillins (piperacillin). Table 54-1 lists the pharmacologic mechanism of penicillins and Table 54-2 lists their pharmacokinetic properties.

Acute oral overdoses of penicillin-containing drugs are usually not life-threatening. The most frequent complaints following acute overdose are nausea, vomiting, and diarrhea. Rarely, hyperkalemia resulting in electrocardiographic abnormalities occurs after the rapid intravenous infusion of potassium penicillin G to patients with renal failure.

Seizures occur in persons given large intravenous or intraventricular doses of penicillins.[35, 136, 150, 175, 241] More than 50 million units intravenously are generally required to produce seizures in adults.[239] Penicillin-induced seizures appear to be mediated through an interaction of the drug with the picrotoxin-binding site on the neuronal chloride channel near the Î³-aminobutyric acid (GABA) binding site (Chap. 14). Binding of the penicillin produces an allosteric change in the receptor that prevents GABA from binding, resulting in a relative lack of inhibitory tone.[66] Penicillin analogs (such as imipenem) also cause seizures in both animal models and humans, presumably through a similar mechanism.[241]

Treatment of patients who develop penicillin-induced seizures include GABA agonists such as the benzodiazepines and barbiturates, if needed. Patients who receive an intraventricular overdose may require cerebrospinal fluid exchange to attenuate seizure activity.[150] There are rare reports of amoxicillin overdose resulting in frank hematuria and renal failure, and a single case report of penicillin-associated hearing loss.[28, 32, 98]

Adverse Effects Associated with Therapeutic Use

Penicillins are associated with a myriad of adverse effects after therapeutic use, the most common of which are allergic reactions. Penicillins are commonly implicated in immune-related reactions such as bone marrow suppression, cholestasis, hemolysis, interstitial nephritis, and vasculitis.[6, 95, 123, 187, 188, 250] Rare effects include pemphigus after penicillin use and corneal damage after the use of methicillin.[20, 278]

Acute Allergy

Penicillins are the pharmaceuticals most commonly implicated in

the development of acute anaphylactic reactions. Anaphylactic reactions are severe life-threatening immune-mediated (IgE) reactions involving multiple organ systems that occur most often immediately after exposure to a triggering agent. Table 54-4 lists the classifications of anaphylactic reactions. Anaphylaxis to penicillin is typically seen after IgE antibody formation, which can only occur after prior exposure to penicillin. Life-threatening clinical manifestations occurring after anaphylaxis can include angioedema, tongue and airway swelling, bronchospasm, bronchorrhea, cardiac dysrhythmias, cardiovascular collapse, and cardiac arrest.[81, 161] The pathophysiology of systemic anaphylaxis is complex and involves multiple pathways. IgE antibodies are cross-linked on the surface of mast cells and basophils, resulting in local and systemic release of preformed mediators of anaphylactic response, including leukotrienes C_4 and D_4, histamine, eosinophilic chemotactic factor, and other vasoactive substances, such as bradykinin, kallikrein, prostaglandin D_2, and platelet-activating factor.

I
Large local contiguous reaction (>15 cm)
II
Pruritus (urticaria) generalized
III
Asthma, angioedema, nausea, vomiting
IV
Airway (asthma, tongue swelling, dysphagia, respiratory distress, laryngeal edema)
Cardiovascular (hypotension, may progress to cardiovascular collapse)

Grade Classification Description

TABLE 54-4. Classification of Anaphylactic Reactions

The incidence of penicillin hypersensitivity is 5% overall, with 1% of penicillin reactions resulting in anaphylaxis. The risk for a fatal hypersensitivity reaction after penicillin administration is 2 per 100,000 (0.002%) patient exposures.[268] All routes of penicillin administration can result in anaphylaxis; however, it occurs most commonly after intravenous administration.

Treatment is supportive with careful attention to airway, breathing, and circulation. If the penicillin was ingested, the patient may theoretically benefit from oral activated charcoal 1 g/kg. This is unlikely to prevent anaphylaxis, as only a few molecules need be absorbed to trigger the immunologic response. Initial drug therapy for anaphylaxis includes epinephrine 0.01 mL/kg (up to 0.5 mL) of 1:1000 dilution subcutaneously (SC) every 10â€“20 minutes. Epinephrine, through Î²-receptor stimulation, results in bronchodilation and increased cardiac output. In addition, its Î±-receptor stimulation results in increased peripheral vascular tone. Oxygen and inhaled $\hat{I}^2_2$ -adrenergic agonists are warranted in severe cases, as are corticosteroids. H_1 -receptor antagonists may be sufficient in patients with mild allergic reactions who do not have pulmonary manifestations or airway concerns.

H_2 -receptor antagonism as a treatment for anaphylaxis is controversial. H_2 -receptors, when stimulated in the peripheral vasculature, cause vasodilation; in the heart, cause positive inotropy, positive chronotropy, and coronary vasodilation; and in the lung, cause increased mucus production.[227] Theoretically, H_2 -receptor antagonists can lead to a decrease in myocardial activity at a time when H_1 -receptor stimulation is causing hypotension, coronary vasoconstriction, and bronchospasm. However, in vitro and animal models demonstrate decreases in coronary circulation and decreases in the overall anaphylactic response following administration of H_1 blockers.[16 , 23] Cimetidine and ranitidine are useful for the treatment of pruritus and flushing after acute allergic reactions involving the skin.[164 , 179] Cimetidine, used

following anaphylaxis, may result in clinical improvement, particularly hypotension and tachycardia.[73 , 279] There is 1 case, however, of chronic ranitidine administration which was postulated to result in heart block after an anaphylactic response to latex.[203] Available data indicate that treatment using H_2 -receptor antagonists should only be considered when other therapies have failed and the patient is adequately H_1 -receptor blocked. Aminophylline, although mentioned in some references for the treatment of anaphylaxis, is inadequately studied and should not be routinely employed. Lastly, glucagon may be of some benefit, particularly in patients who are maintained on Î²-adrenergic antagonists.

Amoxicillin-Clavulanic Acid and Hepatitis

Intrahepatic cholestatic hepatitis occurs 1â€“6 weeks after initiation of therapy with amoxicillin-clavulanate.[7 , 54 , 114] The incidence of hepatotoxicity typically is estimated at 1.1â€“2.7 per 100,000 prescriptions.[94] The mechanism of

hepatotoxicity is not clear, but may be related to clavulanate, a Î²-lactamase inhibitor used to prevent the bacterial destruction of Î²-lactam antibiotics, or one of its metabolites. Treatment is supportive and clinical findings typically resolve after the discontinuation of therapy. However, prolonged hepatitis, ductopenia, and pancreatitis rarely occur.[50 , 215]

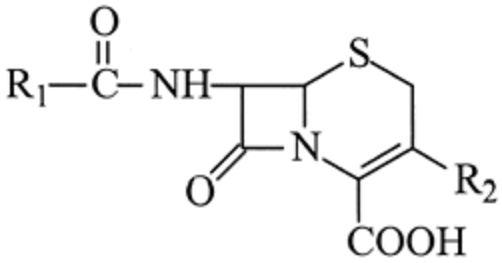
Jarisch-Herxheimer Reaction and Hoigne Syndrome

The most common adverse effects occurring after administration of intramuscular procaine penicillin G are the Hoigne syndrome and the Jarisch-Herxheimer reaction.[12 , 63 , 121 , 131 , 174 , 245 , 285] Both occur after the administration of large intramuscular or intravenous doses of penicillin G.[93 , 106] Hoigne syndrome is

characterized by extreme apprehension and fear, illusions, or hallucinations; changes in auditory and visual perception; tachycardia; systolic hypertension; and, occasionally, seizures that begin within minutes of injection.[267] These effects occur in the absence of signs or symptoms of anaphylaxis. The cause of this syndrome is unknown. Procaine is implicated as the causative agent because of this syndrome's similarity to events that occur after the administration of other pharmacologically similar local anesthetics.[229 , 240 , 264] Hoigne syndrome is 6 times more common in males than females.[244] The reason for this increased prevalence is unclear, but autosomal dominance and influences of prostaglandin and thromboxane A_2 activity in this population may be responsible.[12]

The Jarisch-Herxheimer reaction is a self-limited reaction that develops within a few hours of antibiotic therapy for the treatment of early syphilis or Lyme disease. Clinical findings include myalgias, chills, headache, rash, and fever, which spontaneously resolve within 18â€“24 hours, even with continued antibiotic therapy.[180 , 223] The pathogenesis of this reaction is likely an acute antigen release by lysed bacteria.[193]

Cephalosporins



Cephem Nucleus

Cephalosporins are semisynthetic derivatives of cephalosporin C produced by the fungus *Acremonium* , previously called

Cephalosporium. Cephalosporins have a ring structure similar to that of penicillins. Cephalosporins are generally divided into first, second, third, and fourth generations based on their antimicrobial spectrum. First-generation cephalosporins include cefadroxil, cefazolin, cephalexin, cephapirin, and cephradine. Second-generation cephalosporins include cefaclor, cefamandole, cefonicid, cefotetan, cefoxitin, cefprozil, and cefuroxime. Third-generation cephalosporins include cefdinir, ceftazidime, cefixime, ceftibuten, cefoperazone, ceftizoxime, cefotaxime, ceftriaxone, and cefpodoxime. Finally, of the fourth-generation cephalosporins, cefepime is the first to be marketed.

Effects occurring after acute overdose of cephalosporins resemble those occurring after penicillin exposure. Some cephalosporins have epileptogenic potential similar to penicillin.[98, 270] Case reports have demonstrated seizures after inadvertent intraventricular administration.[34, 156, 280] Management guidelines for cephalosporin overdose are similar to those of penicillin overdose. Table 54-1 lists the pharmacologic mechanism of cephalosporins and Table 54-2 lists their pharmacokinetic properties.

Adverse Effects Associated with Therapeutic Use

Cephalosporins rarely cause an immune-mediated acute hemolytic crisis.[25, 79] Cefaclor is the cephalosporin most commonly reported to cause serum sickness, although it can occur with other cephalosporins.[143, 167] Also like penicillins, cephalosporins are associated with chronic toxicity, including interstitial nephritis and hepatitis with first-generation agents.[187, 188, 277] Cefepime is reported in a single case to cause reversible coma and nonconvulsive seizures.[1]

Cross-Hypersensitivity

The cephalosporins contain a 6-member dihydrithiazine ring instead of the 5-member thiazolidine penicillin ring. The extent of cross-reactivity between penicillins and cephalosporins in an individual patient is largely determined by the type of penicillin allergic response experienced by the patient. The incidence of anaphylaxis to cephalosporins is between 0.0001% and 0.1%, with a 3-fold increase in patients with previous penicillin allergy.[144] Ten percent of patients with prior penicillin-related anaphylactic reactions will have positive skin test for cephalosporin hypersensitivity.[219] A negative skin test predicts a negative allergic response on oral cephalosporin challenge in penicillin-allergic patients. Lastly, the incidence of delayed hypersensitivity reactions after cephalosporin use is 1â€“2.8% in the general population and 8.1% in those with prior penicillin delayed hypersensitivity. Cross-reactivity may be greater with the first- and second-generation cephalosporins that are more structurally similar to penicillin or that are contaminated by penicillin.[8] Antibody binding after cephalosporin exposure occurs at the determinants located on the side-chain groups of the cephalosporin.[14] In fact, IgE directed against a methylene substituent linking the side chain to the penicillin molecule has been identified.[112] These determinants are quite distinct among cephalosporins, which cause the pattern of cross-hypersensitivity among cephalosporins to be much less well-defined than among the penicillins. Caution should be used when considering cephalosporins in penicillin- or cephalosporin-allergic patients; however, if a risk-to-benefit analysis demonstrates a clear benefit to the patient without equivalent alternatives, the cephalosporin should be given.

N -methylthiotetrazole Side-Chain Effects

Cephalosporins containing an *N* -methylthiotetrazole (nMTT) side chain (moxalactam, cefazolin, cefoperazone, cefmetazole, cefamandole, cefotetan) have toxic effects unique to their group

structure. As these cephalosporins undergo metabolism, they release free nMTT, which is responsible for their effects (Fig. 54-1).[176] Free nMTT inhibits the enzyme aldehyde dehydrogenase and, in conjunction with ethanol, can cause a disulfiramlike reaction (Chap. 77).[39]

The nMTT side chain is also associated with hypoprothrombinemia, although a causal relationship is controversial.[107] It is thought that nMTT depletes vitamin K-dependent clotting factors by inhibition of vitamin K epoxide reductase.[197] In a study of children 1 month to 1 year of age who were maintained on a prolonged antibiotic regimen, a significant degree of vitamin K depletion was found.[22] Treatment of patients suspected of hypoprothrombinemia caused by these cephalosporins consists of fresh-frozen plasma, if bleeding is evident, and vitamin K_1 in doses required to resynthesize vitamin K cofactors (Chap. 57).

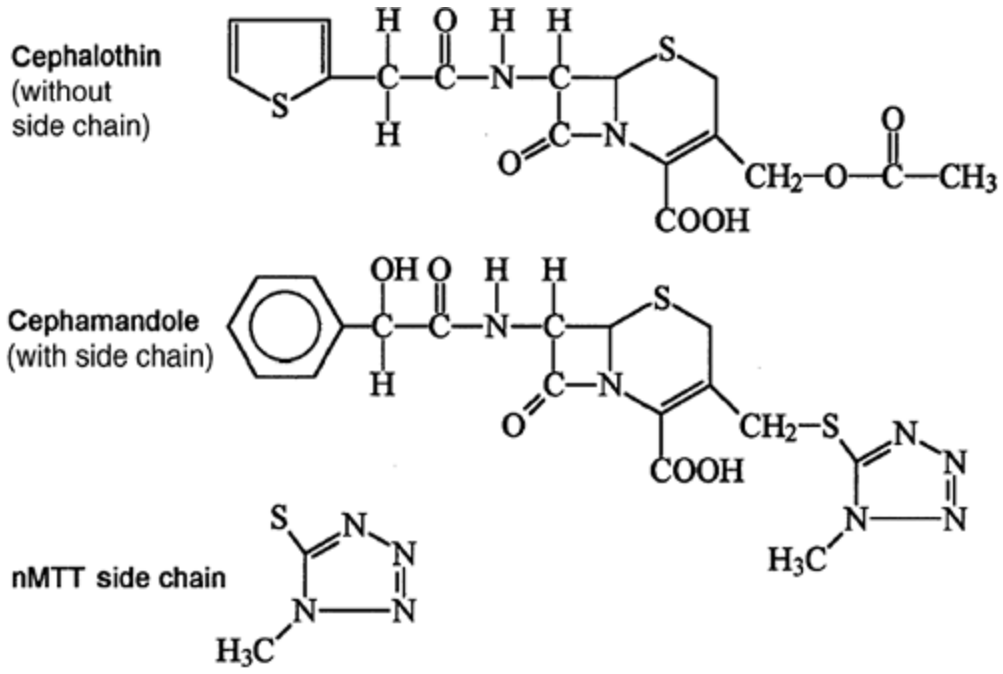
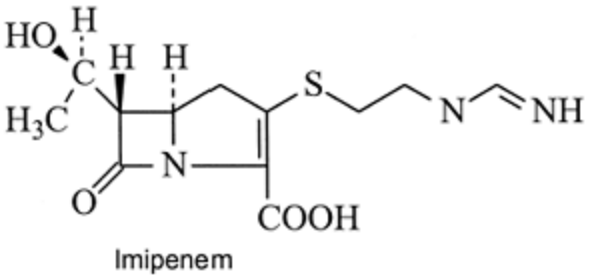
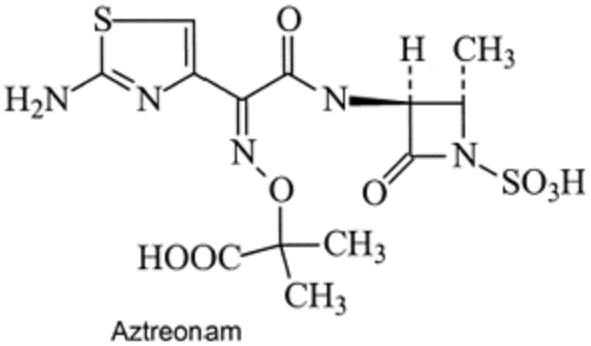


Figure 54-1. Characteristic structures of cephalosporins emphasizing the nMTT side chain.

Other Î²-Lactam Antibiotics



Imipenem



Aztreonam

Figure. No Caption Available.

Included in this group are monobactams such as aztreonam and carbapenems such as imipenem and meropenem. Table 54-1 lists the pharmacologic mechanism of these drugs, and Table 54-2 lists their pharmacokinetic properties.

Effects occurring after acute overdose of other Î²-lactam antibiotics resemble those occurring following penicillin exposure. Imipenem has epileptogenic potential in both overdose and therapeutic dosing (see Adverse Effects Associated with Therapeutic Use). Management guidelines for other Î²-lactam overdoses are similar to those for penicillin overdoses.

Adverse Effects Associated with

Therapeutic Use

Imipenem, a member of the class of carbapenem compounds, can cause seizures in therapeutic doses.[45, 142, 158, 202, 249] The risk factors for seizures include central nervous system disease, prior seizure disorders, and abnormal renal function.[204] The mechanism for seizures appears to be GABA antagonism (similar to the penicillins) in conjunction with enhanced activity of excitatory amino acids.[71, 255]

Cross-Hypersensitivity

Aztreonam is a monobactam that does not contain the antigenic components required for cross-allergy with penicillins, and generalized cross-allergenicity is not expected.[230] However, aztreonam cross-reacts in vitro with ceftriaxone, thought to be the result of the similarity in their side-chain structure.[207] Cross-allergenicity has also been noted between imipenem and penicillin, although the incidence has yet to be determined.

Chloramphenicol

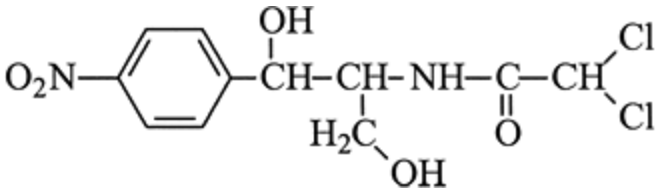


Figure. No Caption Available.

Chloramphenicol was originally derived from *Streptomyces venezuelae* and is now produced synthetically. Antimicrobial activity exists against many Gram-positive and Gram-negative aerobes and anaerobes. Table 54-1 lists the pharmacologic mechanism of chloramphenicol, and Table 54-2 lists its pharmacokinetic properties.

Acute overdose of chloramphenicol commonly causes nausea and vomiting. Effects are caused by its ability to inhibit protein synthesis in rapidly proliferating cells. Metabolic acidosis occurs as a result of the inhibition of mitochondrial enzymes, oxidative phosphorylation, and mitochondrial biogenesis.[90] Infrequently, sudden cardiovascular collapse can occur 5â€“12 hours after acute overdoses. In case series, cardiovascular compromise was more frequent in patients with serum concentrations >50 Âµg/mL.[90 , 145 , 185 , 205 , 260] Because levels are not readily available, all poisoned patients should be closely observed for at least 12 hours after exposure. Orogastric lavage may be useful for recent ingestions when the patient has not vomited, and activated charcoal 1 g/kg should be given orally.

Extracorporeal means of eliminating chloramphenicol are not usually required because of its rapid metabolism (Table 54-2). However, both hemodialysis and charcoal hemoperfusion decrease elevated plasma chloramphenicol levels and may be of benefit in patients with large overdoses, or in patients with severe hepatic or renal dysfunction.[89 , 178 , 246] Exchange transfusion also lowers chloramphenicol serum concentrations in neonates.[145 , 253] Surviving patients should be closely monitored for signs of bone marrow suppression.

Adverse Effects Associated with Therapeutic Use

Chronic toxicity of chloramphenicol is similar to that which occurs following acute poisoning. The classic description of chronic chloramphenicol toxicity is the â€œgray baby syndrome.â€• [89 , 90 , 178 , 253] Children with this syndrome exhibit vomiting, anorexia, respiratory distress, abdominal distension, green stools, lethargy, cyanosis, ashen color, metabolic acidosis, hypotension, and cardiovascular collapse. The majority (90%) of a dose of chloramphenicol is metabolized via glucuronyl transferase, forming

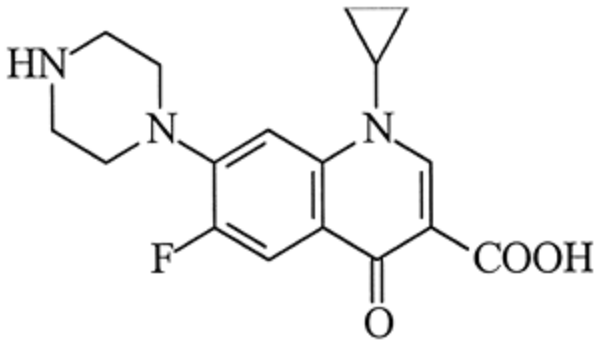
a glucuronide conjugate. The remainder is excreted renally unchanged. Infants, in particular, are predisposed to the gray baby syndrome because they have a limited capacity to conjugate chloramphenicol and, concomitantly, a limited ability to excrete unconjugated chloramphenicol in the urine.[101, 276]

Dose-dependent bone marrow depression occurs with high serum concentrations of chloramphenicol.[127, 128, 238] Clinical manifestations usually occur after several weeks of therapy and include anemia, thrombocytopenia, leukopenia, and very rarely, aplastic anemia. Bone marrow suppression is generally reversible on discontinuation

of therapy. Chloramphenicol causes bone marrow suppression by inhibiting protein synthesis in the mitochondria of marrow cell lines.[189, 190] The development of aplastic anemia after chloramphenicol use is not dose related and generally occurs in susceptible patients within 5 months of treatment (Chap. 24).[77, 282] The dehydro and nitroso bacterial metabolites of chloramphenicol cause human bone marrow cell line injury through inhibition of myeloid colony growth, inhibition of DNA synthesis, and inhibition of mitochondrial protein synthesis.[138]

Other adverse effects associated with chloramphenicol include peripheral neuropathy;[141, 211] neurologic abnormalities, such as confusion and delirium;[162] optic neuritis;[58, 141] nonlymphocytic leukemia;[243] and contact dermatitis.[151]

Fluoroquinolones



Ciprofloxacin

The fluoroquinolones are a structurally similar, synthetically derived group of antibiotics that exhibit a diverse spectrum of antimicrobial activity. The fluoroquinolones include balofloxacin, ciprofloxacin, clinafloxacin, enoxacin, fleroxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, lomefloxacin, moxifloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, pefloxacin, rufloxacin, sparfloxacin, temafloxacin, tosufloxacin, and trovafloxacin. Like other antimicrobials, the fluoroquinolones rarely produce life-threatening effects following acute overdose, and most patients can be safely managed with minimal intervention.[11] Table 54-1 lists the pharmacologic mechanism of fluoroquinolones, and Table 54-2 lists their pharmacokinetic properties.

Rarely, acute overdose of a fluoroquinolone results in renal failure or seizures. The mechanism of renal failure after fluoroquinolone exposure is controversial. In animals, ciprofloxacin and norfloxacin cause pathologic changes in the kidney, especially in the setting of neutral or alkaline urine.[60, 234] In humans, renal failure is reported after both acute and chronic exposure to fluoroquinolones. A hypersensitivity reaction is postulated to explain pathologic changes consistent with interstitial nephritis.[125, 187, 188, 217, 281] Treatment includes discontinuation of the fluoroquinolone and supportive care. Improvement in renal function is usually noticed within several days.

Seizures are reported with ciprofloxacin and may be a result of the inhibition of GABA.[248, 263] Others postulate that the ability of fluoroquinolones to bind efficiently to cations, particularly magnesium, results in seizures. This hypothesis is related to magnesium's inhibitory role at the excitatory NMDA-gated ion channel (Chap. 14).[72, 235] Treatment is supportive, using benzodiazepines and, if necessary, barbiturates to increase GABAergic activity.

Adverse Effects Associated with Therapeutic Use

Several fluoroquinolones are substrates and/or inhibitors of cytochrome CYP isozymes. This can result in drug interactions, which are especially important with drugs that have a narrow therapeutic index.

Serious adverse effects related to fluoroquinolone use consist of central nervous system toxicity, as discussed, cardiovascular toxicity, hepatotoxicity, and articular/tendon toxicity.

Fluoroquinolones cause prolongation of the QTc interval and may cause torsades de pointes.[69, 135, 228] Although the mechanism of this effect is unclear, sequestering of magnesium, resulting in clinical hypomagnesemia, is postulated.[235] Treatment of patients presenting with QTc interval prolongation is supportive, with careful attention to magnesium supplementation if necessary.

The fluoroquinolones rarely result in potentially fatal hepatotoxicity.[51, 52, 91, 103, 115, 154, 169, 220] This adverse effect is most notable with trovafloxacin, although the reason for the increased risk associated with this particular fluoroquinolone is not clear. Consequently, trovafloxacin (Trovan) is now reserved only for the treatment of patients with life-threatening infections in whom the benefits are thought to outweigh the risks. In addition, the manufacturer has initiated a limited distribution

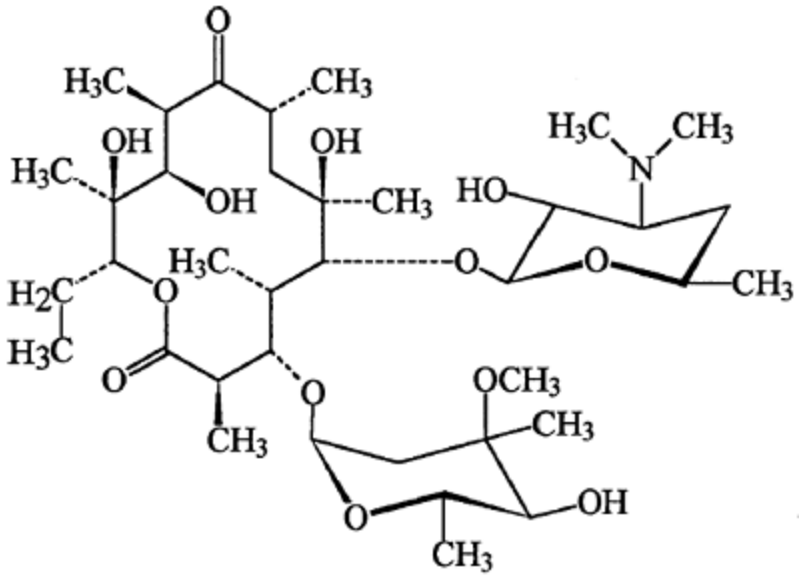
system that allows drug shipment only to pharmacies within inpatient healthcare facilities.

Fluoroquinolones should be used with caution in children and pregnant women because of their potential adverse effects on developing cartilage and bone. Damage to articular cartilage is demonstrated in young dogs and rats, although the extent varies among different fluoroquinolones.[42, 257] There are very limited data regarding damage to articular cartilage as a result of using fluoroquinolones in humans; however, children given ciprofloxacin on a compassionate basis developed complaints of swollen, painful, and stiff joints after 3 weeks of therapy.[137] All signs and symptoms abated within 2 weeks of discontinuation of therapy. However, 29 additional children treated with ofloxacin or ciprofloxacin showed no differences with respect to cartilage thickness, cartilage structure, edema, cartilage-bone borderline, or synovial fluid. Women who received quinolones during pregnancy had larger babies and more caesarean deliveries because of fetal distress than did controls.[19] However, there were no congenital malformations, delay to developmental milestones, or musculoskeletal abnormalities found.

Fluoroquinolones are also implicated as a cause of tendon rupture, which is reported to occur for up to 120 days after the start of treatment and even after the discontinuation of therapy.[206] The fluoroquinolone should be discontinued in patients, particularly athletes who complain of symptoms consistent with painful and swollen tendons.

Other adverse effects include acute psychosis, rash, tinnitus, eosinophilia, serum sickness, and, commonly, photosensitivity.[40, 108, 186, 252]

Macrolides and Ketolides



Erythromycin

The macrolide antibiotics include various forms of erythromycin (base, estolate, ethylsuccinate, gluceptate, lactobionate, stearate), azithromycin, clarithromycin, troleandomycin, and dirithromycin. Ketolides are similar in pharmacology to macrolides; telithromycin is the only available agent at this time. Table 54-1 lists the pharmacologic mechanism of macrolides and ketolides, and Table 54-2 lists their pharmacokinetic properties.

Acute oral overdoses of macrolide antibiotics are usually not life threatening and symptoms which are generally confined to the gastrointestinal tract include nausea, vomiting, and diarrhea. Erythromycin lactobionate causes QTc interval prolongation and torsades de pointes after intravenous use.[198] Oral erythromycin is also implicated in causing prolongation of the QTc interval and torsades de pointes, especially in patients concurrently taking cytochrome P450 (CYP) 3A4 inhibitors.[212] In vitro models demonstrate erythromycin's ability to slow repolarization in a concentration-dependent manner.[192] The cause of widened QTc interval was once thought to be from hypokalemia-induced

promotion of intracellular efflux of potassium.[213] Current data, however, demonstrate that the QTc interval prolongation results from blockade of delayed rectifier potassium currents (Chap. 23).[222] QTc interval prolongation and torsades de pointes are common after intravenous erythromycin lactobionate.[198] More pronounced widening occurs in patients with underlying heart disease and correlates with the infusion rate.[110] Epidemiologic studies note an increased incidence of ventricular dysrhythmias in women treated with erythromycin.[75]

Although there is no acute overdose data regarding ketolide antibiotics, effects are expected to be similar to macrolide antibiotics.

Adverse Events Associated with Therapeutic Use

Drug Interactions

Erythromycin is the prototypical macrolide and, as such, has received the most attention with respect to potential and documented drug interactions. Clarithromycin, erythromycin, and troleandomycin are all potent inhibitors of the CYP3A4 enzyme system; azithromycin does not inhibit this enzyme.[64] Erythromycin inhibits cytochrome P450 after metabolism to a nitroso intermediate, which then forms an inactive complex with the iron (II) of cytochrome P450. Chapter 9 lists substrates for the CYP3A4 system. Clinically significant interactions occur with erythromycin and carbamazepine or cisapride.[43 , 105 , 118 , 124 , 210] Inhibition of cisapride metabolism results in increased concentrations of the parent drug, which is capable of causing a widening of the QTc interval and causing torsades de pointes.[30 , 201] Cases of carbamazepine toxicity are documented when combined with the use of erythromycin.[118] Erythromycin also inhibits CYP1A2, producing clinically significant interactions with clozapine,

theophylline, and warfarin.[218]

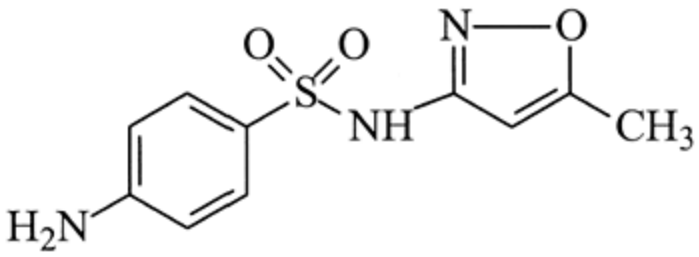
Macrolides may also interact with the absorption and renal excretion of drugs that are amenable to intestinal P-glycoprotein excretion or interfere with normal gut flora responsible for metabolism. This may be part of the underlying mechanism of cases of macrolide-induced digoxin toxicity (Chap. 62).[196]

End-Organ Effects

The most common toxic effect of macrolides after chronic use is hepatitis, which may be immune mediated.[46] Erythromycin estolate is the agent most frequently implicated in causing cholestatic hepatitis.[100 , 132]

Large doses (>4 g/d) of macrolide antibiotics are also associated with reversible high-frequency sensorineural hearing loss.[37 , 237] Renal impairment may be a risk factor.[224 , 256] There are rare case reports in which ototoxicity did not resolve following discontinuation of therapy.[78 , 160] There are insufficient data concerning the ototoxic potential of the other macrolide antibiotics. Other, rare toxic effects associated with macrolides include cataracts after clarithromycin use in animals and acute pancreatitis in humans.[83 , 266] Allergy is rare and reported at a rate of 0.4â€“3%.[70] Telithromycin contains a carbamate side chain that may interfere with the normal function of neuronal cholinesterase. It should be used cautiously in patients with myasthenia gravis, particularly those patients receiving pyridostigmine, because of the risk of cholinergic crisis.[259]

Sulfonamides



Sulfamethoxazole

Sulfonamides antagonize *para* -aminobenzoic acid or *para* -aminobenzyl glutamic acid, which are required for the biosynthesis of folic acid. Table 54-1 lists the pharmacologic mechanism of sulfonamides, and Table 54-2 lists their pharmacokinetic properties. Acute oral overdoses of sulfonamides are usually not life threatening and symptoms are generally confined to nausea, although allergy and methemoglobinemia occur rarely.[87] Treatment is similar to acute oral penicillin overdoses.

Adverse Effects Associated with Therapeutic Use

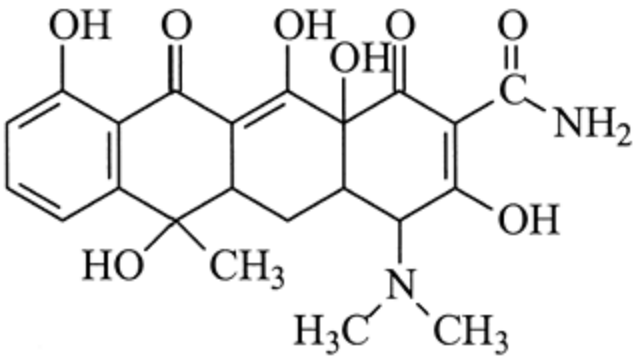
The most common adverse effects associated with sulfonamide therapy are nausea and cutaneous hypersensitivity reactions. Hypersensitivity reactions are thought to be caused by the formation of hapten sulfamethoxazole metabolites, *N* -hydroxy-sulfamethoxazole-NHOH and nitroso-sulfamethoxazole-NO. The degree of hapten binding is mitigated in vitro by cysteine and glutathione.[191] The incidence of adverse reactions to sulfonamides, including allergy, is increased in HIV-positive patients and is positively correlated to the number of previous opportunistic infections experienced by the patient.[157] This may be caused by a decrease in the mechanisms available for detoxification of free radical formation, as cysteine and glutathione levels are low in these patients.[272] Whether supplementation with a glutathione precursor such as *N* -acetylcysteine will reduce the

incidence of these reactions is unknown.[3]

Methemoglobinemia and hemolysis also rarely occur.[76 , 166] The mechanism for adverse reactions is not entirely clear. However, when sulfamethoxazole is exposed to ultraviolet B (UVB) radiation in vitro, free radicals are formed that can participate in the development of tissue peroxidation and hemolysis.[284] This finding may be of particular importance in treating patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency caused by a decrease in reducing capabilities.[4]

The sulfonamides are associated with many chronic adverse effects. Bone marrow suppression is rare, but the incidence is increased in patients with folic acid or vitamin B_{12} deficiency, and in children, pregnant women, alcoholics, dialysis patients, and immunocompromised patients, as well as in those patients who are receiving other folate antagonists. Other adverse effects include hypersensitivity pneumonitis, stomatitis, aseptic meningitis, hepatotoxicity, renal toxicity, and central nervous system toxicity.[26]

Tetracyclines



Tetracyclines

Tetracyclines are derivatives of *Streptomyces* cultures. Currently

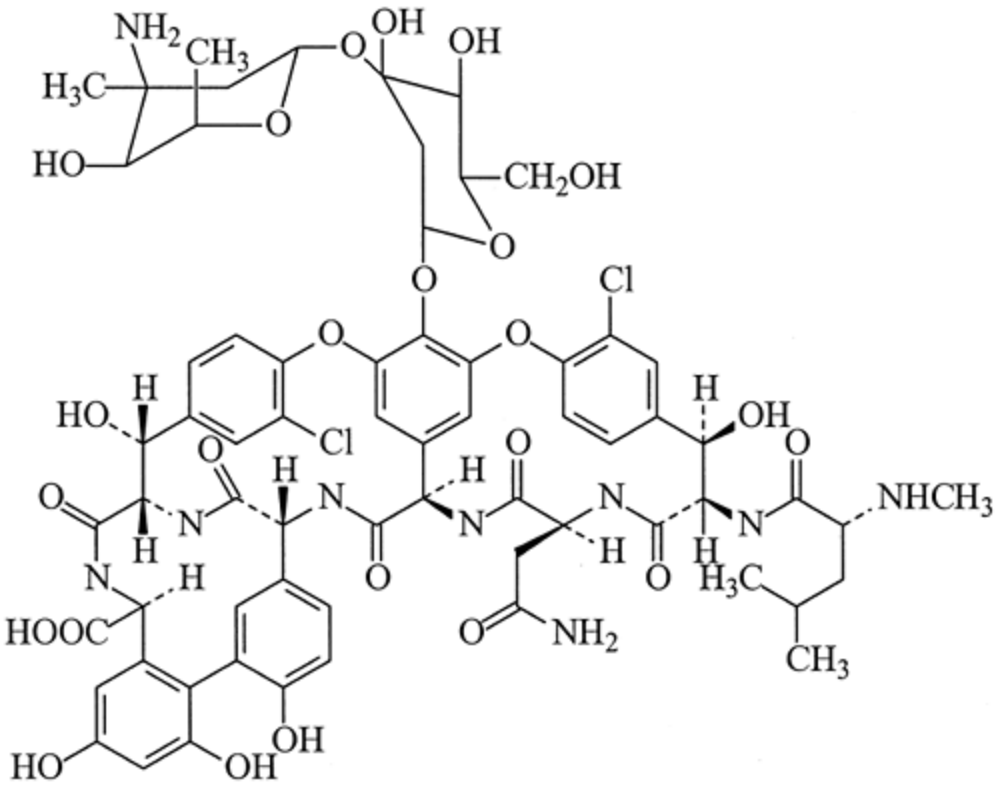
available tetracyclines include demeclocycline, doxycycline, methacycline, minocycline, oxytetracycline, and tetracycline. Table 54-1 lists the pharmacologic mechanism of tetracyclines, and Table 54-2 lists their pharmacokinetic properties. Significant toxicity after acute overdose of tetracyclines is unlikely. Gastrointestinal effects consisting of nausea, vomiting, and epigastric pain have been reported.[38]

Adverse Effects Associated with Therapeutic Use

Tetracycline should not be used in children during the first 6â€“8 years of life or by pregnant women after the 12th week of pregnancy because of the risk of development of secondary tooth discoloration in the children or developing children in utero.

Other effects associated with tetracyclines include nephrotoxicity, hepatotoxicity, skin hyperpigmentation in sun-exposed areas, and hypersensitivity reactions.[46 , 104 , 130 , 258] More severe hypersensitivity reactions, drug-induced lupus, and pneumonitis are reported after minocycline use, as are cases of necrotizing vasculitis of the skin and uterine cervix, and lymphadenopathy with eosinophilia.[171 , 236 , 242] Demeclocycline rarely causes nephrogenic diabetes insipidus.[47] Outdated older formulations, but not newer formulations, of tetracycline are reported to cause hypouricemia, hypokalemia, and a proximal and distal renal tubular acidosis.[56]

Vancomycin



Vancomycin

Vancomycin is obtained from cultures of *Nocardia orientalis* and is a tricyclic glycopeptide. Vancomycin is biologically active against numerous Gram-positive organisms. Table 54-1 lists the pharmacologic mechanism of vancomycin, and Table 54-2 lists its pharmacokinetic properties.

Acute oral overdoses of vancomycin rarely cause significant toxicity and most cases can be treated with supportive care alone. Multiple-dose activated charcoal therapy decreases the half-life of vancomycin and can be considered for patients with large overdoses when the patient is expected to have prolonged clearance.[152]

Adverse Effects Associated with Therapeutic Use

Patients who receive intravenous vancomycin may develop the â€œred man syndrome,â€• through an anaphylactoid reaction in which mast cells and basophils are directly degranulated without antibody mediation.[96] Symptoms include chest pain, dyspnea, pruritus, urticaria, flushing, and angioedema.[221] Signs and symptoms spontaneously resolve, typically within 15 minutes. Other symptoms attributable to red man syndrome include hypotension, cardiovascular collapse, and seizures.[13 , 194]

The incidence of red man syndrome appears to be related to the rate of infusion. The incidence is approximately 14% when 1 g is given over 10 minutes, whereas it is 3.4% when given over 1 hour.[194 , 199] A trial in 11 healthy persons studied the relationship between intradermal skin hypersensitivity and the development of red man syndrome. Each of the 11 subjects underwent skin testing that was followed 1 week later by an intravenous dose of vancomycin 15 mg/kg over 60 minutes. Following intravenous vancomycin, all subjects developed dermal flare responses and erythema, and 10 of 11 subjects developed pruritus within 20â€“45 minutes. After the infusion was terminated, symptoms resolved within 60 minutes.[208]

The signs and symptoms of the red man syndrome are related to the rise and fall of histamine concentrations.[117 , 163] Tachyphylaxis occurs in patients given multiple doses of vancomycin.[116 , 271] Animal models demonstrated a direct myocardial depressant and vasodilatory effect of vancomycin.[59] More serious reactions result when vancomycin is given via intravenous bolus, further supporting a rate-related anaphylactoid mechanism.[21]

Patients most often experience red man syndrome after vancomycin is administered intravenously. In rare cases, oral administration of vancomycin can also result in the syndrome.[18] Treatment includes increasing the dilution of vancomycin and slowing intravenous administration. Antihistamines may be useful

as pretreatment, especially prior to the first dose.[214] A placebo-controlled trial in adult patients studied the incidence of these symptoms in patients given 1 g of vancomycin over 1 hour, as well as the effect of diphenhydramine in the prevention of the syndrome.[271] There was a 47% incidence of reaction without diphenhydramine and a 0% incidence with diphenhydramine.

Chronic use of vancomycin may cause reversible nephrotoxicity, particularly in patients with prolonged excessive steady-state serum levels.[9, 216] Concomitant administration of aminoglycoside antibiotics may increase the risk of nephrotoxicity.[225] Vancomycin also causes, but rarely, thrombocytopenia and neutropenia.[55, 74]

Antifungals

Numerous antifungals are available. Toxicity related to the use of antifungals is variable and is based generally on their mechanism of action.

Amphotericin B

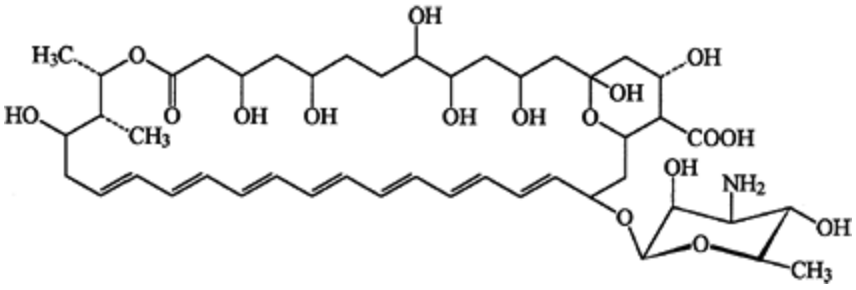


Figure. No Caption Available.

Amphotericin B is a potent antifungal derived from *Streptomyces nodosus.* Amphotericin B is generally fungistatic against fungi that contain sterols in their cell membrane. Table 54-1 lists the pharmacologic mechanism of amphotericin B, and Table 54-2 lists

its pharmacokinetic properties. Development of lipid and colloidal formulations of amphotericin B attenuate the adverse effects associated with amphotericin B.[109] In these preparations, the amphotericin B is complexed with either a lipid or cholesteryl sulfate. On contact with a fungus, lipases are released to free the complexed amphotericin B, resulting in focused cell death.[120]

There are several case reports of amphotericin B overdose in infants and children. Significant clinical findings include hypokalemia, increased aspartate aminotransferase concentrations, and cardiac complications. Dysrhythmias and cardiac arrest have occurred following doses of 5â€“15 mg/kg of amphotericin B.[31 , 57 , 148] Care should be employed in the doses of amphotericin B administered according to dosage form, as these are not interchangeable. For example, intravenous therapy for fungal infections includes a usual dose of 0.25â€“1 mg/kg/d of amphotericin B or 3â€“4 mg/kg/d of amphotericin B cholesteryl. The potential for significant dosage errors and their sequelae is readily apparent in this comparison.

Adverse Effects Associated with Therapeutic Use

Infusion of amphotericin B results in fever, rigors, headache, nausea, vomiting, hypotension, tachycardia, and dyspnea.[172] Pretreatment with acetaminophen, diphenhydramine, ibuprofen, and hydrocortisone is helpful in alleviating the febrile symptoms, as are slower rates of infusion and lower total daily doses.[99 , 265] Doses greater than 1 mg/kg/d and rapid administration of drug in less than 1 hour are not recommended. Infusion concentrations of amphotericin B greater than 0.1 mg/mL can result in localized phlebitis. Slower infusion rates, hot packs, and frequent line flushing with dextrose in water may help to alleviate symptoms.

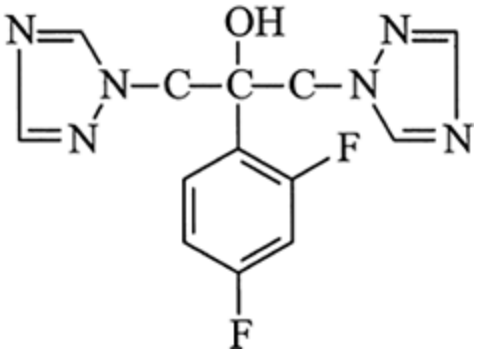
Eighty percent of patients exposed to amphotericin B will sustain some degree of renal insufficiency (Chap. 27).[44] Azotemia is

caused by distal renal tubule damage, which causes renal artery vasoconstriction as a consequence of alterations in tubular and vascular smooth muscle function.[84] Studies in animals show depressed renal blood flow and glomerular filtration rate, and increased renal vascular resistance. It is unclear why this occurs, but at this time, renal nerves, angiotensin II, nitric oxide, and tubuloglomerular feedback are excluded.[226 , 231] The toxic effects associated with amphotericin B may be caused by the vehicle deoxycholate.[283] After large total doses of amphotericin B, residual decreases in glomerular filtration rate may occur even after discontinuation of therapy. This is hypothesized to be the result of nephrocalcinosis. Potassium and magnesium wasting, proteinuria, decreased renal concentrating ability, renal tubular acidosis, and hematuria also occur.[15 , 172] Strategies to reduce renal toxicity after amphotericin B include intravenous saline or magnesium and potassium supplementation.[29 , 85 , 119] Liposomal formulations of amphotericin B resulted in fewer patients with breakthrough fungal infections, infusion-related fever, rigors, or nephrotoxicity.[273] However, chest pain is uniquely reported after use of the liposomal agent.[139]

Other adverse effects reported after treatment with amphotericin B include normochromic, normocytic anemia; decreased erythropoietin release; respiratory insufficiency with infiltrates; and, rarely, dysrhythmias, tinnitus, thrombocytopenia, peripheral neuropathy, and leukopenia.[165 , 170 , 172]

Exchange transfusion may be useful in neonates and infants and should be considered after large intravenous exposures. In adults, extracorporeal elimination is not expected to be useful because of the low water solubility and high bloodâ€“protein binding of the drug.

Azole Antifungals: Triazole and Imidazoles



Fluconazole

Common triazole antifungals include fluconazole, itraconazole, and voriconazole. Common imidazoles include clotrimazole, econazole, ketoconazole, and miconazole. Triazole antifungals are active to treat an array of fungal pathogens, whereas imidazoles are used almost exclusively in the treatment of superficial mycoses and vaginal candidiasis. Severe toxicity is not expected in the overdose setting. Hepatotoxicity, thrombocytopenia, and neutropenia are uncommon.[27] Rare case reports implicate voriconazole in the development of toxic epidermal necrolysis.[126] The majority of toxic effects noted after the use of these drugs result from their drug interactions. Fluconazole, itraconazole, ketoconazole, and miconazole competitively inhibit CYP3A4, the enzyme system responsible for the metabolism of many drugs. Table 54-5 lists other organ system manifestations associated with antifungal agents and other antibiotics.

Antibiotics Specific to the Treatment of Human Immune Deficiency Virus and Related Infections

The evaluation and management of patients infected with the human immunodeficiency virus (HIV) and associated acquired immune deficiency syndrome (AIDS) is ever evolving at a rapid

and progressive pace. Medications used to manage this disorder have increased life expectancy in these patients dramatically as new, more powerful antiviral agents and drug combinations become available. Drug therapy for HIV commonly consists of a combination of agents from different classes (nucleoside reverse transcriptase inhibitor [NRTI], nonnucleoside reverse transcriptase inhibitor [NNRTI], and protease inhibitor) in order to take advantage of the unique mechanism that each drug offers in inhibiting viral replication and minimizing drug resistance. Resistance patterns to the typical agents used in attenuating viral replication and proliferation are a substantial issue and will continue to be addressed with yet more evolution in management in

the foreseeable future. This section focuses on overdoses and major toxic effects from HIV-directed antiviral therapy, as well as from drugs that are specifically used in the management of opportunistic infections.[17] Table 54-6 lists the common antibiotic agents used to treat HIV-related opportunistic infections, and Table 54-7 lists common adverse drug effects and overdose effects, if known, for antibiotics that are specific in their use for HIV-related infections.

Antibiotics
Bacitracin
Immune
Hypersensitivity reactions
Clindamycin
Immune
Hypersensitivity reactions
Gastrointestinal
Nausea/vomiting/diarrhea
Nervous
Dizziness, headache, vertigo
Colistimethate (colistin sulfate)

Renal
Decreased function, acute tubular necrosis
Nervous
Peripheral paresthesias, confusion, coma, seizures, neuromuscular blockade
Griseofulvin
Renal
Proteinuria, nephrosis
Hepatic
Increased liver enzymes
Gastrointestinal
Nausea/vomiting/diarrhea
Immune
Granulocytopenia
Other
Disulfiram reactions, increased porphyrins
Lincomycin
Gastrointestinal
Nausea/vomiting/diarrhea
Immune
Hypersensitivity reactions
Metronidazole
Neurologic
Peripheral neuropathy, seizures
Gastrointestinal
Nausea/vomiting
Other
Disulfiram reactions
Nitrofurazone
Immune
Hypersensitivity reactions
Other
Ointment contains polyethylene glycols (renal dysfunction)
Nitrofurantoin

Gastrointestinal
Nausea/vomiting/diarrhea
Hepatic
Jaundice
Immune
Rash, acute and chronic pulmonary hypersensitivity
Neurologic
Peripheral neuropathy
Novobiocin
Immune
Rash
Gastrointestinal
Nausea/vomiting/diarrhea
Hematologic
Pancytopenia/hemolytic anemia
Polymyxin
Neurologic
Muscle weakness, seizures
B sulfate
Renal
Azotemia, proteinuria
Selenium sulfide
Cutaneous
Contact dermatitis
Hair loss (rare)
Silver sulfadiazine
Cutaneous
Contact dermatitis
Hematologic
Anemia, aplastic anemia
Spectinomycin
Immune
Rash (rare)
Antifungals

Benzoic acid
Gastrointestinal
Nausea/vomiting/diarrhea
Carbol-fuchsin solution (phenol/resorcinol/fuchsin)
Gastrointestinal
Nausea/vomiting/diarrhea
Gentian violet
Gastrointestinal
Nausea/vomiting/diarrhea
Immune
Rash (rare)
Nystatin
Gastrointestinal
Nausea/vomiting/diarrhea
Pradimicins (investigational)
Unknown
Unknown
Salicylic acid
Gastrointestinal and dermal
Higher concentrations are caustic
Undecylenic acid and undecylenate salt
Gastrointestinal
Nausea/vomiting/diarrhea

Drug Organ System Signs, Symptoms, Laboratory

TABLE 54-5. Consequential Organ System Manifestations Associated with Antibiotics and Antifungals

It should be noted that adverse reactions to antibiotics occur at an increased rate in HIV-infected patients. The reason for this occurrence is unclear. Drug interactions related to pharmacokinetic and pharmacodynamic causes are common and problematic in the management of HIV-positive patients.

Specific Antiretroviral Classes

Nucleoside Analog Reverse Transcriptase Inhibitors

The nucleoside analog reverse transcriptase inhibitors inhibit the reverse transcription of viral RNA into proviral DNA. Currently available

agents include abacavir (ABC), emtricitabine (FTC), didanosine (ddI), lamivudine (3TC), stavudine (d4T), zidovudine (AZT, ZDV), and zalcitabine (ddC).

Albendazole
Microsporidiosis
Amphotericin B
Aspergillosis
Coccidiomycosis
Cryptococcus
Histoplasmosis
Leishmaniasis
Paracoccidioidomycosis
Penicilliosis
Antimony (pentavalent)
Leishmaniasis
Atovaquone
Pneumocystis jiroveci pneumonia
Azithromycin
Mycobacterium avium complex
Clarithromycin

Caspofungin
Aspergillosis
Clindamycin

Pneumocystis jiroveci pneumonia
Toxoplasma gondii encephalitis
Dapsone
Pneumocystis jiroveci pneumonia
Ethambutol
Mycobacterium avium complex
Fluconazole
Coccidioidomycosis
Histoplasmosis
Flucytosine
Cryptococcus
Foscarnet
Cytomegalovirus
Fumagillin
Microsporidiosis
Ganciclovir
Cytomegalovirus
Itraconazole
Histoplasmosis
Leucovorin
Pneumocystis jiroveci pneumonia
Toxoplasma gondii encephalitis
Nitazoxanide
Cryptosporidiosis
Microsporidiosis
Paromomycin
Cryptosporidiosis
Pentamidine
Pneumocystis jiroveci pneumonia
Primaquine
Pneumocystis jiroveci pneumonia
Pyrimethamine
Toxoplasma gondii encephalitis
Rifabutin

Mycobacterium avium complex
Sulfadiazine
Toxoplasma gondii encephalitis
TMX-SMX
Pneumocystis jiroveci pneumonia
Toxoplasma gondii encephalitis
Isosporiasis
Trimetrexate
Pneumocystis jiroveci pneumonia
Valganciclovir
Cytomegalovirus
Voriconazole
Aspergillosis
TMX-SMX = trimethoprim and sulfamethoxazole.

Drugs Opportunistic Infection

TABLE 54-6. Antibiotics Used to Treat Common Opportunistic Infections [17]

Albendazole
No reported cases
Increased AST/ALT, nausea, vomiting, and diarrhea. Hematologic toxicity; rareâ€"encephalopathy, renal failure, rash
Antimony (pentavalent)
Acute tubular necrosis
Acute tubular necrosis. Multiorgan system failure
Atovaquone
No clinical relevant effects in reported cases[53]
Rashes, anemia, leucopenia, increased AST/ALT
Caspofungin
No reported cases
Phlebitis, headache, hypokalemia, increased AST/ALT, fever
Flucytosine

No reported cases

Bone marrow suppression, hepatotoxicity, nausea, vomiting, diarrhea, and rash

Foscarnet

No reported cases

Azotemia, hypocalcemia and renal failure are most consequential; may also result in anemia, leukopenia, thrombocytopenia, fever, headache, seizures, genital and oral ulcers, fixed-drug eruptions, nausea, vomiting, diarrhea, headaches, seizures, coma, diabetes insipidus, hypophosphatemia, hypokalemia, and hypomagnesemia

Fumagillin

No reported cases

Neutropenia and thrombocytopenia

Ganciclovir

No clinical relevant effects in reported cases[149]

Leukopenia, worsening of renal function; can also cause nausea, vomiting, diarrhea, increased AST/ALT, anemia, thrombocytopenia, headache, dizziness, confusion, seizures

Nitazoxzanide

No reported cases

Hypotension, headache, abdominal pain, nausea, vomiting; may cause green-yellow urine discoloration

Pentamidine

40 times dosing error in a 17-month-old child resulted in cardiac arrest[275]

Hypoglycemia (early) followed by hyperglycemia, azotemia; can cause hypotension, torsades de pointes, phlebitis, rash, Stevens-Johnson syndrome, hypocalcemia, hypokalemia, anorexia, nausea, vomiting, metallic taste, leukopenia, and thrombocytopenia

Primaquine

No reported cases

Granulocytopenia, hemolytic anemia, methemoglobinemia, leukocytosis; potential for hypertension

Pyrimethamine

	No reported cases	
	Agranulocytosis, aplastic anemia, thrombocytopenia, and leukopenia	
Rifabutin	High doses(>1 g daily): arthralgia/arthritis	Nausea, vomiting, diarrhea; can cause hepatotoxicity, neutropenia, thrombocytopenia, and hypersensitivity reactions
Sulfadiazine	Acute renal failure and hypoglycemia[62]	Rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme; can cause headaches, depression, hallucinations, ataxia, tremor, crystalluria, hematuria, proteinuria, and nephrolithiasis
Trimetrexate	No reported cases; treat similar to methotrexate (Chap. 52)	Myelosuppression, nausea, vomiting, histaminergic reactions
Valganciclovir	No reported cases; expect to be similar to ganciclovir	Anemia, neutropenia, thrombocytopenia; nausea, vomiting, headache, and peripheral neuropathy

TABLE 54-7. Antibiotics Used in the Treatment of HIV-Related Infections [17]

Acute Overdose Effects

Many intentional overdoses of reverse transcriptase inhibitors occur without major toxicologic effect. The most serious adverse effect anticipated after acute overdose of an NRTI is the development of a lactic acidosis, which appears to be more common in women.[49 , 82 , 173] This occurs after incorporation of

the nucleoside analog into mitochondrial DNA by RNA polymerase, causing inhibition of DNA polymerase Î³. This results in decreased production of mitochondrial DNA electron transport proteins, which ultimately inhibits oxidative phosphorylation (Chap. 13). Organ system toxicity follows in addition to the development of lactic acidosis. The reported mortality in patients with NRTI-associated lactic acidosis is 33â€“57%.[82] Resolution of symptoms in survivors is 1â€“24 weeks. Patients with NRTI-associated lactic acidosis may recover more quickly after the use of cofactors such as thiamine, riboflavin, L-carnitine, vitamin C, and antioxidants.[33] The indications for the use of these agents are unclear at this time; however, because of the relative lack of toxicity of these agents, they may be considered in an attempt to attenuate toxicity.

Chronic Effects

Development of lactic acidosis is more commonly associated with therapeutic use of reverse transcriptase inhibitors than with acute overdose. The mechanism is likely identical to that described above. Other common adverse effects are somewhat agent specific and include hematologic toxicity after zidovidine,[68 , 102] pancreatitis with didanosine,[155] hypersensitivity after abacavir,[67] and sensory peripheral neuropathy after zalcitabine, stavudine, and didanosine.[184]

Nonnucleoside Reverse Transcriptase Inhibitors

Nonnucleoside reverse transcriptase inhibitors (NNRTI) bind directly to reverse transcriptase enzymes enabling allosteric inhibition of enzymatic function.[261] Delavirdine (Rescriptor), nevirapine (Viramune), and efavirenz (Sustiva) comprise the currently available agents.

There are no substantial acute overdose data on these drugs, although they generally appear to be safe in overdose. Treatment should include supportive care until more information is available. The NNRTIs are also limited in toxicity after chronic use. Nevirapine and delavirdine use commonly results in hypersensitivity reactions such as rash.[67] Efavirenz is reported to result in dizziness and dysphoria. Otherwise, toxicity can result from the ability of these drugs to either inhibit or enhance CYP isozymes in the metabolism of other drugs.

Protease Inhibitors

Protease inhibitors inhibit the vital enzyme (proteinase), which is required for viral replication.[86] Currently available agents include amprenavir (Agenerase), indinavir (Crixivan), lopinavir (Kaletra), nelfinavir (Viracept), ritonavir (Norvir), and saquinavir mesylate (Invirase).

Data after protease inhibitor overdose are limited. A review of data submitted to the manufacturer of indinavir found that of 79 reports, the complaints were nausea, vomiting, abdominal pain, and nephrolithiasis. Protease inhibitors as a class commonly result in gastrointestinal symptoms and rash.[86] A uniqe finding is an altered fat distribution pattern that, over time, results in central obesity, â€œbuffalo hump,â€• breast enlargement, cushingoid appearance, and peripheral wasting.[86]

Summary

Adverse effects attributable to antibiotics are largely related to chronic administration, although, rarely, acute toxicity does occur. Acute toxic effects of antibiotics are more common after large intravenous administration, drug interactions, or iatrogenic overdose. Careful vigilance on the part of the healthcare provider will prevent the majority of acute toxic manifestations following antibiotic use.

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Chapter 55
Antituberculous Medications

Edward W. Boyer

A 15-year-old girl who had recently emigrated from Vietnam began to sei while at school. Paramedics observed two additional seizures during transport to the emergency department (ED). On arrival at the hospital, her vital signs were: blood pressure, 122/50 mm Hg; pulse, 107 beats/min; respirations, 22 breaths/ min; and temperature 99.4Â°F (37.4Â°C). Physical examination revealed an obtunded young girl without signs of head trauma, who was minimally responsive to painful stimuli. H pupils were 3 mm and sluggishly reactive. Her oropharynx showed no sig of trauma. The lungs were clear to auscultation, and she was tachycardic with no murmurs, rubs, or gallops appreciated on cardiac examination. H abdomen was soft with normal bowel sounds. Her skin was warm, dry, an well perfused. There was an abrasion on her left forearm, but no other extremity injuries.

A peripheral intravenous catheter was established, and she was placed or 100% oxygen via a nonrebreathing face mask. Pulse oximetry demonstrated an oxygen saturation of 100%. A bedside capillary glucose test revealed euglycemia. She received a total of 8 mg IV lorazepam in tl

ED but had another seizure. Additional history obtained from family members revealed that the patient had started taking medicine for a â€œlung problem.â€• On the basis of this information, she was given 5 g of intravenous pyridoxine with cessation of seizure activity. Fifty grams o activated charcoal was instilled via nasogastric tube.

Laboratory values were: a white blood cell count of 13,600/mm^3 ; hemoglobin, 12.9 g/dL; platelets, 287 Ã— 10^3 /mm^3 ; sodium, 142 mEq/L potassium, 3.7 mEq/L; chloride, 103 mEq/L; bicarbonate, 7 mEq/L; blood urea nitrogen (BUN), 7 mg/dL; creatinine, 0.6 mg/dL; serum glucose, 97 mg/dL; and anion gap, 29 mEq/L. Arterial blood gas revealed: pH 7.19; PCO_2 , 33 mm Hg; PO_2 , 105 mm Hg; and 98% oxygen saturation. Creatinine phosphokinase was 1067 U/L. Cerebrospinal fluid (CSF) showe 4 RBC (red blood cells) per mm^3 and 33 WBC (white blood cells) per mm^3 with a normal Gram stain. Cerebrospinal glucose was 76 mg/dL and prote was 27 mg/dL. Serum titers for herpes simplex virus, equine encephalitis virus, and West Nile virus were negative, as were blood and CSF cultures

She was admitted to the intensive care unit (ICU), but her level of consciousness did not improve over the next 6 hours. An electroencephalogram that was performed because of persistent depressi of consciousness showed no seizure activity. The toxicology service recommended that the patient be given an additional 5 g of intravenous pyridoxine. The patient's level of consciousness improved over the next 1 minutes, at which point she revealed that she ingested approximately 8 g of isoniazid in a suicide attempt. The remainder of her hospitalization was uneventful. A computerized tomography scan and magnet resonance imag of the brain were normal. She was discharged from the medical service a transferred to a psychiatric facility.

History and Epidemiology

The global burden of tuberculosis is enormous. Approximately 2 billion people are infected with *Mycobacterium tuberculosis;* 7.96 million new cases are diagnosed each year. An estimated 1.87 million persons die worldwide from the infection annually.[3] The introduction of isoniazid (INH

into clinical practice in 1952 caused the number of US cases of tuberculos (TB) to steadily decrease over the subsequent 30 years. However, betwe 1985 and 1991, there was a resurgence in TB cases in the United States, result of, among other factors, the human immunodeficiency virus (HIV) epidemic, homelessness, deterioration in the healthcare infrastructure, a an increased number of foreign-born persons. Concurrently, multidrug-resistant tuberculosis emerged as a serious health concern. Currently, on third of newly diagnosed cases are resistant to INH and one-fifth are resistant to both INH and rifampin, formerly the two most effective drugs for treating tuberculosis. Containment strategies, such as aggressive cas identification and directly observed therapy, were initiated to slow the spread of the infection.[21 , 22 , 43 , 57] Subsequently, the number of reported cases in the United States in 1998 decreased by 31% from the peak incidence reported in 1992. Populations that remain at risk for tuberculosis are HIV-positive patients, the homeless, intravenous drug users, healthcare workers, prisoners, prison workers, and Native Americans. In addition, the tuberculosis rate in foreign-born persons is 4â€“6 times higher than for US-born persons. The birth countries generating the highest number of US tuberculosis cases are Mexico, the Philippines, and Vietnam.[23 , 24 , 57] The emergence of multidrug-resistan tuberculosis has forced the use of multidrug regimens, as well as the reintroduction of older antituberculous drugs. This approach likely results in an increased incidence of adverse drug effects. Multidrug antitubercul regimens are associated with a 15% incidence of adverse events.[3] Hepatotoxicity, peripheral neuropathy, and ocular neuropathy are often irreversible and potentially fatal. Moreover, many patients receiving antituberculous therapy are chronically ill and have an increased risk of suicidality and intentional overdose.

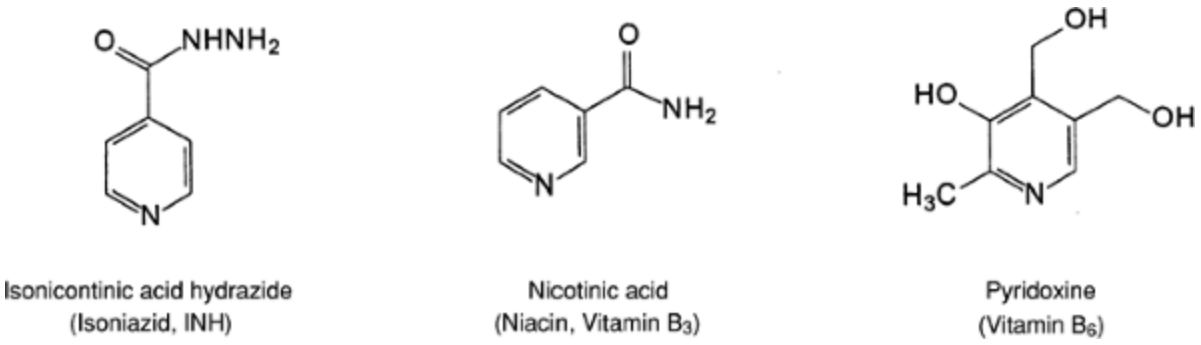


Figure 55-1. INH and related compounds.

Isoniazid

Pharmacology

Isoniazid (INH, or isonicotinic hydrazide) is structurally related to nicotinic acid (niacin, or vitamin B_3), nicotinamide-adenosine dinucleotide (NAD), and pyridoxine (vitamin B_6) (Fig. 55-1). The pyridine ring is essential for antituberculous activity. The mechanism of action of INH involves an interaction with InhA, a mycobacterial enzyme that functions as an enoyl acyl carrier protein (enoyl-ACP) reductase.[83, 84] Isoniazid itself does not directly interact with the InhA enzyme. Instead, INH is a prodrug that undergoes metabolic activation by a mycobacterial catalase-reductase, known as KatG, to produce a highly reactive intermediate.[85, 118] This activated form of INH is either an anion or radical that is stabilized by the pyridine ring. This INH-derived species enters the binding site of InhA where it reacts with the reduced form of nicotinamide adenine dinucleotide (NADH).[85] The covalently linked INH-NADH complex remains bound to the active site of InhA, irreversibly inhibiting the enzyme.[73, 83]

Enoyl-ACP reductases catalyze the NADH-dependent reduction of the double bonds in the growing fatty acid chain linked to acyl carrier protein. InhA is required for the synthesis of very-long-chain lipids known as mycolic acids (containing between 40 and 60 carbons) that are important

components of mycobacterial cell walls.

Pharmacokinetics and Toxicokinetics

When therapeutic doses of 5â€“15 mg/kg are administered orally, INH is rapidly absorbed, reaching peak plasma concentrations within 2 hours.[54] [80] , [81] Isoniazid diffuses into all body fluids with a volume of distribution approximately 0.6 L/kg and has negligible binding to serum proteins. Afte the drug penetrates infected tissue, it persists in concentrations well abo those required for bacteriocidal activity.

Isoniazid is metabolized via a cytochrome P450-mediated process, with approximately 75â€“95% of INH renally eliminated as hepatic metabolites within 24 hours of administration.[71] The primary metabolic pathway for INH is via *N* -acetylation performed by hepatocytes and gut mucosa. *N* -Acetyltransferase, the enzyme responsible for this conversion, exhibits Michaelis-Menten kinetics, although the activity of an individual's enzyme is determined by an autosomal dominant inheritance pattern. Patients wit the polymorphic forms of *N* -acetyltransferase are distinguishable phenotypically as slow and fast acetylators. The slow acetylation isoform found in 50â€“60% of American whites and African Americans, whereas t fast acetylator isoenzymes are found in 90% of Asians and Inuits.[36] Thes isoforms are distinguishable by the following characteristics: (a) Slow acetylators have less presystemic clearance, or first-pass effect, than do fast acetylators; (b) fast acetylators metabolize INH 5â€“6 times faster than slow acetylators; and (c) plasma INH concentrations are 30â€“50% lower in fast acetylators than in slow acetylators. The elimination half-life of INH is approximately 70 minutes in fast acetylators, and 180 minutes i slow acetylators. Twenty-seven percent of INH is excreted unchanged in urine by slow acetylators, as compared with excretion of 11% in fast acetylators. The clearance of INH averages approximately 46 mL/min.[11] , [112] Isoniazid is transformed either via a stepwise process to acetylhydrazine and isonicotinic acid, or directly to hydrazine. In the first instance, INH is initially acetylated to acetylisoniazid and then hydrolyzed to acetylhydrazine. This intermediate may then be oxidized by hepatic

microsomes to reactive intermediates that damage hepatocytes.[109] Figure 55-2 illustrates the metabolism of INH.

Mechanism of Toxicity

Toxic effects of INH are caused by two additive mechanisms. First, INH alters the metabolism of pyridoxine, the coenzyme needed for

transamination, transketolization, and decarboxylation, biotransformation reactions. Isoniazid creates a functional deficiency of pyridoxine by at least two mechanisms (Fig. 55-3). Hydrazone INH metabolites inhibit pyridoxine phosphokinase, the enzyme that converts pyridoxine to its active form, pyridoxal-5â€²-phosphate.[26 , 53 , 67] In addition, INH reacts with pyridoxal phosphate to produce an inactive hydrazone complex that is renally excreted.[67 , 112] Urinary excretion of pyridoxine and its metabolites increases with increasing INH dosage, reflecting the effect of INH on pyridoxine metabolism. The consequences of pyridoxine depletion include impaired activity of pyridoxine-dependent enzyme systems, as well as a decrease in catecholamine synthesis. In addition, INH either replaces nicotinic acid in the synthesis of NAD or reacts with NAD to form inactive hydrazones. Isoniazid disrupts cellular reduction/oxidation capabilities through both of these mechanisms.

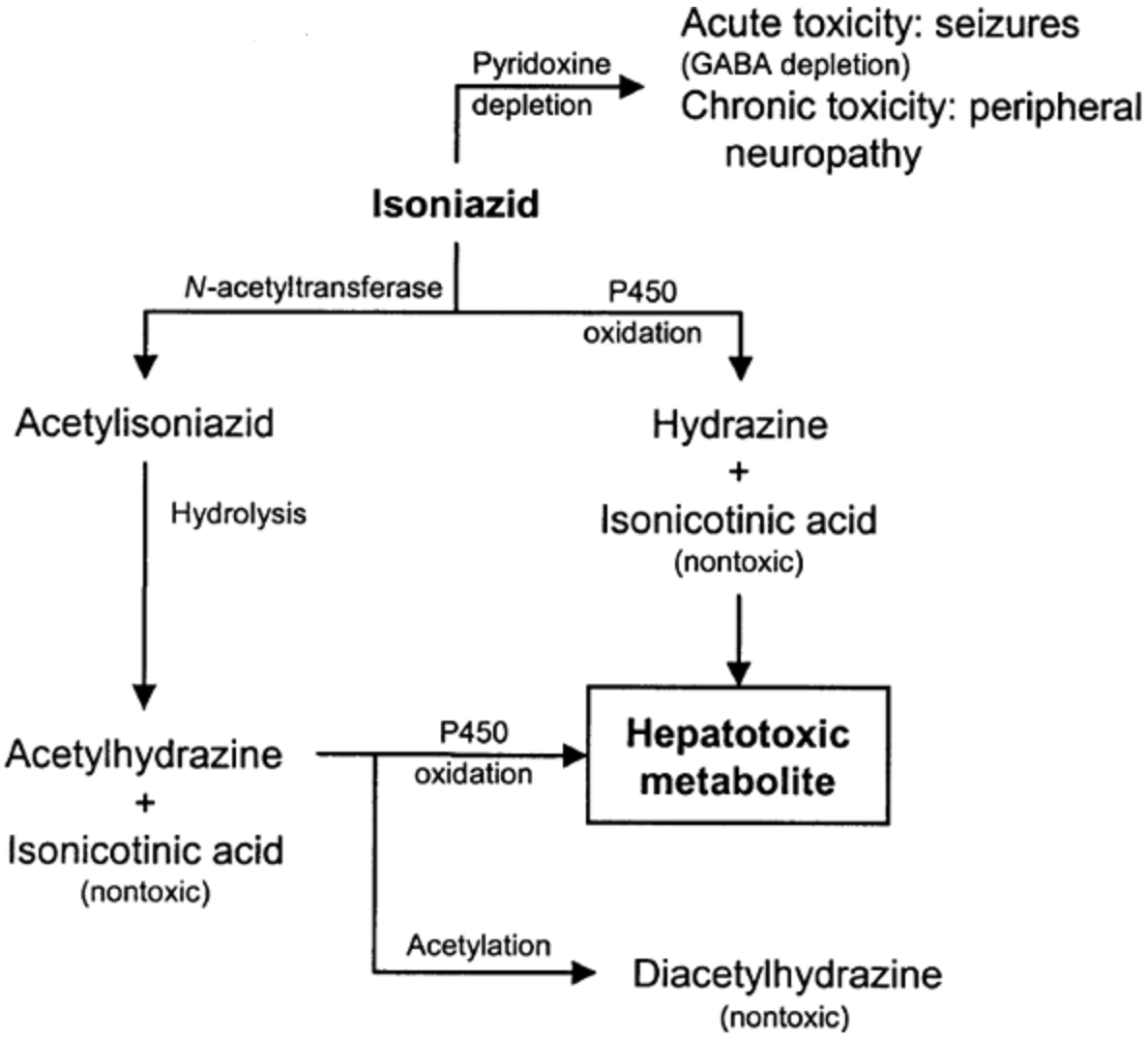


Figure 55-2. Metabolism of INH. Acetylator status is determined by polymorphism in *N* -acetyltransferase.

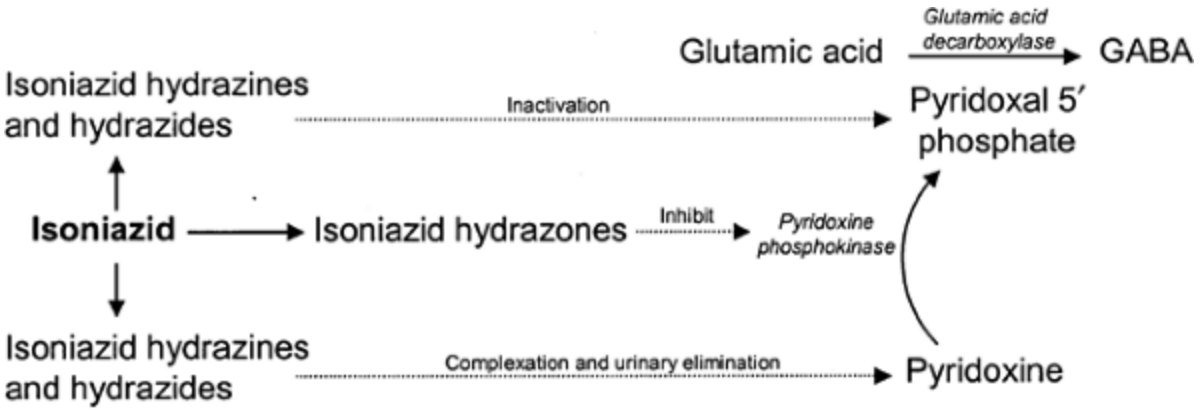


Figure 55-3. The effect of isoniazid on Î³-aminobutyric acid (GABA) synthesis.

Second, isoniazid interferes with the synthesis and metabolism of Î³-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system. Two pyridoxine-dependent enzymes control GABA metabolism: glutamic acid decarboxylase (GAD) and GABA aminotransferase. The former catalyzes GABA synthesis, while the latter degrades the neurotransmitter. The inhibitory effects are greater on GAD which leads to decreased GABA concentrations.[7 , 114] Depletion of GABA thought to be the etiology of INH-induced seizures. Structurally similar chemicals exert similar acute toxic effects. Monomethylhydrazine, a metabolite produced from gyromitrin isolated from the *Gyromitra* species (â€œfalse morelâ€•) mushroom, and the hydrazines used in liquid rocket fuel, have a similar mechanism of action (Chap. 113).

Isoniazid, a class C drug, crosses the placenta to enter the fetal compartment and produce umbilical cord blood concentrations comparable to maternal levels.[113] Mammalian teratogen studies suggest that isoniazid is not a human teratogen, although fetal deformities following acute overdose of INH have been reported.[63 , 112] Administration of INH to pregnant women was not associated with cancer in their offspring. Isoniazid readily enters breast milk, but breast-feeding during therapy is considered acceptable.[90 , 112]

Interactions with Other Drugs and Foods

Isoniazid has an overall incidence of drugâ€“drug interactions of 5.4%.[69,94] Isoniazid potentially inhibits several cytochrome P450 (CYP)-mediated transformations, particularly demethylation, oxidation, and hydroxylation (Chap. 9). Clinically relevant adverse effects are documented with theophylline (CYP1A2), phenytoin (CYP2C9/CYP2C19), warfarin (CYP2C9/CYP2C19), valproate, and carbamazepine (CYP3A4).[52,94] Therapeutic doses of INH induce expression of the CYP2E1 cytochrome subtype. It also binds to CYP2E1 simultaneously to decrease the metabolism of substrate. The binding of INH to the active site inhibits the degradation of the enzyme itself. Intracellular concentrations of CYP2E1 are therefore increased; after INH diffuses from the CYP2E1 active site, greater-than-normal amounts of cytochrome become available to metabolize potential substrates.[94] CYP2E1 catalyzes the formation of NAPQI (*N* -acetyl-*p* -benzoquinoneimine), the acetaminophen metabolite responsible for toxicity.[25] Consequently, INH use may increase the likelihood of acetaminophen-induced hepatotoxicity, although this is unstudied.[25]

Isoniazid has numerous food interactions. Isoniazid is a weak monoamine oxidase inhibitor, and tyramine reactions to foods and serotonin syndrom from meperidine are reported in patients taking INH. Clinical effects include flushing, tachycardia, and hypertension.[31,40,62,102] Furthermore, INH inhibits the enzyme histaminase, leading to exacerbate reactions following the ingestion of histamine in scombrotoxic fish.[4,50,52,94] Table 55-1 summarizes additional INH drug and food interactions.

Clinical Manifestations of INH Toxicity

Acute Toxicity

Isoniazid produces the triad of seizures refractory to conventional therap severe metabolic acidosis, and coma. These clinical manifestations may appear as soon as 30 minutes following ingestion.[48,52,108] The case

fatality rate of a single acute ingestion may be as high as 20%.[15, 18] Although vomiting, slurred speech, dizziness, and tachycardia may represent early manifestations of toxicity, seizures may be the initial sign of acute overdose.[66] Seizures may occur following the ingestion of greater than 20 mg/kg of INH, and invariably occur with ingestions greater than 35â€“40 mg/kg. Patients with underlying seizure disorders, however, may develop seizures at lower doses.[15] Hyperreflexia or areflexia may herald INH-induced seizures. Patients may exhibit improvement in consciousness between seizures.[30, 77] Because GABA, the primary inhibitory neurotransmitter, is depleted in acute INH toxicity, seizure activity may persist until GABA concentrations are restored.

Acute INH toxicity is often associated with a wide anion gap metabolic acidosis associated with a high serum lactate. Typically, serum pH ranges between 6.80 and 7.30, although survival in the setting of an arterial pH 6.49 was reported.[48] Paralyzed animals poisoned with INH do not develop lactic acidemia, a finding that suggests the lactate arises from intense muscular activity.[26, 78] Although not borne out in clinical practice, the acidosis from INH-induced seizures has been described as resolving more slowly

than the lactic acidemia from typical seizures, the mechanism for which may be the formation of NAD hydrazones that prevent the transformation of lactate to pyruvate.[26, 113] Alternate explanations of INH-associated acidosis include the generation of acidic INH metabolites and enhanced fatty acid oxidation leading to increased serum ketoacids.[78, 112]

INH
Acute: seizures, acidosis, coma, hyperthermia, oliguria, anuria
Chronic: elevation of liver enzymes, hepatitis, autoimmune disease (arthritis, anemia, hemolysis, eosinophilia), peripheral neuropathy, optic neuritis, vitamin B_6 deficiency (pellagra)
Rifampin, PZA, ethanol: hepatic necrosis
Acetaminophen: hepatic necrosis
Warfarin: increased prothrombin time

Theophylline: tachycardia, vomiting, seizures, acidosis
Phenytoin: increased phenytoin levels
Carbamazepine: altered mental status
Meperidine: hypertension
Lactose: decreased INH absorption
Antacids: decreased INH absorption
Red wine/soft cheese: tyramine reaction
Fish (scombroid): flushing, pruritus
Liver enzymes, ANA, CBC
HIV enteropathy may decrease absorption; INH should not be given with lactose-containing drug formulations because lactose can form hydrazone and lower INH concentrations
Rifampin
Acute: diarrhea, periorbital edema
Chronic: hepatitis, reddish discoloration of body fluids
Protease inhibitors: decreased serum concentration of protease inhibitor
Delavirdine: increased HIV resistance
Cyclosporine: graft rejection
Warfarin: decreased INR
Oral contraceptives: ineffective contraception
Methadone: opioid withdrawal
Phenytoin: higher frequency of seizures
Theophylline: decreased theophylline levels
Verapamil: decreased cardiovascular effect
If administered with HIV antiretroviral agents, viral titers should be followed. Liver enzymes; monitor serum concentrations of drugs (ie, pheny- toin, cyclosporine) or clinical markers of efficacy (ie, coagulation times)
Interactions of rifampin with several HIV medications are very poorly described; changes in dosing or dosing interval for both rifampin and antiretroviral drugs may be required; has teratogenic effects
Ethambutol
Chronic: optic neuritis, loss of red-green discrimination, loss of peripheral vision

Visual acuity, color discrimination
Contraindicated in children too young for formal ophthalmologic examination
Pyrazinamide
Chronic: hepatitis, decreased urate excretion
INH: increased rates of hepatotoxicity (when extended courses or high dose pyrazinamide used)
Liver enzymes
Courses of therapy of 2 months or less recommended
Cycloserine
Chronic: depression, paranoia, seizures, megaloblastic anemia
INH: increased frequency of seizures
CBC, psychiatric monitoring

Ethionamide
Chronic: orthostatic hypotension, depression
Cycloserine: may increase CNS effects
Follow clinical signs of orthostasis

para -Aminosalicylic acid
Chronic: malaise, GI upset, elevated liver enzymes, hypersensitivity reactions, thrombocytopenia

Liver enzymes, CBC

Capreomycin
Chronic: hearing loss, tinnitus, proteinuria, sterile abscess at IM injectior sites

Audiometry, renal function tests

Drug	Major Adverse Reactions	Drug Interactionsâ€“Clinical Effect	Monitoring	Comment

TABLE 55-1. Adverse Reactions and Drug Interactions of Antituberculous Drugs

Protracted coma typically occurs with acute severe INH toxicity. Coma ma last as long as 24â€“36 hours and persist beyond the termination of seizure activity as well as the resolution of acidemia. The etiology of com is unknown.[48] Additional sequelae from acute INH toxicity include renal failure, hyperglycemia, glycosuria, and ketonuria, along with hypotension and hyperpyrexia.[6,19,112]

Chronic Toxicity

As a consequence of a myriad of INH-induced biochemical changes, chronic, therapeutic INH use is associated with a variety of adverse effec The most disconcerting is hepatocellular necrosis. Although asymptomatic elevation of aminotransferases is common in the first several months of treatment, laboratory testing may reveal the onset of hepatitis up to 1 year after starting INH therapy. In 1978, following several deaths among patients receiving INH therapy, the US Public Health Service reported the incidence of clinically evident hepatitis as 1% of those taking INH; of tha subgroup, 10% died, for an overall mortality of 0.1%.[17,60] Research performed since the resurgence of TB, however, identified a considerably lower rate of hepatotoxicity. Clinically relevant hepatitis occurred in only 11 patients in a population of 11,141 persons receiving INH, an incidence of 0.1%.[76] Additional studies suggest that the death rate from INH hepatotoxicity is only 0.001% (2 of 202,497 treated patients).[88] The decrease in mortality from INH-associated hepatitis may be a

result of improved surveillance protocols allowing for earlier cessation of therapy or decision analysis concerning continued use of INH.

Isoniazid-induced hepatitis can arise via two pathways.[34] The first involv an autoimmune mechanism resulting in hepatic injury that is thought to b idiopathic.[9 , 101 , 112 , 117] The association of hepatitis with lupus erythematosus, hemolytic anemia, thrombocytopenia, arthritis, vasculitis and polyserositis supports an immunologic process.[9 , 101 , 112 , 117] However, symptoms commonly found in autoimmune disorders such as fever, rash, and eosinophilia are usually absent, and rechallenge with isoniazid often fails to provoke recurrence of hepatocellular injury.[34] The second, more common mechanism involves direct hepatic injury by INH o its metabolites. The metabolite believed responsible for hepatic injury is acetylhydrazine, which arises from the acetylation of INH followed by its hydrolysis.[74] Hepatotoxicity is associated with chronic overdosage, increasing age, comorbid conditions such as malnutrition, and combinatio of antituberculous drugs that may serve as cytochrome inducers. Overt hepatic failure often occurs if INH therapy is continued after onset of hepatocellular injury.[34 , 35 , 38 , 47 , 72 , 97] The incidence of hepatitis is 2â€“4 times higher in pregnant women than in nonpregnant women.[39]

Peripheral neuropathy and optic neuritis are known adverse drug effects chronic INH use. Neurotoxicity is probably caused by pyridoxine deficienc aggravated by the formation of pyridoxine-INH hydrazones.[36] Peripheral neuropathy, the most common complication of INH therapy, presents in a stocking-glove distribution that progresses proximally. Although primarily sensory in nature, myalgias and weakness may occur.[98] Peripheral neuropathy is generally observed in severely malnourished, alcoholic, uremic, or diabetic patients; it is also associated with slow acetylator status, an effect which leads to increased INH levels and, consequently, increased pyridoxine depletion.[42] Optic neuritis presents as decreased visual acuity; visual field testing may reveal central scotomata.[44 , 52] Isoniazid is also associated with such findings of CNS toxicity as ataxia, psychosis, hallucinosis, and coma.[1 , 10 , 41 , 87]

Diagnostic Testing

Acute INH toxicity is a clinical diagnosis that may be inferred by history

and confirmed by measuring serum INH concentrations.[93] Acute toxicity from INH has been defined as a serum INH concentration greater than 10 mg/L 1 hour after ingestion, greater than 3.2 mg/L 2 hours after ingestio or greater than 0.2 mg/L 6 hours after the ingestion.[77] Because serum IN concentration measurements are not widely available, clinicians cannot re on serum concentrations to confirm the diagnosis or initiate therapy. Because of the risk of hepatitis associated with chronic INH use, hepatic aminotransferases should be regularly monitored once therapy is started.

Management

Acute Toxicity

The initial management requires termination of seizure activity, fluid resuscitation, and stabilization and correction of vital signs with maintenance of a patent airway. Clinicians should consider the administration of sodium bicarbonate to treat severe acidemia with a pH <7.0. Gastrointestinal decontamination should be performed by administering activated charcoal to awake patients who are able to comp with therapy.[96] Orogastric lavage and emetics are relatively contraindicated unless the patient is intubated when the risk of aspiration is diminished because of the underlying risk of seizures. Delayed absorption of INH has not been observed, suggesting that late gastrointestinal decontamination with charcoal is ineffective in preventing toxicity.[92]

The antidote for INH-induced neurologic dysfunction is pyridoxine. Pyridoxine rapidly terminates seizures, corrects metabolic acidosis, and reverses coma. The efficacy of pyridoxine is correlated with the administered dose; one study identified recurrent seizures in 60% of patients who received no pyridoxine, in 47% of those who received 10% the ideal pyridoxine dose, and in no patients who received the full dose o pyridoxine.[111] To treat acute toxicity, the pyridoxine dose in grams shoul equal the amount of INH ingested in grams, with a first dose of up to 5 g adults. Unknown quantities of ingested INH warrant initial empiric

treatment with a pyridoxine dose of no more than 5 g (pediatric dose: 70 mg/kg to a maximum of 5 g). Pyridoxine should be administered at a rate of 1 g every 2â€“3 minutes. Seizures that persist beyond administration of the initial 5-g dose should be treated by administration of an additional 5 of pyridoxine.[8]

Hospital pharmacies may stock insufficient quantities of pyridoxine to tre even a single patient with a large INH ingestion.[91] In the event that intravenous formulations are unavailable in sufficient quantities, pyridoxi tablets may be crushed and administered with fluids via nasogastric tube

Conventional anticonvulsants demonstrate variable effectiveness in terminating INH-induced seizures. Benzodiazepines may be used to potentiate the antidotal effect of suboptimal doses of pyridoxine, if gram-for-gram replacement doses of the antidote are unavailable. The benzodiazepines act synergistically with pyridoxine, as well as possess inherent GABA-agonist activity, but as single agents they may be ineffective in the treatment of acute INH poisoning.[27, 28, 52, 111] Phenytoin has no intrinsic GABAergic effect and is not recommended as therapy for INH-induced seizures.[52, 77, 86] Barbiturates, which have potent GABA-agonist activity, are expected to be as effective as the benzodiazepines, although the risk of complications is greater with this class of anticonvulsant. The efficacy of propofol in terminating INH-induc seizures has not been evaluated in humans.

Although hemodialysis has been used to enhance elimination of INH in acute overdose, with clearance rates reported as high as 120 mL/min, hemodialysis is rarely indicated. It is usually reserved for patients who develop INH-induced renal failure.[19, 112]

Asymptomatic patients who present to the ED within 2 hours of ingestion toxic amounts of INH should receive prophylactic administration of 5 g of pyridoxine. This recommendation is based on the observation that INH reaches its peak serum concentration within 2 hours of ingestion of therapeutic doses. Asymptomatic patients may be observed for a 6-hour period for signs of toxicity. Acute toxicity is unlikely to manifest more tha 6 hours beyond ingestion.

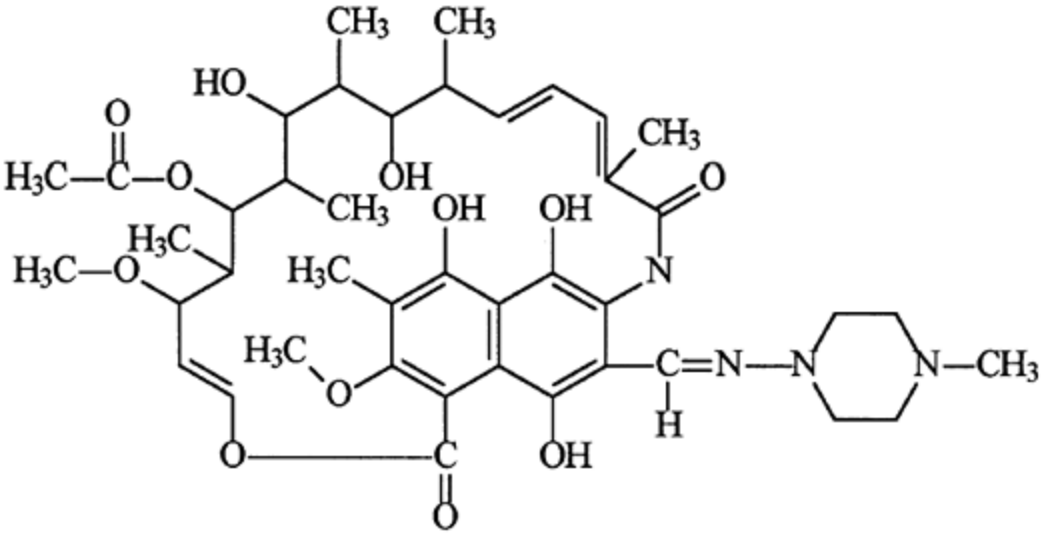
Chronic Toxicity

Hepatitis (defined as aminotransferase concentrations 2â€“3 times baseli levels) resulting from therapeutic INH administration mandates terminati of therapy; malnourished patients may require nutritional support. After resolution of liver injury, INH may be restarted, provided aminotransfera concentrations are closely monitored.[34 , 97] Pyridoxine does not reverse hepatic injury; consequently, surveillance for and recognition of hepatocellular injury remains essential. Cases of hepatitis refractory to medical therapy may require liver transplantation.[37 , 49]

Neurologic toxicity, including peripheral neuropathies, cerebellar findings and psychosis, is commonly treated with as much as 50 mg/d of oral pyridoxine, although doses as low as 6 mg/d appear

to be effective.[1 , 10 , 87 , 103] Because of its effectiveness in preventing neurologic toxicity, pyridoxine is used concurrently with INH therapy.

Rifamycins



Rifampin

Pharmacology

Rifamycins are a class of semisynthetic macrocyclic antibiotics derived fr *Streptomyces mediterranei.* Drugs in this class include rifampin, rifabutin and rifapentine, of which the first two are most commonly used.[65] Rifamp inhibits the initial steps in RNA chain polymerization through the formatic of a stable complex with RNA polymerase. Disruption of RNA synthesis interrupts protein synthesis, leading to cell death. Whereas mycobacteria RNA polymerase is susceptible to rifampin, eukaryotic RNA polymerase is not.[69]

Pharmacokinetics and Toxicokinetics

When administered orally, rifampin reaches peak plasma concentrations i 2â€“4 hours; foods, but not antacids, interfere with absorption.[81] Rifamp is secreted into the bile and undergoes enterohepatic recirculation. Although the recirculating antibiotic is deacetylated, the metabolite retai antimicrobial activity. The half-life of rifampin, which is normally betwee 1.5 and 5 hours, increases in the setting of hepatic dysfunction. After therapy is started, however, rifampin induces its own metabolism to shorten its half-life by approximately 40%. Rifampin is approximately 75 protein-bound, and distributes widely into body compartments. It imparts reddish color to all body fluids, including the CSF, leading to confusion w xanthochromia from subarachnoid hemorrhage.[52 , 69] The reddish discoloration of the skin may be removed by washing.[69] This property distinguishes rifampin from the â€œred man syndromeâ€• associated wi vancomycin, in which extreme flushing produces intense skin discoloratio (Chap. 54).[58]

Rifampin therapy carries greater teratogenic risk than other antituberculous therapies, with an incidence of malformation of 4.4%. Anencephaly, hydrocephalus, and congenital limb abnormality and dislocations are reported.[14 , 105] Rifampin is associated with hemorrhagic disease of the newborn.[14] The antibiotic is compatible with breast-feedin as only minute amounts of rifampin are secreted into breast milk.[103 , 104]

Drugâ€“Drug Interactions

Rifamycins are potent inducers of cytochrome P450 oxidative enzymes, which result in numerous drug interactions (Chap. 9). Of the rifamycins, rifampin has greater activity in inducing CYP3A4 than rifapentine; rifabut has the least inductive activity of the class.[65] In addition, rifampin is thought to induce CYP1A2, CYP2C8, and CYP2C9.[45 , 107] Concurrent administration of rifampin thus affects the metabolism of an array of drug such as warfarin, cyclosporine, phenytoin, opioids, and oral contraceptives.[45 , 95 , 107] Enzyme induction by rifampin therefore may b responsible for a variety of pathophysiologic processes, including insufficient anticoagulation in patients receiving oral anticoagulants, acut graft rejection in transplant patients, graft-versus-host disease, difficulty controlling phenytoin levels, methadone withdrawal, and unplanned pregnancy. Effects arising from CYP3A4 induction begin within 5â€“6 days after rifampin is started, and persist for up to 7 days after therapy is stopped.[70]

The cytochrome isozymes induced by rifampin also control the metabolism of drugs used in the treatment of HIV. Rifampin decreases the concentration of available protease inhibitors by 35â€“92%.[16] The antivi effect of protease inhibitors correlates best with trough concentrations.[10] Lower trough concentrations increase the frequency of drug-resistant mutations in the protease gene and promote the outgrowth of drug-resistant HIV strains. The reduction of serum concentrations of protease inhibitors is of such magnitude that it may not be overcome by increasing the dose of the protease inhibitor. Coadministration of rifampin with protease inhibitors may therefore lead to loss of HIV suppression and to the emergence of resistant HIV strains.[16]

Rifampin also decreases the serum concentrations of nucleoside reverse transcriptase inhibitors such as zidovudine. The efficacy of zidovudine an congeners is not related to the serum concentration of drug, but is, instead, related to the intracellular concentration of the active metabolite a triphosphate derivative. Even though rifampin decreases serum

zidovudine concentrations by 47%, active metabolite is present within ce in sufficient levels for activity. Rifampin, therefore, has minimal effect on the efficacy of nucleoside reverse transcriptase inhibitors. Table 55-1 list the drug interactions of rifampin.

Rifampin suppresses the transformation of antigen-stimulated lymphocyt as well as normal T-cell function, leading to decreased sensitivity to tuberculin, in turn resulting in false-negative purified protein derivative (PPD) test results.

Clinical Manifestations

Acute Toxicity

The most common side effects of acute rifampin overdose are gastrointestinal symptoms consisting of epigastric pain, nausea, vomiting and diarrhea. The presence of diarrhea distinguishes rifampin ingestion from overdose of other antimycobacterial agents.[34] Nonetheless, 3 death are associated with rifampin or rifampicin ingestion; an autopsy performe on 1 of these patients demonstrated the presence of pulmonary edema, although no causation was implied.[12, 56, 82] Other effects include flushing, angioedema, and obtundation. Children who receive an overdose of rifampin can develop facial or periorbital edema. Anterior uveitis is occasionally observed, as are neurologic effects consisting of generalized numbness, extremity pain, ataxia, and muscular weakness.[46, 69] Isolated rifamycin overdose infrequently produces serious acute effects.

Chronic Toxicity

When rifampin was originally introduced as an antituberculous agent, hepatitis was more frequently observed in patients taking combination therapy of rifampin and INH than in those taking INH alone. These findin potentially arise from rifampin's

ability to induce cytochromes responsible for INH hepatotoxicity and may

not result from direct hepatic injury by rifampin itself. Liver injury, when attributable to rifampin alone, is predominantly cholestatic, prompting suggestions that clinical surveillance for hepatic injury may be preferable to regular biochemical monitoring.[34, 79] Rifampin alters the metabolism of other xenobiotics, such as INH and acetaminophen, to increase their potential for hepatotoxicity.[34, 75] Although more prevalent in combined regimens, adverse effects are uncommon; the increased efficacy of multidrug regimens generally outweighs the risks associated with their us One report underscores the risks of the 9-month isoniazid, 2-month rifampin and pyrazinamide regimen that has resulted in 2 fatal cases of severe hepatitis following treatment for latent tuberculosis.[22]

A condition similar to a viral syndrome may result from a hypersensitivity reaction that is associated with rifampin therapy. The syndrome, which occurs in 20% of patients receiving high doses, includes fever, chills, myalgias, and a nonproductive cough. Eosinophilia, hemolytic anemia, thrombocytopenia, and interstitial nephritis can develop in severe cases.[7, 71] Intermittent dosing of rifampin is also a risk factor for renal failure, the mechanism for which is unknown. Renal failure is rarely oliguric and i usually self-limited; patients usually recover with supportive care, althou rechallenge with rifampin should be undertaken only with caution.[79]

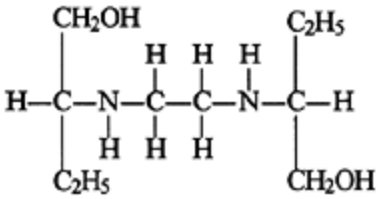
The concomitant administration of rifampin and protease inhibitors result in increased rates of arthralgias, uveitis, leukopenia, and skin discoloration. Identical side effects occurred during the simultaneous administration of rifampin and CYP3A4 inhibitors such as clarithromycin, suggesting that toxic effects arise from elevated serum rifampin concentrations.[16] Current recommendations are that rifampin dosing be decreased when administered with nelfinavir, indinavir, and amprenavir. The administration of rifampin with ritonavir is not recommended.[16, 20]

Therapeutic Testing and Management

Management of patients with acute rifampin overdose is primarily supportive. Stabilization of vital signs and administration of activated charcoal are usually adequate, although clinicians should remain vigilant

for coingestants. For chronic toxicity, recognition of interactions between rifampin and other drugs is critical. Hepatic function should be monitored because of rifampin's ability to augment the hepatotoxicity of other pharmaceuticals and xenobiotics. Treatment for hepatic injury involves withholding rifampin therapy and reassessing the appropriateness of othe drugs administered to the patient. Supportive care for hepatotoxicity may be required. Influenzalike symptoms and renal failure secondary to rifampin may respond to decreasing the interval between administration o the drug.[79] Although rifampin interacts with protease inhibitors, the utilit of therapeutic drug monitoring is uncertain because the correlation of clinical events with serum concentrations of rifampin and antiretroviral drugs is unknown.[16]

Ethambutol



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Pharmacology and Pharmacokinetics

Ethambutol, an antibiotic to which almost all strains of *M. tuberculosis* ar sensitive, has no effect on other bacteria. Ethambutol binds to arabinosyltransferases, which are enzymes that incorporate glycan subunits into cell wall polymers known as arabinogalactan and lipoarabinomannan.[64] Only the D(+) isomer is used therapeutically, but both enantiomers are bacteriocidal.[52] The drug is active only in growing cells, where bacteriostatic effects appear approximately 24 hours after ethambutol is incorporated by mycobacteria.[69]

Maximum serum concentrations are reached within 4 hours of oral

administration and are proportional to the dose. Both foods and antacids decrease absorption.[16] Ethambutol is approximately 20â€“30% protein bound and has a half-life of between 4 and 6 hours.[61, 69] Three-fourths a standard dose is excreted unchanged into the urine by a combination of glomerular filtration and tubular secretion. Consequently, ethambutol accumulates in patients with renal failure, making adjustments in dosing necessary.[69]

Ethambutol is considered safe for use during pregnancy as a first-line agent. Although a 2.2% incidence of congenital abnormalities was identified in women undergoing ethambutol therapy, no consistent patter of abnormalities occurred in their offspring.[14] Even though ethambutol is excreted into breast milk in approximately a 1:1 ratio with serum, it is compatible with breast-feeding.[14]

Clinical Manifestations and Management

Acute overdosage of ethambutol is generally well tolerated, although dea is reported.[56] More commonly, nausea, abdominal pain, confusion, visual hallucinations, and optic neuropathy occur following acute ingestions of greater than 10 g.[33] Although stabilization of vital signs and GI decontamination with activated charcoal remain the hallmarks of therapy, clinicians must remain vigilant for coingestants, particularly INH. Hemodialysis is rarely used as treatment for multidrug ingestions includir ethambutol.[33]

Although peripheral neuropathy and asymptomatic hyperuricemia occur with chronic therapy, the most significant effect of the therapeutic use of ethambutol is dose-related optic or retrobulbar neuritis, which may be unilateral or bilateral.[55, 99] Approximately 15% of patients receiving 50 mg/kg/d, 5% of patients receiving 25 mg/kg/d, and fewer than 1% of those receiving 15 mg/kg/d develop optic neuritis.[79] Patients may develo subclinical ocular disease within 30 days of starting ethambutol.[115] If clinically apparent, patients may complain of decreased visual acuity, loss of red-green discrimination, and loss of peripheral vision. The loss of peripheral vision and color discrimination that occurs in patients with opt

neuropathy caused by ethambutol distinguishes this condition from optic neuropathy secondary to INH.[52, 79]

Management of chronic toxicity from ethambutol involves cessation of therapy, although improvement may be hastened by treatment with hydroxocobalamin.[52] Recovery is less likely in older patients and is relate to the degree of visual impairment.[110]

Optic neuritis may be related to derangements in mitochondrial copper or zinc metabolism; ethambutol chelates both metals.[29] The visual abnormalities induced by ethambutol have clinical features similar to a hereditary condition known as Leber optic neuropathy. In this disorder, t mechanism of visual loss is defective mitochondrial metabolism of copper.[59] Ethambutol is suspected of mimicking this condition by binding intracellular copper, altering mitochondrial function, and producing neuronal injury.[51, 59] Alternatively, optic neuritis may be related to zinc metabolism. Ethambutol

chelates intracellular zinc to induce reversible vacuolar degeneration in retinal cultures. Progressive degeneration leads to irreversible neuronal destruction.[116] The clinical effect of this injury is a shift in the threshold for wavelength discrimination without changing the absolute sensitivity o the cone system, which patients discern as loss of red-green discrimination.[100]

Diagnostic Testing

All patients should receive neuro-ophthalmic testing prior to ethambutol therapy. The use of visual-evoked potentials is especially useful in identifying subclinical optic nerve disease. Furthermore, patients should receive regular visual acuity examinations, and clinicians should encoura patients to report any subjective symptoms related to vision. The use of ethambutol may be relatively contraindicated in children who are unable comply with an ophthalmic examination.[52, 79]

Pyrazinamide

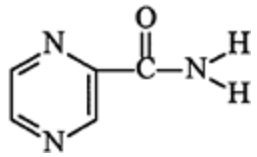

Figure. No Caption Available.

Pharmacology and Pharmacokinetics

Pyrazinamide (PZA) is a structural analog of nicotinamide whose mechanism of action is similar to that of INH. Like INH, PZA is a prodrug. Pyrazinamide requires deamidation by pyrazinamidase, an endogenous bacterial enzyme, to pyrazinoic acid, the active form of the drug. The precise cellular functions inhibited by pyrazinoic acid have not been defined, but an acid pH is required for activity. Pyrazinamide is effective against both active and dormant bacteria and its use in antituberculosis regimens shortens the course of therapy.[5] If PZA is administered during the first 2 months of treatment with INH and rifampin, a course of chemotherapy may be shortened to only 6 months, producing the shortes effective regimen.[81] After oral administration, PZA is rapidly absorbed, with maximum concentrations occurring within 1 hour of administration. The volume of distribution of PZA is 0.7 L/kg and approximately 10% remains bound to plasma protein. Pyrazinamide is metabolized to pyrazinoic acid and 5-hydroxypyrazinoic acid, which are then renally excreted. The drug has a half-life of approximately 9 hours.[69]

When introduced in the 1950s, PZA was administered in doses of 40â€“50 mg/kg for extended periods of time. The dosages produced hepatitis, witl clinical manifestations of highly elevated aminotransferase and bilirubin concentrations. Among patients taking high-dose PZA, elevations in aminotransferases were identified in 20%, and symptomatic hepatitis was identified in 10%. A small number of the latter population succumbed aft a fulminant course. As a result of these findings, PZA was believed to be

highly hepatotoxic and its use was discouraged. The resurgence of multidrug-resistant mycobacteria, however, has forced clinicians to reassess the role of PZA. Modern dosing regimens of 30 mg/kg for brief courses of 2 months infrequently produce hepatic injury, with some studi suggesting that addition of PZA to multidrug TB regimens confers no additional risk for hepatotoxicity.[34 , 80 , 81]

Pyrazinamide is rarely used in pregnancy because the risk of birth defects is poorly defined. Animal studies suggest that PZA has no teratogenic potential at therapeutic doses.[2] Pyrazinamide is minimally excreted into breast milk and is presumed safe for breast-feeding.[14]

Clinical Manifestations and Management

Proper dosing of PZA and short courses of therapy are the two most important factors in preventing toxicity. Treatment for hepatotoxicity involves cessation of PZA therapy in conjunction with supportive care.[34] Pyrazinamide inhibits the renal excretion of uric acid, and hyperuricemia observed. More than 90% of children treated with short courses develope elevated uric acid concentrations.[89] Most patients, regardless of age, remain asymptomatic and do not develop symptoms of gout, but polyarthralgias responsive to probenecid or allopurinol may be observed.[8] Toxic effects from acute overdose of pyrazinamide have not been reporte

Cycloserine

Cycloserine is used in conjunction with other tuberculostatic agents when treatment with primary agents (INH, rifampin, ethambutol, and streptomycin) has failed. Cycloserine, a structural analog of alanine, inhibits reactions in which D-alanine is required for cell wall biosynthesis. After oral doses, 70â€“90% of the drug is absorbed. Peak concentrations the drug are reached in 3â€“4 hours. Cycloserine is distributed throughou all tissues and body fluids and easily crosses the bloodâ€–brain barrier. Very little of the antibiotic is metabolized, and the drug is excreted unchanged in the urine.[69]

Toxicity, occurring in as many as 50% of patients taking cycloserine, is dose dependent. Neurologic effects consist of somnolence, headache, tremor, dysarthria, vertigo, confusion, irritability, and seizures. Psychiatr manifestations include paranoid reactions, depression, and suicidal ideation. These effects are thought to be caused by agonism of glycine B receptors by cycloserine. Cycloserine is contraindicated in patients with a history of either seizures or depression. If used, cycloserine should be introduced slowly to avoid CNS toxicity.[52, 79, 81] Toxicity is potentiated by alcohol, usually appears within the first 2 weeks of therapy, and cease upon termination of the drug. Because cycloserine is renally excreted, patients with renal failure may be predisposed to toxicity; it is removed b hemodialysis. Although no teratogenic effects were noted in 3 women exposed to cycloserine during the first trimester, cycloserine is not recommended for use during pregnancy. Cord blood concentrations are approximately 70% of serum levels, and no adverse effects occurred in breast-fed infants. Consequently, cycloserine is considered to be safe in women who are breast-feeding.[14] Reports of overdose are lacking in the English medical literature.

Other Antimycobacterials

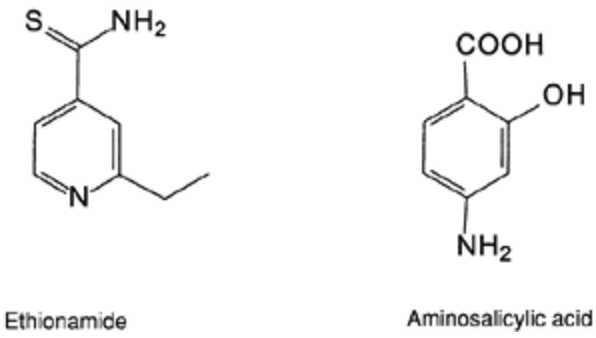

Figure. No Caption Available.

Ethionamide, a congener of INH, is thought to have a similar mechanism action to INH. Oral doses yield peak serum concentrations within

approximately 3 hours of administration. The half-life of the drug is approximately 2 hours. Toxic effects include orthostatic hypotension, depression, and drowsiness. Rash, purpura, and gynecomastia are observed, as are tremor, paresthesias, and olfactory disturbances. Approximately 5% of patients receiving ethionamide develop hepatitis. Treatment for toxicity involves withholding ethionamide therapy.[69] Birth defects were observed in 7 of 23 newborns antenatally exposed to ethionamide, although a consistent pattern of anomalies was lacking. Dat regarding the safety of ethionamide are lacking.[14] Reports of toxicity fro ethionamide overdose are absent from the English literature.[32]

para -Aminosalicylic acid (PAS) is thought to inhibit enzymes responsible for folate biosynthesis in mycobacteria but not in other organisms. PAS is readily absorbed from the gut and is rapidly distributed into all tissues, especially the pleural fluid and caseous material. *para* -Aminosalicylic aci has a half-life of minutes and is renally excreted. Adverse effects associated with PAS use include nausea, vomiting, diarrhea, sore throat, and malaise. Between 5 and 10% of patients receiving PAS develop hypersensitivity reactions characterized by high fever, rash, and arthralgias. Hematologic abnormalities of agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, and acute hemolytic anemia have been observed.[69] *para* -Aminosalicylic acid may be removed by hemodialysis in patients with renal failure.[68] Adverse effects associated with chronic therapy may be treated with withdrawal of the drug. Data regarding the safety of PAS in pregnancy and breast-feeding are lacking.[14]

Capreomycin is a cyclic polypeptide with an unknown mechanism of actio Because of poor absorption after oral dosing, capreomycin must be administered intramuscularly. Toxicity associated with capreomycin use includes hearing loss, tinnitus, proteinuria, and electrolyte disturbances, although severe renal failure is rare. Eosinophilia, leukocytosis, and rash have been described. Pain and sterile abscesses at the site of capreomyc injection have been reported.[69] Data regarding the safety of capreomycir in pregnancy and breast-feeding are lacking.[14]

Summary

In overdose antituberculous drugs represent a significant toxicologic threat. Patients acutely poisoned with INH require immediate and appropriate action to reverse seizures, acidosis, and coma. As an antidote to INH overdose, pyridoxine is effective therapy, although its action may be augmented by the use benzodiazepines. Although less common than previously believed, hepatocellular injury resulting from therapeutic dosing of INH nonetheless requires surveillance to prevent fulminant hepatic failure.

Other antituberculous agents cause significant adverse effects. In particular, rifampin has numerous drugâ€“drug interactions, including several with anti-HIV therapies. Because antituberculous therapies are common in the HIV population, potential interactions between rifampin and antiretroviral agents should remind clinicians to remain vigilant for unanticipated adverse effects. Patients receiving ethambutol, pyrazinamide, and other antituberculous agents benefit from surveillance for specific effects such as decreased visual acuity, hepatic injury, and psychiatric manifestations. Despite the toxicity of this class of drugs, poisoning is often responsive to intervention if recognized and treated appropriately.

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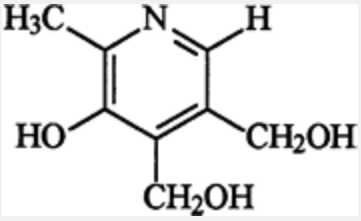
Antidotes in Depth

Pyridoxine

Mary Ann Howland



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Pyridoxine (vitamin B_6), a water-soluble vitamin, is administered as an antidote for overdoses of isonicotinic acid hydrazide (isoniazid, INH), hydrazine, methylated hydrazines, and perhaps

ethylene glycol. With the exception of ethylene glycol, all of the named xenobiotics produce seizures by the competitive inhibition of pyridoxal-5â€²-phosphate (PLP) Pyridoxine overcomes this inhibition. Also, the administration of pyridoxine may enhance the less-toxic pathway of ethylene glycol metabolism to form benzoic and hippuric acid, as opposed to oxalic acid.[6] Hydrazine and methylated hydrazines (1,1-dimethylhydrazine [UDMH], monomethylhydrazine [MMH]) are used as rocket fuels, and MMH is also found in *Gyromitra esculenta* mushrooms.[3]

History

Pyridoxine deficiency was first identified in 1926 and was mistakenly attributed to the absence of vitamin B_2.[33] Ten years later, the deficiency was fully characterized and attributed to vitamin B_6.[22] A rare genetic abnormality that produced pyridoxine-responsive seizures in newborns was recognized in 1954.[5]

Chemistry

The active form of pyridoxine is the phosphate ester of pyridoxal (PLP).[27] Pyridoxine, an alcohol; pyridoxal, an aldehyde; and pyridoxamine, an aminomethyl form are all naturally occurring related compounds that are metabolized by the body to PLP.[27] Pyridoxine was chosen by the Council on Pharmacy and Chemistry to represent vitamin B_6.[27] Pyridoxine hydrochloride was chosen as the commercial preparation because of its stability.[47]

Pharmacology

PLP is an important cofactor in more than 100 enzymatic reactions, including decarboxylation and transamination of amino acids, and the metabolism of tryptophan to 5-hydroxytryptamine and methionine to cysteine.[21,27] Iatrogenic pyridoxine deficiency in animals produces seizures associated with reduced

concentrations in the brain of PLP, glutamic acid decarboxylase, and Î³-aminobutyric acid (GABA).[15]

Pharmacokinetics

Pyridoxine is not protein bound, has a volume of distribution of 0.6 L/kg, and easily crosses cell membranes; in contrast PLP is nearly entirely plasma protein bound.[47] Pyridoxine is rapidly metabolized at extrahepatic sites to pyridoxal, PLP, and 4-pyridoxic acid, with only 7% excreted unchanged in the urine.[47] After intravenous infusion of 100 mg of pyridoxine over 6 hours, PLP concentration increases rapidly in serum and in erythrocytes.[47] Pyridoxal rises from 37 nmol/L to 2183 nmol/L in serum and from undectable to 5593 nmol/L in erythrocytes, with peak levels achieved at the end of the infusion.[47] Oral pyridoxine in doses of 600 mg is 50% absorbed within 20 minutes of ingestion by a first-order process with rapid achievement of peak plasma concentrations of pyridoxine, PLP, and pyridoxal.[46] The concentration of PLP appears to be tightly controlled in the serum and related to alkaline phosphatase activity.[22,46] Oral doses of pyridoxine from 10â€“800 mg result in PLP concentrations of 518â€“732 nmol/L 4 hours after ingestion.[46] Chronic alcoholics have lower baseline PLP serum levels, as acetaldehyde enhances the degradation of PLP in erythrocytes, through stimulation of an erythrocyte membrane-bound phosphatase that hydrolyzes phosphate-containing B_6 compounds.[26]

Mechanism of Hydrazide- and Hydrazine-Induced Seizures

The antidotal role of pyridoxine in the management of INH and methylated hydrazines like MMH poisoning is based on the interference of these xenobiotics with the normal use and function of pyridoxine as a coenzyme. INH produces a syndrome resembling

cerebral vitamin B_6 deficiency, which results in seizures. Specifically, INH and other hydrazides and hydrazines inhibit the enzyme pyridoxine phosphokinase that converts pyridoxine to PLP.[21] In addition, hydrazides directly combine with PLP, causing inactivation through the production of hydrazones that are rapidly excreted by the kidney.[21] PLP is a coenzyme for L-glutamic acid decarboxylase that facilitates the synthesis of GABA from L-glutamic acid. Animal studies suggest that this interference with PLP disrupts the formation of GABA.[21,43] The decreased GABA formation reduces cerebral inhibition, which may contribute in part to the seizures resulting from exposure to INH and methylated hydrazines.[35,45]

Animal Studies

In a dog model of INH-induced toxicity, pyridoxine reduced the severity of seizures, increased the time to seizure, and prevented the mortality of a previously lethal dose of INH in a dose-dependent fashion.[12,13] Lower molar ratios prevented deaths and higher molar ratios prevented both deaths and seizures.[13] When used as a single agent, phenobarbital, pentobarbital, phenytoin, ethanol, and diazepam were ineffective in controlling seizures and mortality, but when combined with pyridoxine, each protected the animals from seizures

and death.[12] Other small-animal experiments have documented the effectiveness of pyridoxine against MMH-induced seizures when used alone[21,29,40] and when used in combination with diazepam.[18] Anticonvulsant efficacy is also demonstrated in cat[36] and monkey[38] models.

Rat studies with intraperitoneal dimethylhydrazine (UDMH) also demonstrate the protective effects of pyridoxine given intraperitoneally 90 minutes later.[14] Pyridoxine prevented seizures and death in a model that produced 94% mortality and 100%

seizures without pyridoxine.[14] When intraperitoneal UDMH and pyridoxine IV 20 minutes later were administered to rats 17% died at 24 hours, as compared to a 100% mortality without pyridoxine.[14] Other studies in dogs and monkeys also demonstrate the effectiveness of pyridoxine in preventing seizures and mortality, and in treating seizures.[4] Pyridoxine IM protected the monkeys from death and stopped the seizures caused by an IV UDMH dose.

Human Data

Clinical experience with the use of pyridoxine for INH overdose in humans demonstrates favorable results.[3,11] Rapid seizure control with no morbidity or mortality was achieved when the ratio in grams of pyridoxine administered to INH ingested ranged from 0.14 to 1.3, although in practice, most patients receive approximately gram-for-gram amounts. In 5 patients, the use of gram-for-gram amounts of pyridoxine resulted in the complete control of seizures and a resolution of the metabolic acidosis.[42] In 8 patients with intentional INH overdoses, basic poison management, intensive supportive care, and a mean dose of 5 g of pyridoxine IV resulted in no fatalities.[8] Seizures were controlled in a 22-month-old boy given 100 mg of IV pyridoxine, after an estimated INH ingestion of 5 g.[41] Variable results are reported when relatively small doses of pyridoxine are used.[28] Seizures were reported in 2 patients following the ingestion of INH-pyridoxine combination tablets, although the actual amount of pyridoxine ingested was not noted.[39]

In addition to controlling seizures, the administration of pyridoxine also appears to restore consciousness. Two patients, who remained obtunded for as long as 72 hours after the apparent resolution of the seizures, were reported to awaken immediately after 3â€“10 g of IV pyridoxine was administered.[10] A third patient who was lethargic awakened with IV pyridoxine. This work

suggests that mental status abnormalities associated with INH overdose, and conceivably hydrazine overdoses, may be responsive to pyridoxine and also may require repetitive dosing.[11,42] Patients treated with large doses of pyridoxine awaken more rapidly even after experiencing sustained seizure activity or status epilepticus.

MMH poisoning can be encountered in a variety of clinical situations. In the aerospace industry, where MMH is used as a rocket propellant, percutaneous or inhalational poisoning may occur. Ingestion of the false morel mushroom, *G. esculenta*, can also produce toxicity when its major toxic compound, gyromitrin, is metabolized to MMH (Chap. 113).

The neurologic effects of MMH poisoning are similar to those of INH toxicity and include seizures and respiratory failure. Severe liver damage similar to INH-induced hepatotoxicity is also described.[15] As in the case of INH hepatotoxicity, there is no evidence that MMH-induced hepatotoxicity can be treated by administration of pyridoxine.[9]

A patient who was exposed to hydrazine became comatose 14 hours later and remained comatose for 60 hours until 25 mg/kg of pyridoxine aroused him.[23] Another case report describes improvement in the mental status of a confused, lethargic, and restless man who had ingested a mouthful of hydrazine and was treated with a 10-g dose of pyridoxine.[20] This improvement developed over 24 hours and may have been unrelated to pyridoxine therapy. A severe sensory peripheral neuropathy lasting for 6 months developed 1 week following the overdose and was most likely a result of the hydrazine ingestion and not the pyridoxine. Six patients exposed to an Aerozine-50 (hydrazine and UDMH) spill were effectively treated with pyridoxine after developing twitching, clonic movements, hyperactivity, or GI symptoms.[17]

Ethylene Glycol

PLP is a cofactor in the conversion of glycolic acid to nonoxalate compounds (Chap. 103). Patients poisoned with ethylene glycol should receive 100 mg/d of pyridoxine IV in an attempt to shunt metabolism preferentially away from the production of oxalic acid. This approach is supported by an animal model[6] and by the study of primary hyperoxaluria,[19] but has not been studied adequately in humans with ethylene glycol poisoning.[31]

Safety Issues

Pyridoxine is clearly neurotoxic to animals and humans when administered chronically in supraphysiologic doses.[23,24,32] Delayed peripheral neurotoxicity occurred in patients taking daily doses of 200 mg to 6 g of pyridoxine for 1 month.[30,34,35] Healthy volunteers given 1 or 3 g/d developed a small- and large-fiber distal axonopathy, with sensory findings and quantitative sensory threshold abnormalities occurring after 1.5 months in the high-dose and 4.5 months in the low-dose regimens. Once symptoms occurred, the pyridoxine was immediately stopped, but symptoms progressed for 2â€“3 weeks, leading to speculation that it took time for the reversal of neuronal metabolic manifestations.[7]

Pyridoxine may also induce a sensory neuropathy when massive doses are administered, either as a single dose or over several days.[1,25,41] Ataxia occurred in dogs receiving 1 g/kg of pyridoxine.[41] Larger doses of pyridoxine produce incoordination, ataxia, seizures, and death.[41] Death after pyridoxine administration was sometimes delayed for 2â€“3 days.[41] Two patients treated with 2 g/kg of IV pyridoxine (132 and 183 g, respectively) over 3 days developed severe and crippling sensory neuropathies.[1] One year later, both patients were unable to walk. Inadequate information is available to determine the maximal single acute nontoxic dose in humans; however, there appears to be a wide margin of safety. Doses of pyridoxine ranging from

70â€“375 mg/kg or doses equivalent to the milligram-per-kilogram historical dose of ingested INH have been administered without adverse effects.[42]

Dosing

Considering all of the available data, a safe and effective pyridoxine regimen for INH overdoses in adults is 1 g of pyridoxine for each gram of INH ingested, to a maximum of 5 g or 70 mg/kg. Initial doses of pyridoxine in children probably should not exceed 70 mg/kg.[42] These doses are sufficient in the majority of patients, but the dose can be repeated if necessary. The best way to administer pyridoxine in a patient after an INH overdose has not been

established. For a patient who is actively seizing, pyridoxine may be given by slow IV infusion at approximately 0.5 g/min until the seizures stop or the maximum dose has been reached. When the seizures stop, the remainder of the dose should be infused over 4â€“6 hours to maintain pyridoxine availability while the INH is being eliminated. The dose should be repeated if seizures persist or recur, or if the patient exhibits mental status depression. In the intravenous pyridoxine, pyridoxine should be administered orally.[33]

For hydrazine and methylated hydrazines (ie, MMH, UDMH) poisoning, there is no established dose.[45] Using the same dosage regimen as for INH is theoretically reasonable, but has never been tested in humans.

Pyridoxine should not be the sole agent used for INH or MMH poisoning. A benzodiazepine should be used with pyridoxine in an attempt to achieve synergistic control of seizures. If the seizures do not respond to both of these measures, they can be repeated, followed by intravenous agents such as propofol, pentobarbital, or phenobarbital, and, if necessary, neuromuscular blockade and

general anesthesia. When neuromuscular blockade is achieved without extinguishing the central nervous system (CNS) seizure activity, irreversible neuronal damage may result. Although metabolic acidosis is probably a result of the seizures and should therefore resolve once the underlying condition is controlled, severe or refractory metabolic acidosis may require appropriate quantities of sodium bicarbonate.

Availability

Pyridoxine HCl is available parenterally at a concentration of 100 mg/mL in 1-mL ampules from various manufacturers. Thus a 5-g IV dose of pyridoxine requires fifty 1-mL ampules containing 100 mg/mL. This is an exception to the rule that appropriate doses of medications rarely require multiple dosages of this magnitude. This also emphasizes the necessity of keeping an adequate supply available in the emergency department, as well as in the pharmacy. Oral pyridoxine is available in many tablet strengths from 10â€“500 mg from various manufacturers.

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Chapter 56
Antimalarials

G. Randall Bond

A 30-year-old man stumbled into the emergency department (ED) appeari agitated. However, he was quite coherent. He complained of inability to s a continuous ringing in his ears, and the sensation of â€œa train rushing

He stated that he took â€œa bunch of pills,â€• drank some wine, and we before coming to the ED. On awakening approximately 6 hours later, he w balance.

His mother related an extensive family, medical, and social history: The taking many medications. In addition, he took â€œwater pills,â€• later i control hypertension. The patient, she said, took aspirin â€œfor arthritis,â for malaria.â€• She insisted that he used no illicit drugs and seldom drar packs of cigarettes per day. She further noted that he had been extreme loss of his unemployment benefits. In addition, he had had a quarrel on t

Physical examination revealed a well-developed, talkative, anxious man, v blood pressure, 100/40 mm Hg; pulse, 100 beats/ min; respiration, 18 97.2Â°F (36.2Â°C). The skin was warm, dry, anicteric, and without pallor

Ophthalmic examination revealed fixed, widely dilated pupils (right eye 7

unresponsive to light and accommodation. Assessment of visual acuity d of distant shadows but no perception of close objects. The fundi were ea were pale and flat. There was severe arteriolar constriction starting at th vessels. The veins appeared normal in diameter. The arteriovenous ratio movements were intact.

Examination of the ears revealed normal tympanic membranes. The patien fork on each side, but could not hear the ticking of a watch. The remainc was normal except for a soft systolic ejection murmur.

Blood samples were drawn and an electrocardiogram (ECG) was obtained. with dextrose 5% in water (D_5 W), and 1 g/kg of body weight of activate orally.

The initial laboratory data revealed a hematocrit of 37.6%; a hemoglobin blood cell count (WBC) of 8600/mm^3 with 80% polymorphonuclear cells, monocytes, and 1% eosinophils. The platelet count and international norr normal.

The electrolyte analysis revealed sodium, 143 mEq/L; potassium, 4.4 mE bicarbonate, 29 mEq/L; blood urea nitrogen (BUN), 9 mg/dL; and glucose phosphokinase (10,250 IU/L), lactic dehydrogenase (700 IU/L), and aspa IU/L) were all elevated. The urinalysis was normal, with a negative urine salicylates. The ECG showed a normal sinus rhythm at 96 beats/min, an a waves in leads II, III, and aVF. Peaked T waves were present in V2 to V4 were both normal. The chest radiograph was normal. The patient was adr unit.

The ophthalmic and auditory symptoms rapidly resolved without any addi addition, the pupillary and funduscopic examination returned to normal. T vasculature and color within 24 hours. Blood pressure returned to normal abnormal auditory and visual findings entirely resolved within 48 hours. subsequently discovered that he had taken ten (300-mg) quinine tablets, treatment of the *Plasmodium falciparum* malaria.

History and Epidemiology

The malaria parasite has caused untold grief throughout human history. T

population live in areas where malaria is endemic. More than 300 million infection, and 1 million die from the infection each year.[122] Included amor infected are 50 million travelers from industrialized countries who visit th year. In spite of using prophylactic medications (Table 56-1), 30,000 wi

The bark of the cinchona tree, the first effective remedy for malaria, was than 350 years ago.[107] The toxicity of its active ingredient, quinine, was use. In this century, the need to fight wars in malaria-infested areas, and pharmaceutical advances funded largely by the military during World Wa amodiaquine, pyrimethamine) and later during the Vietnam conflict (me Chloroquine, hydroxychloroquine, primaquine, amodiaquine, mefloquine, a related to quinine, but have different patterns of toxicity. Other xenobioti include the folate inhibitors proguanil and pyrimethamine (frequently used atovaquone), the sulfonamide sulfadoxine, or the sulfone dapsone, as wel macrolides (Chap. 54).

Quinine sulfate
Not used
650 mg tid Ã— 7 days[b]
Chloroquine phosphate
500 mg/wk as single dose
1000 mg STAT then 500 mg at 6 h, 24 h, and 48 h
Hydroxychloroquine sulfate
400 mg/wk as single dose
Rarely used
Primaquine phosphate
30 mg of base/d Ã— 14 days[c]
30 mg of base/d Ã— 14 days
Halofantrine
Not used
500 mg q6h Ã— 3 doses, repeat in 7 days
Amodiaquine
Not used
10 mg of base/kg/d Ã— 3 days
Mefloquine

250 mg/wk as single dose
750 mg STAT, then 500 mg 8 h later
Pyrimethamine-sulfadoxine
Not used
75 mg pyrimethamine + 1500 mg sulfadoxine as single dose
Artemisinin
Not used
10 mg/kg Ã— 7 days
Artesunate
Not used
2 mg/kg PO BID on day 1 then 2 mg/kg/d Ã— 6[d] or

2.4 mg/kg IV on day 1 then 1.2 mg/kg/d IV or PO Ã— 6 days
Artemether
Not used
3.2 mg/kg IM on day 1 then 1.6 mg/kg/d IM or PO Ã— 6 days
Artemether-lumefantrine
Not used
80 mg artomether + 480 mg lumefantrine at 0, 8, 24, 36, 48, and 60 h
Doxycycline
100 mg/day
100 mg BID[e]
Proguanil-atovaquone
100 mg proguanil + 250 mg atovaquone once per day
400 mg proguanil + 1000 mg atovaquone per day Ã— 3 days
Proguanil-chloroquine
200 mg proguanil + 100 mg chloroquine once per day
Not used
[a] Choice, duration, and dosage may vary with malarial species and freque
geographic area.
[b] Usually with doxycycline, tetracycline, or clindamycin for chloroquine-r
[c] After leaving *P. vivax* or *P. ovale* area.
[d] Often with mefloquine 15 mg/kg in a shorter course.

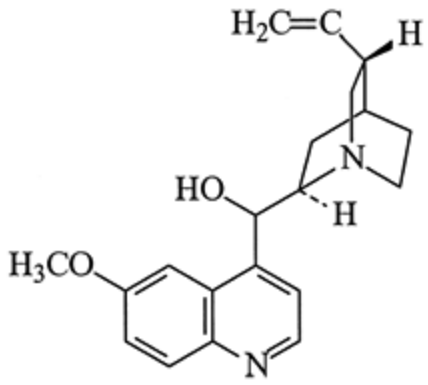
[e] With quinine sulfate for chloroquine-resistant cases.

Drug Prophylactic Dose (Adult) Upper Dose Range, Treatment

TABLE 56-1. Common Adult Doses of Antimalarials Used Worldwi

With the introduction of each new xenobiotic, resistance developed, parti Asia, and Africa.[104, 107] In some places, quinine is again the first-line th In the last two decades, the search for active agents has returned to a r herb qinghaosu.[58, 116] Artemisinin, the active ingredient, is widely used resistant malaria.[116] With increased leisure travel, a greater number of N prophylactic agents with potential toxicity.

Quinine



Quinine
MW = 324.41 daltons

Figure. No Caption Available.

In addition to its use as an antimalarial, quinine is also available in small been used for muscle cramps and, because of an extremely bitter taste si adulterant in drugs of abuse.

Pharmacokinetics and Toxicodynamics

Quinine is rapidly and almost completely absorbed orally (Table 56-2). P achieved within 3 hours, with 85â€“95% of quinine protein bound, primari glycoprotein.[99 , 113] The apparent volume of distribution is 1.8â€“4.6 L/k concentrations are achieved at 3â€“6 hours. The average therapeutic plas 9â€“15 hours. In overdose, the elimination half-life is approximately 25â kidneys, and muscles metabolize 80% of the ingested dose to a variety Approximately 20% is excreted unaltered in urine. Quinine passes transpl milk.

If high doses of cinchona alkaloids are ingested during pregnancy, resulta induce abortion or premature labor. Because of this mechanism, in the pa commonly as an abortifacient (Chap. 28).[69] Chloroquine continues to be parts of the developing world.[6 , 86]

Quinine and quinidine are optical isomers and share similar pharmacolog and antimalarials. Because of the tissue toxicity of quinine, intravenous q States when a parenteral form is needed to treat severe or resistant mal effects on

the GI tract and stimulates the center in the brainstem responsible for na the cardiac and endocrine toxicity of quinine can be attributed to its effec channels.

Bioavailability (%)
76
80
74
>85
Low, varies
>95
90
Time to peak (oral)
1â€“3 h
2â€“5 h
1â€“3 h
8â€“24 h

4â€“7 h
2â€“6 h
3â€“6 h
Protein bound (%)
93
50â€“65
â€”
98
â€”
87
70â€“80
Volume of distribution (L/kg)
1.8â€“4.6
>100
3
15â€“40
>100
3
0.5â€“1
Half-life
9â€“15 h
40â€“55 d
5â€“7 h
15â€“27 d
1â€“6 d
3â€“4 d
21â€“30 h
Urinary excretion (%)
20
55
4
<1
â€”
16â€“32

20

[a] For additional information, see references 5 ,25 ,37 ,43 ,45 ,63 ,86 .

	Quinine	Chloroquine	Primaquine	Mefloquine	Halofantrine

TABLE 56-2. Pharmacokinetic Properties of Antimalarials[a]

Pathophysiology

As in the case of quinidine, the anti- and prodysrhythmic effects of quinir effect on the cardiac sodium channels and potassium channels (Chaps. 23 blockade decreases inotropy, slows the rate of depolarization, slows conc potential duration. Inhibition of the rapid inward sodium current is increas (called *use-dependent blockade*), leading to a rate-dependent widening of the potassium channels suppresses the repolarizing delayed rectifier the rapidly activating component. The resultant increase in the effective dependent, causing greater repolarization delay at slower heart rates. Th predisposes to the development of torsades de pointes. As a result, syncc occur. In addition, syncope may be the result of vasodilation from the Î- quinine.

The mechanism of quinine-induced inhibition of hearing is multifactorial.[1] of the outer hair cells of the cochlea and organ of Corti occurs.[2 , 40] Addit local prostaglandin inhibition within the organ of Corti may contribute to Inhibition of the potassium channel may also be responsible for hearing lo that the homozygous absence of gene products that form part of some p Lange-Nielson syndrome) causes deafness and prolonged QTc intervals (C

The ophthalmic toxicity of quinine is most likely a direct retinal toxic effe studies demonstrate a rapid and direct effect on the retina (decreased p doses of quinine.[37] These early retinographic changes, as well as histolo and ganglion cell layers, provide evidence of direct damage.[37] Changes ir suggesting changes in the retinal pigment epithelium, parallel changes in electrophysiologic, angiographic, or morphologic experimental evidence fo felt to be contributory) has been found.[37 , 41] Quinine may also antagoni

neurotransmission in the inner synaptic layer.

Another effect of quinine is the inhibition of the adenosine triphosphate channels of the pancreatic Î² cells, which results in the release of insulin, sulfonylureas (Chap. 48).[26] The clinical significance of quinine-induced h limited to those patients receiving high-dose IV quinine and to patients v such as concurrent malaria, pregnancy, malnutrition, and alcohol consum

Clinical Manifestations

The margin between therapeutic and toxic dosing of quinine is very smal therapeutic doses often experience a syndrome known as â€œcinchonism, nausea, vomiting, decreased hearing acuity, tinnitus, headache, vertigo, tachycardia, diarrhea, and abdominal pain.[31 , 45 , 58 , 76 , 107] The skin m

The average oral lethal dose of quinine is 8 g, although a dose as small a death.[33 , 45] Delirium, coma, and seizures are uncommon, usually occurri overdoses.[14]

Cardiovascular manifestations of quinine use are related to myocardial dru those of quinidine.[11] They manifest on the ECG as prolongation of the PR QTc interval, and as ST depression with or without T-wave inversion.[11] Pa heart block or dysrhythmias.[11] Patients on high doses of quinine must be pointes, ventricular tachycardia, and ventricular fibrillation. Quinine toxicity significant hypotension, because of vasodilation and probably a concomita contractility.

Ophthalmic presentations include blurred vision, visual field constriction, color perception, mydriasis, photophobia, scotomata, and sometimes con Onset of blindness is invariably delayed and usually follows the onset of least 6 hours. The pupillary dilation that occurs is usually nonreactive an of visual loss. Vermiform motion or tonic pupil with denervation supersen Funduscopic examination may be normal, but usually demonstrates extre associated with optic disc and retinal edema. Normal arteriolar caliber ma manifestations such as vessel attenuation and disc pallor may develop as Improvement in vision can occur rapidly, but is usually slow, occurring ov severe exposure. Initially, improvement occurs centrally and is followed la

peripheral vision. The pupils may remain dilated even after return to nor greatest exposure may develop optic atrophy.

Eighth-nerve dysfunction results in tinnitus and deafness. This causes a r acuity with a flattening of audiograms. The decreased acuity is not usua the patient recognizes tinnitus.[91] These findings usually

resolve within 48â€“72 hours, and permanent hearing impairment is unli

Although mild hyperinsulinemia may occur, hypoglycemia is rare following , [55] , [119] Hypoglycemia with elevated plasma insulin levels following therap patient with severe congestive heart failure,[55] and in a healthy patient w quantity of alcohol.[55] It also has occurred in a healthy patient following

A number of hypersensitivity reactions are described. These are the resul antiquinineâ€“hapten antibodies cross-reacting with a variety of membra Asthma sometimes occurs. Dermatologic manifestations include urticaria cutaneous vasculitis, lichen planus, and angioedema.[90] Hematologic mani are rare, but include thrombocytopenia (Chap. 24), agranulocytosis, mi anemia, and disseminated intravascular coagulation (DIC), which can lea and renal failure.[49] , [95] Hemolysis may also occur in patients with gluco deficiency. Hepatitis is a rare hypersensitivity reaction.[30] Acute respirator and a sepsislike syndrome are also reported.[52]

Diagnostic Testing

Urine thin-layer chromatography is sensitive enough to confirm the prese the ingestion of tonic water.[119] However, this test might not reliably diff quinidine, if the latter is a clinical possibility.

Immunoassay techniques are the most reliable, but quantitative serum tes available. Quinidine immunoassays cannot be substituted. In any case, no be used to determine a unique management intervention, although serum higher in individuals who develop severe toxicity, including blindness. Af serum quinine levels greater than 10 Âµg/mL are associated with tempora Âµg/mL are associated with increased risk of permanent visual damage,[11 [45] Similar levels in individuals who are severely ill with malaria do not re

because of the increase in Î±$_1$ -acid glycoprotein and consequent reductio present.[94 , 99]

Management

Although patients may frequently vomit on their own, emetic agents shoul dysrhythmias, and hypotension can occur rapidly. Because activated char quinine, orogastric lavage should only be performed for patients with rec and no spontaneous emesis. Otherwise, standard overdose management activated charcoal (1 g/kg), and supportive techniques such as oxygen, c infusion, and dextrose as needed. Because toxic manifestations are seru measures to enhance elimination may be effective in preventing or reduc

Cardiac

The cardiotoxic manifestations of quinine make the choice of serum alka intervention. In a case report of a patient with quinine overdose, alkalin was dramatically effective in narrowing the QRS complex, but torsades d perhaps because of hypokalemia combined with quinine-induced potassiu torsades de pointes was responsive in this case only to an overdrive pac should only be given if there is a clear indication of cardiotoxicity. Prolong be treated with sodium bicarbonate alkalinization to achieve a serum pH done in the patients with cardiotoxicity associated with cyclic antidepress Depth: Sodium Bicarbonate). Hypertonic sodium bicarbonate may result exacerbating the effect of potassium channel blockade. The QTc should b prolongation. If necessary, interventions for torsades de pointes, includi potassium supplementation, and overdrive pacing, should be initiated (Ch

Class IA, IC, or III antidysrhythmic agents, those with sodium channel- blocking activity, should not be used to treat a quinine-, quinidine-, or because they may exacerbate the toxin-related conduction disturbances o agents, such as lidocaine, may be useful (Chap. 61).

Extracorporeal membrane oxygenation (ECMO) was used in one case of s bradydysrhythmia and refractory hypotension[105] to stabilize the cardiovas quinidine-activated charcoal bezoar was removed, and the patient metab

A similar approach should be considered for intractable quinine toxicity.

Ophthalmic

Funduscopic examination, visual field examination, and color testing may diagnostic studies. Electroretinography, electrooculogram, visual-evoked p adaptation may be helpful in assessing the injury, but are not practicable equipment that is not portable or readily available in most clinical setting effective treatment for quinine retinal toxicity.[37 , 38] Hyperbaric oxygen (H who recovered vision, but the role of HBO in that recovery was not estab

Hypoglycemia

Serum glucose should be supported with an adequate infusion of dextrose QTc interval should be monitored during correction and maintenance. Diaz serum glucose.[80] Octreotide, a somatostatin analog that blocks insulin sec hypoglycemia. It was administered intravenously in a dose of 50 Âµg/h t hyperinsulinemia in adult malaria victims.[80 , 81] In volunteers, quinine-in suppressed within 15 minutes following a 100-Âµg intramuscular dose of Depth: Octreotide).[81]

Enhanced Elimination

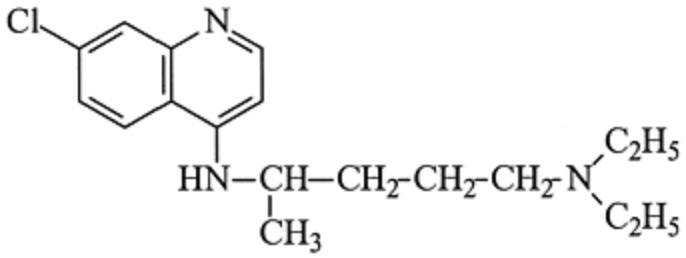
The effect of multiple-dose activated charcoal (MDAC) on quinine eliminati experimental human model as well as in symptomatic patients.[59 , 84] In t decreased the half-life of quinine from approximately 8 hours to about 4. clearance by 56%.[84] Although numerous studies show that activated char life,[8 , 57 , 84] it is unclear whether this reduction in half-life improves cl because ophthalmic, CNS, and cardiovascular toxicity are related to serur to reduce concentrations as quickly as practicable; thus, activated charco administered every 2â€“4 hours unless otherwise contraindicated.

There is conflicting evidence about a benefit of urinary acidification in en However, because of the increased potential for cardiotoxicity associated technique is never recommended. Forced diuresis is similarly not helpful a

single study, the mean half-life of quinine in the forced acid diuresis grou compared to 26.5 hours in the control group.[8]

Because quinine has a relatively large volume of distribution and is highl dialysis, hemoperfusion, hemodialysis, and exchange transfusion have only removal.[8,14,62,68,94,107] Although the blood compartment can be cl these techniques, total body clearance is only marginally altered. After tl occurs, there is little impact on the total body burden because of the rela distribution and the very extensive protein binding.

Chloroquine, Hydroxychloroquine, and Am



Chloroquine

The structurally related compounds chloroquine and amodiaquine were on malaria prophylaxis. However, with the development of resistance, they a regions. Amodiaquine is also rarely used because of a higher incidence o

Hydroxychloroquine is similar to chloroquine in therapeutic, pharmacokin properties.[32,62] The side-effect profiles of the two are slightly different, malarial prophylaxis and hydroxychloroquine use as an antiinflammatory

Pharmacokinetics and Toxicodynamics

Oral chloroquine is rapidly and completely absorbed (Table 56-2) and is tissues, particularly kidney, liver, and lung, and to erythrocytes.[13,40] Co very large apparent volume of distribution of >100 L/kg.[107] Whole-blood reflects tissue distribution and correlates with mortality.[22] About half of eliminated in the urine, as much as 70% as the parent molecule, and the

hepatic metabolites.[54, 62] An exceedingly long half-life, averaging 41 da
Hydroxychloroquine has a similarly rapid absorption and a half-life of 40
However, half-life in overdose is reported to be 15â€“30 hours.[47]

Pathophysiology

Like quinine, chloroquine has a small toxic-to-therapeutic margin. Severe
usually associated with ingestions of 5 g or more in adults, or with serur
Âµg/mL. The cardiovascular effects of chloroquine and hydroxychloroquine
quinine, including QRS prolongation, atrioventricular (AV) block, ST- and
U waves, and QTc interval prolongation, but other features of cinchonism
xenobiotics have low toxicity when used in therapeutic doses. Because of
first-line drug for malaria prophylaxis and treatment in areas where *Plasr*
changes are not described with prophylactic doses but occur rarely with
hydroxychloroquine for arthritis. The variation in individual risk for this
understood. Recent evidence suggests an early, pathological role for mer
the ganglion cells of the retina.[70] Melanin granules are also noted in the
the retina, but this occurs late.[58, 70] A related process involving skin me
pruritus frequently noted in Africans who use these drugs (8â€“20%).[58]

In some hosts, amodiaquine metabolism produces a quinone imine metabo
hapten to induce a hypersensitivity reaction.[16] This has led to reduced us
prophylactic agent, particularly among Western travelers. Nonetheless, the
tropical countries for treatment of acute and chronic malaria.

Clinical Manifestations

Symptoms usually occur within 1â€“3 hours of ingestion.[88] The range of
chloroquine toxicity is quite similar to quinine, but the frequencies of va
Nausea, vomiting, diarrhea, and abdominal pain are less common than w
depression often occurs. Apnea, hypotension, and cardiovascular compron

Hypotension is a more prominent feature than with quinine.[45] Electrocardio
associated with chloroquine use include QRS prolongation, AV block, ST-
increased U waves, and QTc interval prolongation, but these are less frec
Significant hypokalemia is invariably associated with the cardiac manifes

results from direct chloroquine-induced intracellular shifts.

The neurologic manifestations include CNS depression, dizziness, headach dystonic reactions occur.[77] Transient parkinsonism has been reported fol

The ophthalmic manifestations are infrequent in acute toxicity, usually le in nature.[45 , 58] More severe and irreversible vision and hearing changes with the use of chloroquine and hydroxychloroquine as antiinflammatory neuropathy, and cardiomyopathy also are described in this context.[5 , 114 hypersensitivity reactions similar to those associated with quinine are de oxidant stress from chloroquine may result in hemolysis in patients with dehydrogenase (G6PD) deficiency (Chap. 24).

Acute hydroxychloroquine toxicity is similar to chloroquine toxicity.[47 , 63 doses include nausea and abdominal pain, hemolysis in G6PD-deficient pa damage, sensorineural deafness, and hypoglycemia.[10 , 46 , 98] Hypersensit myocarditis and hepatitis, are described.[34 , 61]

One report of amodiaquine toxicity suggests that neurologic toxicity incl muscle stiffness, dysarthria, syncope, and seizures may occur.[45] Amodiaq hypersensitivity hepatitis and neutropenia in prophylactic use, but not th overdose experience reported.

Management

Early, aggressive management of severe chloroquine toxicity decreased th from 91% to 9%.[88] The protocol involves the use of epinephrine for ch and myocardial depression, and diazepam for possible direct cardiovascula minimize CNS-based cardiac excitation.[89] Other experiences validate this

Patients should receive early endotracheal intubation and mechanical ven used to facilitate intubation, its use immediately preceded sudden cardiac after chloroquine overdose.[22] An adequate FiO_2 , tidal volume, and venti Orogastric lavage should be performed for patients with recent and subs charcoal should be administered. During decontamination, 2 mg/kg IV dia minutes, and then 1â€“2 mg/kg/d for 2â€“4 days. Simultaneously, epine should be given IV with D_5 W, and adjusted incrementally until a systolic

100 mm Hg is achieved. Even after this initial therapy, some patients ma cardiovascular compromise and require additional epinephrine and other complex width is increased, sodium bicarbonate should be administered a potassium concentrations should be monitored and potassium supplemen aggressive replacement therapy is discouraged, because hypokalemia rep total-body potassium depletion.[21 , 45 , 47]

Because chloroquine and hydroxychloroquine have high volumes of distri binding, and long terminal elimination half-lives, enhanced elimination pr [, 45]

Primaquine

Pathophysiology

Primaquine causes RBC oxidant stress. Clinically insignificant methemoglo Methemoglobinemia and hemolysis can occur in normal individuals given toxicity of primaquine in therapeutic use has been hemolysis in G6PD-de contraindicated in pregnant women because the fetal G6PD status is unk suppression can occur.

Clinical Manifestations

Overdose with primaquine is rarely reported. Nausea, headache, and abd A case of extreme, iatrogenic overdose (1260 mg followed by 15 mg/d for hallucinations, abdominal cramps, nausea, jaundice, hepatitis, and black 7.4 mg/dL. Aminotransferases peaked at aspartate aminotransferase (AST) aminotransferase (ALT) 2654 IU/L. Renal function, hemoglobin, and white reported. Resolution occurred over 1 month.

Management

In the event of overdose, therapy should be directed at minimizing abso decontamination, reversing significant methemoglobinemia with methylene Antidotes in Depth: Methylene Blue), supporting adequate circulating red

necessary, and preventing hemoglobin-induced renal injury by maintaining alkalinizing the urine to a pH greater than 6, if necessary (Chap. 10 , Ant Bicarbonate , and Antidotes in Depth: Activated Charcoal).

Mefloquine

Pharmacokinetics and Toxicodynamics

Mefloquine is slowly absorbed (Table 56-2).[96] Absorption is enhanced wit protein bound and has a very large volume of distribution (22 L/kg).[49 , 9 in an inactive metabolite, with a terminal elimination half-life of 18 days variation occurs.[96] Because it has such a long half-life, it may take sever state, delaying the onset of toxic manifestations.

Clinical Manifestations

Common effects with prophylactic and therapeutic dosing include nausea, These effects are noted particularly in children and older adults, or with are expected in acute overdose.[90 , 116]

Mefloquine has a mild cardiodepressant effectâ€”less than that of quinine clinically significant in prophylactic dosing or with therapeutic administrat neither the PR interval nor the QRS complex is prolonged, but QTc prolo Clinically insignificant bradycardia is common.[58 , 74] Reports of torsades increase in QTc and risk of torsades de pointes are increased when meflo chloroquine, or, most particularly, with halofantrine.[58 , 73 , 74] Risk is als acute overdose. The long half-life of mefloquine, about 18 days, means th taken with therapeutic use of these xenobiotics when breakthrough mala prophylaxis, or within 28 days of mefloquine therapy. Given the lack of quinine is often used.

During prophylactic use, many patients experience insomnia, an alteration dizziness, headache, fatigue, mood alteration, and vertigo.[96 , 110] In only effects significant enough to cause the traveler to â€œfeel sickâ€• or to [97] Intolerance occurs more commonly in women.[7 , 79 , 110] Seizures occur and therapeutic use.[83 , 92] In many of these cases, there is a history of

first-degree relative, or other risk factors. Other neuropsychiatric sympto â€œcloudedâ€• consciousness, toxic encephalopathy, anxiety, depression, delirium with psychosis, comprise the bulk of serious adverse event repor related to the serum or CNS concentration. The frequency of hallucination about 1:10,000 with prophylaxis to as high as

1:200 with therapeutic dosing.[25,90] In at least one case report, the se manifestations of mefloquine were reversed with physostigmine, suggesti etiology.[102] Risk of CNS toxicity is increased by administration of quinine mefloquine. A self-resolving postmalaria neurologic syndrome including c tremor is associated with therapeutic use of mefloquine for severe malari

The effect of mefloquine on the pancreatic potassium channel is much less resulting in only a mild increase in insulin secretion.[26,27] Symptomatic h reported as an effect of mefloquine alone in healthy individuals, but has of alcohol and in a severely malnourished patient with AIDS.[4,27,58] In accompanied by alcohol use or recent starvation, this hypoglycemia may

Rare events reported with prophylaxis include urticaria, alopecia, erythem necrolysis, myalgias, mouth ulcers, neutropenia, and thrombocytopenia.[6] likely hypersensitivity reactions. It is unclear which, if any, would be sign large dose ingestion. ARDS was linked to therapeutic dosing in 1 case.[108]

In therapeutic use, mefloquine is associated with an increased incidence quinine and a group of other antimalarial medications.[75] Mefloquine was n increased incidence of abortion, low birth weight, mental retardation or implications for an overdose in the absence of malaria are not clear, but instituted.

In contrast, the consequences of excessive dosing are not only severe, b permanent. Two cases of daily mefloquine overdosing resulted in confusi speech difficulties, and high-frequency hearing loss in 1 case, and nausea depression, disorientation, and paresthesia in the other. In the first case, year, except for residual hearing loss.[56] In the second case, symptoms p another case, a man ingested 5.25 g of mefloquine over 6 days.[15] Sympto myalgia, vertigo, visual accommodation difficulties, mild hypotension (90/5 beats/min) with occasional ventricular premature complexes, minimal incre

and prolonged INR. His symptoms resolved over 5 days, except for the v 2 months. The INR corrected over 2 weeks. In this case, cardiovascular s significant than were neurologic symptoms. A fourth man ingested mefloc 3250 mg, and sulfadoxine-pyrimethamine 175 mg/3500 mgâ€”2.5 times t eachâ€”over 3 days.[18] He suffered encephalopathy that was unresolved 8 patient took mefloquine 2 g over 2 days (the usual therapeutic dose is 1: malaria.[72] At presentation he experienced nausea, constipation, and abdor headache, vertigo, insomnia, anxiety, confusion, hallucinations, and paran findings. ECG and laboratory findings were normal. No other drugs were d elevated mefloquine level of 1.8 Âµg/mL (upper limit of therapeutic 1 Âµ with only supportive care.

Management

In overdose, supportive care is the primary therapy. Decontamination wit indicated if the patient presents soon after the ingestion. Specific monito hypoglycemia, and liver injury should be provided. Patients should be foll nerve complications.

In 2 renal-failure patients taking mefloquine, prophylactic hemodialysis di Given the large volume of distribution and high degree of protein binding unlikely to be effective.

Halofantrine

Pharmacokinetics and Toxicodynamics

Halofantrine is slowly and incompletely absorbed (Table 56-2).[17 , 45] It i metabolite, *N* -desbutylhalofantrine.[17] The half-life of halofantizine is 1â€ the QTc interval is proportional to the dose and serum halofantrine conc percent of children receiving a therapeutic course of halofantrine will have msec.[101]

Clinical Manifestations

The primary toxicity from therapeutic and supratherapeutic doses is torsa fibrillation associated with prolongation of the QTc interval.[23 , 39 , 73 , 10 and syncope may occur. First-degree heart block is common, but bradyca QTc interval duration is related to serum concentration, dysrhythmias wou Dysrhythmias are also likely in the context of combined overdose or con with other drugs that cause QTc interval prolongation, particularly meflo

Other side effects, including nausea, vomiting, diarrhea, abdominal cramp headedness, which frequently occur in therapeutic use, are also expected frequently described side effectsâ€”pruritus, myalgias, and rigorsâ€”can oc seizures, minimal liver enzyme concentration elevation, and hemolysis ar Whether these manifestations are related to halofantrine or to the underl

Management

Management of halofantrine overdose should also focus on decontaminati monitoring for QTc interval prolongation and associated dysrhythmias. Trea prolonged QTc interval and torsades de pointes is discussed above under

Proguanil, Pyrimethamine, Sulfadoxine, Dap Atovaquone

Pharmacokinetics and Toxicodynamics

Proguanil, pyrimethamine, sulfadoxine, and dapsone all interfere with fola used in combination. Proguanil (chloroguanide) may be used alone, but is (Lapdap), chloroquine, or the antiparasitic atovaquone (Malarone) for pr the de novo pyrimidine synthesis that is necessary for protozoal survival unnecessary in mammalian cells. Based on the relative side-effect profile, physicians are

switching from mefloquine to atovaquone/proguanil for routine antimalari Atovaquone and proguanil may now be the most common antimalarial age Pyrimethamine is used in combination with sulfadoxine (Fansidar) or with growing malarial resistance has limited the usefulness of these two drug

for pharmacokinetic profile). Genetic polymorphism is described in the m dapsone.[48 , 87] This may be the cause of the significant hypersensitivity dapsone.[87]

Clinical Manifestations

Information on proguanil overdose is limited. The side effects of proguan nausea, diarrhea, and mouth ulcers.[58] Because of interference with folate rare complication. Folate supplementation may be required in pregnancy neutropenia, thrombocytopenia, rash, and alopecia are also noted.[25] In a hypersensitivity hepatitis was described.[25] When used to treat malaria, vomiting, sometimes severe, in a significant portion of patients (15â€“45 associated with elevated liver function tests.[90]

Atovaquone alone, primarily used to treat *Pneumocystis carinii* in AIDS p tolerated.[78] Side effects include maculopapular rash, erythema multiform complaints, and mild aminotransferase elevations. Three cases of 3- to 4 dosing have been reported.[20] No symptoms occurred in 1 case (at 3 tim Rash occurred in another, and in the third case, methemoglobinemia was overdose of dapsone.

Dapsone and the sulfonamides have a long history of causing idiosyncrat neutropenia, thrombocytopenia, eosinophilic pneumonia, aplastic anemia, [90] The rare occurrence of life-threatening erythema multiforme major, a sulfadoxine prophylaxis, has limited the use of this combination for prop

Acute ingestion of dapsone may result in nausea, vomiting, and abdomina dapsone produces RBC oxidant stress leading to methemoglobinemia and, sulfhemoglobinemia (Chap. 122).[19 , 59] The onset of hemolysis may be delayed.[121] Other symptoms, particularly tachycardia, dyspnea, dizziness seizure, syncope, and coma resulting from end-organ hypoxia, can occur. described in overdose include hepatitis and peripheral neuropathy.[45]

Overdose of pyrimethamine alone is rare. In children, it results in nausea seizures, fever, and tachycardia.[1 , 45] Blindness, deafness, and mental re Seizures were attributed to sulfadoxine-pyrimethamine in an overdose of 1 dose is 3 tablets taken once).[72] Chronic high-dose use may be associated

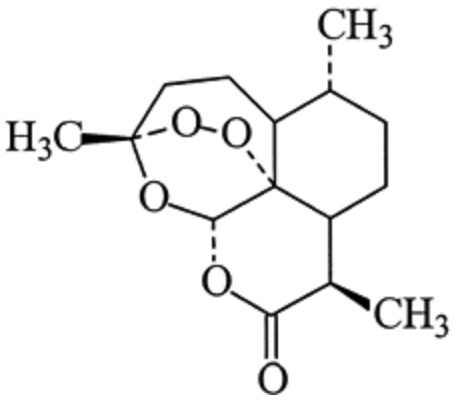
requiring folate replacement (Chap. 24 and Antidotes in Depth: Folic Acid).[1]

Management

Folate supplementation should be considered after overdose of proguanil in Depth: Folic Acid and Leucovorin [Folinic Acid]). Other efforts should

Following dapsone ingestion, clinically significant methemoglobinemia shou blue (Antidotes in Depth: Methylene Blue). Sulfhemoglobinemia is irreve insignificant portion of total hemoglobin. Both hemodialysis and multidose elimination of dapsone during therapy.[71 , 121] Multidose activated charcoa the treatment of dapsone overdose.[3] Required support may include RBC alkalinization if hemolysis is extensive (Antidotes in Depth: Sodium Bicar

Artemisinin and Derivatives



Artemisinin

Pharmacokinetics and Toxicodynamics

Artemisinin and its derivatives: artemether, arteether, dihydroartemisinin the Chinese herb qinghaosu. They were introduced in the 1980s in China and since then millions of doses have been used in Asia and Africa.

The parent drug artemisinin has poor solubility and limited bioavailablilty

absorption and some may be used parenterally, but are rapidly degraded half-life. Because these xenobiotics have a short half-life, prolonged cours prevent recrudescence of malaria. To provide a shorter, more effective tr emergence of malarial resistance, artemesinins are frequently used in co Recently the oral combination drug artemether/lumefantrine was introduc evaluating a combination of artemisinin and naphthoquine.[112]

The efficacy and toxicity of artemisinin is thought to be a result of the al core to form intracellular free radicals, particularly in the presence of hen brainstem nuclei is consistently produced following prolonged, high-dose These findings are associated with prolonged CNS exposure to parenteral xenobiotics.[35 , 90] Embryonic loss has also been observed in animals.[90]

Clinical Manifestations

In contrast to the experience with animals, the experience of more than shows that these xenobiotics have a very low incidence of side effects.[90] include nausea, vomiting, abdominal pain, diarrhea, and dizziness.

Prospective studies have failed to identify an increased incidence of adve particularly related to the brainstem.[51 , 90] Rare reports of adverse CNS suggest the possibility of CNS depression, seizures, or

cerebellar symptoms following intentional self-poisoning. In children with incidence of seizures and a delay to recovery from coma were noted in a neurologic difference was noted in long-term follow-up. In an artemether adults with severe malaria, recovery from coma was also prolonged in th number (<1%) of patients receiving an artemisinin derivative in two oth transient dizziness or cerebellar signs.[66 , 85] Most recovered within days. suffered prolonged symptoms, 1 month and 4 months, respectively, but [85] The attribution of these symptoms to artemisinin compounds, as oppos malaria, is debatable.

When serial ECGs were obtained, a small, but statistically significant fall i coincident with peak drug levels.[66] In one therapeutic trial, 7% of adult had an asymptomatic QTc interval prolongation of at least 25%.[43] Change

noted.

In contrast to the effects of quinine therapy, hypoglycemia is not reporte neutropenia, reticulocytopenia, anemia, eosinophilia, and elevated concer aminotransferases.[90]

There is little experience with the toxicity of lumefantrine alone. Lumefa related to mefloquine and halofantrine, but similar toxicity has not been product artemisinin-lumefantrine is well tolerated.[117] Studies of the com lumefantrine do not show an increase in QTc or evidence of cardiac toxic [111] Cough and angioedema were described in one case.[53]

Management

Overdose patients should be managed with supportive measures and exp cardiovascular monitoring. CNS manifestations are the most likely.

Summary

A variety of xenobiotics are used in the prevention and treatment of mala consequently, the most widely available xenobiotics, change rapidly with resistance. Most antimalarials have significant toxicity in acute overdose. are related to quinine, even within the quinine group, the pattern of prec xenobiotic dependent. Effects at the low doses associated with prophylaxi vomiting, headache, and confusion. Autoimmune-mediated idiosyncratic re most of the antimalarials. In overdose, cardiovascular, neurologic, and h predominate. Dysrhythmias are the effects that are the most life-threate derivatives and especially with chloroquine. These result from sodium ch potassium channel blockade, and myocardial depression. Other significant and neurologic injury, particularly to the special senses. Primaquine and oxidant stress resulting in methemoglobinemia. Little is known of the acu agent, artemisinin.

Decontamination, including the administration of activated charcoal, is r specific symptoms are anticipated and specific management strategies fol resulted, particularly for chloroquine poisoning. Multidose activated charc for quinine and dapsone ingestions.

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Chapter 57
Anticoagulants

Mark Su

Robert S. Hoffman

A 66-year-old man presented to the emergency department with a compl of 24 hours of lower abdominal pain that radiated to his left groin. The pa had increased in intensity and resulted in syncope. His past medical histo was significant for atrial fibrillation, hypertension, congestive heart failur colonic polyps, diverticulosis, cataracts, and sciatica. His medications inc warfarin 2.5 mg daily, oxybutynin chloride 2 mg twice daily, labetalol 300 three times daily, quinapril 40 mg daily, rofecoxib 25 mg daily, and zolpi 10 mg as needed for sleep.

On physical examination, he was awake and alert, but ill appearing and p Vitals signs were blood pressure, 101/38 mm Hg; pulse, 92 beats/min; respiratory rate, 18 breaths/min; temperature, 98.6Â°F (37Â°C); symptomatic orthostasis was present. Examination of the head, eyes, ear nose, and throat was unremarkable. His chest was clear to auscultation bilaterally, and heart examination revealed an irregularly irregular rate. T patient's abdomen was noted to be moderately distended and tender in th left upper quadrant and left flank with scrotal edema. Rectal examination

testing for occult blood were negative. The skin and extremities were nor with no evidence of petechiae or ecchymoses.

The patient was immediately given 100% oxygen via a non-rebreather m treated with intravenous 0.9% sodium chloride via 2 large-bore catheters and blood was drawn for laboratory studies. An electrocardiogram demonstrated atrial fibrillation, at a rate of approximately 100 beats per minute, without evidence of acute myocardial ischemia or infarction.

Initial laboratory studies showed a white blood cell (WBC) count of $14,000/mm^3$, hemoglobin 10.3 g/dL, hematocrit 32.1%, and platelets $317,000/mm^3$. The initial prothrombin time (PT) was 66.7 seconds (international normalized ratio [INR] of 5.7), and activated partial thromboplastin time (PTT) was 81.4 seconds. Urinalysis revealed a specif gravity of 1.025; small bilirubin; trace ketones; 100 mg/dL protein; and red blood cells.

After discovering the patient's coagulopathy, he was given 10 mg of vitar K_1 subcutaneously. He was also given 4 units of fresh-frozen plasma base his weight and then taken emergently for a noncontrast abdominal compu tomography (CT) scan of the abdomen, which revealed a large retroperit hematoma, extending from the inferior pole of the spleen into the pelvis 57-1). On repeat abdominal computed tomography scan with contrast 3 hours later, the retroperitoneal hematoma was noted to have increased in size.

The patient was admitted to the surgical intensive care unit where his re coagulation studies were significant for a PT of 27 seconds, an INR of 2.3 and a PTT of 56.2 seconds. His hematocrit decreased to 22.6%, and he received an additional 6 units of fresh-frozen plasma and 6 units of packe red blood cells prior to surgery. Intraoperatively, a large hematoma with was evacuated and although no active bleeding was visualized at the time the retroperitoneal blood was believed to originate from his psoas muscle The patient had an uneventful course postoperatively and was discharged home 5 days later.

History and Epidemiology

Anticoagulants have numerous clinical applications, including the treatmer coronary artery disease, cerebrovascular events, deep venous thrombosis and pulmonary embolism.

The origins and discovery of anticoagulants are extraordinary.[1, 18, 74] The discovery of modern-day oral anticoagulants originated following investigations of a hemorrhagic disorder in Wisconsin cattle in the early 2 century that resulted from the ingestion of spoiled sweet clover silage. Th hemorrhagic agent, eventually identified as bishydroxycoumarin, would be precursor to its synthetic congener warfarin (named after the *W* isconsin lumni *R* esearch *F* oundation). This knowledge also led to the use of warf as a rodenticide. â€œSuperwarfarinsâ€• were subsequently developed as selective pressure caused rats to develop genetic resistance to warfarin. These potent agents permitted either small, repetitive ingestions or singl larger ingestions to successfully function as rodenticides.

Like warfarin, the origins of the anticoagulant heparin are equally fascina A medical student initially attempting to study ether-soluble procoagulant agents derived from porcine intestines,

serendipitously found that, over time, these apparent â€œprocoagulantsâ actually prevented the normal coagulation of blood. The phospholipid anticoagulant responsible for this effect would later be identified as an ea form of heparin. Shortly thereafter, the water-soluble mucopolysaccharid termed *heparin* (because of its abundance in the liver) was then discover *Unfractionated* heparin is a mixture of polysaccharide chains with varying molecular weights. Following the identification of the active pentasacchar segment of heparin in the 1970s, multiple *low-molecular-weight* heparins were isolated and synthetic forms created.

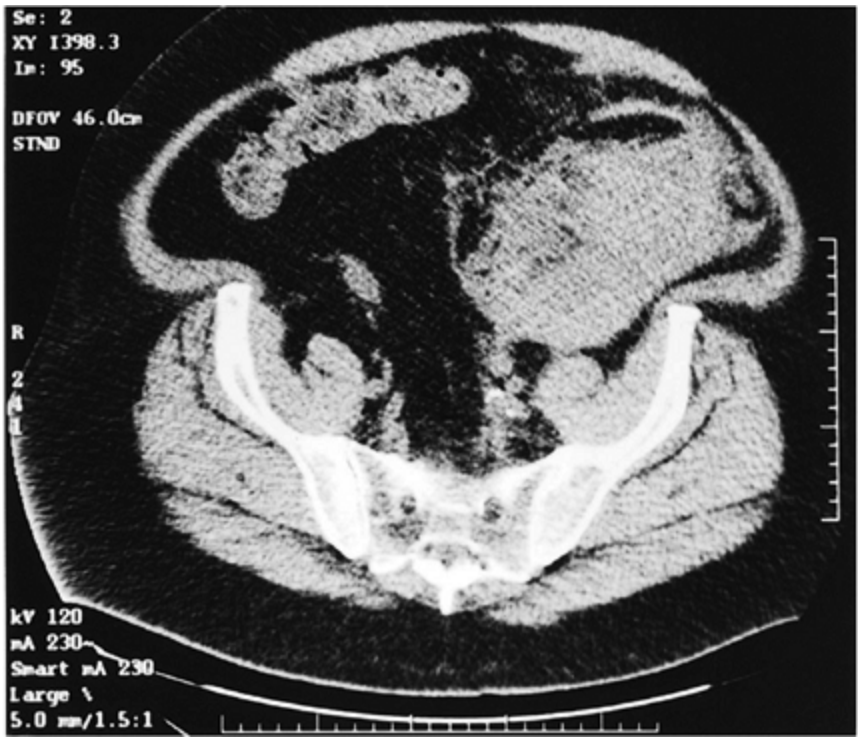


Figure 57-1. Abdominal CT scan illustrating a large left-sided retroperit hematoma in a patient with an INR of 5.7 presenting with left flank pain radiating to the groin.

In the late 19th century, human urine was noted to have proteolytic activ with a specificity for fibrin. A substance found to be an activator of endogenous plasminogen leading to the consumption of fibrin, fibrinogen, other coagulation proteins was isolated and purified and given the name *urokinase.* Streptokinase, a protein produced by Î²-hemolytic streptococc tissue plasminogen activator (t-PA), and other synthetic thrombolytic age were later discovered. Although known to exist for many years, ancrod (Arvin; a purified derivative of snake venom) and hirudin (a product of leeches) only recently gained attention as naturally occurring antithromb therapeutic agents.

The diversity of these anticoagulant and fibrinolytic agents has led to eve increasing use in many fields of medicine. Warfarin is the most common anticoagulant in use today because of its uses in patients with cerebrovascular disease, cardiac dysrhythmias, and thromboembolic dise

During the period of 1999â€“2003, the total number of cases of reported warfarin exposures to the Toxic Epidemiologic Surveillance System was 11,544 with 22 deaths (Chap. 130). Throughout this time, there was a general trend toward an increasing number of reports. Additionally, beca the common problem of excessive warfarin effects leading to hemorrhage poorly quantitated as an adverse drug reaction, it frequently goes untabulated. Thus, as long as warfarin continues to be routinely prescribe is likely that the incidence of adverse drug events will increase. Physician must be cognizant of the complications of warfarin and other anticoagula as well as their various therapeutic modalities, while balancing the poten for their risk and benefits.

Physiology

Balance Between Coagulation and Anticoagulation

An understanding of the normal function of the coagulation pathways is essential to appreciate the etiology of a coagulopathy. This section summarizes the critical steps of the coagulation cascade. For additional detail, the reader is referred to Chap. 24 and several reviews.[64 , 125 , 15

Coagulation consists of a series of events that prevent excess blood loss assist in the restoration of blood vessel integrity. Although the traditional understanding of the events that occur in the coagulation cascade,[49 , 110 discussed below, adequately describe in vitro events, the current understanding emphasizes some distinct differences that occur in vivo.[64 , 151] Despite these differences, an understanding of the traditional model most useful for interpreting the results of diagnostic tests of coagulation.

Within the cascade, coagulation factors exist as inert precursors and are transformed into enzymes when activated. Activation of the cascade occu through one of two distinct pathways, the intrinsic and extrinsic systems 57-2).[49 , 110] Once activated, these enzymes catalyze a series of reactio that ultimately converge and lead to the generation of thrombin and the

formation of a fibrin clot.

The intrinsic pathway is activated by the complexation of factor XII (Hag factor), with high-molecular-weight kininogen (HMWK) and prekallikrein, vascular subendothelial collagen. This results in sequential activation of XII, active kallikrein, active factors IX to XI, and prothrombin (factor II) 57-2). Prothrombin is converted to thrombin in the presence of factor V, calcium, and phospholipid. The integrity of this system is usually evaluate determining the partial thromboplastin time (PTT).

In the extrinsic, or tissue factor-dependent pathway, a complex is formed between factor VII, calcium, and tissue factor, which is released following injury. A calcium and lipid-dependent complex is then created between fa VII and X. The factor VII-X complex subsequently converts prothrombin t thrombin, which promotes the formation of fibrin from fibrinogen (Fig. 57 The integrity of this pathway is usually assessed by determining the prothrombin time (PT or INR).

Activation of factor X provides the important link between the intrinsic ar extrinsic coagulation pathways. Additional evidence that tissue factors ca activate both factors IX and X suggests that there are more interrelations between the two pathways.[137] Furthermore, cell surfaces facilitate the process of clotting. Platelets are also known to interact with proteins of t coagulation cascade through surface receptors for factors V, VIII, IX, and X.[67, 114, 168] As a final step, factor XIII assists in the cross-linking of fi to form a stable thrombus.

Antithrombin III (AT), protein C, and protein S serve as inhibitors, maintaining the homeostasis that is required to prevent spontaneous clot and keep blood fluid. Protein C, when aided by protein S, inactivates two plasma factors, V and VIII.[27, 41, 64] AT complexes with all the serine protease coagulation factors (factor Xa, factor IXa, and contact factors, including XIIa, kallikrein, and HMWK), except factor VII.[27, 64, 151]

Thrombolytic agents such as streptokinase, urokinase, anistreplase, and recombinant tissue plasminogen activator (rt-PA) enhance the normal processes that lead to clot degradation.[125]

Thrombosis is initiated when exposed endothelium or released tissue fact leads to platelet adherence and aggregation, the formation of thrombin, a cross-linking of fibrinogen to form fibrin

strands.[64 , 125 , 151] This results in a hemostatic plug or thrombus forma Thrombus formation, in turn, leads to generation of plasmin from plasminogen, which causes fibrinolysis and eventual dissolution of the hemostatic plug.[43 , 44] Thus the fibrinolytic system may be thought of as natural balance against unregulated coagulation. Thrombolytic therapy increases fibrinolytic activity by accelerating the conversion of plasminoge plasmin, which actively degrades fibrin.[43 , 44] Following the administration thrombolytic agents, a consequential drug-induced coagulopathy ensues, fibrin degradation products are elevated secondary to the rapid turnover clot.

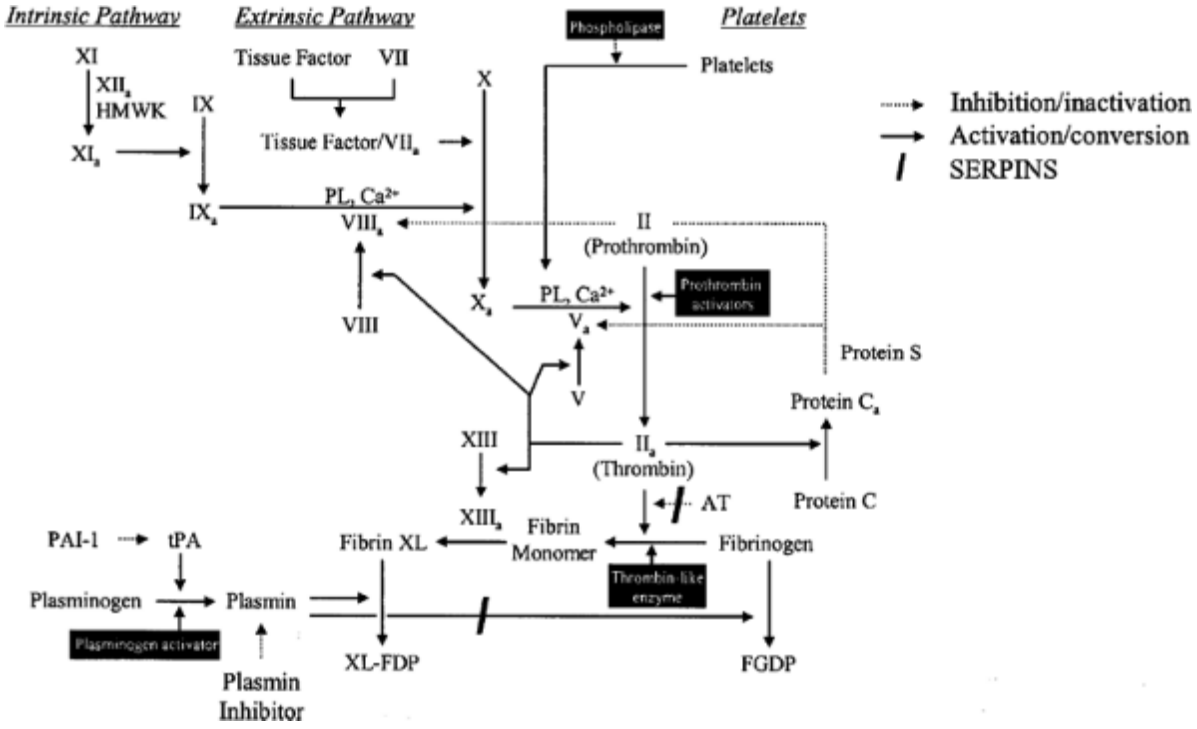


Figure 57-2. The figure presents a schematic overview of the coagulatio and fibrinolytic pathways and indicates where phospholipids on the platel surface interact with the coagulation pathway intermediates. Arrows are shown from platelets to phospholipids involved in the tissue factor VII_a a

the factor IX_a â€“$VIII_a$ interactions to avoid confusion. Interactions of selected venom proteins are indicated in the black boxes. The diagram is complete with reference to the multiple sites of interaction of the SERPIN (serine protease inhibitors) to avoid overcrowding.[115] PL = platelets; XL cross-linked.

Development of Coagulopathy

Impaired coagulation results from decreased production or enhanced consumption of coagulation factors, the presence of inhibitors of coagula activation of the fibrinolytic system, or abnormalities in platelet number function. Platelets are involved in the initial phases of clotting following b vessel injury by assisting in the formation of the fibrin plug. For the purp of this chapter, a discussion of platelet-related abnormalities is excluded. Some of this information can be found in Chap. 24 .

Decreased production of coagulation factors results from congenital and acquired etiologies. Although congenital disorders of factor VIII (hemoph factor IX (Christmas factor), factor XI, and factor XII (Hageman factor) a all reported, their overall incidence is still quite low. Clinical conditions th result in acquired factor deficiencies are much more common and result f either a decrease in synthesis or activation. Factors II, V, VII, and X are entirely synthesized in the liver,[64 , 125 , 151] making hepatic dysfunction common cause of acquired coagulopathy. In addition, factors II, VII, IX, X require postsynthetic activation by an enzyme that uses vitamin K as a cofactor,[173 , 178 , 179] such that vitamin K deficiency (from malnutrition, changes in gut flora secondary to xenobiotics, or malabsorption), or inhil of vitamin K cycling (from warfarin, as will be described), is capable of impairing coagulation.

Excessive consumption of coagulation factors usually results from massiv activation of the coagulation cascade. Massive activation occurs during s hemorrhage, or disseminated intravascular coagulation. The latter results from infection, such as sepsis, and from conditions that introduce tissue factor into the blood, such as neoplasms, snake envenomations, stagnant

blood flow, diffuse endothelial injury secondary to hyperthermia, ruptured aortic aneurysm, or aortic dissection. The hallmark of a consumptive coagulopathy is a depressed level of fibrinogen with an elevation of fibrin degradation products. This combination suggests the rapid turnover of fil in the coagulation process. In the other coagulopathic conditions, the fail to activate the coagulation cascade is associated with normal or high fibr levels and low fibrin-degradation products because of limited clot formati

Inhibitors of the coagulation cascade (circulating anticoagulants) are of t types: immunoglobulin and nonimmunoglobulin. Immunoglobulins, which often antibodies to existing coagulation factors, may occur without obviou cause. They may be part of a systemic autoimmune disorder or as a resul repeated transfusions with exogenous factors (as occurs in hemophilia).[7 105 , 163] The clinical syndromes associated with antibody inhibitors are s to those associated with deficiencies of the particular coagulation factors involved. Antibodies to factors V, VII to XI, and XIII are described in the literature.[22 , 163] Alternatively, nonimmunoglobulin neutralizers of coagulation occur in conditions associated with rapid white blood cell turnover.[22] These lysosomal cationic proteins are neutralizers that

compete with coagulation factors for negatively charged phospholipid membrane surfaces. Although they prolong in vitro coagulation times, the are rarely responsible for clinical coagulopathy because of the excess of phospholipid surface area available in vivo.[77 , 105]

Oral Anticoagulants

Warfarin and â€œWarfarinlikeâ€• Anticoagulants

Oral anticoagulants can be divided into two groups: (a) hydroxycoumarin including warfarin (commonly called by its trade name Coumadin), difenacoum, panwarfarin, warficide, coumachlor, coumafuryl, fumasol, pr ethyl biscoumacetate (Tromexan), phenprocoumon, dicumarol

bishydroxycoumarin, and acenocoumarin (Sintrom); and (b) indanediones including chlorophacinone, pindone, pivalyn, diphacinone, diphenadione, phenindione, and anisindione. Regardless of the classification, the mecha of action involves inhibition of the vitamin K cycle. Vitamin K is a cofactor the postribosomal synthesis of clotting factors II, VII, IX, and X (Fig. 57- The vitamin K-sensitive enzymatic step that occurs in the liver involves t Î³-carboxylation of 10 or more glutamic acid residues at the amino termi end of the precursor proteins, to form a unique amino acid Î³-carboxyglutamate.[54, 173, 178, 179] These amino acids chelate calcium in vivo, which allows the binding of the four vitamin K-dependent clotting fa to phospholipid membranes during activation of the coagulation cascade.[1

Vitamin K is inactive until it is reduced from its quinone form to a quinol hydroquinone) form in hepatic microsomes. This reduction of vitamin K m precede the carboxylation of the precursor factors. The carboxylation act is coupled to an epoxidase activity for vitamin K, whereby vitamin K is oxidized simultaneously to vitamin K 2,3-epoxide (Fig. 57-3).[178, 198] Th inactive form of the vitamin is converted back to the active form by two successive reductions.[54, 112, 141] In the first step, an epoxide reductase (known as vitamin K 2,3-epoxide reductase) uses reduced nicotinamide adenine dinucleotide (NADH) as a cofactor to convert vitamin K 2,3-epox to a quinone form.[133, 178] Subsequently, the quinone is reduced to the a vitamin K quinol form (see Antidotes in Depth: Vitamin K_1).

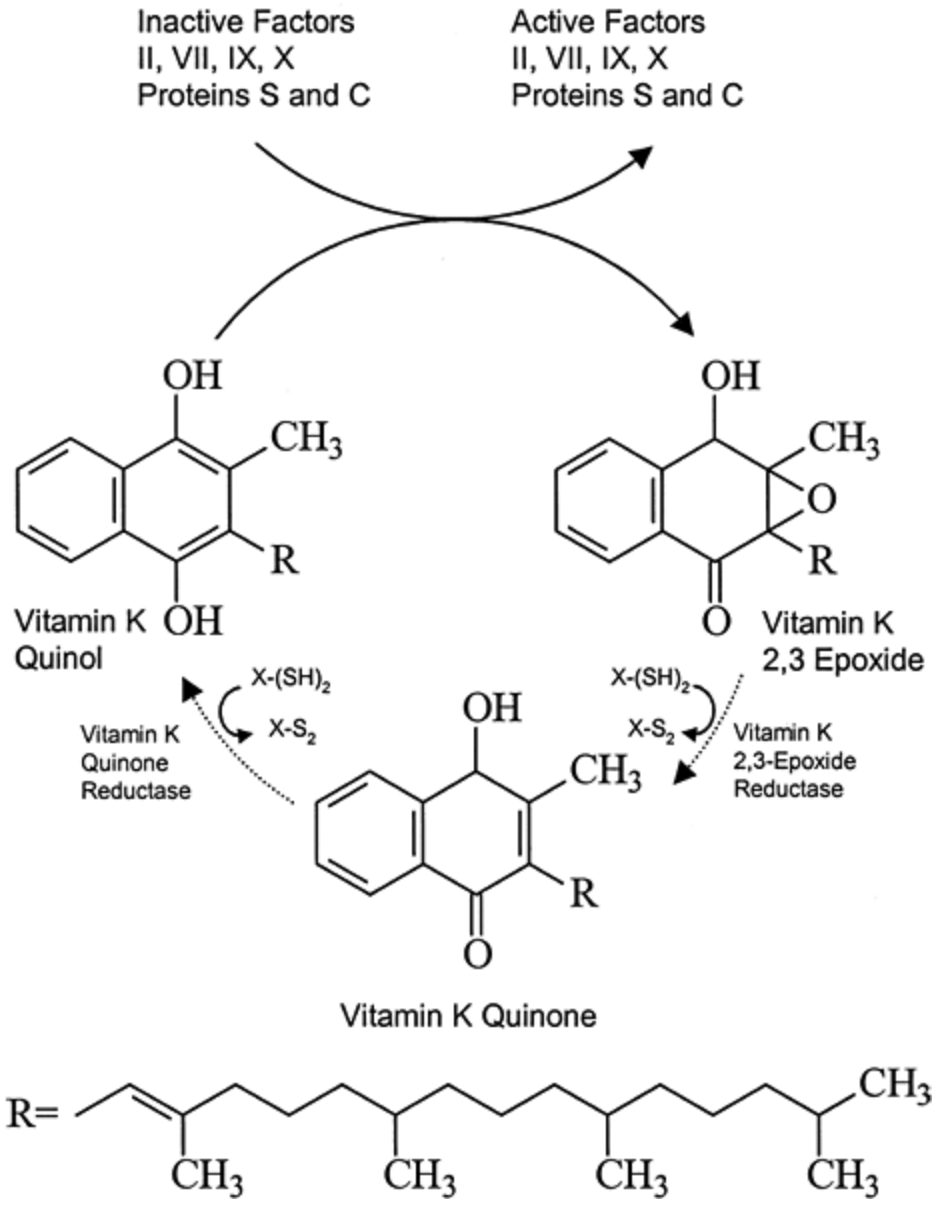


Figure 57-3. The vitamin K cycle. Dotted lines represent pathways that c be blocked with warfarin and warfarinlike anticoagulants. The aliphatic si chain (R) of vitamin K is shown below the metabolic pathway.

Warfarin is a racemic mixture of R warfarin and S warfarin enantiomers. rodents, S warfarin is 3â€“6 times more potent than R warfarin at produc hypoprothrombinemia.[30] In humans, S warfarin may only be about 1.5 ti as potent as R warfarin.[31] Warfarin and all warfarinlike compounds inhibit activity of vitamin K 2,3-epoxide reductase, as can be demonstrated by t

observation of elevated levels of vitamin K 2,3-epoxide, in orally anticoagulated subjects.[39, 201] Additional evidence suggests that another enzyme, vitamin K quinone reductase, is also inhibited by warfarin and its related compounds (Fig. 57-3).[54, 57] This reduction in the cyclic activat of vitamin K subsequently inhibits the formation of activated clotting fact

Pharmacology of Warfarin

Orally ingested warfarin is virtually completely absorbed, and peak plasm concentrations occur approximately 3 hours after drug administration.[177] Because only the free warfarin is therapeutically active, concurrent administration of xenobiotics that alter the level of free warfarin, either b competing for binding to albumin or by inhibiting warfarin metabolism, m markedly influence the anticoagulant effect.[14, 62, 177] Table 57-1 lists t xenobiotics that interfere with or potentiate warfarin's effects. Although vitamin K regeneration is altered almost immediately, the anticoagulant of warfarin, as well as other oral anticoagulant agents, is delayed until th existing stores of vitamin K are depleted and the active coagulation facto are removed from circulation. Because vitamin K turnover is rapid, this e is dependent on factor half-life ($t_{1/2}$), with factor VII ($t_{1/2}$ ~5 hours)

depleted most rapidly.[62] For a prolongation of the INR to occur, factor le must fall to approximately 25% of normal values. Assuming complete inhibition of the vitamin K cycle, this suggests that in most patients who not originally anticoagulated, at least 15 hours (three factor VII half-lives are required before warfarin's effect is evident.[62] In fact, complete inhib does not occur and hence, the onset of coagulation is even further delaye

Acetaminophen
Allopurinol
Amiodarone
Anabolic steroids
Aspirin
Carbenicillin
Clarithromycin

Cephalosporins
Chloral hydrate
Cimetidine
Clofibrate
Cyclic antidepressants
Disulfiram
Erythromycin
Ethanol
Fluconazole
HMG-CoA Reductase Inhibitors
Isoniazid
Ketoconazole
Metronidazole
Nonsteroidal anti-inflammatory agents
Omeprazole
Phenytoin
Propafenone
Propoxyphene
Quinidine
Quinolones
Sulfonylureas
Tamoxifen
Tetracycline
Thyroxine
Trimethoprim- Sulfamethoxazole
Vitamin E
Antacids
Barbiturates
Carbamazepine
Cholestyramine
Colestipol
Corticosteroids
Griseofulvin
Oral contraceptives

Phenytoin	
Rifampin	
Vitamin K	

Potentiation Antagonism

TABLE 57-1. Common Drug Interactions With Warfarin Anticoagulation

Because the half-life of warfarin in humans is 35 hours, its duration of ac may be as long as 5 days.[30 , 62 , 177] On average, it takes approximately days of warfarin administration to reach a steady-state anticoagulant eff

R warfarin is metabolized by isozymes CYP1A2 and CYP3A4, and S warfari metabolized by CYP2C9 of the hepatic microsomal P450 enzyme system. I warfarin is metabolized by side-chain reduction to secondary alcohols tha subsequently excreted by the kidney, whereas S warfarin is metabolized hydroxylation to 7-hydroxy warfarin, which is excreted into the bile.[62 , 1 The elimination of S warfarin is more rapid than that of R warfarin.[31]

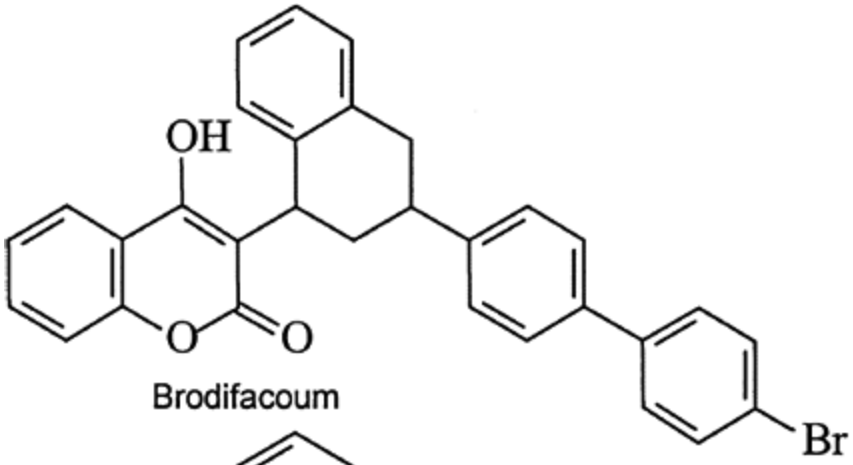
The therapeutic dose of warfarin is established for both adults and childr Typical adult recommendations are to give a starting dose of 5 mg/d with subsequent doses based on nomograms, computer programs, and/or clin experience.[65] Previous recommendations of initiating with a â€œloadingâ dose appear to be unnecessary.[3] Wide variability of maintenance dosing exists, depending on, for example, individual responsiveness, comorbid h conditions, and age. For children, the suggested starting dose of warfarin 0.2 mg/kg, followed by continued loading over 3 days, followed by a daily maintenance dose to maintain the INR between 2 and 3.[124 , 148]

Pharmacology of Long-acting Anticoagulan

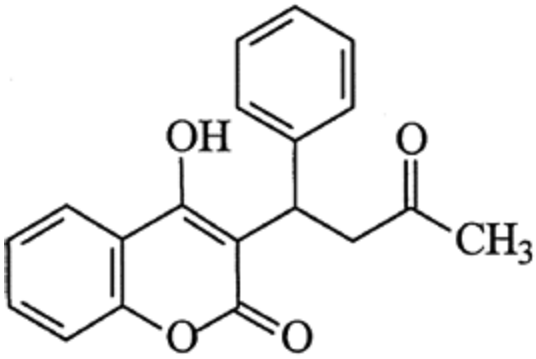
Within the coumarin group are two 4-hydroxycoumarin derivativesâ€”difenacoum and brodifacoum. These agents differ from wa by their longer, higher-molecular-weight polycyclic hydrocarbon side cha (Fig. 57-4). Together with chlorophacinone, an indandione derivative, th

are known as â€œsuperwarfarins,â€• or long-acting anticoagulants.

Long-acting anticoagulants were designed to be effective rodenticides in warfarin-resistant rodents.[109] Their mechanism of action is identical to th the traditional warfarinlike anticoagulants, as demonstrated by the measurement of increased concentrations of vitamin K 2,3-epoxide after acting anticoagulant administration.[28 , 29 , 32 , 106 , 140] The ability of th xenobiotics to perform as superior rodenticides is attributed to their high solubility and concentration in the liver.[106 , 109 , 140] They also may satu hepatic enzymes at very low levels, as demonstrated by zero-order elimination following overdose.[32] These factors make them about 100 tim more potent than warfarin on a molar basis.[106 , 109 , 140] In addition, the have a longer duration of action than the traditional warfarins.[106 , 109 , 1 For example, to obtain 100% lethality in a mouse, more than 21 days of feeding with a warfarin-containing rodenticide (0.025% anticoagulant by weight of bait) is required.[109] Similar efficacy can be achieved with a sin ingestion of brodifacoum (0.005% anticoagulant by weight of bait).[109]



Brodifacoum



Warfarin

Figure 57-4. Structural comparison of prototypical short-acting (warfari and long-acting (brodifacoum) anticoagulants.

Many animals have been poisoned with long-acting anticoagulants, either secondary to the unintentional ingestion of rodenticides, or intentionally scientific investigation. In rats, the half-life of brodifacoum is reported to 156 hours.[8] The half-life in dogs is reported to be between 6 and 120 days.[202] Horses intentionally poisoned with brodifacoum had a half-life of 1.22 days.[24] The veterinary literature is replete with reports of fatalities of animals that remained anticoagulated in excess of 1 month.[126, 175]

Likewise, many cases of intentional overdose of long-acting anticoagulant humans are also described in the literature. Table 57-2 summarizes these cases. These patients' clinical courses are characterized by a severe coagulopathy that may last weeks to months, often accompanied by consequential blood loss. The most common sites of bleeding are the

gastrointestinal and genitourinary tracts. Although initial parenteral vitar K_1 doses as high as 400 mg have been required for reversal,[34] daily oral vitamin K_1 requirements may be in the range of 50â€“100 mg. Recent experience in both animals and humans suggests that parenteral vitamin therapy might not be required (see Antidotes in Depth: Vitamin K_1).[32, 2] It should also be noted that although ingestions of these xenobiotics are most common route of exposure and subsequent cause of toxicity, derma absorption of certain xenobiotics can occur, resulting in a significant coagulopathy.[172]

Patients with unintentional ingestions must be distinguished from those w intentional ingestions, because the former individuals demonstrate a low likelihood of producing coagulation abnormalities and have only rare morbidity or mortality. Prolongation of the INR is unlikely with a single s ingestion of a superwarfarin rodenticide. Clinically significant anticoagula is even rarer. In a combined pediatric case series, prolongation of the IN occurred in only 8 of 142 children (5.6%) reported with single small ingestions of long-acting anticoagulants.[17, 94, 96, 170] Only 1 child in th group was reported to have â€œabnormal prolonged bleeding,â€• but th required no medical attention.[170] In a single case report, a 36-month-old child developed a coagulopathy manifested by epistaxis and hematuria, w anticoagulation persisting for more than 100 days after a presumed, but unwitnessed, single unintentional ingestion of brodifacoum.[183] Clinically significant coagulopathy can result, however, following small repeated ingestions. Two children reportedly became poisoned by repeated ingesti of a long-acting anticoagulant. One child presented with a neck hematom that compromised his airway, and the other with a hemarthrosis.[70] Simila a 7-year-old girl required multiple hospitalizations over a 20-month perio following repeated nonsuicidal ingestions of brodifacoum.[195] Finally, a 24 month-old child who presented with unexplained bruising and a PT >125 seconds,

was the victim of brodifacoum poisoning because of a Munchausen syndro by proxy.[7]

Babcock[7]
2
Brodifacoum
Purpura

9 mo
Baker[10]
42 M
Brodifacoum
Upper and lower extremity swelling; multiple ecchymoses
PT > 100
â€œSeveral weeksâ€•
Barlow[11] (Reingestion)
17 F
Difenacoum
None
GI bleeding
15
5 wk
42 d
Barnett[12]
27 F
Brodifacoum
Hemoptysis
7
â€”
Basehore[13]
Unknown
Brodifacoum
Epistaxis, hematuria, death
5
â€”
Berry[20]
57 F

Brodifacoum
Wound bleeding

â€”
Bruno[12]
52 M
Brodifacoum
Hematuria, oral bleeding
6
46 d
Burucoa[34]
20 F
Chlorophacinone
Hematuria
8
49 d
60 F
Chlorophacinone
Hematuria, menorrhagia
7
25 d
23 M
Chlorophacinone
Oral bleeding
6
132 d
Butcher[35]
M
Difenacoum
Hematuria
6
10 wk
Canser[36]
61 F

Brodifacoum
Ecchymoses, GI/vaginal bleeding

>14 wk
Chong[38]
20 M
Brodifacoum
Oral bleeding, hematuria
2
8 mo
Chow[40]
27 F
Bromadiolone
Bruising, menorrhagia, epistaxis, petechiae
PT 35.6 s
3 wk
Corke[47]
26 M
Brodifacoum
Hematuria, oral bleeding, mesenteric hematoma

>5 wk
Exner[56]
25 F
Brodificoum
Hemoptysis
7
>8 mo
Helmuth[78]
25 M
Brodifacoum
CNS bleeding, death
>6
â€”

Hoffman[82]
30 M
Brodifacoum
Hematuria, GI bleeding
10
64 d
Hollinger[84]
38 M
Brodifacoum
Hematuria
11
114 d
Hui[88]
76 M
Brodifacoum
Hematuria, GI bleeding
>10
>3 mo
Huic[89]
35 F
Unknown
Epistaxis, hematomas, metrorrhagia

>6 wk
Jones[93]
17 M
Brodifacoum
Hematuria
>10
55 d
Kruse[99]
25 M
Brodifacoum
Upper GI bleeding; fatal CNS bleed

4
15 wk[a]
LaRosa[103]
17 M
Brodifacoum
Mucosal and skin bleeding
PT 48 s
>1 year
Lipton[108]
31 F
Brodifacoum
Abortion
6
300 d[a]
McCarthy[119]
41 M
Difenacoum
Ecchymoses, hematuria, GI bleeding
>10
>7 mo[a]
Murdoch[129]
37 F
Chlorophacinone
None
4
3 mo
Palmer[139]
15 F
Brodifacoum
Pulmonary hemorrhage, death

â€”
Rauch[146]
26 M

Brodifacoum
Calf hematoma, hematemesis
9
24 mo[a]
37 F
Brodifacoum
Ecchymoses
>8
6 mo
42 M
Brodifacoum
Hematuria, epistaxis
>4
>3 mo
Ross[154]
62 M
Brodifacoum
Hematuria
4
3 mo
Routh[155]
29 F
Brodifacoum
Death
9
â€”
Seidelman[161]
24 M
Unconfirmed
None
>12
>37 d
Sheen[164]
39 M

Brodifacoum
Hematuria
>12
>152 d
Soubiron[171]
51 F
Difenacoum
Multiple hematomas, ecchymoses; spontaneous hemoperitoneum
>7
>9 d
Swigar[180]
52 M
Unconfirmed
Compartment syndrome

>82 d
Tecimer[181]
37 M
Brodifacoum
Hematuria, occult GI bleeding
8
17 d
Tsutaoka[184]
23 M
Brodifacoum
Mild gingival bleeding; hematuria and flank pain (26 days later)
37.8, 189
>30 days
Walker[191]
71 M
Bromadiolone
Acute coronary syndrome; upper GI bleeding
7.0
â€”

Wallace[192]
36 M
Brodifacoum
Upper GI bleeding
10
â€”
Weitzel[196]
20 F
Brodifacoum
Melena, menorrhagia, hematuria
>4
>11 mo
25 M
Brodifacoum
Epistaxis, compartment syndrome
>4
100 d
37 M
Brodifacoum
Hematuria
>5
>150 d

[a] Denotes possible repeat ingestion.

Reference	Age (y), Sex	Xenobiotic	Complications	Initial PT/INR	Duration Coagulopa

TABLE 57-2. Intentional Long-acting Anticoagulant Overdoses

Most patients (usually children) are entirely asymptomatic and have a nc coagulation profile following an acute unintentional exposure. Knowing th the risk of coagulopathy is low and that it takes days to develop, most authors recommend supportive care only.[95 , 170] Despite the fact that

significant toxicity from superwarfarins is rare, it should be recognized th the reported benign courses of pediatric exposures may be misleading. Multiple retrospective studies suggest that children with unintentional acu exposures do not require any followup coagulation studies.[33, 127, 142] However, this conclusion and approach to management may be an unjus attempt to decrease the cost of â€œunnecessaryâ€• coagulation studies. There are clearly insufficient data to justify this conclusion, as many of t â€œexposedâ€• children were never documented to have ingested long-acting anticoagulants (see Chap. 130). We recommend that clinicians continue to manage these children as possible significant exposures, and all children be followed up with daily INR

studies for at least 48 hours. A baseline INR study may also be performed determine if a child has been chronically ingesting the superwarfarin.

Clinical Manifestations

Typical warfarin rodenticides contain only small concentrations of anticoagulant, 0.025% (or 25 mg of warfarin per 100 g of product). Using data previously listed, a 10-kg child would require an initial dose of 2.5 m warfarin (or 10 g of rodenticide). These quantities are far greater than th that occur in typical â€œtastes.â€• Thus, single unintentional ingestions warfarin-containing rodenticides pose virtually no threat to either normal anticoagulated patients.[95] In contrast, intentional and large unintentional ingestions of pharmaceutical-grade anticoagulants have the potential to produce a coagulopathy and consequential bleeding. In one study describ 12 patients with surreptitious ingestion of oral anticoagulants, 9 were healthcare professionals.[134] These patients presented with bruising, hematuria, hematochezia, and menorrhagia, the typical manifestations of impaired coagulation. Hemorrhage into the neck with resultant airway compromise is a rare but life-threatening complication that has occurred.

Although intentional ingestions of warfarin-containing products are uncommon, adverse drug events resulting in excessive anticoagulation ar bleeding frequently occur. The risk of hemorrhage during oral anticoagula

therapy depends on a myriad of factors, including the intensity of anticoagulation, patient characteristics, and comorbid conditions such as hypertension, renal insufficiency, hepatic dysfunction, malignancy, length anticoagulant therapy, and indications for anticoagulationâ€”cerebrovasc disease, prosthetic heart valves, atrial fibrillation, ischemic heart disease, venous and arterial thromboembolism. Although the significance of each these clinical conditions varies among different reports, most studies demonstrate that there is a greater incidence of bleeding complications w increasing INR,[42] increasing intensity (or variation) of coagulation, advar age, a history of previous bleeding episodes while on therapeutic warfari drug interactions, impaired liver function, and dietary changes.[60 , 62 , 72 , 145 , 200] Clearly, the most serious complication of excessive anticoagula is intracranial hemorrhage, which is reported to occur in as many as 2% patients on long-term therapy.[62] This complication is associated with a fatality rate as high as 77%.[117]

An Outpatient Bleeding Risk Index was created and shown to be more accurate than physician judgment in classifying patients according to the of major bleeding.[21] The index was based on 4 independent risk factors: 65 years or older; history of cerebrovascular accident; history of gastrointestinal bleeding; and history of recent myocardial infarction, hematocrit <30%, serum creatinine >1.5 mg/dL, or diabetes mellitus. Th sum of the number of risk factors successfully predicted major bleeding a months to be 3% in low-risk (0 risk factors), 12% in intermediate-risk (1 risk factors), and 53% in high-risk (3â€“4 risk factors) patients. Because physicians had little ability to accurately estimate the probability of bleed use of the Outpatient Bleeding Risk Index seems appropriate to improve awareness and treatment of these high-risk patients.

In a study of 32 patients who developed life-threatening hemorrhage whil warfarin therapy, most patients had multiple risk factors including excess anticoagulation.[200] The gastrointestinal tract was identified as the source bleeding in 67% of the patients.[200] Sixty-six percent of patients were giv vitamin K_1 , 50% were given fresh-frozen plasma (FFP), and 7% were giv both therapies.[200]

Laboratory Assessment

Established screening tests are helpful for diagnosis. Four studiesâ€”PT (PTT, thrombin time, and fibrinogen concentrationâ€”are usually adequate Prothrombin time is calculated by adding standardized thromboplastin re (phospholipid and tissue factor) to a sample of the patient's citrated plas (the citrate removes calcium to prevent clotting). Calcium is then introdu and the time to clotting measured. With the exception of factor X, the PT unaffected by the presence or absence of factors VIII to XIII, platelets, prekallikrein, and HMWK. An individual's PT was formerly expressed as a (PT observed-to-PT control). Because this ratio is directly affected by bot laboratory methodology and the source of the thromboplastin reagent use the generated results suffered from significant variability. Thus, a standa the INR, was developed in an attempt to limit interlaboratory variability.[7] [131] The INR is derived by raising the PT ratio to a power value known as International Sensitivity Index (ISI): $(\text{PT ratio})^{\text{ISI}}$. The ISI is a measure responsiveness of the particular thromboplastin to warfarin. Although the of the INR does not completely eliminate variability,[80 , 130] it does impro the potential for standardized interpretation and limits interinstitutional variations. It should be noted that in patients taking oral anticoagulants, INR is extremely effective at monitoring the extent of anticoagulation. However, in patients with acute fulminant hepatic failure of various etiol the INR is extremely variable and occasionally misleading as a consequer of the variability in thromboplastins.[150] This may be less of a problem in United States because of the use of recombinant human preparations of thromboplastin, which results in greater consistency.[37]

The partial thromboplastin time is measured by adding kaolin or celite to citrated plasma in order to activate the â€œcontactâ€• components of th intrinsic system. This mixture is then recalcified and the time to clotting observed. Some tests use phospholipids in the reagent to activate the remaining coagulation factors, thereby giving rise to the term *activated partial thromboplastin time* (aPTT). Because the PTT and aPTT are essen interchangeable, the term PTT is used hereafter to represent the concept. PTT is not affected by alterations in factors VII, XIII, or platelets.

The thrombin time, determined by adding exogenous thrombin to citrated plasma, evaluates the ability to convert fibrinogen to fibrin, and is thus unaffected by abnormalities of factors II, V, VII to XIII, platelets, prekallikrein, or HMWK. Finally, either a fibrinogen level or a determinatic fibrin degradation products will help distinguish between problems with c formation and consumptive coagulopathy. An evaluation of the combinatic normal and abnormal results of these tests usually determines a patient's clotting abnormality (Table 57-3).

Inhibitors can be diagnosed by â€œmixing studies,â€• because only a sr percentage of the coagulation factors present in normal plasma are neces to have normal clotting studies. If the patient with an abnormal PT or PTT suffers from even a severe factor deficiency, restoration of that factor ac to 50% of normal will completely normalize the PT or PTT. Thus the pres of an abnormal PT or PTT that will not correct by incubation of the patien plasma with an equal volume of normal plasma is diagnostic of an inhibitc coagulation. Heparin-induced anticoagulation results in an elevated PTT t corrects when mixing studies are performed. More sophisticated

studies can be used to identify specific coagulation-factor deficiencies. Th reader is referred to one of several standard references for a more detail discussion of the approach to patients with abnormal coagulation studies.

PT normal, PTT prolonged, bleeding
- Deficiencies of factors VIII, IX, XI
- Von Willebrand disease

PT normal, PTT prolonged, no bleeding
- Deficiencies of factor XII, prekallikrein, high-molecular-weight-kininoge inhibitor syndrome

PT prolonged, PTT normal
- Deficiency of factor VII
- Warfarin therapy (early)
- Vitamin K deficiency (mild)

Liver disease (mild)

PT and PTT prolonged, thrombin time normal, fibrinogen normal
Deficiencies of factors II, V, IX; vitamin K deficiency (severe)
Warfarin therapy (late)

PT and PTT prolonged, thrombin time abnormal, fibrinogen normal
Heparin effect
Dysfibrinogenemia

PT and PTT prolonged, thrombin time abnormal, fibrinogen abnorm
Liver disease
Disseminated intravascular coagulation
Fibrinolytic therapy
Crotaline envenomation

TABLE 57-3. Evaluation of Abnormal Coagulation Times

Although warfarin levels may be useful to confirm the diagnosis in unkno cases and to study drug kinetics,[73 , 132] the routine use of simple and inexpensive measures such as INR determination seems more appropriat

Laboratory Evaluation of Long-acting Anticoagulants

For patients who have ingested long-acting anticoagulants and who are considered likely to develop a coagulopathy, baseline coagulation studies not usually helpful, but they may provide information about chronic exposures. If the history is reliable and the patient is healthy, baseline studies can be avoided. Serial INRs at 24 and 48 hours should identify all patients at risk of coagulopathy.[170] Depending on the social situation, th studies can be obtained while the patient remains in the home setting.

In contrast, all patients with intentional ingestion of long-acting anticoagulants should be presumed to be at risk for a severe coagulopath

fact, most patients do not seek medical care until bruising or bleeding is evident.[11,32,34,38,56,78,82,93,94,96,99,108,129,155,180] These events often occur many days after ingestion, which obviates the r for gastric decontamination unless there is a suggestion of repetitive ingestion. These patients should be managed as described below.

For patients who have suspected long-acting anticoagulant overdose, daily twice-daily INR evaluations for 2 days should be adequate to identify mos patients at risk for coagulopathy. Early detection through coagulation fac analysis may be preferred,[73] however, and levels of long-acting anticoagulants can now be measured.[59,100,132]

General Management and Antidotal Treatm

Gastrointestinal decontamination should be performed on patients who ar believed to have potentially significant life-threatening ingestions unless already present with significant bleeding. For patients who present after a hours of ingestion, gastric emptying is not indicated (see Chap. 8). Altho convincing data on the efficacy of either single- or multiple-dose activate charcoal (possible enterohepatic circulation) are lacking, at least a single dose of AC should be administered unless it is contraindicated. Oral cholestyramine can also be used to enhance warfarin elimination,[147] but studies are available that compare these two therapies or evaluate the ro combined activated charcoal and cholestyramine therapy. Although in ani models phenobarbital also enhances elimination, it is contraindicated in humans because of the decreased ability to reliably monitor the mental s of a patient who has the possibility of spontaneous intracranial hemorrha and subsequent increased risk of falling. In addition to general supportive measures, the patient should be placed in a supervised medical and psychiatric environment that offers protection against external or self-in trauma, and permits observation for the onset of coagulopathy.

Blood transfusion is required for any patient with a history of blood loss c active bleeding who is hemodynamically unstable, has impaired oxygen transport, or is expected to become unstable. Although a transfusion of packed red blood cells is ideal for replacing lost blood, it cannot correct a

coagulopathy, and thus patients will continue to bleed. Whole blood conta both the cellular elements the patient is losing and the necessary coagula factors to reverse the coagulopathy. Transfusion of whole blood may be considered in severe cases because whole blood contains many compone including platelets, white blood cells, and nonâ€“vitamin K-dependent fa However, because whole blood contains only relatively small amounts of vitamin K-dependent factors, selective use of specific blood products is generally preferred. These products include packed red blood cells, FFP, cryoprecipitate or other factor concentrates, such as factor IX complex (Konyne 80), recombinant factor VIIA (rFVIIa), and prothrombin complex concentrate.

Life-threatening hemorrhage secondary to oral anticoagulant toxicity sho be immediately reversed with FFP, followed by vitamin K_1 . FFP is rich in active vitamin K-dependent coagulation factors and will reverse oral anticoagulant-induced coagulopathy in most patients. In general, approximately 15 mL/kg of FFP should be adequate to reverse any coagulopathy.[48] However, the specific factor quantities and volume of ea unit may be varied, leading to an unpredictable response.[113] A recent stu comparing the efficacy of FFP and various clotting factor concentrates (prothrombin complex concentrate, factor VII concentrate, and Prothrom T [factors II, VII, IX and X]) in rapid reversal of anticoagulation, showed despite significant reduction in the INR, FFP had an extremely varied effe factor IX repletion. These clotting factor concentrates not only significant decreased the INR, but completely corrected it, and factor IX replacemen was much more consistent.[113] Furthermore, multiple FFP transfusions ma also be required because of the rapid degradation of coagulation factors i the absence of vitamin K.

Preliminary data using rFVIIa, a compound originally developed for the treatment of bleeding complications in patients with hemophilia, demons it to be a useful pharmacologic therapy for bleeding secondary to warfari induced excessive anticoagulation.[52 , 123] There is also a single case rep demonstrating efficacy at reversing severe bleeding caused by enoxapari Further experience with rFVIIa is necessary to determine its safety and

efficacy in anticoagulant-induced hemorrhage.

Several issues influence the decision to administer vitamin K_1 to a patien with a suspected overdose of a warfarinlike anticoagulant. Answers to the following questions should always be considered. Does the ingestion invol warfarin-containing rodenticide or a pharmaceutical preparation? Is the ingestion unintentional or intentional? Does the patient require maintena of therapeutic anticoagulation? Moreover, although vitamin K_1 administra is required to reverse the blockade of coagulation factor activation, it car be relied on for the patient with acute and consequential hemorrhage (se Antidotes in Depth: Vitamin K_1). Treatment with vitamin K_1 takes severa hours to activate enough factors to reverse the patient's coagulopathy,[11] [141] and this delay may be potentially fatal.

Repetitive, large doses of vitamin K_1 (on the order of 60 mg/d) may be required in some patients.[73] , [134] If complete reversal of INR prolongatio occurs or is desirable (as in most cases of life-threatening bleeding), and patient's underlying medical condition still requires some degree of anticoagulation, they can then receive controlled anticoagulation with he once the bleeding is controlled and they are otherwise stable. Heparin anticoagulation was used without apparent bleeding complications in 25% patients in one cross-sectional study.[200]

Vitamin K_1 is preferable over the other forms of vitamin K; the other forr are ineffective[93] , [129] , [133] , [185] and are potentially toxic.[9] (Vitamins K_3 [menadione] and K_4 [menadiol sodium diphosphate] can cause oxidative stress on neonatal erythrocytes and produce hemolysis, hyperbilirubinem and kernicterus.) Parenteral administration of vitamin K_1 (phytonadione) traditionally preferred as initial therapy by many authors, but success als can be achieved with early oral therapy.[32] In most cases reviewed, the patient was switched to oral vitamin K_1 preparations for long-term care. Vitamin K_1 can be administered intramuscularly, subcutaneously, intradermally, or intravenously. Although intravenous therapy has the mo rapid onset of action of all routes of delivery, its use as the sole therapeu agent is still associated with a delay of several hours[112] , [141] and carries added risk of anaphylactoid reactions.[149] The use of low doses and slow

of administration reduces this risk,[167] but we generally prefer that vitami be administered by other than the intravenous route (see Antidotes in De Vitamin K_1). In cases where oral administration is undesirable, for exam significant gastrointestinal hemorrhage, the subcutaneous route may be realizing that absorption may be erratic. Furthermore, if a patient is anticoagulated or overanticoagulated, administration of vitamin K_1 by the intramuscular route may result in a large hematoma. Caution should be exercised if this route of administration is chosen.

For patients with nonâ€“life-threatening hemorrhage, the clinician must consider whether anticoagulation is required for long-term care. In patien not requiring chronic anticoagulation, even small elevations of the INR m be treated with vitamin K_1 alone to prevent a deterioration in coagulation status and reduce the risk of bleeding. Because in most cases, coagulopa persists only for several days, there may be a rationale for prophylactic vitamin K_1 administration in known warfarinlike anticoagulant ingestions patients not requiring anticoagulation. In contrast to ingestions of warfar prophylactic vitamin K_1 should never be given to asymptomatic patients unintentional ingestions of long-acting anticoagulants because (a) if the patient is a child who develops a coagulopathy, it will last for weeks, and 1 or 2 doses of vitamin K_1 given will not prevent complications; (b) a gra decline in coagulation factors occurs over the first day of anticoagulation, no child would be expected to develop a life-threatening coagulopathy in 2 days; and (c) after vitamin K_1 is administered, the onset of an INR abnormality will be delayed, which could impair the clinician's ability to diagnose any coagulation abnormality, possibly requiring the patient to undergo an unnecessarily prolonged observation period.

For patients requiring chronic anticoagulation, The American College of C Physicians has issued guidelines for management of patients with elevate INRs (Table 57-4). Moreover, the use of a regression formula may assist calculating the amount of oral vitamin K_1 necessary to partially correct th INR, without completely discontinuing the oral anticoagulant. If validated, would be extremely useful prior to minor surgery or dental procedures in patients requiring chronic anticoagulation, while theoretically decreasing likelihood of thromboembolism.[197]

Treatment of Long-acting Anticoagulant Overdoses

Treatment of a patient with a long-acting anticoagulant overdose is essentially the same as the treatment of oral anticoagulant toxicity with certain exceptions.

â€¢
<5.0; no significant bleeding
Lower dose or omit next dose of warfarin
â€¢
â‰¥5.0â€“9.0; no significant bleeding
Discontinue warfarin for several doses. Alternatively, omit next dose and oral vitamin K_1 (1â€“2.5 mg) especially if at increased risk of bleeding. If more rapid reversal is necessary, give oral vitamin K_1 (â‰¤5 mg) and w 24 hours. Give additional vitamin K_1 orally (1â€“2 mg) as needed.
â€¢
â‰¥9.0; no significant bleeding
Hold warfarin therapy and give a higher dose of oral vitamin K_1 (5â€“10 and wait 24 hours. Give additional vitamin K_1 if necessary.
â€¢
Serious bleeding at any concentration or life-threatening bleeding
Hold warfarin therapy and give vitamin K_1 (10 mg by slow parenteral[b] infusion) supplemented with fresh-frozen plasma or prothrombin complex concentrate; recombinant factor VIIa may be used instead of prothrombi complex concentrate. Vitamin K_1 administration may need to be repeated h.

[a] If continued warfarin therapy is indicated after high doses of vitamin K_1 then anticoagulation with heparin or LMWH can be concomitantly given. I values >4.5 are also less reliable than values at or near the therapeutic range.

[b] Although parenteral infusion of vitamin K_1 is recommended, we urge ca with this route of administration because there may not be an appreciable

difference in onset of therapeutic effect and, although rare, may cause s anaphylactoid reactions.
Adapted from American College of Chest Physicians Consensus Conferenc 2004 guidelines.[3]

INR Recommendations

TABLE 57-4. Recommendations for Management of Elevated INF with and without Bleeding, in Patients Requiring Chronic Anticoagulation[a]

Long-acting anticoagulants are metabolized by the hepatic mixed-functior oxidase system (cytochrome P450 [CYP]).[8,133] In a rat model, the dura of coagulopathy was shortened by administering phenobarbital, a CYP3A4 inducer.[8] Although a phenobarbital effect has never been systematically studied in humans, this approach was employed by several authors in isc human cases of long-acting anticoagulant toxicity.[34,93,108,183,195] Although these anecdotal reports suggest some improvement with phenobarbital therapy, the risks of producing sedation in a patient who n be prone to bleeding complications appear consequential.

Patients with long-acting anticoagulant overdose should be followed until coagulation studies remain normal while off therapy for several days. Thi usually requires daily or even twice-daily INR measurements until the INF at the lower limit of the therapeutic range. Monitoring of serial INR measurements should allow for a gradual decrease in vitamin K_1 requirer over time. Periodic coagulation factor analysis, however, may provide an early clue to the resolution of toxicity.[82] The patient may require weeks t months of close observation for both psychiatric and medical managemer Emphasis has been placed on determining a critical superwarfarin concentration below which anticoagulation does not occur.[34] In one case report, brodifacoum was observed to follow zero-order elimination kinetic If this type of toxicokinetics is consistent in the analysis of other long-ac anticoagulants, these laboratory measurements may prove more reliable

the current empiric end points of therapy.

Parenteral Anticoagulants

Heparin

Conventional or unfractionated heparin is a heterogeneous group of mole within the class of glycosaminoglycans.[92] The heparin precursor molecule composed of long chains of mucopolysaccharides, a polypeptide, and carbohydrates. The main carbohydrate components of heparin molecules include uronic acids and amino sugars in polysaccharide chains. Heparin f pharmaceutical use is extracted from bovine lung tissue and porcine intestines.[160]

As a therapeutic agent, heparin inhibits thrombosis by accelerating the binding of the protease inhibitor antithrombin III (AT) to thrombin (factor and other serine proteases involved in coagulation.[111 , 153] Thus, factors to XII, kallikrein, and thrombin are inhibited. Heparin also affects plasminogen activator inhibitor, protein C inhibitor, and other components coagulation. Heparin's therapeutic effect is usually measured through the activated PTT. The activated blood coagulation time (ACT) may be more useful for monitoring large therapeutic doses or in the overdose situation

Low-molecular-weight heparins (LMWHs) are 4000- to 6000-Dalton fracti obtained from conventional (unfractionated) heparin.[63] As such, they sha many of the pharmacologic and toxicologic properties of conventional heparin.[26] The various LMWHs (e.g., Fraxiparine, enoxaparin, dalteparin) prepared by different methods of depolymerization of heparin; consequer they each differ to a certain extent regarding their pharmacokinetic prop and anticoagulant profiles. The major differences between LMWHs and conventional heparin are greater bioavailability, longer half-life, more predictable anticoagulation with fixed dosing, targeted activity against activated factor X, and less targeted activity against activated factor II.[2(As a result of this targeted factor X activity, LMWHs have minimal effect the activated PTT, thereby eliminating either the need for, or the usefuln

of, such monitoring. As such, they are administered on a fixed-dose sche

LMWHs have been investigated for prevention of thromboembolic disease after hip surgery and trauma, in patients with stroke or deep venous thrombosis, in pregnancy, and in other conditions where anticoagulation heparin would otherwise be indicated (e.g., at the onset of oral anticoagulation therapy). Although these xenobiotics are presumed to hav minimal risk in pregnancy[121] because they do not cross the placenta,[61 ,] they are not yet approved for treatment or prophylaxis of thromboemboli disease in pregnancy. Most studies demonstrate a lower incidence of embolization; however, there is still a trend toward increased bleeding.[19 , 107]

Pharmacology

Because of heparin's large size and negative charge it is unable to cross cellular membranes. These factors also eliminate oral administration as a therapeutic route, and heparin must be administered by either subcutane injection or continuous intravenous infusion. Following parenteral administration, heparin remains in the intravascular compartment, in par bound to globulins, fibrinogen, and low-density lipoproteins, resulting in a volume of distribution of 0.06 L/kg in humans.[55 , 135] Because of its rapi metabolism in the liver by a heparinase, heparin has a short duration of effect.[111] Although the half-life of elimination is dose dependent and ran from 1â€“2.5 hours,[111 , 118 , 135] the duration of anticoagulant effect is usually reported as 1â€“3 hours.[111] Dosing errors or drug interactions wi thrombolytic agents, antiplatelet drugs, or nonsteroidal antiinflammatory drugs may increase the risk of hemorrhage.[76]

Clinical Manifestations

Intentional overdoses with heparin are rare.[116] Most reported cases invol unintentional poisoning in hospitalized patients.[66 , 69 , 116 , 138 , 159] The cases have involved the administration of large amounts of heparin as a consequence of misidentification of heparin vials, during the process of

flushing intravenous lines, and secondary to intravenous pump malfunctio Significant bleeding complications occurred in several cases, including 1 fatality.[66]

Although no overdoses of LMWHs are reported, LMWHs are renally elimin and patients with severe renal insufficiency (creatinine clearance <30 mL/min), or end-stage renal disease, are at increased risk of toxicity.[188] Similar adverse effects to unfractionated heparins are also reported to in epidural/spinal hematoma, intrahepatic hemorrhage,[85] abdominal wall hematomas,[4] psoas hematoma after lumbar plexus block,[97] and intracrar hemorrhage in patients with malignancy in the brain.[53] These complicatio were all reported in patients who received the LMWH enoxaparin.

Evaluation and Treatment

After stabilization of the airway and breathing, and circulation are assure the physician should be prepared to replace blood loss and reverse the coagulopathy, if indicated. Because of the relatively short duration of act of heparin, observation alone might be indicated if significant bleeding ha not occurred. For the patient requiring anticoagulation, serial PTT determinations will indicate when it is safe to resume therapy. If significa bleeding occurs, either removal of the heparin or reversal of its anticoag effect

is indicated. Because heparin has a very small volume of distribution, it c be effectively removed by exchange transfusion.[159] Although this techniq has been used successfully in neonates, it is not generally applicable to c children and adults.

When severe bleeding occurs, heparin may be effectively neutralized by protamine sulfate.[2] Protamine is a low-molecular-weight protein found in sperm and testes of salmon, which forms ionic bonds with heparin and renders it devoid of anticoagulant activity.[111] One milligram of protamine sulfate injected intravenously neutralizes 100 U of heparin.[111] The dose c protamine should be calculated from the dose of heparin administered if known and assuming heparin's approximate half-life to be 60â€“90 minut

the amount of protamine should not exceed the amount of heparin expec to be found intravascularly at the time of infusion. As with other foreign proteins, protamine administration is associated with numerous adverse effects such as hypotension, bradycardia, and allergic reactions. Because approximately 0.2% of patients receiving protamine experience anaphyla a complication that carries a 30% mortality rate, most authors commonly recommend that protamine be reserved for patients with life-threatening hemorrhage (see Antidotes in Depth: Protamine).[83] It should also be no that excess protamine administration may result in paradoxical anticoagulation.

Because of the severe adverse effects associated with protamine, researc has focused on safer methods to reverse heparin anticoagulation. These agents include heparinase,[122] synthetic protamine variants,[189 , 190] and platelet factor 450, but these therapies are not widely available.

If life-threatening bleeding occurs following LMWH administration, patien should be treated supportively. The newer experimental protamine variar appear to be effective against LMWHs but are not yet unavailable.[189 , 19

Nonbleeding Complications of Anticoagular

Warfarin therapy is associated with three nonhemorrhagic lesions of the urticaria,[158] purple toe syndrome,[58] and warfarin skin necrosis.[45 , 98 , 10 120 , 187] Although warfarin skin necrosis was once thought to be a rare a idiosyncratic reaction,[98 , 102] more recent evidence suggests a link betwe this disorder and protein C deficiency.[102 , 187] Protein C is also dependen vitamin K.[41] Patients who are homozygotes for protein C deficiency have increased incidence of thrombosis and embolic events, such that they oft require long-term anticoagulant therapy.[41] Because the half-life of protein is shorter than that of many of the vitamin K-dependent coagulation fact protein C levels fall rapidly during the first hours of warfarin therapy. In protein C-deficient patient, protein C levels fall dramatically prior to a reduction in coagulation factors. This results in an imbalance that actually favors coagulation, and skin necrosis results due to microvascular throm in dermal vessels.[120 , 187] Although warfarin skin necrosis is more commo

patients with protein C deficiency, this disorder is also described in patie with protein S and AT deficiencies.[45] Unfortunately, these deficiencies are neither necessary nor sufficient to account for the incidence of warfarin necrosis.[45] If necrosis occurs, warfarin should be discontinued and hepar should be initiated to decrease thrombosis of postcapillary venules. Some patients may also require surgical dÃ©bridement.[185] The purple toe syndrome, in contrast to warfarin-induced skin necrosis, is presumed to from small atheroemboli that are no longer adherent to their plaques by

An additional major nonhemorrhagic complication of warfarin therapy rela to its use in pregnant women. Most warfarin-induced fetal abnormalities during weeks 6 to 12 of gestation, but CNS and ocular abnormalities can develop at any time during gestation.[75 , 174]

Heparin therapy is associated with a transient and mild thrombocytopenia called heparin-induced thrombocytopenia (HIT) that occurs in approximat 25% of patients during the first few days of therapy.[194] Although this syndrome results from heparin-induced platelet aggregation, a more seve form of thrombocytopenia, heparin-induced thrombocytopenia and throm syndrome (HITTS; formerly known as HIT-2 or the white clot syndrome), occurs in 1â€“5% of patients between days 7 and 14 of therapy.[112] In patients who were previously treated with heparin, these events can occu earlier than 7 days. Heparin stimulates platelets to release platelet factor which subsequently complexes with heparin to provoke an IgG response. These antibodies against the heparinâ€“platelet factor 4 complex activate platelets, which may lead to plateletâ€–fibrin thrombotic events.[6 , 111 , 2] Patients may present with either hemorrhagic or thromboembolic complications. Previously reported not to occur,[193] LMWH is also associat with thrombocytopenia (isolated HIT) and HITTS, although less frequently Consequently, once HITTS occurs, LMWH is contraindicated.[193] In addition HIT and HITTS, necrotizing skin lesions[144] and hyperkalemia from aldost suppression[136] also rarely occur in patients receiving heparin therapy.

Some additional complications of heparin use include osteoporosis, which mostly occurs in patients on long-term therapy with unfractionated hepar A small percentage of these patients may develop bone fractures if treate

continuously for more than 3 months. Data for LMWHs are limited and the incidence of osteoporosis may be less compared to unfractionated hepari

Fibrinolytic Agents and other Anticoagulan

Thrombolytic Agents

The fibrinolytic system is designed to remove unwanted clots, while leavi those clots protecting sites of vascular injury intact. Plasminogen exists a proenzyme and is converted to the active form, plasmin, by various plasminogen activators.[43, 44] t-PA is released from the endothelium and under the inhibitory control of two inactivators known as tissue plasmino activator inhibitors 1 and 2 (t-PAI-1 and t-PAI-2).[43, 44, 112, 125] Plasmi actions are nonspecific in that it degrades not only fibrin clots but also so plasma proteins and coagulation factors.[112] Inhibition of plasmin occurs through $\hat{I}\pm_2$ -antiplasmin.

With their diverse indications in acute myocardial infarction, unstable an arterial and venous thrombosis and embolism, and cerebrovascular disea the thrombolytic agents (streptokinase, urokinase, alteplase, and anistreplase) are commonly used.[16] The reader is referred to a number o reviews for specific indications and dosing regimens.[46, 104, 112, 143, 1 199] Although all xenobiotics enhance fibrinolysis, they differ in their spec sites of action and durations of effect. Alteplase (t-PA) is specific for clot does not increase fibrinolysis in the absence of a thrombus), whereas streptokinase, urokinase, and anistreplase are not clot-specific. Alteplase

has the shortest half-life and duration of effect (5 minutes and 2 hours, respectively), and anistreplase the longest (90 minutes and 18 hours, respectively).[143, 169] Streptokinase has the additional risk of severe alle reaction on rechallenge, limiting its use to once in a lifetime.

Newer thrombolytic drugs such a reteplase, and some noncommercially available agents, including monteplase, lanoteplase, pamiteplase, and staphylokinase are being evaluated for therapeutic use. These agents hav

longer half-life in plasma and may be administered via single or repeated bolus injections. They also have increased fibrin selectivity, but no improvement in long-term mortality is demonstrated.[5] Although the incid of bleeding requiring transfusion may be as high as 7.7% following high- (150 mg) alteplase and 4.4% following low-dose alteplase,[46] the incidenc intracranial hemorrhage with alteplase appears to be similar to the newe agents (monteplase, tenecteplase, reteplase, and lanoteplase).[186] The addition of heparin to the thrombolytic regimen increases the risk of blee Reviews of multiple trials suggest that life-threatening events such as intracranial hemorrhage occur in 0.30â€“0.58% of patients receiving anistreplase, 0.42â€“0.73% of patients receiving alteplase, and 0.08â€–0.30% of patients receiving streptokinase.[199] Regardless of the thrombolytic agent used the frequency of bleeding events is similar even the newer agents, with the exception that lanoteplase may have a decrea incidence of significant bleeding.[51] Supportive care is indicated for patie with minor bleeding complications; however, for patients with significant bleeding, fibrinogen and coagulation factor replacement with cryoprecipit and FFP should be administered.[156]

Snake Venoms

A detailed discussion of snake envenomations is found in Chap. 117 ; onl few specific issues are discussed here. Snake venoms may be composed c vast number of complex proteins and peptides that interact with compon of the human hemostatic system. In general, their functions may be thou of as being procoagulant, anticoagulant, fibrinolytic, vessel wall interacti platelet active, or as protein inactivators. Additionally, they may more specifically also be classified based on their specific biologic activity; som the various mechanisms include individual factor activation, inhibition of protein C and thrombin, fibrinogen degradation, platelet aggregation, and inhibition of serine protease inhibitors (SERPINS). Currently, there are m than 100 different snake venoms that affect the hemostatic system;[90 , 9] Figure 57-2 is an overview of their multiple interactions with the coagula and fibrinolytic systems.[115]

Some of these venom proteins are being used as therapeutic agents for human diseases. Ancrod, a purified derivative of the Malayan pit viper, *Calloselasma rhodostoma* (formerly known as *Agkistrodon rhodostoma*), therapeutically used because of its defibrinogenating property.[15] The mechanism of action of ancrod and other similar agents is to link fibrinog end-to-end and subsequently prevent cross-linking. It has been investiga in the treatment of deep vein thrombosis, myocardial infarction, pulmona embolus, acute cerebrovascular thrombosis, HIT, and warfarin-related vascular complications. In a multicenter study of 500 patients with acute progressing ischemic neurologic events, ancrod showed a favorable bene to-risk ratio compared to placebo.[166] As expected, an increased risk of hemorrhage is observed; however, the risk appears to be less than that v thrombolytic agents.[166] Monitoring of fibrinogen levels is essential to avo potential complications, as no specific antidote exists. For envenomation other snake venoms (such as from the Crotalinae family) that induce hemorrhage, antivenin treatment may be required.

Hirudin

Hirudin, a 65-amino-acid polypeptide produced by the salivary glands of medicinal leech (*Hirudo medicinalis*), irreversibly blocks thrombin withou need for AT.[162] Unlike heparin, the small size of hirudin allows it to enter clots and inhibit clot-bound thrombin, offering the distinct advantage of restricting further thrombus formation. Hirudin demonstrates enhanced bioavailability and a longer half-life than unfractionated heparin. In addit there are no known natural inhibitors of hirudin, such as platelet factor 4 Desirudin, is a recombinant hirudin which is used in acute coronary synd in the prevention of thromboembolic disease and in patients with heparin induced thrombocytopenia.[23 , 157 , 162] Both of these compounds appear be at least as effective as unfractionated heparin, and without increased bleeding or thrombocytopenia. However, in the Global Use of Strategies t Open Occluded Coronary Arteries (GUSTO) IIb study of patients with uns angina/nonâ€“Q-wave myocardial infarction, there was an increase in the number of blood transfusions in patients who received desirudin as comp to those who received heparin.[68]

Summary

The ever-increasing frequency of anticoagulant therapeutic use is associa with complications and adverse outcomes. A complete understanding of t normal mechanisms of coagulation, anticoagulation, and thrombolysis, combined with an understanding of the pharmacology of the agent and th patient's clinical needs, will allow the clinician to better choose among th complex therapies currently available. Supportive care is often adequate certain complications associated with these therapies; however, occasion more aggressive interventions and specific antidotes are necessary depe on the particular agent and medical condition of the patient.

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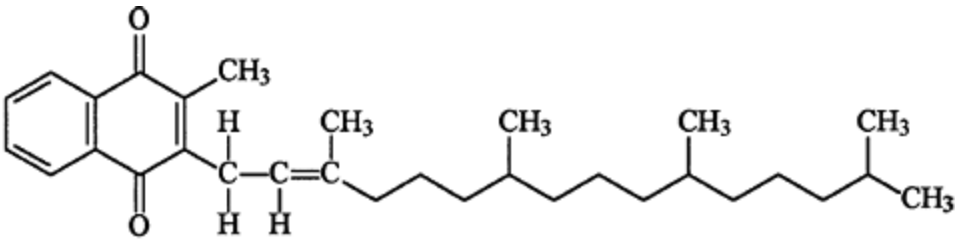
Antidotes in Depth

Vitamin K_1

Mary Ann Howland



Vitamin K_1

Vitamin K_1 (phytonadione) is indicated for the reversal of elevated prothrombin times and international normalized ratios (INRs) in patients with xenobiotic-induced vitamin K deficiency. Vitamin K deficiency is typically induced following the therapeutic administration of warfarin, or following the overdose of warfarin or the long-acting anticoagulant rodenticides (LAARs), such as brodifacoum. The optimal dosage regimen of vitamin K_1 to treat patients who develop an elevated INR while receiving warfarin has been reviewed and a revised guideline regarding the dose and route of administration published.[1,7] Oral administration of

vitamin K_1 is used safely and successfully. Because intravenous administration of vitamin K_1 is associated with anaphylactoid reactions, it should be avoided unless serious or life-threatening bleeding is present. Subcutaneous administration should only be considered an appropriate route of therapy when a patient is unable to tolerate oral vitamin K therapy yet is not clinically compromised enough to necessitate intravenous vitamin K_1 .[7]

History

It was noted in 1929 that chickens fed a poor diet developed spontaneous bleeding. In 1935, Dam and coworkers discovered that incorporating a fat-soluble substance in the diet could correct the bleeding and they named this substance a â€œkoagulation factor,â€• hence vitamin K.[19 , 28]

Chemistry

Vitamin K is an essential fat-soluble vitamin. The name *vitamin K* is actually a broad term that encompasses at least two distinct natural forms. Vitamin K_1 (phytonadione, phylloquinone) is the only form synthesized by plants and algae. Vitamin K_2 (menaquinones) is actually a series of compounds with the same 2-methyl-1,4-naphthoquinone ring structure as phylloquinone, but with a variable number (1â€“13) of repeating 5-carbon units on the side chain. Bacteria synthesize vitamin K_2 (menaquinones). Most of the vitamin K ingested in the diet is phylloquinone (vitamin K_1).

Daily Requirement

The human daily requirement for vitamin K is small; the Food and Nutrition Board set the recommended daily allowance at 1 Âµg/kg/d of phylloquinone for adults, although 10 times that amount is required for infants to maintain normal hemostasis.[27]

Extrahepatic enzymatic reactions that are vitamin K-dependent relate to carboxylation of proteins in the bone, kidney, placenta, lung, pancreas, and spleen, and include the synthesis of osteocalcin, matrix Gla protein, plaque Gla protein, and one or more renal Gla proteins.[27 , 28 , 32] Note that variations in an individual's dietary vitamin K intake while receiving chronic oral anticoagulation can significantly result in either over- or under-anticoagulation.[12]

Pharmacokinetics of Dietary Vitamin K

Dietary vitamin K in the form of phylloquinone and menaquinones is solubilized with the bile salts, free fatty acids, and monoglycerides to enhance absorption. Vitamin K, bound to chylomicrons, enters the circulation via the lymphatic system and then is taken up by the liver.[28] In the plasma, vitamin K is primarily in the phylloquinone form, whereas liver stores are 90% menaquinones and 10% phylloquinone.[28] Following 3 days of low vitamin K intake, a group of surgical patients showed a 4-fold lowering of liver vitamin K concentrations.[31] Rats given a vitamin K-deficient diet develop severe bleeding within 2â€“3 weeks.

Pharmacology

Activation of coagulation factors II, VII, IX, and X, and proteins S and C require Î³-carboxylation of the glutamate residues in a vitamin K-dependent process. Only the reduced (quinol, hydroquinone) form of vitamin K manifests biologic activity (Fig. 57-3). The quinone form of vitamin K can be activated to the quinol form directly by a nicotinamide adenine dinucleotide phosphate (NADPH)-dependent pathway that is relatively insensitive to warfarin.[28 , 32] During the carboxylation step, the K quinol form is converted to an epoxide. This 2,3-epoxide is reduced and recycled to the active K quinol in a two-step process that is inhibited by warfarin. For further detail, the reader is

referred to an in-depth model of the chemical basis of this reaction.[9 , 34]

Vitamin K Deficiency and Monitoring

Vitamin K deficiency can result from inadequate intake, malabsorption, or interference with the vitamin K cycle. Malnourishment and any condition in which bile salts or fatty acids are inadequate, such as extrahepatic cholestasis or severe pancreatic insufficiency, can lead to vitamin K deficiency. There are multifactorial etiologies that place newborns at risk for hemorrhage. Phylloquinone does not readily cross the placenta, and breast milk contains less phylloquinone than vitamin K-fortified formula. Fetal hepatic stores of phylloquinone are low and maternal anticonvulsant therapy may lead to increased vitamin K metabolism.[28 , 32] Although

menaquinones are produced in the colon by bacteria, it is unlikely that enteric production contributes significantly to vitamin K stores or that eradication of the bacteria with antibiotics, without a coexistent dietary deficiency of vitamin K, results in deficiency.[28] Determination of vitamin K deficiency is usually established on the basis of a prolonged prothrombin time (PT), which is a surrogate marker of specific coagulation factors. Measurement of the vitamin K-dependent factors, II, VII, IX, and X, appears to be an effective way to determine the adequacy of vitamin K_1 dosing.[15] Serial measurements of factor VII, the factor with the shortest half-life, allows for the early detection of inadequate vitamin K in the diet or a therapeutic regimen.[6] Direct measurement of serum vitamin K serum levels is done by high-performance liquid chromatography (HPLC) analysis. The human serum vitamin K concentration required for adequate production of activated clotting factors in the presence of LAARs is still unclear. One study in a patient who overdosed on brodifacoum suggested that a serum vitamin K concentration of 0.2â€“0.4 Âµg/mL was sufficient, in contrast to

the 1 Âµg/mL reported as necessary in rabbits.[6 , 23]

Mechanism of Action for Xenobiotic-Induced Vitamin K Deficiency

Oral anticoagulants are vitamin K antagonists that interfere with the vitamin K cycle, causing the accumulation of vitamin K 2,3-epoxide, an inactive metabolite. Warfarin is a strong irreversible inhibitor of the dithiol-dependent vitamin K reductases (epoxide reductase and quinone reductase), which maintain vitamin K in its active (quinol, hydroquinone) form.[3] The superwarfarins are even more potent vitamin K reductase inhibitors. Without exogenous interference, vitamin K is recycled and only 1 Âµg/kg is required in adults to maintain adequate coagulation. NADPH-dependent quinone reductase is a warfarin-insensitive enzyme capable of reducing vitamin K_1 to its active hydroquinone form, but it is incapable of regenerating vitamin K from vitamin K epoxide following carboxylation of the coagulation factor (Fig. 57-3).[3] Thus, in the presence of warfarin or superwarfarin, additional vitamin K_1 must be administered to supply this active cofactor for each and every carboxylation step, as it can no longer be recycled.[6] The minimum vitamin K_1 requirement in the presence of a LAAR is unknown. Other compounds have varying degrees of vitamin K antagonistic activity and include the *N* -methyl-thiotetrazole side-chain-containing antibiotics such as moxalactam and cefamandole (Chap. 54), as well as salicylates (Chap. 35).[28]

Vitamin K_1 (phylloquinone, phytonadione)
Mephyton
AquaMEPHYTON
Oral
SC, IV
5 mg
2 mg/mL

Commercial Preparation	Route of Administration	Strength	Comments
		10 mg/mL	Best for anticoagulant-induced prolonged prothrombin time. Oral route preferred; divided doses may be necessary for large requirements; IV reserved for life-threatening situations. Must be carefully diluted and slowly infused (IV) to avoid anaphylactoid reactions; SC for small doses.

TABLE A16-1. Available Vitamin K_1 Products

Availability of Different Forms of Vitamin K

Table A16-1 lists the currently marketed vitamin K products. Vitamin K_1 (phylloquinone, phytonadione) is the only vitamin K preparation that should be used to reverse anticoagulant-induced vitamin K deficiency or to treat infants, pregnant women, or patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency because of the increased risks of hemolysis with other vitamin K preparations. Vitamin K_1 is superior to the other previously commercially available vitamin K preparations because it is more active, thus requiring comparatively smaller doses, because it works more rapidly (6 vs. 12 hours), and because it has fewer associated risks.[13, 30]

Vitamins K_3 (menadione) and K_4 (menadiol sodium diphosphate) can produce hemolysis, hyperbilirubinemia, and kernicterus in neonates, and hemolysis in G6PD-deficient patients. The only advantage that menadione and menadiol sodium diphosphate have is that these preparations are absorbed directly from the intestine by a passive process that does not require the presence of bile salts. Theoretically, these agents are advantageous for patients

with cholestasis or severe pancreatic insufficiency. However, they are neither interchangeable with vitamin K_1 , nor a substitute for vitamin K_1 , when anticoagulants such as warfarin or LAAR are responsible for coagulation deficits. Therefore, for a patient deficient in bile salts who requires vitamin K_1 , exogenous bile salts, such as ox bile extract 300 mg or dehydrocholic acid 500 mg, should be given with each dose of oral vitamin K_1 .[24]

Pharmacokinetics and Pharmacodynamics of Administered Vitamin K_1

There are only a limited number of pharmacokinetic studies of vitamin K_1 .[6 , 14 , 23 , 35] One study evaluated the pharmacokinetics of vitamin K_1 in healthy volunteers, brodifacoum-anticoagulated rabbits, and a patient poisoned with brodifacoum.[23] In the volunteers and the poisoned patient, a 10-mg IV dose of vitamin K_1 had

a half-life of 1.7 hours. After oral administration of doses of 10 and 50 mg of vitamin K_1 , peaks of 100â€“400 ng/mL and 200â€“2000 ng/mL, respectively, occurred at 3â€“5 hours. Bioavailability varied significantly between patients (10â€“65%) for both doses, and in individual patients with the 50-mg dose. Oral vitamin K_1 (phytonadione, phylloquinone) is absorbed in an energy-dependent saturable process in the proximal small intestine, and this likely contributes to the variability.[23] In maximally brodifacoum-anticoagulated rabbits, IV vitamin K_1 (10 mg/kg) increased prothrombin complex activity (PCA) from 14â€“50% by 4 hours, and to 100% by 9 hours, after which it declined with a half-life of 6 hours. High doses of oral vitamin K_1 were used to treat a patient anticoagulated with brodifacoum.[6] The pharmacokinetics of oral and IM vitamin K_1 were compared in 8 healthy female volunteers. Baseline serum vitamin K

concentrations were 0.23 ng/mL. Following the oral administration of 5 mg of vitamin K, peak serum concentrations of 90 ng/mL were achieved between 4 and 6 hours. These levels dropped to a steady state of 3.8 ng/mL and exhibited a half-life of about 4 hours. The pharmacokinetics were distinctly different after IM administration and quite variable. IM administration of 5 mg of vitamin K resulted in peak serum concentrations of only 50 ng/mL with delays from 2â€“30 hours following administration and with the maintenance of a plateau for about 30 hours.[14] Consequently, IM administration is not recommended; either oral or intravenous is more appropriate and the route will be defined by the severity of bleeding. Only in the case of acute gastrointestinal disease in a patient without life-threatening overanticoagulation is subcutaneous route an appropriate alternative to the oral route.

Routes of Administration and Adverse Effects

Although vitamin K_1 can be administered orally, subcutaneously, intramuscularly, or intravenously, the oral route is preferred for maintenance therapy. When administered orally, vitamin K_1 is virtually free of adverse effects, except for overcorrection of the INR in the setting of a patient who requires maintenance anticoagulation. The only preparation available for intravenous administration is AquaMEPHYTON, which is associated with rare anaphylactoid reactions. This preparation is not available in solution but as an aqueous colloidal suspension of a polyoxyethylated castor oil, dextrose, and benzyl alcohol because of vitamin K's lipid solubility. Intravenous administration has resulted in death secondary to anaphylactoid reactions, probably as a result of the preparation's colloidal formulation.[4,8,20] Numerous anaphylactoid reactions have been reported, even when it is properly diluted and administered slowly.[22] New liposomal preparations are under development, which may become safer

alternatives.

Onset of Effect

The time necessary for the INR to return to a safe or normal range is very variable and depends on the rate of absorption of vitamin K_1 , the serum concentration achieved, and the time necessary for the synthesis of activated clotting factors. A decrease in the INR can often occur within several hours, although it may take 8â€“24 hours to reach target values.[5 , 11 , 21 , 25] Maintenance of a normal INR depends on the half-life of the vitamin K_1 , maintenance of an effective serum concentration, and the half-life of the anticoagulant involved. The IV route is unpredictably faster than the oral route in restoring the INR to a safe range.[14 , 18] A comparison of oral versus intravenous vitamin K_1 therapy for excessive anticoagulation, without major bleeding, demonstrated that those individuals with INRs 6â€“10 had similarly improved INRs at 24 hours and that the IV group was more often overcorrected to an INR <2.[18]

Dosing and Administration

The optimal dosage regimen for vitamin K_1 remains unclear. Variables include the vitamin K_1 pharmacokinetics and the amount and type of anticoagulant ingested.[26] Reported cases of LAAR poisoning have required as much as 50â€“250 mg of vitamin K_1 daily for weeks to months.[2 , 6 , 10 , 16 , 17 , 29 , 33] A reasonable starting approach for a patient who has overdosed on LAAR is 25â€“50 mg of vitamin K_1 , orally 3â€“4 times a day for 1â€“2 days. The INR should be monitored and the vitamin K_1 dose adjusted accordingly. Once the INR is <2, a downward titration in the dose of vitamin K_1 can be made on the basis of factor VII analysis. For an ingestion of brodifacoum, serial serum levels of brodifacoum may be helpful in determining the ultimate duration of treatment.[6] See Table 57-4 for the management of patients

with elevated INRs secondary to excessive warfarin.

IV administration of vitamin K_1 should be reserved for life-threatening bleeding and serious bleeding at any elevation of INR (Table 57-4).[1] Under these circumstances, patients may be supplemented with prothrombin complex concentrate; fresh-frozen plasma or recombinant factor VIIa can be considered as an alternative to prothrombin complex concentrate. A starting dose of 10 mg of vitamin K_1 is reasonable. To minimize the risk of an anaphylactoid reaction, the preparation should be diluted with preservative-free 5% dextrose, 0.9% sodium chloride, or 5% dextrose in 0.9% sodium chloride, and administered slowly, at a rate not to exceed 1 mg/min in adults. Precautions should be anticipated in the event of an anaphylactoid reaction.

Because the duration of action of vitamin K_1 is short-lived, the dose must be repeated 2â€“4 times daily. The onset of the effect of vitamin K_1 is not immediate, regardless of the route of administration.

Vitamin K_1 is available orally as a 5-mg tablet.

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Antidotes in Depth

Protamine

Mary Ann Howland

History

Protamine is a rapidly acting antidote that is used for reversing the anticoagulant effects of unfractionated heparin (UFH) and potentially low-molecular-weight heparin (LMWH). The antidotal property of protamine was recognized in the late 1930s, and it was approved for use as an antidote for heparin overdose in 1968.[48] However, the largest body of literature pertaining to protamine originates from its use in neutralizing heparin following cardiopulmonary bypass and dialysis procedures.

Pharmacology

The protamines are a group of simple basic cationic proteins found in fish sperm that bind to heparin to form a stable salt. Commercially available protamine sulfate is derived from the sperm of mature testes of salmon and related species. On hydrolysis, it yields basic amino acids, particularly arginine,

proline, serine, and valine, but not tyrosine and tryptophan. The effects of protamine sulfate and protamine chloride appear to be comparable.[39] The molecular weight of heparin ranges from 3,000â€“30,000 daltons and is composed of approximately 45 monosaccharide chains.

One milligram of protamine will neutralize approximately 100 U (1 mg) of UFH (mean molecular weight [MW] ~12,000 daltons). However, there is no proven method for neutralizing LMWH. Protamine neutralizes approximately 60% of the antifactor Xa activity of LMWH. Because the interaction of protamine and heparin is dependent on the MW of heparin, the lower-molecular-weight heparin (mean MW 4500 daltons) has reduced protamine binding. This protamine-resistant fraction in LMWH is an ultralow-molecular-weight fraction with low sulfide charge.[12] It is suggested that 1 mg enoxaparin equals ~100 antifactor Xa units. There are no human studies that have robust evidence either demonstrating or refuting a beneficial effect of protamine on bleeding related to LMWH. Within the first 8 hours following administration, the recommendation for reversal of the antithrombotic effect of LMWH is to administer 1 mg protamine per 100 antifactor Xa units of LMWH. A second dose of 0.5 mg protamine should be administered per 100 antifactor Xa units if bleeding continues.[24]

In animal studies, synthetic protamine variants were effective in reversing the anticoagulant effects of LMWH and are reported to be less toxic than protamine. These agents are not available for clinical use.[24,29,59,60]

Mechanism of Action

Heparin is a large electronegative substance that is rapidly complexed by the electropositive protamine, forming an inactive salt. Heparin is an indirect anticoagulant, requiring a cofactor. This cofactor formerly called antithrombin III, now referred to simply

as AT,[24] alters its stereochemistry and thereby catalyzes the subsequent inactivation of thrombin and other clotting factors. Only about one-third of an administered dose binds to AT and this fraction is responsible for most of its anticoagulant effect.[3,41] LMWH has a reduced ability to inactivate thrombin caused by lesser AT binding, but the smaller fragments of LMWH inactivate factor Xa almost as well as the larger molecules of UFH, allowing for equal efficacy.[24] Immunoelectrophoresis demonstrates that because of its net positive charge, protamine has a greater affinity for heparin than AT, producing a dissociation of the heparinâ€“AT complex in favor of a protamine-heparin complex.[49]

Adverse Effects, Risk Factors, and Safety Issues

Since the advent of cardiopulmonary bypass surgery, protamine has been routinely employed in the neutralization of heparin at the completion of the procedure. Millions of patients are exposed to protamine each year and approximately 100 deaths are reportedly associated with the use of protamine under these circumstances. It is largely in this setting that the adverse effects of protamine are also documented and studied.[26,27,42] It is often difficult to separate the adverse effects caused by protamine from those of the protamineâ€“heparin complex and those actually related to that of heparin. Adverse effects associated with protamine include both rate- and nonâ€“rate-related hypotension,[15,16,17 and 18,20,31,34,53,56] anaphylactic[30] and anaphylactoid reactions,[33,44,46] bradycardia,[1] thrombocytopenia,[64] leukopenia, decreased oxygen consumption,[61,63] acute lung injury,[4,58] pulmonary hypertension,[6] and anticoagulant effects.[2]

The mechanisms for these adverse effects are multifactorial. The strong net-positive charge of protamine may be responsible for some of the adverse effects and probably directly injures a variety of organelles, including platelets.[9,65] The protamineâ€“heparin

complex activates the arachidonic acid pathway and the production of thromboxane is at least partly responsible for some of the hemodynamic changes, including pulmonary hypertension.[6,11,25,45,65] Pretreatment with indomethacin limits these effects.[11,25,45,65] Free protamine or protamine complexed with heparin can convert L-arginine to nitric oxide (formerly called endothelium-derived relaxing factor), which, in turn, causes vasodilation and inhibits platelet aggregation and adhesion.[50] Protamine administered in the absence of heparin, or in an amount exceeding that necessary for heparin neutralization, can act as an anticoagulant and may inhibit platelet function, resulting in weaker clot formation.[32,61] This anticoagulant effect may result from effects on factor VII and/or AT. Protamine in excess of heparin can enter the myocardium and decrease cyclic adenosine monophosphate (cAMP), causing myocardial depression.[6] Protamine and protamineâ€“heparin complexes can activate the complement pathway and contribute to vasoactive events.[6,51] Protamine stimulates mast cells in the human heart and skin to release histamine.[6] Risk factors for protamine-induced adverse reactions include prior exposure, which may occur during a previous

surgery, history of nonprotamine medication allergy, a rapid rate of infusion, or a history of allergy to fish.[51] A prospective study reported a 0.06% incidence of anaphylactic reactions to protamine in all patients undergoing coronary artery bypass, but a 2% incidence in diabetics using neutral protamine Hagedorn (NPH) insulin.[7] The resultant elevation of histamine levels, the activation of complement, and elevated IgE, IgA, and IgG concentrations are also suggested as mechanisms for the adverse effects.[40,57,66,67] Diabetic patients receiving daily subcutaneous injections of a protamine-containing insulin (NPH) have a 40â€“50% increased risk of adverse reactions.[19,22,30,38,56]

Occasionally, patients manifesting a protamine allergy are

presumed to have insulin allergy.[37] In diabetic patients receiving protamine insulin injections, the presence of serum antiprotamine IgE antibody is a significant risk factor for acute protamine reactions. Only patients with previous exposure to protamine insulin injections had serum antiprotamine IgE antibodies. However, in the group without previous protamine insulin exposure, antiprotamine IgG antibody was noted as a risk factor for protamine reactions.[67] Either naturally occurring cross-reacting antibodies, or perhaps previously unrecognized protamine exposure, was responsible for the generation of these IgG antibodies.

Alternatives to Protamine in Patients at High Risk for an Adverse Drug Reaction

There are limited options for the reversal of heparin in patients who have previously experienced anaphylaxis following protamine therapy, or in patients who are expected to be at high risk for a protamine reaction. Clotting factors may be replaced, or exchange transfusion instituted in neonates, and protamine avoided, or protamine may be used while preparing to treat anaphylaxis expectantly. Several alternatives are under investigation and include the placement of heparin removal devices in the coronary artery bypass extracorporeal circuit, as well as the use of hexadimethrine, methylene blue, platelet factor 4, and heparinase as antidotes.[7,36] Pretreatment with antihistamines and corticosteroids may be sufficient for immune-mediated mechanisms, but will probably not be beneficial for pulmonary vasoconstriction and nonâ€“immune-mediated anaphylactoid reactions.[28]

Dosing in Cardiopulmonary Bypass

Protamine is most frequently used at the end of cardiopulmonary bypass operations to reverse the effects of heparin. There are many regimens used for protamine dosing, including (a) giving an arbitrary amount of protamine (eg, 0.2 mg/kg); (b) giving protamine in a ratio of 0.6â€“1.5:1 times the initial heparin dose, resulting in an activated coagulation time (ACT) of about 480 seconds; and (c) giving protamine in a ratio of 0.75â€“2.1:1 times the total operative heparin dose.[68] Two additional methods of calculating the protamine dose to improve accuracy and avoid excess protamine are proposed.[32,68] One advocates an initial protamine dose based on ACT, with subsequent doses based on the ratio of the change in thrombin time to the heparin-neutralized thrombin time. If this ratio is greater than 12 seconds, then 10-mg incremental protamine doses should be administered.[32] The other uses a nomogram based on heparin activity in mg/kg versus ACT.[68] Both methods demonstrate efficacy with 2-mg/kg doses of protamine, about one-half of the dose previously used. With these approaches, the ACT responded to protamine within 5 minutes, decreasing in value from between 550 and 700 seconds to a control of 150 seconds. Other investigators suggest a variety of monitoring methods and dosing schemas in this setting.[13,23,54]

Heparin Rebound and Redosing of Protamine

A heparin anticoagulant rebound effect is noted after cardiopulmonary bypass and is attributed to the presence of detectable circulating heparin several hours after apparently adequate heparin neutralization with protamine. The incidence of heparin rebound and the need for additional protamine range from 4â€“42% depending on the neutralization protocol.[21,43,52] It is likely that larger heparin doses may prolong the clearance of heparin, contributing to higher than expected heparin levels.[52] When 300 U/kg of body weight doses of heparin were reversed at

the end of cardiopulmonary bypass with 3 mg/kg of protamine, a 14% incidence of small but detectable concentrations of circulating heparin was noted at 2 hours, which lasted less than 1 hour in all but 1 case.[43] The prothrombin time was prolonged and thrombocytopenia was noted, but there was no increase in blood loss.

Dosing Considerations

Approximately 1 mg of protamine will neutralize about 100 U (1 mg) of heparin (UFH). A limited number of studies suggest incomplete neutralization by protamine of the LMWHs enoxaparin, dalteparin, and tinzaparin. Present recommendations are to administer 1 mg protamine per 100 antifactor Xa units where 1 mg enoxaparin equals 100 antifactor Xa units. A second dose of 0.5 mg protamine should be administered per 100 antifactor Xa units if bleeding continues.[14] A number of tests can directly measure heparin levels or indirectly measure heparin's effect on the clotting cascade.[8,10,13] These tests may be helpful in determining the appropriate dose of protamine. Because excessive protamine can act as an anticoagulant, the dose chosen should always be an underestimation of that which is needed. In the case of unintentional overdose, the half-life of heparin should be considered, because half of the administered dose of heparin is eliminated within 60â€“90 minutes. In the case of an unintentional overdose without bleeding, the short half-life of heparin and the potential risks of protamine administration usually argue for a conservative approach of patient observation, rather than protamine reversal of anticoagulation. If protamine use is necessary to treat active bleeding, the dose must be administered intravenously over 15 minutes to limit rate-related hypotension.[35,62]

Dosing in the Overdose Setting

When faced with a patient believed to have received an overdose of an unknown quantity of heparin, the decision to use protamine should be determined by the presence of a prolonged activated partial thromboplastin time (aPTT) and the presence of persistent bleeding.

In each circumstance, the potential risks of protamine use (especially in those who have had a prior life-threatening reaction to protamine as well as in a diabetic receiving a protamine-containing insulin) and the risks of continued heparin anticoagulation should be evaluated. A baseline ACT, thrombin time, heparin-neutralized thrombin time, heparin activity, platelets, prothrombin time (PT)/partial thromboplastin time (PTT), hemoglobin, and hematocrit should be obtained. Because of the routine nature of heparin reversal following cardiopulmonary bypass, consultation with members of the bypass team may be helpful. An empiric dose of protamine may be suggested by the baseline ACT: (a) an ACT of 150 seconds necessitates no protamine; (b) an ACT of 200â€“300 seconds necessitates 0.6 mg/kg; and (c) an ACT of 300â€“400 seconds necessitates 1.2 mg/kg. These doses have not been tested outside the operating room. The ACT should be repeated 5â€“15 minutes following the protamine dose and in 2â€“8 hours (to evaluate the potential for heparin rebound), and further dosing should be based on these values.

When the ACT is not available, 25â€“50 mg of protamine can be administered to an adult and adjusted accordingly. Repeat dosing in several hours may be necessary if heparin rebound occurs. The dose should be administered intravenously slowly over 15 minutes with resuscitative equipment immediately available. Neonates should not receive protamine that has been reconstituted with bacteriostatic water containing benzyl alcohol.

Future interventions for bleeding following heparin may include activated factor VII and adenosine triphosphate. Activated factor

VII therapy was recently shown to be successful in treating postoperative bleeding in a patient with renal failure who was given LMWH and aspirin.[47] Adenosine triphosphate completely reversed clinical bleeding related to LMWH in a rat model. These agents have not been FDA approved for clinical use in this setting.[14]

Availability

Protamine is available either as a parenteral solution ready for injection or as a powder to be reconstituted with 5 mL of sterile or bacteriostatic water for injection. When the vials containing 50 mg of protamine are used, they should be shaken vigorously after the water is added. The final solution of either preparation contains 10 mg of protamine per mL.

Summary

Protamine is an effective, rapidly acting antidote used to reverse the anticoagulant effect of unfractionated heparin, while its ability to reverse the effects of LMWH is less clear. This antidote should only be used for a prolonged aPTT in the presence persistent bleeding, since potential risks of its use include hypotension, anaphylactic reactions, dysrhythmias, leukopenia, thrombocytopenia and acute lung injury. Activated factor VII and adenosine triphosphate may be used in the near future to treat heparin-induced bleeding.

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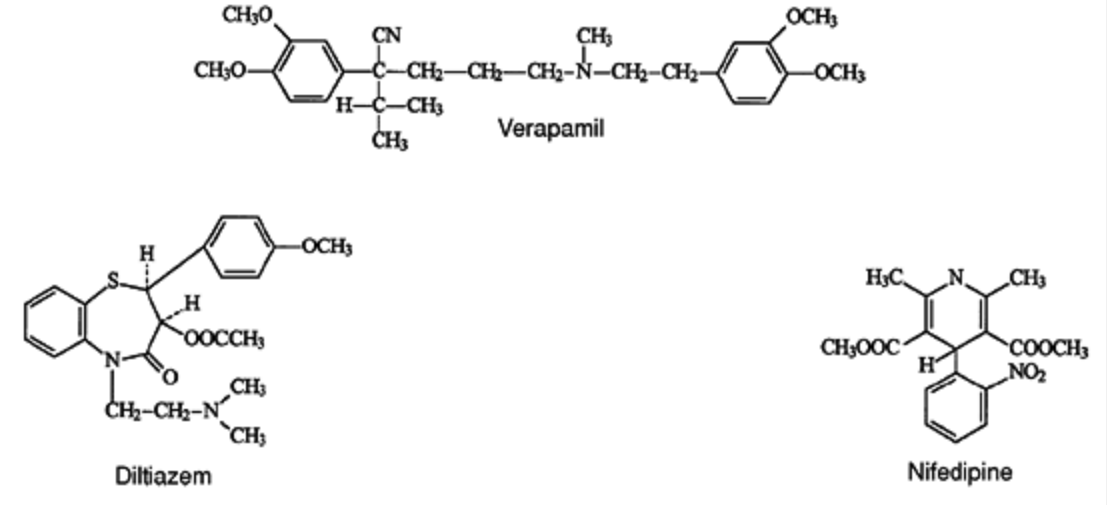
Chapter 58
Calcium Channel Blockers

Francis DeRoos



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A 40-year-old woman with a history of insulin-dependent diabetes

mellitus, coronary artery disease, and depression presented to the hospital with multiple nonspecific complaints, including â€œnot feeling well,â€• dyspnea, weakness in the legs, and lightheadedness. Physical examination revealed a morbidly obese woman in no distress whose initial vital signs were: blood pressure, 120/70 mm Hg; heart rate, 100 beats/min; respiratory rate, 18 breaths/min; temperature 98.9Â°F (37.2Â°C). The lungs were clear to auscultation, and cardiac examination revealed normal S_1 and S_2, and an S_4 gallop, but no murmurs or rubs. Her abdomen was obese with active bowel sounds and no tenderness. Neurologic assessment revealed a normal mental status and no focal deficits.

Because of the nonspecific complaints in a patient with significant medical conditions, a broad diagnostic evaluation was begun that included a rapid bedside glucose measurement, a urinalysis, electrolytes, renal function testing, liver enzymes, complete blood count, and an electrocardiogram (ECG). The ECG demonstrated a sinus rhythm at 100 beats/min, with normal PR and QRS intervals, left atrial enlargement, and evidence of an old anterior wall infarction (Fig. 58-1). There was no change from previous ECGs on file at the hospital.

Approximately 4 hours into her evaluation and hospital stay, the patient complained of lightheadedness and weakness. Repeat physical examination revealed a slightly lethargic but arousable and cooperative woman. Her blood pressure was 70/30 mm Hg with a heart rate of 90 beats/min and regular. A repeat ECG revealed normal sinus rhythm and first degree heart block, with a PR interval of 240 msec (Fig. 58-2). At this time, she confided in the physician that the true reason for her visit was that she ingested 20 diltiazem (90-mg) tablets in a suicide attempt just prior to coming to the hospital.

Initial therapy included boluses of 0.9% sodium chloride, calcium chloride (2 g intravenously), glucagon (1 mg intravenously), and intravenous infusions of dopamine and isoproterenol which resulted

in transient improvement in systolic blood pressure to 98 mm Hg. One hour after her initial hypotensive episode, the patient suffered a cardiac arrest with junctional rhythm of 65 beats/min and no measurable blood pressure (Fig. 58-3). With aggressive therapy, including cardiopulmonary resuscitation (CPR), endotracheal intubation, atropine (3 mg intravenously), high-dose intravenous infusions of dopamine and isoproterenol, and a glucagon bolus (5 mg intravenously), the systolic blood pressure returned to between 40 and 65 mm Hg with a heart rate of 50â€“60 beats/min. Over the next 3 hours multiple pharmacologic agents, including repeat boluses of calcium chloride and continuous infusions of glucagon (5 mg/h), amrinone (200-mg bolus then 800 mg/h), and phenylephrine were initiated, without improvement in blood pressure. During this period the patient's serum glucose had risen from 250â€“800 mg/dL and an insulin infusion was begun.

Because of only limited improvement after multiple pharmacologic agents, a transcutaneous pacer was applied but was unable to capture. A transvenous right-ventricular pacemaker was then placed with intermittent capture at 70 beats/min, but the systolic blood pressure remained below 80 mm Hg. An intraaortic balloon pump (IABP) was placed, and within 15 minutes the blood pressure improved to 100/50 mm Hg. The patient was maintained on the IABP and transvenous pacemaker, and slowly weaned off the multiple inotropic agents and vasopressors over the next 24 hours. After a complicated 3-week hospitalization, the patient was discharged to an inpatient psychiatric facility with complete neurologic recovery.

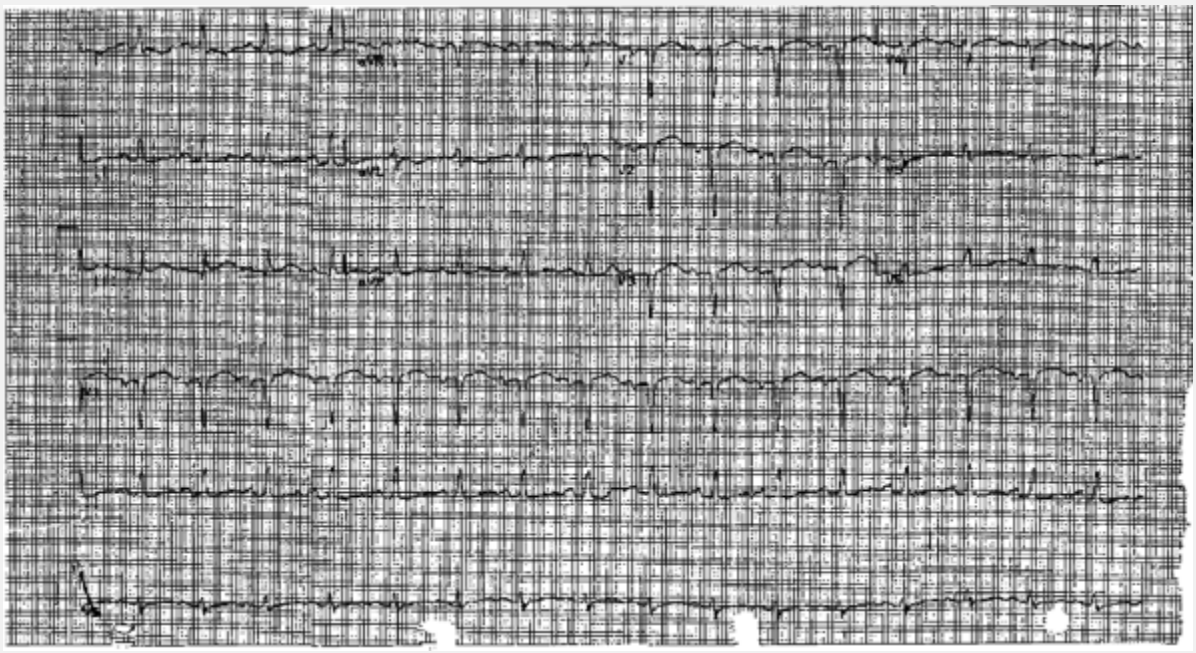

Figure 58-1. This 12-lead electrocardiogram taken 2 hours postingestion of 1800 mg of sustained-release diltiazem demonstrates a sinus tachycardia at 100 beats/min with a normal QRS axis, normal intervals, left atrial enlargement, and an old anterior wall myocardial infarction.

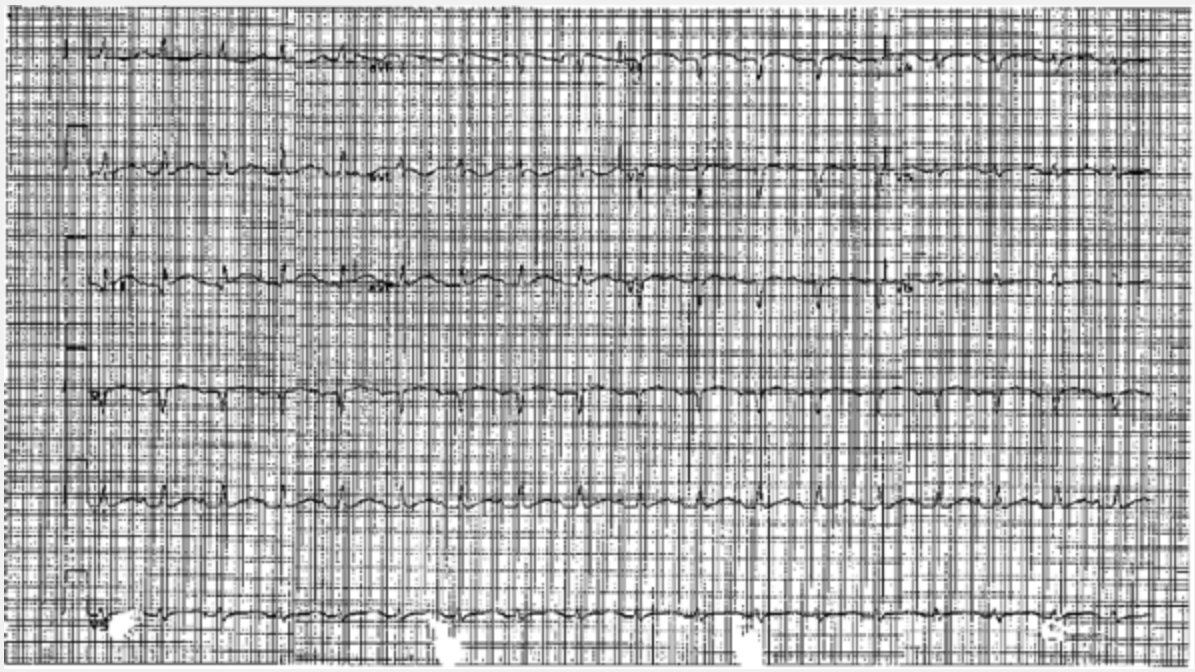

Figure 58-2. This 12-lead electrocardiogram, taken 6 hours postingestion of 1800 mg of sustained-release diltiazem, demonstrates first-degree heart block with a PR interval of 260 msec and no other changes as compared to the patient's previous electrocardiogram (Fig. 58-1).

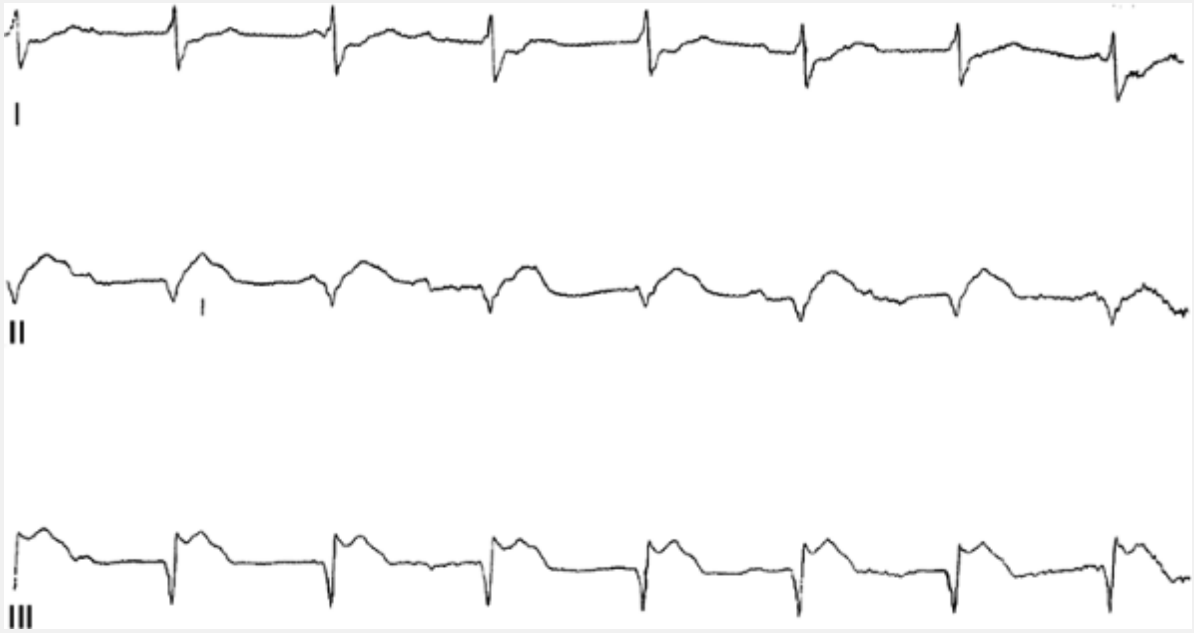

Figure 58-3. This 3-lead rhythm strip was obtained 9 hours postingestion of 1800 mg of sustained-release diltiazem, shortly after the patient became obtunded, hypotensive, and bradycardic. The electrocardiogram demonstrates a junctional bradycardia at 65 beats/min with widened QRS interval of 130 msec and possible inferior ischemia.

Calcium channel blockers (CCBs) were first used experimentally in the 1960s, and their use has steadily risen to the point where they are some of the most frequently prescribed cardiovascular drugs.[47] Mirroring this widespread use, poisonings involving CCBs have also risen. The combination of compliance-improving sustained-release formulations and potent hemodynamic effects complicates the management of patients poisoned with these drugs. The hallmarks of toxicity include hypotension, from vasodilation and impaired myocardial contractility, and bradydysrhythmias. In severely

poisoned patients, no therapeutic intervention is demonstrated to be consistently effective. Management decisions must be made on an individual patient basis with careful assessment of the physiologic response to each treatment.

TABLE 58-1. Classification of Calcium Channel Blockers Available in the United States

Class	Specific Compounds
Phenylalkylamine	Verapamil (Calan, Isoptin, Verelan)
Benzothiazepine	Diltiazem (Cardizem, Dilacor, Tiazac)
Dihydropyridines	Nifedipine (Adalat, Procardia) Isradipine (DynaCirc) Amlodipine (Norvasc) Felodipine (Plendil) Nimodipine (Nimotop) Nisoldipine (Sular) Nicardipine (Cardene)
Diarylaminopropylamine ether	Bepridil (Vascor)
T-channel blocker	None (Mibefradil withdrawn)

Epidemiology

CCBs were first introduced to the US pharmaceutical market in the late 1970s. Currently, there are 10 CCB agents available in either regular or sustained-release formulations (Table 58-1). They are used for a variety of medical conditions, including hypertension, stable angina, dysrhythmias, migraine headaches, Raynaud phenomenon, and subarachnoid hemorrhage.

In 1986, more than 1200 exposures and 7 deaths related to CCBs were reported to the American Association of Poison Control Centers. In 2003, those figures increased to 9650 exposures, including 2042 characterized by moderate to major toxicity, and an additional 57 deaths (Chap. 130). This significant rise in fatalities is most likely the result of the increased use and access to these drugs, although the introduction of sustained-release preparations in 1988 may also play a role.

Pharmacokinetics and Toxicokinetics

All CCBs are well-absorbed orally and undergo hepatic oxidative metabolism predominantly via CYP3A subgroup of the cytochrome P450 (CYP) enzyme system.[45,62,119] Norverapamil, formed by *N*-demethylation of verapamil is the only active metabolite and retains 20% of the parent compound's activity.[78] Diltiazem is predominantly deacetylated into minimally active deacetyldiltiazem, which is then eliminated via the biliary tract.[62] In overdose, these hepatic enzymes become saturated, reducing the

potential control of the first-pass effect and increasing the quantity of active drug absorbed systemically. This saturation of drug metabolism contributes to the prolongation of the half-lives reported following overdose of various CCBs.[19,43,44,146] All CCBs are highly protein bound.[87,119] Volumes of distribution are large for verapamil (5.5 L/kg)[120] and diltiazem (5.3 L/kg),[119] and somewhat smaller for nifedipine (0.8 L/kg).[93] Although not well-studied, the substantial protein binding and the large volumes of distribution make it unlikely

that extracorporeal drug removal with hemodialysis or hemoperfusion would be of any value in overdose. Several case reports offer clinical support for this conclusion.[149,151,169]

One interesting aspect of the pharmacology of CCBs is their potential for drugâ€“drug interactions. CYP3A, which metabolizes most CCBs, is also responsible for the initial oxidation of numerous other drugs. Verapamil and diltiazem specifically compete for this isozyme and can decrease the clearance of many drugs including carbamazepine, cisapride, quinidine, various Î²-hydroxy-Î²-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, cyclosporine, tacrolimus, most HIV-protease inhibitors, and theophylline.[1,140] In June 1998, mibefradil, a structurally unique CCB, was voluntarily withdrawn following several reports of serious adverse drug interactions caused in part by mibefradil's potent inhibition of the CYP3A.[7,104] Whereas other inhibitors of CYP3A4, such as cimetidine, fluoxetine, some antifungals, macrolide antibiotics, and even the flavonoids in grapefruit juice, may raise serum concentrations of several CCBs, the clinical significance of this effect remains unclear.[1]

In addition to affecting CYP3A, verapamil and diltiazem also inhibit P-glycoproteinâ€“mediated drug transport into peripheral tissues. This inhibition results in elevated serum concentrations of drugs, such as cyclosporine and digoxin, which use this transport system.[34,72] Unlike diltiazem and verapamil, nifedipine and the other dihydropyridines do not appear to affect the clearance of other agents via CYP3A or P-glycoproteinâ€“mediated transport.[2]

Pathophysiology

Calcium plays an integral part in excitation-contraction coupling and myocardial conduction (Fig. 58-4). Initially, Ca^{2+} is driven intracellularly down large concentration and electrical gradients through calcium-specific voltage-sensitive channels. These channels, specifically identified as L-type calcium channels, are located in the plasma membrane of all types of muscle cells[81] and are composed of

homologous protein subunits, also found in some sodium and potassium channels.[85] The Î±$_{1c}$ subunit is the pore-forming portion of this channel and is where all CCBs bind to prevent Ca^{2+} transport.[64] There are many other types of calcium channels, including N, P, T, Q, and R types, that can be found either intracellularly on the sarcoplasmic reticulum or on cell plasma membranes, particularly in neuronal and secretory tissue.[153] They may be stimulated by cellular stretch (stretch-operated), specific neurohormonal binding (receptor-operated), or voltage changes (voltage-sensitive).[144] Skeletal muscle depends exclusively on intracellular Ca^{2+} stores for excitation contraction coupling, so intracellular influx of Ca^{2+} does not add much to the total Ca^{2+} pool required for contraction. In cardiac and smooth muscle cells, however, this influx is critical.

In smooth muscle, the rapid influx of calcium binds calmodulin, and the resulting complex stimulates myosin light-chain kinase activity.[3] The myosin light-chain kinase phosphorylates, and thus activates, myosin, which subsequently binds actin, causing a contraction to occur (Fig. 58-4).[82,128] In myocardial cells, this slow Ca^{2+} influx creates the plateau phase (phase 2) of the action potential.[125] The Ca^{2+} then acts as a second messenger by binding to and opening a receptor-operated calcium channel on the sarcoplasmic reticulum which releases Ca^{2+} from the vast stores of the sarcoplasmic reticulum into the cytosol.[73,74] This is often termed calcium-induced calcium release.[40,183] Calcium then binds troponin C, which causes a conformational change that displaces troponin and tropomyosin from the actin allowing actin and myosin to bind, resulting in a contraction (Chap. 23; Fig. 58-4).[84]

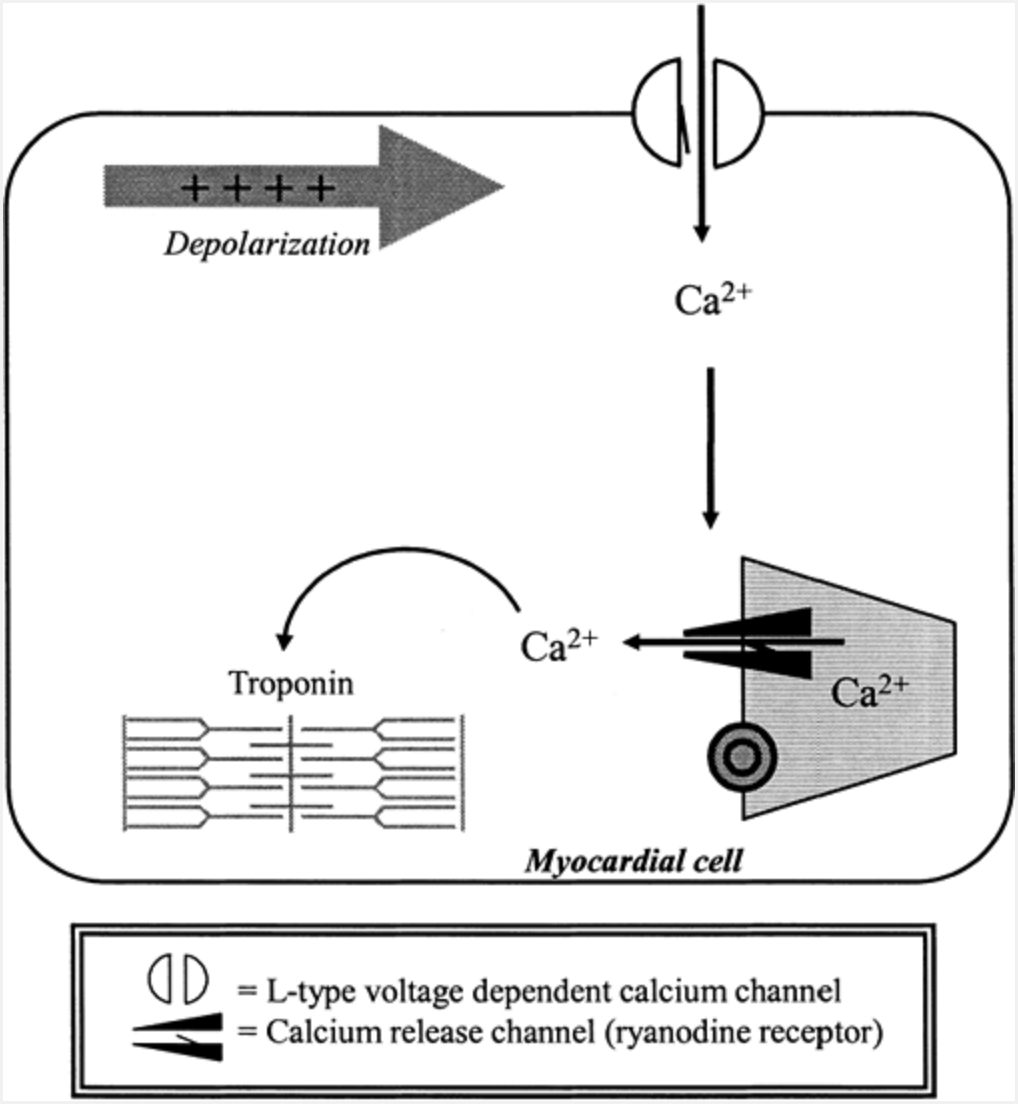

Figure 58-4. Normal contraction of myocardial cells. The L-type voltage sensitive calcium channels open to allow calcium ion influx during myocyte depolarization. These calcium ions cause the concentration-dependent release of more calcium ions from the sarcoplasmic reticulum that ultimately produce cardiac contraction.

In addition to its role in myocardial contractility, Ca^{2+} influx is also

important in myocardial conduction. Calcium influx plays an important role in the spontaneous depolarization (phase 4) of the action potential in the sinoatrial (SA) node.[125] This Ca^{2+} influx also allows normal propagation of electrical impulses via the specialized myocardial conduction tissues particularly the atrioventricular (AV) node.[147] After opening, the rate of recovery of these slow calcium channels, in both the SA and AV nodal tissue, determines rate of conduction.[89,173]

All commercially available CCBs exert their physiologic effects by antagonizing L-type voltage-sensitive calcium channels.[83,175] The differences among their pharmacologic effects is related to a combination of specific receptor affinity and types of antagonism. This impairs Ca^{2+} influx into muscle cells, particularly the myocardial and smooth muscle, which are dependant on this influx for normal function. In the vascular smooth muscle, the cytosolic Ca^{2+} concentration maintains basal tone and any

decrease of Ca^{2+} influx results in relaxation and arterial vasodilation.[77] In the myocardium, this impaired Ca^{2+} flow results in a decreased force of contraction. In addition, the delay in recovery of the slow calcium channels in the specialized SA and AV nodal tissue results in decreased heart rate and conduction.[121]

The CCBs currently available in the United States are classified into four structural groups (Table 57-1). Each group binds a slightly different region of the $Î±_{1c}$ subunit of the calcium channel and thus has different affinities for the various L-type calcium channels, both in the myocardium and the vascular smooth muscle.[111,123,124,166,175] For several reasons, verapamil, a phenylalkylamine, has the most profound inhibitory effects on the SA and AV nodal tissue, whereas diltiazem has less profound effects and dihydropyridines have little, if any, direct myocardial effects in therapeutic dosing.[86,123,124] First, in therapeutic dosing, nifedipine does not alter the normal calcium channel recovery within the myocardium.[89,100] Second, not only do verapamil and, to a lesser extent, diltiazem impede Ca^{2+} influx and

channel recovery, but their blockade is potentiated as the frequency of channel opening increases.[55,89,137] Finally, dihydropyridines bind the calcium channel best at less-negative membrane potentials. Because the resting potential for myocardial muscle (-90 mV) is lower than that of vascular smooth muscle (-70 mV), dihydropyridines bind preferentially in the peripheral vascular tissue.[137] As a class, dihydropyridines have the most potent vasodilatory effects. Verapamil is the next most potent, followed by diltiazem. Consequently, verapamil is the most effective at decreasing heart rate, cardiac output, and blood pressure, whereas nifedipine produces the greatest decrease in systemic vascular resistance. Because nifedipine, and all the dihydropyridines, have little myocardial effect at therapeutic levels, the baroreceptor reflex remains intact and a slight increase in heart rate and cardiac output may occur.[166] Isradipine is the only dihydropyridine whose inhibitory effect on the SA node is significant enough to blunt any reflex tachycardia.[46]

These receptor-binding differences among the CCB classes determine the potential therapeutic role of each. Verapamil and diltiazem are used in the management of hypertension, to reduce myocardial oxygen demand, to achieve rate control in atrial flutter and atrial fibrillation, and to abolish supraventricular reentrant tachycardias.[2] Dihydropyridines are typically used to treat diseases with increased peripheral vascular tone such as hypertension, Raynaud phenomenon, Prinzmetal angina, esophageal spasm, vascular headaches, and post-subarachnoid hemorrhage vasospasm.[24,51,158]

Bepridil is unique because in addition to its calcium channel-blocking effects, it is a potent fast sodium channel and potassium channel blocker.[66] This impairs both myocardial contractility and conduction and results in prolongation of the effective refractory period of the AV node, the action potential itself, and myocardial repolarization.[66] Bepridil prolongs the QTc interval and may precipitate malignant ventricular dysrhythmias, including torsade de pointes.[6,66] This dysrhythmogenic effect is potentiated in the setting of hypokalemia.

Bepridil is classified and used as an antidysrhythmic agent, but because of its dysrhythmogenic potential its use is limited to patients who are refractory to all other therapy.[66]

Clinical Manifestations

The life-threatening toxicity of CCBs is manifest largely within the cardiovascular system and is an extension of their therapeutic effects. Myocardial depression and peripheral vasodilation occur, producing bradycardia and hypotension.[152] Myocardial conduction may be impaired, producing AV conduction abnormalities, idioventricular rhythms, and complete heart block.[12,42,68,75,105,113,131,139] Junctional escape rhythms frequently occur in patients with significant poisonings.[17,28,36] The negative inotropic effects may be so profound, particularly with verapamil, that ventricular contraction may be completely inhibited.[14,36,58] Patients may present initially asymptomatic but deteriorate rapidly into severe cardiogenic shock.[157,177]

Hypotension is the most common abnormal vital sign finding following an overdose.[142,143] The associated clinical findings represent the degree of cardiovascular compromise and hypoperfusion of the patient's central nervous system. Early or mild symptoms include dizziness, fatigue, and lightheadedness, whereas more severely poisoned patients may manifest lethargy, syncope, altered mental status, coma, and death.[29,60,68,99,131,148] Cases of seizures,[60,68,116,134,162] cerebral ischemic events,[150,155,179] ischemic bowel,[54,56,161,178] and renal failure,[113,139] occurring in the setting of CCB-induced cardiogenic shock, also are reported. Severe CNS depression is distinctly uncommon, and if respiratory depression or coma is present without severe hypotension, coingestants or other causes of altered mental status must be considered. Gastrointestinal symptoms, such as nausea and vomiting, are also uncommon.[70]

Although receptor selectivity is lost in overdose, and all CCBs can produce severe bradycardia, hypotension, and death,[152] there are

some subtle variations in presentation, depending on the agent. The CCBs with the most significant myocardial effects, verapamil and, to a lesser extent, diltiazem, are associated with more negative inotropic and chronotropic effects.[135,138] In a prospective, poison control center-based study, AV nodal block occurred much more frequently in the setting of verapamil poisoning.[142] In contrast, nifedipine, because of its limited myocardial binding, may produce tachycardia or a â€œnormalâ€• heart rate initially, with bradycardia developing only in patients with more substantial ingestions.[27,63,178,182] Deaths associated with dihydropyridines occur, although they are relatively uncommon.[99,108,135]

Numerous reports document hyperglycemia in patients with severe CCB poisoning.[18,29,38,60,68,113,122,139,162,177] Insulin release from the Î²-islet cells in the pancreas is dependent on calcium influx via an L-type calcium channel.[107,115] In CCB overdose, this channel is also antagonized, impairing normal calcium influx and reducing insulin release.[31] The hyperglycemic effect may be exacerbated in a diabetic patient, or if glucagon is used as inotropic therapy (Chap. 48).[170]

Acute pulmonary injury is also associated with CCB poisoning.[18,50,63,71,80,109] Although the mechanism is unknown, precapillary vasodilation may cause an increase in transcapillary hydrostatic pressure.[71,80] The elevated pressure gradient results in increased pulmonary capillary transudates and, ultimately, interstitial edema.

Several factors, including the CCB involved, the dose ingested, the product formulation, and the patient's underlying cardiovascular health, may play a role in the ultimate degree of toxicity. Coingestion with other agents that have cardiovascular activity, such as Î²-adrenergic antagonists and digoxin, may potentiate conduction abnormalities.[23,48,79,101,188]

The product formulation (immediate or regular vs. sustained release) affects the onset of symptoms and duration of toxicity. With regular-

release formulations, toxicity is often present within 2â€“3 hours of ingestion.[13,143] With sustained-release products, however, initial signs or symptoms may be delayed for 6â€“8 hours, and delays

of up to 15 hours are reported.[13,143,160,172] In addition, with ingestion of sustained-release products, the drug's apparent half-life is prolonged and toxicity may last longer than 48 hours.[9,12,36,103]

Comorbidity and age are two factors that negatively impact on both morbidity and mortality in patients with CCB poisoning. Elderly patients, and those with underlying cardiovascular disease such as congestive heart failure, are much more sensitive to the myocardial depressant effects of CCBs.[27,118] Even at therapeutic doses, these individuals may develop symptoms of mild hypoperfusion, such as dizziness and fatigue, much more frequently.[59,69,75,127]

Diagnostic Testing

All patients with a suspected CCB ingestion should be attached to a cardiac monitor and have a 12-lead ECG performed to assess both their heart rate and rhythm, as well as the presence of any conduction abnormalities. Careful assessment of the degree of hypoperfusion, if any, may include a chest radiograph, pulse oximetry, and serum chemistry analysis for metabolic acidosis. Assays for various CCB serum concentrations are not routinely available and are not used to manage patients after overdose. If a patient presents with bradydysrhythmias of unclear origin, assessment of electrolytes, particularly potassium and magnesium, renal function, and a digoxin concentration may be helpful, although careful history taking often provides the most valuable clues. If hyperkalemia is present, cardioactive steroid poisoning should be considered, particularly in the absence of renal failure. Because calcium channel antagonist poisoning can impair insulin secretion from the pancreas, hyperglycemia may be detected.

Management

Any patient with a suspected CCB ingestion should be immediately evaluated, even if there are no symptoms and the vital signs are normal. Intravenous access and continuous electrocardiographic monitoring should be initiated. A 12-lead ECG should be repeated at least every 1â€“2 hours for the first several hours. If the patient's condition normalizes, ECGs can be repeated at longer intervals subsequently. Initial treatment should begin with adequate oxygenation and airway protection (as clinically indicated), and aggressive gastrointestinal decontamination. If the patient is hypotensive and there is no evidence of congestive heart failure, an initial fluid bolus of 10â€“20 mL/kg of crystalloid should be given, and repeated as needed.

Gastrointestinal decontamination is a critical intervention. Induced emesis should be avoided because CCB-poisoned patients can rapidly deteriorate and become severely hypotensive. Orogastric lavage should be considered for all patients who present early (1â€“2 hours postingestion) after large ingestions, and for those patients who are critically ill. Although the effects of orogastric lavage in an overdose involving a sustained-release CCB have not been specifically studied, and although most of these formulations tend to be large and poorly soluble, because of their significant danger in overdose, orogastric lavage should still be strongly considered. When performing orogastric lavage in a CCB-poisoned patient, it is important to remember that lavage may increase vagal tone and potentially exacerbate any bradydysrhythmias.[171] Pretreatment with a therapeutic dose of atropine may prevent this. All patients with CCB ingestions should receive 1 g/kg of activated charcoal orally. Multiple doses (0.5 g/kg) of activated charcoal (MDAC) without a cathartic should be administered to all patients with either sustained-release pill ingestions or signs of continuing absorption. Although data are limited, there is no evidence that MDAC increases CCB clearance from the serum.[146,168] Rather, its efficacy may be a result of the

continuous presence of activated charcoal throughout the gastrointestinal tract, which adsorbs any active drug from its slow-release formulation. Whole-bowel irrigation (WBI) with polyethylene glycol solution (1â€“2 L/h via nasogastric tube in adults, up to 500 mL/h in children) should be initiated for patients who ingest sustained-release products [20,167] and may be the most effective way of achieving gastrointestinal decontamination for ingestions involving these formulations.[91] Dosing should be continued until the rectal effluent is clear.

The importance of early initiation of MDAC and WBI, even for well-appearing patients with a history of sustained-release CCB ingestion, particularly children, cannot be overemphasized. It is imperative to minimize any absorption and prevent delayed cardiovascular toxicity, which can be profound and difficult to reverse. Several reports describe patients who presented with mild signs of poisoning, in whom gastrointestinal decontamination was not performed aggressively and who subsequently displayed severe toxicity.

Pharmacotherapy should focus on maintenance or improvement of both cardiac output and peripheral vascular tone.[88] Although many agents, including atropine, calcium, insulin, glucagon, isoproterenol, dopamine, epinephrine, norepinephrine, and phosphodiesterase inhibitors, have been used with reported success in CCB-poisoned patients, no single agent has consistently demonstrated total efficacy.[68,135,138,142,143] Little prospective or basic research specifically evaluates effective treatment modalities.

Therapy should begin with crystalloids and atropine, but more critically poisoned patients will not respond to these initial efforts, and inotropes and vasopressors will be needed. Although it would be ideal to initiate each agent individually and monitor the patient's hemodynamic response, in the most critically ill patients, multiple therapies should be administered simultaneously. A reasonable treatment sequence includes calcium followed by a catecholamine such as norepinephrine, high-dose insulin infusion, glucagon, and a

phosphodiesterase inhibitor. The evidence for the use of each of these drugs is discussed below.

Atropine

Atropine is considered the drug of choice for patients with symptomatic bradycardia. In an early dog model of verapamil poisoning, atropine improved heart rate and cardiac output.[49] In one prospective study, 2 of 8 bradycardic CCB-poisoned patients also had an improvement in heart rate with atropine therapy.[142] Clinical experience, however, demonstrates atropine to be largely ineffective in improving heart rate in severe CCB-poisoned patients.[29,38,74,138,148,157,179] Initial treatment with calcium might improve the efficacy of atropine.[37,70,76] Given its availability, efficacy in mild poisonings, and safety profile, atropine should still be considered as initial therapy in patients with symptomatic bradycardia. Dosing should begin with 0.5â€“1.0 mg (0.02 mg/kg in children) IV every 2 or 3 minutes up to a maximum dose of 3 mg in all patients with symptomatic bradycardia. However, because of its limited efficacy in severely poisoned patients, treatment failures should be anticipated. In patients in whom WBI or MDAC will be used, the use of atropine must be

carefully considered, weighing the potential benefits of improved heart rate, and thus cardiac output, against the anticholinergic effects potentially decreasing GI motility.

Calcium

Pharmacologically, Ca^{2+} appears to be a logical choice to treat patients with CCB toxicity. Pretreatment with intravenous Ca^{2+}, prior to verapamil use for supraventricular tachydysrhythmias, prevents hypotension without diminishing the antidysrhythmic effects.[33,156,180] This is also observed in the overdose setting where Ca^{2+} tends to improve blood pressure more than it does the heart

rate. Although the exact mechanism is unclear, boluses of Ca^{2+} increase the extracellular Ca^{2+} concentration and increase the intracellular concentration gradient. This may drive Ca^{2+} intracellularly through unaffected calcium channels. Calcium salts are beneficial in experimental models of CCB poisoning.[37,49,58] In verapamil-poisoned dogs, improvement in inotropy and blood pressure was demonstrated after increasing the serum [Ca^{2+}] by 2 mEq/L with an intravenous infusion of 10% calcium chloride at 3 mg/kg/min.[58]

Calcium ion reverses the negative inotropy, impaired conduction, and hypotension in humans poisoned by CCBs.[21,57,61,63,105,106,110,112,126,127,136,181,184] Unfortunately, this effect is often short-lived and more severely poisoned patients may not improve significantly with calcium salt administration.[26,29,38,43,50,53,74,146,151] Some authors believe that these failures might represent inadequate dosing.[20,70,106] Unfortunately, the exact dosing of calcium salts is unclear. Reasonable recommendations for poisoned adults include an initial intravenous bolus of approximately 13â€“25 mEq of Ca^{2+} (10â€“20 mL of 10% calcium chloride or 30â€“60 mL of 10% calcium gluconate) followed by either repeat boluses every 15â€–20 minutes up to 3â€–4 doses or a continuous infusion of 0.5 mEq/kg/h of Ca^{2+} (0.2â€–0.4 mL/kg/h of 10% calcium chloride or 0.6â€–1.2 mL of 10% calcium gluconate).[88,90,135] Careful selection of the calcium salt used is critical for dosing. Although there is no difference in efficacy of calcium chloride or calcium gluconate, 1 g of calcium chloride contains 13.4 mEq of calcium, which is more than 3 times the 4.3 mEq found in 1 g of calcium gluconate. Consequently, to administer equal doses of Ca^{2+}, 3 times the volume of standard calcium gluconate is required. If repeat dosing or continuous infusions are used, the serum [Ca^{2+}] and PO_4^{-3} should be closely monitored to detect if hypercalcemia or hypophosphatemia develop. These concerns are not unfounded, and may in fact significantly limit Ca^{2+} therapy.[99] Other adverse effects of intravenous Ca^{2+} include nausea,

vomiting, flushing, constipation, confusion, and angina.[90] If there is any suspicion that a cardioactive steroid such as digoxin is involved in an overdose, Ca^{2+} should be avoided until after digoxin-specific Fab is administered because it may worsen digoxin toxicity (Chap. 62).[16]

Inotropes and Vasopressors

Catecholamines are the next line of therapy in the treatment of CCB poisoning. Numerous case reports describe the success or failure of a wide variety of vasopressors, including epinephrine (success,[8,26] failure,[60,113]), norepinephrine (success,[68,122] failure[113,116]), dopamine (success,[9,39,179] failure[8,26,35,53,60,113,122,177]), isoproterenol (success,[52,113,131,139,169] failure[8,28,60,177]), dobutamine (success,[139] failure[29,35,113]), and vasopressin.[49,97,165] Experimentally, no single therapy is consistently effective. This is not surprising given the significant variability in both the CCBs and the patients involved. Mechanistically, however, either stimulation of $\hat{I}^2_1$-adrenergic receptors on the myocardium or of $\hat{I}\pm_1$-adrenergic receptors on the peripheral vascular smooth muscle are the most logical targets, but which one depends upon the etiology of the hypotension.

$\hat{I}^2$-Adrenergic agonists activate adenylate cyclase via G_s protein.[154] This results in formation of cyclic adenosine monophosphate (cAMP), which stimulates protein kinase A to phosphorylate the $\hat{I}\pm_1$ subunit of various calcium channels (Fig. 58-6).[159] It is unclear whether this phosphorylation allows calcium channels to remain open longer,[27,145] or if it opens dormant channels within the plasma membrane.[21,90] In addition, protein kinase A also phosphorylates phospholamban, which improves calcium release from troponin after contraction.[164] In the myocardium, this multifactorial increase in intracellular calcium results in improved chronotropy, dromotropy, and inotropy (Chap. 59).

In the peripheral vascular smooth muscle, $\hat{I}\pm_1$-adrenergic receptor

agonists activate receptor-operated calcium channels. This opening of nonpoisoned calcium channels allows calcium influx (Fig. 58-5),[145] which makes Î±$_1$-adrenergic agonists such as norepinephrine and phenylephrine logical choices if the hypotension is primarily the result of peripheral vasodilation, as would occur most typically with the dihydropyridine CCBs. Based on these pharmacologic mechanisms, norepinephrine appears to be an appropriate initial catecholamine to use in hypotensive CCB-poisoned patients. Its significant Î²$_1$-adrenergic activity combats

the myocardial depressant effects, while its Î±$_1$-adrenergic effects increase peripheral vascular resistance. There is some theoretical concern about using pure Î²-adrenergic receptor agonists, such as isoproterenol and, to a lesser extent, dobutamine, because Î²$_2$-adrenergic receptor agonist-induced peripheral vasodilation may worsen hypotension, particularly at high doses.

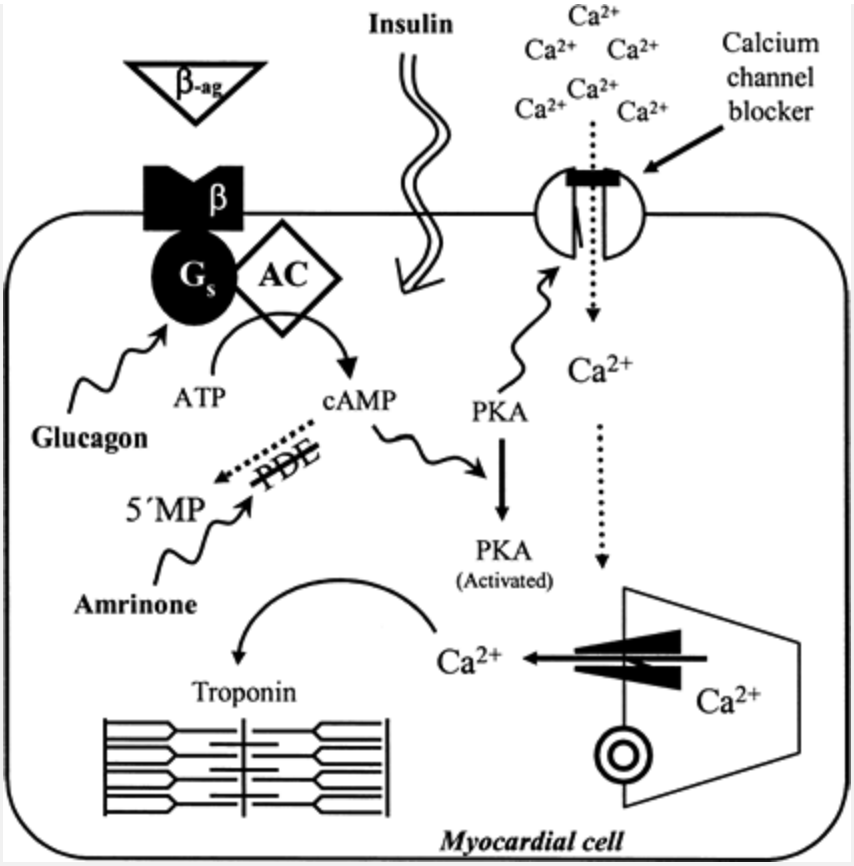

Figure 58-5. Myocardial toxicity of calcium channel blockers and antidotal therapies. Calcium channel blockers reduce ion influx through the L-type calcium channel and thus reduce contractility. Mechanisms to increase intracellular calcium include recruitment of new or dormant calcium channels by increasing cyclic adenosine monophosphate (cAMP) either by stimulating its formation by adenylate cyclase (AC) with catecholamines or glucagon (see text), or by inhibiting its degradation with amrinone. Increasing the calcium concentration gradient across the cellular membrane to futher its influx, may improve contractility. The mechanism by which insulin therapy enhances inotropy is undefined. Phophodiesterase, PDE; protein kinase A, PKA.

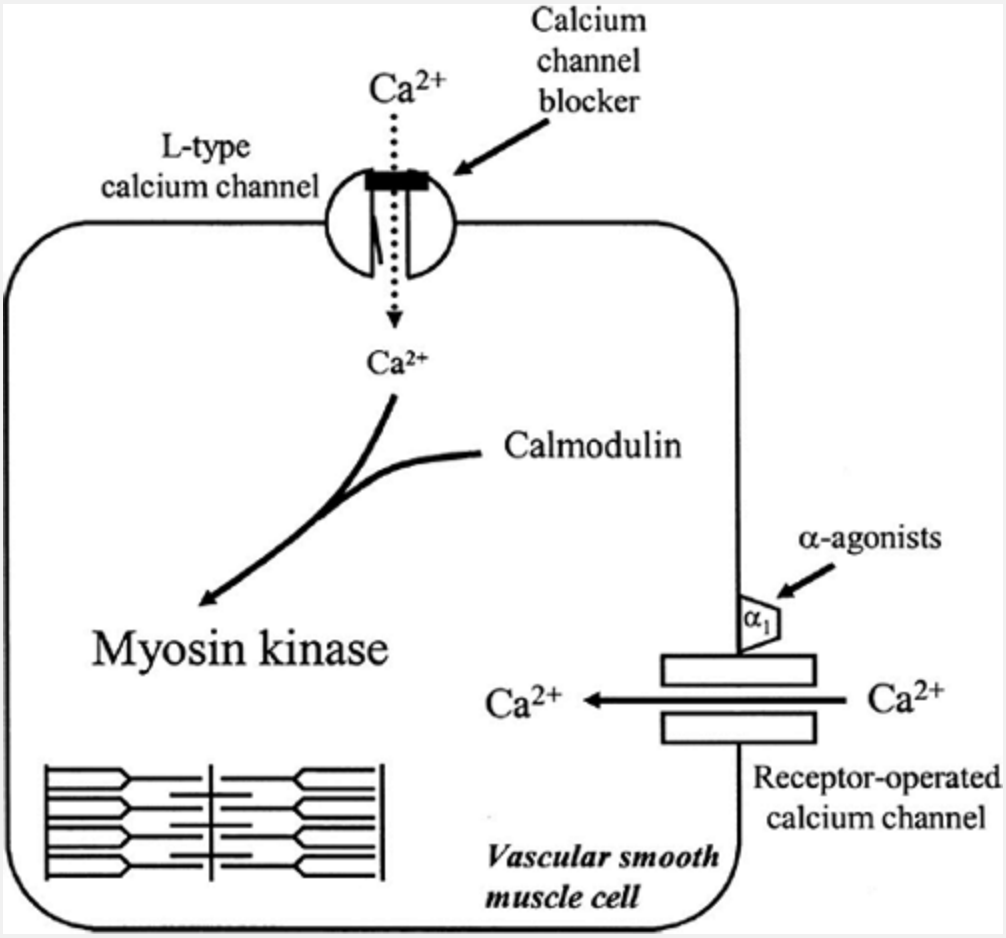

Figure 58-6. Vascular toxicity of calcium channel blockers and antidotal therapies. Calcium's entry via voltage-sensitive channels initiates a cascade of events that result in actinâ€“myosin coupling and contraction; this is inhibited by calcium channel blockers. Mechanisms to increase intracellular calcium include activation of receptor-operated calcium channels with Î±$_1$-adrenergic agonists or increasing the calcium ion gradient across the cellular membrane to further its influx.

Dopamine is predominantly an indirect acting pressor which acts by stimulating the release of norepinephrine from the distal nerve

terminal, and not by direct Î±- and Î²-adrenergic receptor stimulation.[65] This may limit its effectiveness in severely stressed patients who may have catecholamine depletion.[177] Published clinical experience of patients with severe CCB poisonings support these concerns.[8,28,35,52,60,113,122,177] Improvement in blood pressure may be noted with dopamine at high dosing, when the drug has additional direct Î±- and Î²-adrenergic effects.[65]

The choice of a sympathomimetic drug is based on numerous factors, including the pharmacologic profile of each drug, the patient's underlying physiologic condition, and the physician's familiarity and comfort with the drug. If one sympathomimetic drug is unsuccessful, determining the cardiac output and systemic vascular resistance may be helpful in assessing whether the myocardial depressant or peripheral vasodilatory effects are responsible for the hypotension.[138] This knowledge will help guide the subsequent choice of pharmacologic agents.

Insulin and Glucose

The most promising treatment for patients who are severely poisoned with CCBs may be hyperinsulinemia/euglycemia therapy. It is long known that high-dose insulin has positive inotropic effects.[41] Although some indirect evidence suggests that increased Ca^{2+} entry may be involved,[41,102] there is growing support for the hypothesis that improved myocardial use of carbohydrates is responsible for clinical improvement.[96] Verapamil poisoning alters the normal metabolism of the myocardial cell, which primarily relies on fatty acids and forces carbohydrate dependence.[95,97,98] At the same time, CCBs impede use of carbohydrates by inhibiting calcium-mediated insulin secretion from the Î²-islet cells in the pancreas,[31,129] and by somehow increasing myocardial insulin resistance.[96] In a canine model of verapamil toxicity, high-dose insulin, in conjunction with continuous dextrose infusion to maintain euglycemia, improved survival when compared to calcium, epinephrine, or glucagon.[94,98] It

is postulated that although epinephrine and glucagon increase myocardial contractility, they do so at the expense of increased myocardial oxygen consumption, and that insulin improves overall myocardial efficiency. The use of insulin is particularly interesting, because severe CCB toxicity often produces significant hyperglycemia and insulin infusions are often initiated.[38,162]

There are now several reported cases of CCB-poisoned patients in whom adjuvant high-dose insulin therapy successfully improved hemodynamic function.[17,117,187] Notably, there was little effect on heart rate in any of these patients, and in 1 patient, an improvement in ejection fraction from 10 to 50% was described.[187] Reports of the failure of this treatment have also been published,[30] but often represent initiation of therapy in terminally ill patients with multiple organ failure.

Because of the promising animal evidence, the relative lack of other demonstrably effective therapeutics, the seriousness and potentially fatal nature of CCB poisoning, and the growing clinical successes with this therapy, early initiation of hyperinsulinemia/euglycemia therapy for CCB-poisoned patients is recommended. Based on the canine data and published clinical experience, if the serum glucose is <250 mg/dL an initial bolus of 25â€“50 g of dextrose (0.5â€“1 g/kg), should be followed by a dextrose infusion of 0.25â€“0.5 g/kg/h. Then administer an initial insulin bolus of 0.1 U/kg followed by an insulin infusion at a rate of 0.5 U/kg/h, which should be increased if there is no hemodynamic response within 60 minutes. Remember that this increase should be done in a stepwise manner with concomitant increases in the dextrose infusion to maintain euglycemic control. Serum glucose levels should be closely monitored throughout therapy, particularly during the first few hours, and should be continued for several hours after discontinuation of the insulin infusion. Because insulin's hemodynamic effects are mediated via alterations in myocardial metabolism, the hemodynamic response is typically delayed for 30â€“60 minutes, necessitating the simultaneous use of catecholamines in profoundly hypotensive

patients.

Glucagon

Glucagon is an endogenous polypeptide hormone secreted by the pancreatic Î± cells in response to hypoglycemia and catecholamines. In addition, it has significant inotropic and chronotropic effects.[25,133] Glucagon is a therapy of choice for Î²-adrenergic antagonist poisoning (Chap. 59) because of its ability to bypass the Î²-adrenergic receptor and activate adenylate cyclase via a G_s protein in the myocardium.[186] Thus, glucagon is unique in that it is functionally a â€œpureâ€• $Î²_1$ agonist, with no peripheral vasodilatory effects. However in CCB poisoning, because the cellular lesion is â€œdownstreamâ€• from adenylate cyclase, glucagon offers no pharmacologic advantage over more traditional Î²-adrenergic agents (Fig. 58-6).

There are reports of CCB-poisoned patients who failed to respond to fluids, Ca^{2+}, or dopamine and dobutamine, but who had significant increases in both heart rate and blood pressure after glucagon administration.[35,132,176] Many other much more severely poisoned patients demonstrated no hemodynamic benefit with glucagon therapy.[8,28,60] Several animal models demonstrated glucagon's efficacy in improving CCB-induced myocardial depression.[10,79,163,189,190] Unfortunately, none of these studies compared other therapies, including Ca^{2+}, high-dose insulin, and catecholamines, with glucagon. Although the data are limited, given its experimental and anecdotal efficacy, glucagon should be considered in the management of refractory hypotension in patients with CCB poisoning. Dosing for glucagon is not well established. An initial dose of 3â€“5 mg intravenously slowly over 1â€“2 minutes is reasonable in adults, and if there is no hemodynamic improvement within 5 minutes, retreatment with a dose of 4â€“10 mg might be effective. The initial pediatric dose is 50 Âµg/kg. Because of

glucagon's short half-life, a maintenance infusion should be initiated, once a desired effect is achieved. Maintenance infusion dosing should begin at the â€œresponse doseâ€• of glucagon per hour. For example, if an initial dose of 4 mg of glucagon effectively improved blood pressure, the infusion should be started at 4 mg/h (see Antidotes in Depth: Glucagon). Adverse effects include vomiting and hyperglycemia, particularly in diabetics or during continuous infusion.[170]

Phosphodiesterase Inhibitors

Another class of therapeutics that have demonstrated usefulness in treating CCB poisoning are the phosphodiesterase inhibitors: inamrinone, milrinone, and enoximone. These agents inhibit the breakdown of cAMP by phosphodiesterase, thereby increasing cAMP concentrations. These noncatecholamine inotropic agents do not disproportionately increase myocardial oxygen demand and have been traditionally used for congestive heart failure.[11,15] They specifically inhibit phosphodiesterase III, the enzyme responsible for cAMP breakdown found in cardiac and vascular tissue (Fig. 58-6).[32] This inhibition results in increased cAMP, increased intracellular calcium, and improved inotropy. Inamrinone improved myocardial contractility in two canine models of verapamil poisoning.[5,114] In addition, inamrinone was clinically successful in patients with CCB poisoning when used in combination with another inotropic agent, such as isoproterenol or glucagon.[53,185] This â€œtwo-prongedâ€• approach to increase myocardial cAMP concentrations, by stimulating its formation and inhibiting its breakdown, is pharmacologically rational. However, because of inamrinone nonselective inhibition of phosphodiesterase III, cAMP is also increased in the vascular smooth muscle. This causes smooth muscle relaxation, peripheral vasodilation, and, often, hypotension, which may severely limit its usefulness in many CCB-poisoned patients.[92] Phosphodiesterase inhibitors should be used only as second-line agents, in combination with another inotropic agent, and in patients with hemodynamic

monitoring. Dosing in the treatment of CCB-poisoned patients is not well defined, but should be based on traditional dosing for congestive heart failure. For inamrinone, the experimental data and the case reports suggest that an initial bolus of 1 mg/kg over 2 minutes followed by a continuous infusion of 5â€“20 Âµg/kg/min is appropriate.[5,32,52,53,185]

Experimental Pharmaceutical Agents

Digoxin is being experimentally evaluated as a therapeutic agent in CCB poisoning. Cardioactive steroids inhibit sodium/potassium/ adenosine triphosphatase (ATPase), which increases the intracellular sodium concentration and decreases the transmembrane sodium concentration gradient. This concentration gradient is the driving force for the sodiumâ€“calcium exchanger in the cell membrane. When it is decreased, less Ca^{2+} can exit the cell in exchange for Na^{+} during cellular repolarization.[130] In a canine model of verapamil poisoning, digoxin, in conjunction with atropine improved both myocardial dromotropy and inotropy and increased peripheral vascular resistance. A trupine was added to block the vagally mediated inhibitory effects of digoxin on heart rate and AV nodal conduction.[141] However, because digoxin takes a significant amount of time to distribute into tissue, and because limited efficacy data and no safety data have yet been collected, much more work is required before digoxin should be administered to patients with CCB poisoning.

Adjunctive Hemodynamic Support

Many of the most severely poisoned patients may not respond to any pharmacologic intervention.[36,60] Transthoracic or intravenous cardiac pacing may be required to improve heart rate, as several case reports demonstrate.[39,157,177] However, in a prospective cohort of CCB poisonings, 2 of 4 patients with significant bradycardia requiring electrical pacing had no electrical capture.[142] In addition, even if

electrical pacing is effective in increasing the heart rate, blood pressure often remains unchanged.[19,67,68,131]

Intraaortic balloon counterpulsation is another invasive supportive option to be considered in cases refractory to pharmacologic therapy. Intraaortic balloon counterpulsation was used successfully to improve cardiac output and blood pressure in a patient with a mixed verapamil and atenolol overdose.[48] The synchronized inflation and deflation is dependent on regular cardiac electrical activity, so cardiac pacing is often required in addition to the intraaortic balloon.[174] It is important to understand that overdosed patients who may be candidates for intraaortic balloon counterpulsation support have a much better prognosis than do patients with severe left ventricular failure from ischemic heart disease, in whom this technology is traditionally used. Between 24 and 48 hours of assisted cardiac output allows metabolism and elimination of the CCBs and a return of baseline myocardial function.

Much more invasive and technologically demanding, emergent open and percutaneous cardiopulmonary bypass has also been used to support patients with severe CCB poisoning for days, with subsequent full recoveries.[36,60,67] The major limitation of all these technologies, however, is that they are available only at tertiary care facilities.

Disposition

Every patient who manifests any signs or symptoms of toxicity should be admitted to an intensive care setting. Because of the potential for delayed toxicity, despite some recent recommendations to the contrary,[13] any patient ingesting sustained-release products should be admitted for 24 hours to a monitored setting, even if asymptomatic. This is particularly important for toddlers and small children in whom even one or a few tablets may produce significant toxicity.[13,17,60,108,134] All admitted patients should be treated with activated charcoal, and those with a history of sustained-release

product ingestion should be treated with WBI. Only patients with a reliable history of an â€œimmediate-releaseâ€• preparation ingestion who have received adequate gastrointestinal decontamination, who have serial ECGs over 6â€“8 hours that have remained unchanged, and who are asymptomatic, can be â€œmedically cleared.â€•

Summary

Calcium channel blockers are commonly used to treat hypertension, stable and vasospastic angina, dysrhythmias, migraine headaches, Raynaud phenomenon, and subarachnoid hemorrhage. Because of the increasing frequency of use, CCB exposures continue to rise, resulting in numerous deaths from poisoning annually. Hallmarks of toxicity include bradydysrhythmias and hypotension, which are an extension of the pharmacologic effects of these agents. Although most patients develop symptoms of hypoperfusion, such as lightheadedness, nausea, or fatigue, within hours of a significant ingestion, sustained-release formulations may result in significant delays in any hemodynamic consequences and certainly may prolong toxicity. Because of the significant lethality of large ingestions of sustained-release CCBs, it is imperative to make gastrointestinal decontamination with whole-bowel irrigation a high priority. Aggressive decontamination of patients with exposures to sustained-release products should begin as soon as possible and should not be delayed by waiting for signs of toxicity. Once hemodynamic toxicity develops, in addition to supportive care, pharmacologic treatment with calcium boluses, followed by high-dose insulin and glucose infusions, should be initiated. Traditional catecholamines are also typically needed but their use alone may not be sufficient in the most critically poisoned patients. Other options include glucagon and phosphodiesterase inhibitors. Patients who fail to respond to all pharmaceutical interventions should be considered for extracorporeal mechanical support whenever available.

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Chapter 59
Î²-Adrenergic Antagonists

Jeffrey Brubacher

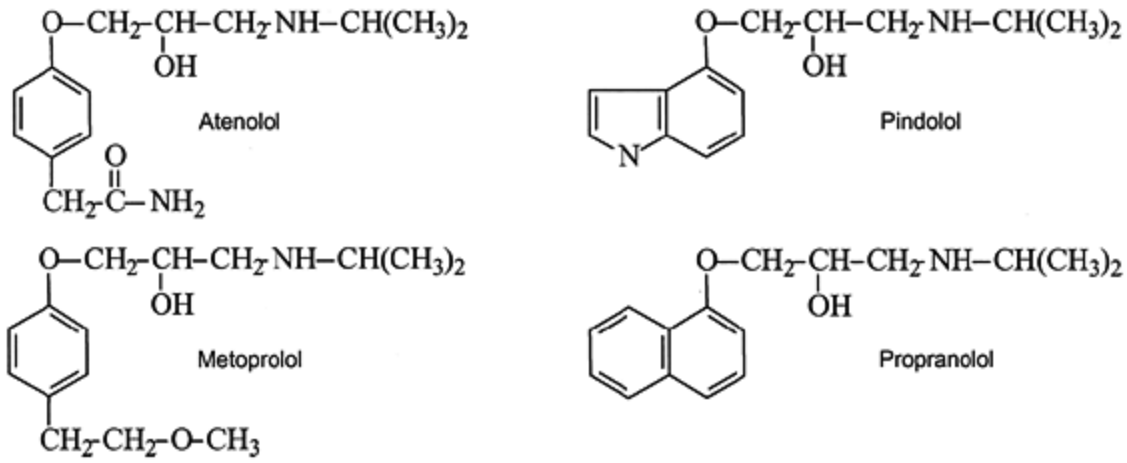

Figure. No Caption Available.

A 64-year-old man was brought to the emergency department (ED) by ar emergency medical personnel found him hypoventilating with a blood press a respiratory rate of 10 breaths/min. They intubated him and gave him 2 NaCl solution. During transport to hospital, the patient had a generalized arrival at the ED he was comatose with a blood pressure of 85 mm Hg by

96.8Â°F (36Â°C). On 100% oxygen the patient's oxygen saturation was 9
mg/dL. Physical examination was otherwise unremarkable except for occa
no murmurs. Pupils were 6 mm and reactive, skin was cool, and bowel so
dextrose IV, 100 mg thiamine IV, and 2 mg naloxone IV with no response

Blood was obtained for laboratory analysis and sent for a complete blood
phosphokinase. Arterial blood was sent for blood gas analysis. A 12-lead
of 280 msec and a QRS duration of 140 msec. During the next several m
pressure decreased to 75 mm Hg and his pulse decreased to 40 beats/min
atropine and another 500 mL of 0.9% NaCl solution, which resulted in lit
pacing was instituted, which increased his pulse to 70 beats/min, but the
discontinued. A central venous line was inserted, and dopamine was titrat

Further history was obtained from the patient's son. The patient was prev
hypertension. The patient stopped taking antidepressants several months
medication and no one else in the family took any pills. The family stated
and displayed apathy, decreased appetite, and an inability to sleep. On th
breakfast, took a shower, and went for a walk before he returned home to
his nap, but 2 hours later when the family could not arouse him for lunch
to return home and bring all medication bottles to the ED. A call was pla

The history of depression, seizures, hypotension, and widened QRS interv
bradycardia, and the patient was given an IV bolus of 100 mEq of hypert

vital signs following this, and a repeat electrocardiogram was essentially u
msec. A bicarbonate infusion was started. Because of the possibility of a
g of calcium chloride intravenously. Following this, his systolic blood pressu
beats/min.

The family physician returned the call and stated that the propranolol had
patient's daughters returned with all of the medication bottles that she c
analgesics were almost full; however, the propranolol bottle was empty. As

With this additional information, the patient was given a total of 5 mg of
blood pressure to 105/60 mm Hg and his pulse to 55 beats/min. A glucag
admitted to the intensive care unit. Laboratory analysis was negative for
complete blood count, and arterial blood gas values were all within norma

resolved on repeat analysis performed after the patient's vital signs had

By the next day, the patient regained consciousness and was able to mai stopped. He was extubated and stated that he had taken an overdose of a psychiatrist who suggested that his depression was exacerbated by th were restarted. A calcium channel blocker was prescribed for hypertension service. On followup 1 month later, he was doing well with no complaints. controlled.

History

In 1948, Raymond Alquist postulated that epinephrine's cardiovascular act the existence of two distinct sets of receptors that he generically named â€œantiepinephrineâ€• agents, such as phenoxybenzamine, reversed the epinephrine. According to Alquist's theory these drugs acted at the Î± re catecholamine-induced tachycardia. The British pharmacist, Sir James Blac potential clinical benefit of a Î²-adrenergic antagonist. In 1958, Black sy drug was briefly marketed as â€œAlderlin,â€• named after Alderly Park, was discontinued because it produced thymic tumors in mice. Propranolol incomplete anagram of Alderlin) in the United Kingdom in 1964,[19 , 155] ar adrenergic antagonists, the management of angina was limited to drugs s venous capacitance vessels and increased myocardial oxygen delivery by clinicians the ability to decrease myocardial oxygen use. This new approa ischemic heart disease.[86] New drugs soon followed, and by 1979, 10 Î²- Unfortunately, it soon became apparent that these agents were dangerous toxicity and deaths from Î²-adrenergic antagonist overdose were reporte antagonists (Table 59-1). They are commonly used in the treatment of and tachydysrhythmias. Additional indications for Î²-adrenergic antagonist benign essential tremor, panic attack, stage fright, and hyperthyroidism are also used in the treatment of glaucoma.[65]

Epidemiology

Intentional Î²-adrenergic antagonist overdose, although relatively uncommo From 1985 to 1995, there were 52,156 Î²-adrenergic antagonist exposure

of the American Association of Poison Control Centers (Chap. 130). Thes antagonists were implicated as the primary cause of death in 38. The otl antagonists because of the presence of cardioactive coingestants, such as than age 6 years accounted for 19,388 exposures, but no fatalities were this series was a 7 year old. More than half of the fatalities developed c number of exposures to Î²-adrenergic antagonists reported to TESS increas 2003. Each year in this period, Î²-adrenergic antagonist exposures resulte 20â€“40 deaths (Chap. 130).

Compared to the other Î²-adrenergic antagonists, propranolol accounts fo and deaths.[84 , 104] This may be explained by the fact that propranolol is anxiety, stress, and migraine, who may be more prone to suicide attempt and membrane-stabilizing properties.[58 , 130]

Pharmacology

The Cardiac Cycle

Normal cardiac electrical activity involves a complex series of ion fluxes Electrical activity of the heart is coupled to cell contraction and relaxatio concentrations. Cardiac electrical and mechanical activity is closely regula

In normal conditions, heart rate is determined by the rate of spontaneou sinoatrial (SA) node (Fig. 59-1). Pacemaker cells are also found in the depolarizations of pacemaker cells are a result of

several inward cation channels that are under autonomic control. Î²-Adre spontaneous depolarization of pacemaker cells by incompletely understood caused by a direct, phosphorylation-independent action of cyclic adenosir Depolarization of cells in the SA node spreads to surrounding atrial cells, initiates an electric current that spreads along specialized pathways to de cardiac excitation, is linked to mechanical activity of the heart by the p (Chap. 23).

Acebutolol

Î²1
Yes
Yes
No
Low
25%
40%
2â€“4
Hepatic/renal
1.2
Atenolol
Î²1
No
No
No
Low
<5%
40â€“50%
5â€“9
Renal
1
Betaxolol (ophthalmic and tabs)
Î²1
No
Yes
Yes (calcium channel blockade)
Low
50%
80â€“90%
14â€“22
Hepatic/renal
NA
Bisoprolol
Î²1

No
No
No
Low
30%
80%
9â€“12
Hepatic/renal
NA
Bucindolol
$\hat{I}^2_1$, $\hat{I}^2_2$
$\hat{I}^2_2$ agonism

Yes ($\hat{I}^2_2$ agonism)
Moderate

30%
8 = 4.5
Hepatic
NA
Carteolol (ophthalmic)
$\hat{I}^2_1$, $\hat{I}^2_2$
Yes
No
Yes ($\hat{I}^2_2$ agonism and nitric oxide mediated)
Low
30%
85%
5â€“6
Renal
NA
Carvedilol
$\hat{I}\pm_1$, $\hat{I}^2_1$, $\hat{I}^2_2$
No

Yes (Î±$_1$ blockade)
Moderate
~98%
25â€“35%
6â€“10
Hepatic
115
Celiprolol
Î±$_2$, B$_1$
Î²$_2$ agonism

Yes (Î²$_2$ agonism)
Low
22â€“24%
30â€“70%
5
Hepatic
NA
Esmolol
Î²$_1$
No
No
No
Low
50%
NA
~8 min
RBC esterases
2
Labetalol
Î±$_1$, Î²$_1$, Î²$_2$
No
Low

Yes (Î±$_1$ antagonism)
Moderate
50%
20â€“33%
4â€“8
Hepatic
9
Levobunolol (ophthalmic)
B$_1$, Î²$_2$
No
No
No
NA
NA
NA
6
NA
NA
Metipranolol (ophthalmic)
Î²$_1$, Î²$_2$
No
No
No
NA
NA
NA
3â€“4
NA
NA
Metoprolol (long-acting form available)
Î²$_1$
No
Low
No

Moderate
10%
40â€“50%
3â€“4
Hepatic
4
Nadolol
Î²1 , Î²2
No
No
No
Low
20â€“30%
30â€“35%
10â€“24
Renal
2
Nebivolol
Î²1
No

Yes (nitric oxide mediated?)
Moderate
98%
12â€“96%
8â€“32
Hepatic
10â€“40
Oxprenolol
Î²1 , Î²2
Yes
Yes
No
Moderate

80%
20â€“70%
1â€“3
Hepatic
1.3
Penbutolol
Î²1 , Î²2
Yes
No
No
High
90%
~100%
5
Hepatic/renal
NA
Pindolol
Î²1 , Î²2
Yes
Low
No
Moderate
50%
75â€“90%
3â€“4
Hepatic/renal
2
Propranolol (long-acting form available)
Î²1 , Î²2
No
Yes
No
High
90%

30â€“70%
3â€“5
Hepatic
4
Sotalol
Î²1 , Î²2
No
No
No
Low
0%
90%
9â€“12
Renal
2
Timolol (ophthalmic)
Î²1 , Î²2
No
No
No
Moderate
60%
75%
3â€“5
Hepatic/renal
2
ISA = intrinsic sympathomimetic activity.
[a] Agents in italics are *not* FDA approved. The notation â€œ*NA* â€• indica
references [41, 58, 65, 111, 113, 122, and 163].

Adrenergic Blocking Activity	Partial Agonist Activity (ISA)	Membrane Stabilizing Activity	Vasodilating Property	Lipid Solubility	Pr Bi

TABLE 59-1. Pharmacologic Properties of the Î²-Adrenergic Anta

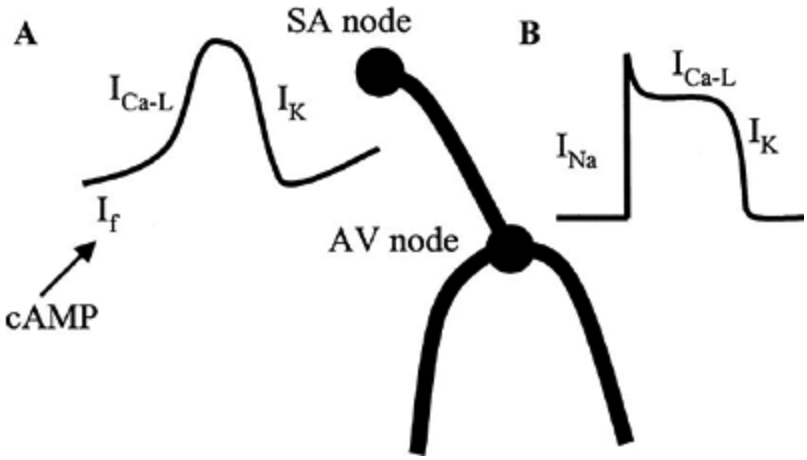

Figure 59-1. Cardiac conduction system: A. The cardiac cycle begins wh spontaneously due to inward â€œpacemakerâ€• currents (I_f). Adrenergi heart rate via a direct effect of cAMP. Cholinergic stimulation hyperpolariz pacemaker cell depolarization and hence bradycardia. Pacemaker cells lac the opening of L-type calcium channels (I_{Ca-L}) and the impulse is transr depolarization generates an impulse sufficient to open fast sodium channe specialized pathways to depolarize the atria and ventricles.

Myocyte Calcium Flow and Contractility

During systole, voltage-sensitive slow calcium channels (L-type channels) depolarization and allow extracellular calcium to flow down its concentrati channels are located primarily at the sarcolemmalâ€“sarcoplasmic reticulur channels (ryanodine receptors) in the SR. A small increase in local calciu through a single L-type calcium channel, triggers the opening of an array calcium from the SR, a phenomenon known as calcium-induced calcium r proportional to the magnitude of the calcium influx via the L-type calciun myocyte calcium concentrations. Actinâ€“myosin interaction is also mod ischemia, intracellular pH, and myofilament stretch.[12 , 16 , 138]

During diastole, several ion pumps actively remove calcium from the cyto

drop during diastole, calcium dissociates from troponin and relaxation oc calcium adenosine triphosphatase (ATPase) that pumps cytosolic calcium i exchanges 1 calcium ion for 3 sodium ions. The activity of the SR calciur

Î²-Adrenergic Receptors and the Heart

Î²-Adrenergic receptors are divided into $Î²_1$, $Î²_2$, and $Î²_3$ subtypes. The receptor, but there also are cardiac $Î²_2$ - and $Î²_3$ -adrenergic receptors. T increases with heart failure.[156] $Î²_1$ -Adrenergic receptors mediate increase protein kinases (Fig. 59-3). $Î²_1$ -Adrenergic receptors are coupled to G_s stimulated. This increases the intracellular production of cAMP, which binds dependent protein kinases.[93] Protein kinase A, in turn, phosphorylates ir voltage-sensitive calcium channels, and troponin.[56 , 160] L-type calcium the influx of calcium during each cell depolarization, triggering greater re [153] Phosphorylation of phospholamban removes its inhibition of the SR ar resulting in increased SR calcium stores and hence enhanced contractility results in more rapid removal of cytoplasmic calcium during diastole, anc phosphorylation facilitates calcium unbinding, thus improving cardiac perf Activated protein kinase A (PKA) also phosphorylates SR calcium release calcium release from the SR.[16] $Î²_1$ -Adrenergic receptors increase chronot at least in part, direct cAMP interaction with pacemaker channels.[2 , 23]

Like $Î²_1$ -adrenergic receptors, the cardiac $Î²_2$ -adrenergic receptors med subcellular mechanisms are less-well understood than for $Î²_1$ -adrenergic excitatory G_s proteins but are also coupled to inhibitory G_i proteins, and relaxation, and chronotropy, independent of global increases in cytoplasmic adrenergic-receptorâ€“induced increases in cAMP (via G_s protein stimulat receptors causes increases in cAMP and PKA activity that remain localized the G_i protein counteracts these effects elsewhere in the cytoplasm, perl down cAMP) and protein phosphatases (that counteract the action of PKA) contractility by increasing cytoplasmic pH independent of G protein activ

The role of the $Î²_3$ -adrenergic receptor in humans is incompletely underst plays a role in thermogenesis and lipolysis[35] and is also found in human mediates negative inotropy caused by G_i protein linkage

and subsequent inhibition of cAMP production and stimulation of nitric ox stimulation resulted in G_S protein stimulation and positive inotropy.[78] The substantially from that of the other Î² receptors. Whereas isoproterenol is adrenergic antagonists actually act as agonists at the $Î²_3$ -adrenergic rec

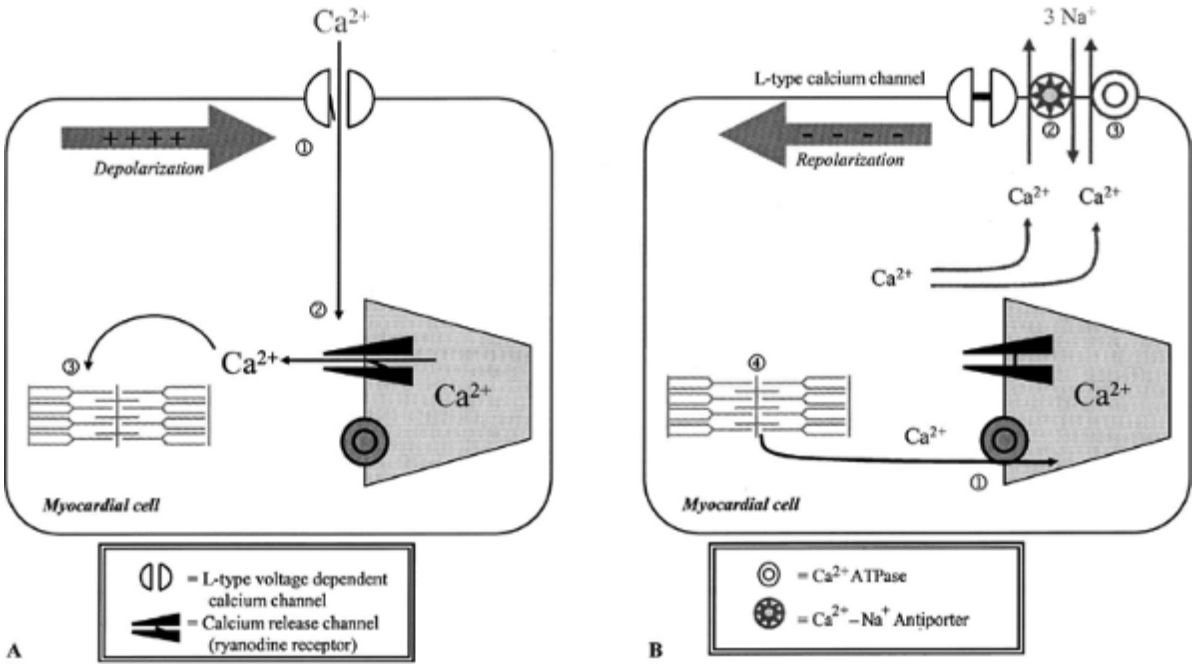

Figure 59-2. A. Fluctuations in calcium concentrations couple myocyte c relaxation. â‘ Depolarization causes voltage sensitive calcium channels to into the myocyte. â‘¡ This calcium current triggers the opening of calcium pours out of the SR. The amount of calcium released from the SR is prop of calcium stored in the SR. â‘¢ At rest, actinâ€“myosin interaction is pre inhibition is removed, and actin and myosin slide relative to each other, a actively removed from the myocyte to allow relaxation. â‘ Most calcium is calsequestrin. Calcium stored in the SR is thus available for release dur ATPase is inhibited by phospholamban. (See Fig. 59-3 .) â‘¡ The calcium sodium flow in one direction to that of a single molecule of calcium in th electrochemical gradients, which usually favor the inward flow of sodium c therefore inhibited by high intracellular sodium or extracellular calcium c conditions, the pump may â€œrun in reverse.â€• â‘¢ Some calcium is act myocyte calcium concentrations fall, calcium is released from troponin an

Noncardiac Effects of Î²-Adrenergic Recept

Î²-Adrenergic agonists have important non cardiac effects. $Î²_2$ -Adrenergi organs. Relaxation of arteriolar smooth muscle by $Î²_2$ -adrenergic stimula blood pressure. This counteracts Î±-adrenergicâ€“mediated arteriolar cons bronchodilation. Third trimester uterine tone and contractions are inhibited both $Î²_1$ - and $Î²_2$ -adrenergic stimulation.

Î² Receptors play a role in the immune system. Mast cell degranulation is epinephrine in aborting and treating severe allergic reactions. Polymorph stimulation, resulting in the increased white blood cell counts with catech epinephrine seen with pain or physiological stress.

Î²-Adrenergic agonists also have important metabolic effects. Insulin secre Despite increased insulin levels, the net effect of $Î²_2$ -adrenergic receptor skeletal muscle glycogenolysis and hepatic gluconeogenesis and glycogen from pancreatic alpha cells.[85] Î²-Adrenergic agonists act at fat cells to c adrenergic receptors results in breakdown of triglycerides and release of increased by $Î²_2$ -adrenergic stimulation, resulting in hypokalemia, explain hyperkalemia. Finally, renin secretion is increased by $Î²_1$ -adrenergic stin

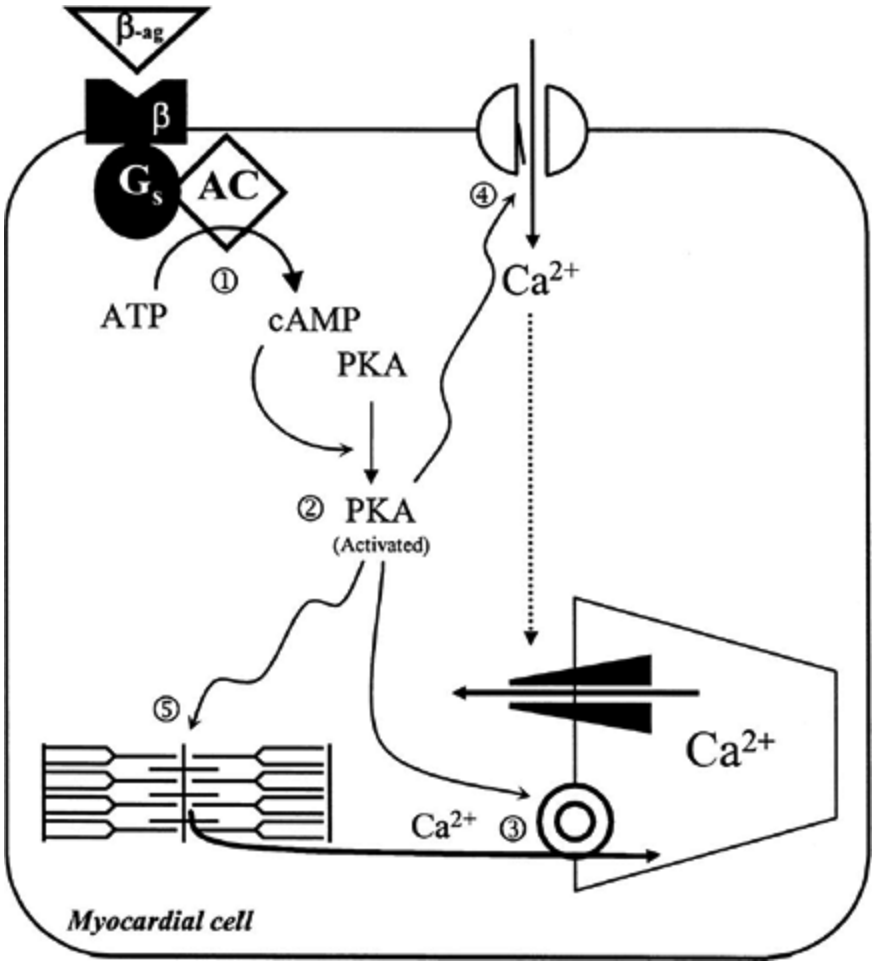

Figure 59-3. Î²-Adrenergic agonists are positive inotropes by virtue of th Adrenergic receptors are coupled to G_S proteins which activate adenyl cyc increased formation of cAMP from ATP. â‘¡ Increased cAMP levels activate receptor stimulation by phosphorylating key intracellular proteins. â‘¢ Ph reticulum (SR) calcium ATPase resulting in increased SR calcium stores a Phosphorylation of voltage sensitive calcium channels increases calcium in phosphorylation improves cardiac performance by facilitating calcium unb

Action of Î²-Adrenergic Antagonists

Î²-Adrenergic antagonists competitively antagonize the effects of catechola chronotropic and inotropic response to catecholamines. Bradycardia and h

conduction defects and in those persons who take calcium channel blocke
in those patients without underlying heart disease, the effects of Î²-adrer
may produce hypotension and bradycardia. In addition to slowing the rat
ectopic pacemakers and slow conduction through atrial and AV nodal tiss
congestive heart failure and have become standard of care for patients w
stable New York Heart Association (NYHA) class III or IV disease.[1,52,1
exacerbate symptoms in patients with decompensated congestive heart f

The antihypertensive effect of Î²-adrenergic antagonists is counteracted b
effect is augmented by the $Î²_2$ -adrenergic antagonism of nonselective Î²
vascular resistance, $Î²_2$ -adrenergic antagonists rarely may worsen perip

Patients with reactive airways disease may suffer severe bronchospasm a
of $Î²_2$ -adrenergicâ€“mediated bronchodilation. Catecholamines inhibit mas
Interference with this may predispose to life-threatening effects, followin

Î²-Adrenergic antagonists prevent catecholamine-mediated potassium uptak
serum potassium, especially after exercise. Although $Î²_2$ -adrenergic stim
seldom lower insulin levels and Î²-adrenergic antagonists may actually ca
gluconeogenesis. $Î²_2$ -Adrenergic antagonists also impair the ability to re
discharge that serves to warn of hypoglycemia. This combination of effec
hypoglycemic episodes.[65] Î²-Adrenergic antagonists also alter lipid metabo
tissue is inhibited, patients taking Î²-adrenergic antagonists sometimes ha
decrease in high-density lipoproteins.

Pharmacokinetics

The oral bioavailability of the Î²-adrenergic antagonists ranges from appr
Volumes of distribution range from about 1 L/kg for atenolol to more thar
minutes. Half-lives of the other Î²-adrenergic antagonists range from about
nebivolol. Some of these pharmacokinetic differences can be explained by
antagonists. The highly lipid soluble drugs cross lipid membranes rapidly
rapid entry into the central nervous system (CNS), and typically result in
protein-bound drugs are poorly excreted by the kidneys and require hepa
drugs tend to accumulate in patients with liver failure. Propranolol is the
water-soluble drugs, in contrast, cross lipid membranes slowly and distribu

absorbed, poorly protein bound, renally eliminated, and slow to enter the and generally have less CNS toxicity. Esmolol, although water soluble, is accumulate in patients with renal failure.[132] Atenolol is the most water- also differ in their Î²$_1$ -adrenergic selectivity, intrinsic sympathomimetic a [, 122 , 129 , 161]

Î²$_1$ Selectivity

Î²$_1$ -Selective drugs may avoid some of the adverse effects of the nonsel

drugs appears to be safe in patients with mild to moderately severe reac with diabetes mellitus or peripheral vascular disease. The Î²$_1$ -adrenergic agents. The Î²$_1$ -adrenergic selectivity of these agents is incomplete, and may occur with even therapeutic dosage.[65 , 95]

Membrane Stabilizing Effects (Acebutolol,

Î²-Adrenergic antagonists that inhibit fast sodium channels are said to po antidysrhythmic activity). No significant membrane stabilization occurs wit QRS complex duration prolongation and hypotension, both manifestations explain, in part, the greater clinical toxicity of propranolol than the othe

Intrinsic Sympathomimetic Activity (Acebu Pindolol)

These antagonists act as partial agonists at Î²-adrenergic receptors and a property is unrelated to Î²$_1$ -adrenergic selectivity. Use of these drugs ma with Î²-adrenergic antagonism in susceptible patients, but their clinical be

Potassium Channel Blockade (Acebutolol,

Sotalol is a nonselective Î²-adrenergic antagonist, with low lipophilicity, n because of its ability to block the delayed rectifier potassium current (I_{Kr} potential duration and is manifested on the electrocardiogram by a prolo torsades de pointes, and ventricular dysrhythmias may complicate the th

common in patients taking sotalol therapeutically who have renal failure, predisposing factors for QTc prolongation, such as hypokalemia, hypoma Some authors suggest that QT dispersion is a better predictor of sotalol i difference between the longest and shortest QT interval on the 12-lead EC pointes.[29] Acebutolol also prolongs the QTc interval, presumably secondar

Vasodilation (Betaxolol, Bucindolol, Carteo Nebivolol)

Labetalol and the newer â€œthird-generationâ€• Î²-adrenergic antagonis nebivolol) are also vasodilators. Labetalol and carvedilol are nonselective antagonist activity. Nebivolol is a selective $\hat{I}^2_1$ -adrenergic antagonist tha carteolol, and celiprolol are $\hat{I}^2_1$ -adrenergic antagonists that vasodilate be Carteolol also vasodilates because of nitric oxide-mediated effects. Bucindo currently available only as an ocular preparation. Betaxolol vasodilates be). Î²-Adrenergic antagonists with vasodilating properties may be particula These drugs may also have a role in managing patients with coronary ar $\hat{I}^2_2$ -adrenergic agonist activity may prove useful for patients with reacti

Î²-Adrenergic antagonists are contraindicated in situations of catecholamin these conditions, $\hat{I}^2_2$ -adrenergicâ€“mediated vasodilation is essential to Adrenergic antagonists may result in an â€œunopposed Î±â€• adrenergi resistance (Chap. 74). Agents with combined Î±- and Î²-adrenergic ant example, is 5- to 10-fold more potent as a Î²-adrenergic antagonist than -adrenergic agonist properties can avoid the â€œunopposed Î±â€• effect, investigated.[49 , 65 , 111 , 163]

Other Preparations (Ophthalmic, Sustained

Therapeutic use of ophthalmic solutions containing Î²-adrenergic antagonis grade AV block, heart failure, bronchospasm, and depression.[20 , 42 , 115] combination of the calcium channel blocker felodipine and metoprolol has medication (Logimax, Astra-Zeneca, Wilmington, Delaware) is marketed in United States or Canada. Another combination product containing nifedipin antihypertensive.[33]

Pathophysiology

Most of the toxicity of Î²-adrenergic antagonists is a result of their abilit cardiac Î²-adrenergic receptors. The peripheral effects of Î²-adrenergic an Adrenergic Antagonists above). Î²-Adrenergic antagonists also appear to catecholamine receptors. For example, in catecholamine-depleted, spontan sotalol all decreased heart rate and contractility.[31] Surprisingly, these eff hearts,[89] suggesting that antagonism of the Î²-adrenergic receptor is not membrane-depressant effect may contribute to the cardiac depressant effe depressant effects of most of the other Î²-adrenergic antagonists. It may depression, at least in part, by an action independent of either catechola

Other investigators studied the role of extracellular ions and cardiac me

toxicity. Î²-Adrenergic antagonists interfere with calcium uptake into the stimulate calcium-sensitive outward potassium channels, and result in m bradycardia. Lowering extracellular potassium, or raising extracellular sod atenolol toxicity in isolated rat hearts.[72] In another series of experiments poisoned with Î²-adrenergic antagonists. This may have been the result o

Although cardiovascular effects are most prominent in overdose, Î²-adre effect is centrally mediated and appears to be an important cause of dea antagonism toxicity.[90] There is evidence that propranolol may interfere w effects noted in propranolol overdose.[50]

Clinical Manifestations

Toxicity generally occurs early following Î²-adrenergic antagonist poisoning the rapid development of seizures, coma, and dysrhythmias. In a retrosp antagonist overdose, there were 39 symptomatic patients with well-docum these patients had ingested a sustained-release product. Thirty-one patien symptoms at 4 hours, and everyone developed symptoms within the first documented reports of immediate-release Î²-adrenergic antagonist overdos ingestion.[96] The authors of an Australian series also noted that, in their symptoms began within 6 hours of ingestion.[130] These observations do no

delayed toxicity, or to sustained-release products.

Î²-Adrenergic antagonist overdose in healthy people is generally quite ben
Î²-adrenergic overdose remained asymptomatic.[34 , 98 , 161] This is partia
often well tolerated in healthy persons who do not rely on sympathetic s
unintentional ingestions in children rarely result in significant toxicity.[14] A
no deaths or serious cardiovascular morbidity following unintentional Î²-ad
years.[106]

Î²-Adrenergic antagonists severely impair the heart's ability to respond t
contractility caused by other xenobiotics. Therefore, even relatively benig
coingested with Î²-adrenergic antagonists.[43] According to one author, the
antagonist overdose is likely to be the presence of a cardioactive coinges
to cause symptoms in persons with congestive heart failure, sick sinus sy
stimulation to maintain heart rate or cardiac output. Nevertheless, severe
have ingested Î²-adrenergic antagonists alone.[40 , 130 , 154] In patients wi
who ingest a Î²-adrenergic antagonist with membrane-stabilizing activity.

Patients with symptomatic Î²-adrenergic antagonist overdose are usually
results in sinus bradycardia, sinus pauses, or sinus arrest. Impaired atric
high-grade AV block, occurs rarely. Prolonged QRS and QTc intervals may
Congestive heart failure often complicates Î²-adrenergic antagonist overdo
the setting of severe hypotension, but may also occur with normal blood
agents.[40 , 130] Respiratory depression and apnea may have an additional
patients with propranolol toxicity and 6% of those with atenolol toxicity h
Respiratory depression following Î²-adrenergic antagonist overdose typically
is reported in awake patients.[117] Hypoglycemia may complicate Î²-adrene
in acutely poisoned adults. In a series of 15 cases of Î²-adrenergic antag
whereas both of the 2 children had symptomatic hypoglycemia.[40] Broncho
antagonist overdose and appears to occur only in susceptible patients. In
bronchospasm,[40] and in a review of 39 cases of symptomatic adults witl
bronchospasm.[96] Clinical use of Î²-adrenergic antagonists slightly increas
rarely complicates acute overdose.

Î²â Selectivity (Acebutolol, Atenolol, Betax

In overdose, cardioselectivity is largely lost, and deaths caused by the Î² atenolol,[104] betaxolol,[18] and metoprolol,[134 , 154] are reported. There is a toxicity.[165]

Membrane-Stabilizing Effects (Acebutolol,

Propranolol possesses the most membrane-stabilizing activity of this class seizures, hypotension, bradycardia, impaired atrioventricular conduction, [104] Hypotension may be disproportionate to bradycardia, and deaths from betaxolol, and oxprenolol also possess significant membrane-stabilizing act (Table 59-1).[18 , 58 , 75 , 122 , 128]

Lipid Solubility

In overdose, the more lipophilic Î²-adrenergic antagonists may cause delir hypotension.[40 , 130] Atenolol, the least lipid soluble of the Î²-adrenergic a antagonists when taken in overdose.[58] In one series of Î²-adrenergic anta overdose

had seizures, compared with 8 of 28 patients with propranolol overdose.[1] toxicity and cardiovascular death.[104 , 124 , 157]

Intrinsic Sympathomimetic Activity (Acebu Pindolol)

There is little experience with overdose of these agents but ISA would th Î²-adrenergic antagonists. Sympathetic stimulation with mild tachycardia this drug appears to be relatively safe in overdose.[40 , 84 , 129] In addition membrane-stabilizing activity, making them dangerous in overdose.[40 , 58

Potassium Channel Blockade (Acebutolol,

In 6 patients with sotalol overdose, the average QTc interval was 172% including multifocal ventricular extrasystoles, ventricular tachycardia, an complicated by hypotension, bradycardia, and asystole,[5 , 120] and fatalitie

Sotalol overdose can cause delayed and prolonged toxicity, although elect 6 patients with sotalol overdose, all had prolonged QTc interval noted on after ingestion. We are not told whether these patients were taking sotalo the prolonged QTc on the initial electrocardiogram was present prior to t hours after ingestion and the risk of ventricular dysrhythmias was highest developed ventricular tachycardia did so after 4 hours, and in 2 patients, ingestion. One patient continued to have ventricular dysrhythmias at 48 h long as 100 hours after ingestion. In this series, the average sotalol half- the QTc interval was 82 hours.[120] Acebutolol-induced QTc interval prolong that occur with severe acebutolol toxicity.[32 , 97 , 104]

Vasodilation (Bucindolol, Carteolol, Carvedi

The Î±$_1$ -adrenergic antagonism of labetalol and carvedilol would theoreti toxicity. Conversely, the low membrane-stabilizing effect of these drugs m labetalol appears to be similar clinically to that of other Î²-adrenergic ar features.[79 , 80 , 150] Experience with carvedilol overdose is extremely lim dopamine, without significant bradycardia, and had a benign course.[54] In complicated by bradycardia, lethargy, and hypoglycemia. The patient rece has occurred following betaxolol poisoning.[18] Overdose with bucindolol, ca

Other Preparations (Ophthalmic, Sustained

There is very little published experience with overdoses of the sustained- expect that overdose will result in both a delayed onset and prolonged d antagonists is not reported. Patients who take mixed overdoses with calc difficult to manage because of synergistic toxicity.[140 , 144 , 151] Overdoses blocker preparations are not reported, but these combinations may be qu

Differential Diagnosis of Bradycardia

Bradycardia can result from numerous xenobiotic exposures and medical bradycardia are calcium channel blockers (Chap. 58), Î²-adrenergic anta Other xenobiotic causes of bradycardia include Î±$_1$ -adrenergic agonists, as clonidine and other imidazolines (Chap. 60), cholinergic agents, such

); opioids (Chap. 38); and most sedative hypnotics, such as the barbitu blockers (Chap. 71) usually cause tachycardia but can cause bradycardia bradycardia, but overdoses are rare. Many patients with xenobiotic causes Non-xenobiotic causes of bradycardia include hyperkalemia, hypothermia, episodes, intracranial hypertension, and benign physiologic bradycardia in discussed in detail in Chap. 23 .

Diagnostic Testing

All patients who intentionally overdose with a Î²-adrenergic antagonist sh monitoring. Serum glucose should be measured regardless of mental sta hypoglycemia. A chest radiograph and measurement of oxygen saturation s congestive heart failure. For patients with bradycardia of uncertain etiolo enzymes, and digoxin concentrations may prove helpful. Serum concentra routine clinical use but may prove helpful in making a retrospective diagn

Management

The initial management of the critically ill patient who ingests Î²-adrenerg is important to have an organized approach to the care of these patients

maintained with endotracheal intubation if necessary. Because laryngoscopy atropine prior to intubation of the bradycardic patient. This is particularly complication. The initial treatment of bradycardia and hypotension consists insufficient in patients with severe toxicity, but may suffice in patients w

Gastrointestinal decontamination is warranted for all persons who have i Induction of emesis is contraindicated because of the potential for catastr because vomiting increases vagal stimulation and can worsen bradycardia significant symptoms such as seizures, significant hypotension, or bradycar Orogastric lavage is also recommended for all patients who present shortl propranolol or one of the other more toxic Î²-adrenergic antagonists (ac orogastric lavage causes vagal stimulation and carries the risk of worseni

standard doses of atropine. Activated charcoal alone is recommended for

of the more water-soluble Î²-adrenergic antagonists and who present mo polyethylene glycol should be considered in patients who have ingested Bowel Irrigation and Other Intestinal Evacuants).

The following categories of toxicity are to be used as a guide only. Some require more aggressive treatment. Clinical judgement is required. See A

Asymptomatic

1. Activated charcoal
2. Consider orogastric lavage within the first hour postingestion
3. Consider whole-bowel irrigation with polyethylene glycol electrolyte la preparations

Mild Toxicity

Mild hypotension (BP <100 mm/Hg systolic) or bradycardia (HR <60 b

1. All of the above plus:
2. Atropine 1 mg for bradycardia
3. Fluid boluses (20â€“40 mL/kg of 0.9% NaCl solution) for hypotension

Moderate Toxicity

Failure of the above therapy, or

severe bradycardia (HR <40 beats/minute), or

hypotension (BP <80 mm/Hg systolic), or clinical evidence of hypope consciousness

1. All of the above plus:
2. Monitor ventilation and intubate if necessary
3. Glucagon: 3â€“5 mg IV over 1â€“2 minutes (may give up to 10 mg) t
4. Atropine up to 3 mg for bradycardia
5. Calcium salts for hypotension: 1â€“3 g calcium chloride slow IV push
6. High-dose insulin: regular insulin 1U/kg bolus followed by regular ins (eg, 10 mL/kg/h of 10% dextrose or 2 mL/kg/h of 50% dextrose); gl tapered, or increased, as required

Severe Toxicity

Failure of the above therapy, or evidence of severe hypoperfusion such

1. All of the above plus:
2. Increase glucagon infusion to 10 mg/h
3. Intra-arterial and pulmonary artery pressure monitoring and frequen
4. Catecholamine infusion: *Very high doses of the following are typicall*
   a. Isoproterenol (Î²$_1$, Î²$_2$ agonistâ€”caution for Î²$_2$ -mediated vasod
   b. Epinephrine (Î±, Î² agonistâ€”caution for â€œunopposed Î±â€• e
   c. Dobutamine (Î²$_1$ agonistâ€”theoretically useful but limited experie
   d. Norepinephrine (Î±, Î²$_1$ agonistâ€”caution for â€œunopposed Î±â€
5. Phosphodiesterase inhibitors:
   a. Milrinone: 50 Âµg/kg IV bolus over 2 min, then 0.25â€“1.0 Âµg/k
   b. Amrinone (Inamrinone): 0.75 mg/kg IV bolus over 2 min (may re
6. Ventricular pacing: *This intervention often increases heart rate witho*
7. Intraaortic balloon pump or extracorporeal circulation

TABLE 59-2. Management of Patients with Î²-Adrenergic Antagon

Seizures or coma associated with cardiovascular collapse are treated by a relatively normal vital signs should be treated with benzodiazepines follo seizures are rare in Î²-adrenergic antagonist overdose.

Specific Management

Patients who fail to respond to atropine and fluids require management w time permits, it is preferable to introduce new medications sequentially so by calcium, high-dose insulin, a catecholamine pressor, and, if this fails, the critically ill patient, there may not be enough time for this approach, Advanced hemodynamic monitoring, when available, is advisable to guide phosphodiesterase inhibitors. Mechanical life support with intraaortic ballo medical management fails.

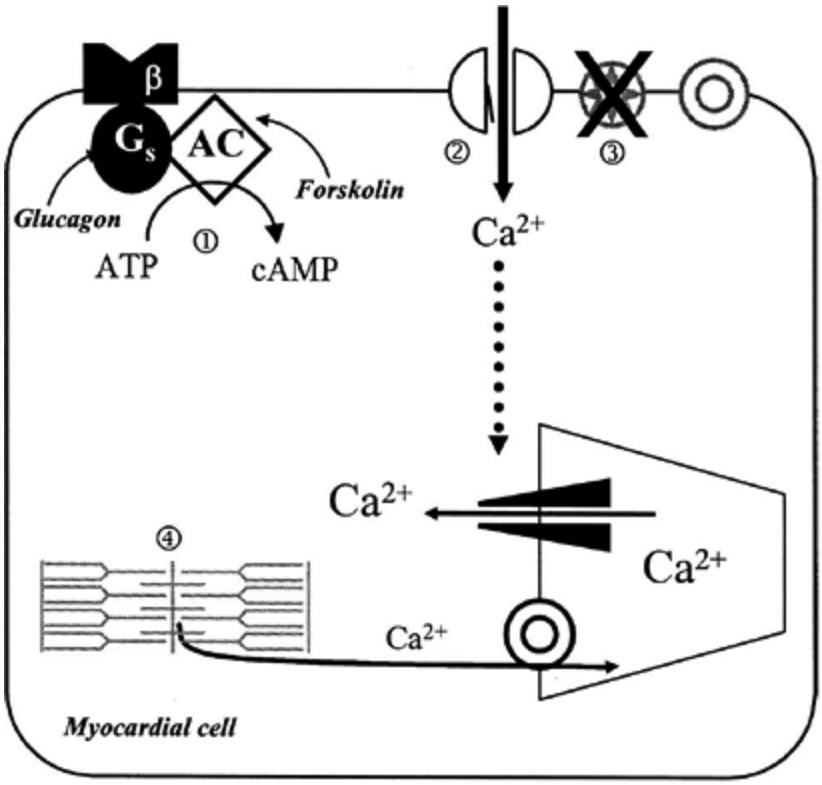

Figure 59-4. Positive inotropes improve cardiac function by a number o calcium. â‘ xenobiotics that increase cAMP: Glucagon receptors and Î²-ac binding increases cAMP by activation of adenyl cyclase. Phosphodiesterase Forskolin increases cAMP by directly activating adenyl cyclase. â‘¡ Calcium depolarization and result in higher intracellular calcium stores. â‘¢ xenobi exchange pump: Digoxin and sodium channel openers that increase intra prolong the action potential duration alter the electrochemical gradients in that increase the sensitivity of the contractile elements to calcium: Angiot alkalosis. Experimental xenobiotics that directly increase the sensitivity of

Glucagon

Humans have cardiac glucagon receptors[174] that, like Î²-adrenergic recept adenyl cyclase activity, independent of Î²-adrenergic receptor binding.[181] phosphodiesterase and thereby prevent cAMP breakdown.[114]

A recent comprehensive review found no controlled trials of glucagon in Nevertheless, with more than 30 years of clinical use,[82 , 171] glucagon is

adrenergic antagonist toxicity.[126 , 161 , 175] This is supported by several glucagon is also effective in correcting symptomatic bradycardia and hyp use.[105] Glucagon is a vasodilator, and in animal models of propranolol p output, and heart rate than in restoring blood pressure.[11 , 103]

The initial adult dose of glucagon for Î²-adrenergic antagonist toxicity is 3 pediatric dose is 50 Âµg/kg. If there is no response to the initial dose, hig response occurs, a glucagon infusion is started. Most authors recommend recommend glucagon infusions as high as 10 mg/h. Glucagon infusion sho example, if the patient receives 7 mg of glucagon before a response occu full dose of glucagon fails to restore blood pressure and heart rate, and we would still recommend starting an infusion of glucagon at 10 mg/h, a Glucagon may cause vomiting with the risk of aspiration. Other side effec hypocalcemia,[68] both of which should be treated appropriately if they de

Calcium

Calcium salts effectively treat hypotension from calcium channel-blocker o but not heart rate, in animal models of Î²-adrenergic antagonist toxicity.[8 patients with Î²-adrenergic antagonist overdose,[24 , 124] and in combined toxicity.[59] The adult starting dose of calcium chloride is 1 g of the 10% s calcium chloride initially. Calcium gluconate contains one-third as much ele proportionately higher. Calcium gluconate is less irritating and is generally calcium gluconate is always preferred for children. The initial pediatric dose repeated up to a total of 180 mg/kg (see Antidotes in Depth: Calcium). significantly higher doses, serum calcium concentrations should be asses

Insulin and Glucose

High-dose insulin combined with glucose and potassium improves cardiac myocardial infarction.[36 , 108 , 109 and 110] High-dose insulin is effective in for patients with severe calcium channel blocker poisoning (Chap. 58). of glucose, proved effective in a series of 5 patients with severe calcium benefit of high-dose insulin for severe calcium channel-blocker toxicity.[21] understood, but may involve inhibition of fatty acid metabolism, enhanced

calcium handling.

There is evidence that high-dose insulin, combined with sufficient glucose antagonist poisoning. In a canine model of propranolol toxicity, all 6 anim of 6 in the glucagon group, 1 of 6 in the epinephrine group, and no survi atenolol and amlodipine had a beneficial response to high-dose insulin.[182] glucose is monitored), and does not require invasive monitoring. There is severely poisoned with calcium channel antagonists. For these reasons, a antagonist poisoning, we recommend using insulin and glucose infusions t fluids, atropine, and glucagon. We recommend a bolus dose of regular ins start at 0.5 U/kg/h. This can be increased up to 1.0 U/kg/h until the pa Glucose should be given at an initial rate of 1 g/kg/h, monitored every 30 euglycemia. The response to insulin is typically delayed for 15â€“60 minu infusion before the full effects of insulin are apparent. Insulin can cause as necessary. Insulin can also cause hypophosphatemia. The effects of ins deterioration is unlikely to occur. It is important to continue monitoring g discontinued.

Catecholamines

Patients who do not respond to the preceding therapies usually require a somewhat controversial. Theoretically, the pure Î²-adrenergic agonist isopro overcome Î²-adrenergic blockade without causing any Î±-adrenergic effec drawbacks that limit its efficacy. In the presence of Î²-adrenergic antago catecholamines are frequently required.[128, 133, 161, 167] One author su the usual effective rate may be required.[28] Individual case reports docum these high doses, the $\hat{I}^2_2$ -adrenergic effects of isoproterenol cause perip Furthermore, isoproterenol is very dysrhythmogenic and is thus potentiall causes of hypotension and bradycardia. Nevertheless, in some animal mo even more effective than glucagon in reversing Î²-adrenergic antagonist validated this in humans. In a review of reported cases, glucagon increase time.[175] In contrast, isoproterenol was effective in increasing heart rate or time. Epinephrine was more effective than isoproterenol.[175] The selective associated with isoproterenol; it has been used successfully to treat Î²-a expected to be especially effective following overdose of the cardioselec

approved and prenalterol therapy is limited, as its relatively long half-life adrenergic agonist, with relatively little effect on vascular resistance, that and dobutamine is not always effective in patients with Î²-adrenergic an antagonism, catecholamines with substantial Î±-adrenergic agonist proper improving contractility, resulting in acute cardiac failure. Severe hypertensi vasodilation is another potential adverse reaction from this so-called un problems, we recommend that catecholamine use be guided by hemodyn bioimpedance techniques or echocardiographic) monitoring of cardiac perf usual rates and then increased rapidly until a clinical effect is obtained. I adrenergic antagonist overdose is fairly certain, it is reasonable to begin monitoring of the patient's blood pressure and clinical status. The infusion hypotensive or develops congestive heart failure.

Phosphodiesterase Inhibitors

The phosphodiesterase inhibitors (PDIs) amrinone, milrinone, and enoxim overdose because they inhibit the breakdown of cAMP by phosphodieste PDIs increase inotropy in the presence of Î²-adrenergic antagonism, in bo appear to be as effective as glucagon in animal models of Î²-adrenergic to demonstrate an additional benefit of these agents over glucagon.[102] , therapy and, in fact, are used clinically to treat Î²-adrenergic antagonist hypotension secondary to peripheral vasodilation. Furthermore, these drug (30â€“60 minutes for milrinone, 2â€“4 hours for amrinone, and approxim PDIs should generally only be considered for patients who have arterial

Ventricular Pacing

Ventricular pacing is not a particularly useful intervention in patients with heart rate in some patients.[71] Unfortunately, there will frequently be failur increase in cardiac output or blood

pressure.[4] , [84] , [87] , [161] In fact, some authors have noticed that ventricu secondary to loss of organized atrial contraction, or impaired ventricular

Extracorporeal Removal

Extracorporeal removal is ineffective for the lipid-soluble Î²-adrenergic an
Hemodialysis may remove water-soluble renally eliminated Î²-adrenergic
hemodialysis is technically difficult in these patients because of hypotens
indicated in patients with Î²-adrenergic antagonist overdose but may be

Mechanical Life Support

It is important to remember that the patient with severe hypotension fro
ventilation and circulation can be maintained until the xenobiotic is elimin
appropriate to consider the use of an intraaortic balloon pump or extrac
recoveries following the use of these therapies for refractory Î²-adrenerg
antagonist and calcium channel blocker overdose.[39 , 178] A recent case s
membrane oxygenation) for patients with cardiac arrest caused by cardiov
were attributed to delayed institution of ECMO. The other 4 patients surv

Experimental Treatment

Aminophylline increases heart rate and contractility by several mechanis
and, at supratherapeutic doses, phosphodiesterase inhibition. Aminophylline
was effective in a dog model of propranolol poisoning.[176] Aminophylline w
atenolol, quinapril, and fluvoxamine.[135]

Forskolin, a drug derived from the root of *Coleus forskolii* , directly activ
is used as a tonic in traditional East Indian medicine, has been investigat
[17] and improves the performance of human myocardium in vitro.[25 , 125] C
improves myocardial contractility to the same extent as dobutamine.[76 , 1
poisoning.[176]

The calcium sensitizers levosimendan and pimobendan interact with the c
clinically to treat heart failure. These drugs may prove to have a role in

Pyruvate is an effective and apparently safe inotrope when given via the
alone or in synergy with catecholamines to improve both systolic and dias
understood but likely involves improved cardiac energy delivery. Unfortuna
administration is unlikely to be effective.[60 , 61] Intracoronary pyruvate infu
patients with severe Î²-adrenergic antagonist poisoning.[61]

Special Circumstances

The preceding discussion applies to the generic management of Î²-adrer unique properties that modify their toxicity. The management consideratio

Sotalol

Sotalol toxicity may result in a prolonged QTc interval and ventricular dy bradycardia and hypotension. Sotalol-induced bradycardia and hypotension However, extreme care must be used to avoid hypokalemia, which is cor Specific management of patients with sotalol overdose includes correction magnesium infusions may be effective for sotalol-induced torsades de po torsades de pointes.[9] In the future, potassium channel openers such as sotalol-induced torsades de pointes.[148 , 162 , 172]

Peripheral Vasodilating Effect (Labetalol, Bet Carvedilol, Nebivolol)

Treatment of patients who have overdosed with one of the vasodilating Î ingest other Î²-adrenergic antagonists, although a greater emphasis on i about the need for vasopressors should be guided by clinical findings. If with Î±-adrenergic agonist properties (eg, norepinephrine or Neo-Synephr antagonism is prominent, agents that act to increase intracellular cAMP m

Membrane-Stabilizing Effects (Acebutolol, Ox

It might be expected that hypertonic sodium bicarbonate would be benefi these drugs. Unfortunately, there is limited experience with the use of bi mixed. Bicarbonate was not beneficial in a canine model of propranolol to narrowing in the bicarbonate group.[101] In models with propranolol-poison beneficial.[72 , 73] Perhaps most compelling is that bicarbonate appeared to poisoning.[32] Because bicarbonate is a relatively safe and simple interventi therapy for Î²-adrenergic-antagonistâ€“poisoned patients with QRS widen Bicarbonate would not be expected to be beneficial in sotalol-induced ve actually increase the risk of torsades de pointes. The usual dose of hype

bolus. This may be followed by an infusion, or repeated boluses may be g
alkalosis or hypokalemia (see Antidotes in Depth: Sodium Bicarbonate).

Observation

All patients who have bradycardia, hypotension, abnormal ECGs, or CNS
be observed in a intensive care setting until

these findings resolve. Toxicity from regular-release Î²-adrenergic antagor
within the first 6 hours.[96 , 100 , 130] Consequently, patients without any fi
Î²-adrenergic antagonist, other than sotalol, can be discharged from medic
remain asymptomatic with normal vital signs and a normal electrocardiogr
activated charcoal. Ingestion of extended-release preparations may cause
24 hours in an intensive care unit. Patients who may have delayed absor
gastrointestinal disease may also require longer observation. Sotalol toxic
occurring as late as 9 hours after ingestion.[120] We recommend that all pa
hours. Patients who remain stable without QTc prolongation can be discha

Summary

Î²-Adrenergic antagonists are commonly used to treat hypertension, angi
Overdoses of Î²-adrenergic antagonists are relatively uncommon, but conti
world. Patients who develop symptoms after ingesting regular-release Î²-a
ingestions are an exception to this and may cause delayed and prolonge
delayed toxicity and require 24 hours of observation. Patients with Î²-ac
develop bradycardia and hypotension. Propranolol and other Î²-adrenergi
lipid solubility are the most toxic in overdose. These drugs cause prolong
and apnea. Hypoglycemia is rare in adults following Î²-adrenergic antago
Bronchospasm may occur in acute Î²-adrenergic antagonist toxicity in susc
QTc interval, and sotalol toxicity often results in refractory ventricular dys
magnesium infusions. In addition to supportive care, the most important
doses of insulin together with glucose provide a promising new treatment
should be closely monitored and large doses are typically required. Patien
catecholamines are critically ill and may respond to phosphodiesterase in
most patients respond to simpler measures, and this aggressive therapy

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Antidotes in Depth

Glucagon

Mary Ann Howland

Glucagon is a polypeptide counterregulatory hormone with a molecular weight of 3500 daltons, secreted by the Î± cells of the pancreas. Glucagon was discovered in 1923, 2 years after the discovery of insulin.[8] Previously animal derived, the current FDA-approved form is synthesized by recombinant DNA technology since 1998. Its traditional role was to reverse life-threatening hypoglycemia in diabetic patients who were unable to ingest dextrose in the outpatient setting. In medical toxicology, however, glucagon is used in the management of Î²-adrenergic antagonist and calcium channel blocker overdoses.

Mechanism of Action

Administration of ^{125}I-labeled glucagon to cats demonstrates the presence of a specific glucagon receptor, and binding is closely correlated with activation of cardiac adenylate cyclase.[25] A large number of glucagon binding sites are demonstrated, and as little as 10% occupancy produces near maximal stimulation of adenylate

cyclase. Glucagon receptors are identified in the human heart and brain, and resemble those on the pancreas.[65] The binding of glucagon to its receptor results in coupling with two isoforms of the G_S protein, catalyzing the exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP) on the Î± subunit of the G_S protein.[24,53,70] One isoform is coupled to Î² agonists, while both isoforms are coupled to glucagon.[70] The GTP-G_S units stimulate adenylate cyclase to convert adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP).[34,42] In addition, it now appears that in human atrial heart tissue glucagon, along with $Î²_2$ agonists, histamine, and serotonin (but not $Î²_1$ agonists), also activates G_i, which inhibits cAMP formation.[29]

Stimulation of glucagon receptors in the liver and adipose tissue increases cAMP synthesis, resulting in glycogenolysis, gluconeogenesis, and ketogenesis.[34] Other properties of glucagon include relaxation of smooth muscle in the lower esophageal sphincter, stomach, small and large intestines, common bile duct, and ureters.[21,24,32]

Pharmacokinetics and Pharmacodynamics

The volume of distribution of glucagon is 0.25 L/kg. The elimination half-life is 8â€“18 minutes, and the plasma, liver, and kidney extensively metabolize glucagon. After a single IV bolus, the effects of glucagon on the heart in human volunteers begin within 1â€“3 minutes, are maximal within 5â€“7 minutes, and persist for 10â€“15 minutes.[48] The time to maximal glucose concentration is 5â€“20 minutes, with a duration of action of 60â€“90 minutes.[19] Smooth muscle relaxation begins within 1 minute and lasts 10â€–20 minutes.[19]

Tachyphylaxis or desensitization may occur with continual dosing. Experimental heart preparations exposed to glucagon for varying

lengths of time demonstrated a decrease in the amount of cAMP generated.[27,71] Calcium or isoproterenol administration after glucagon desensitization improved contractility and cAMP rose. Possible explanations for tachyphylaxis include uncoupling from the glucagon receptor and or phosphodiesterase (PDE) hydrolysis of cAMP.[27,67,71,74] Other experiments demonstrated a transient effect of glucagon on contractility and hyperglycemia, also suggesting tachyphylaxis.[23,28]

Cardiovascular Effects

Investigations of the mechanism of action of glucagon on the heart have been performed on cardiac tissue obtained from patients during surgical procedures and in a variety of in vivo and ex vivo animal studies. The results are often species specific and are affected by the presence or absence of congestive heart failure. The inotropic action of glucagon appears to be related to an increase in cardiac cAMP levels.[13,34,42] Resulting positive inotropic[2,17,40,48] and chronotropic[2,13,17,30,32,40,42,48,68] actions of glucagon are very similar to those of the Î²-adrenergic agonists, except that they are not blocked by Î²-adrenergic antagonists.[70] Although in some canine experiments glucagon was associated with ventricular tachycardia, glucagon was not found to be dysrhythmogenic in studies in patients with severe chronic congestive heart failure or myocardial infarction-related acute congestive heart failure, or in postoperative patients with myocardial depression.[28,36,41,44] The effects of glucagon are markedly diminished as the severity and chronicity of congestive heart failure increases.[48]

Evidence now suggests an additional mechanism of action for glucagon, independent of cAMP, and dependent on arachidonic acid.[59] Cardiac tissue metabolizes glucagon, liberating mini-glucagon, an apparently active smaller terminal fragment.[59,67] Mini-glucagon stimulates phospholipase A_2, releasing arachidonic

acid. Arachidonic acid acts to increase cardiac contractility through an effect on calcium. The effect of arachidonic acid, and therefore of mini-glucagon, is synergistic with the effect of glucagon and cAMP.[58]

Volunteer Studies

The cardiovascular effects of glucagon were extensively studied in 21 patients with heart failure who were given varied doses and durations.[49] Eleven patients who received 3â€“5 mg via IV bolus had increases in the force of contraction, as measured by maximum dP/dT (upstroke pattern on apex cardiogram), heart rate, cardiac index, blood pressure, and stroke work. There was no change in systemic vascular resistance, left ventricular end-diastolic pressure (LVEDP), or stroke index. Additionally, glucose increased by 50% and the potassium fell. A study of 9 patients demonstrated a 30% increase in coronary blood flow following a 50 Âµg/kg IV dose.[44] Patients who received 1 mg via IV bolus also had an increase in cardiac index, but systemic vascular resistance fell, probably secondary to splanchnic and hepatic vascular smooth muscle relaxation.[49] Patients who received an infusion of 2â€“3 mg/min for 10â€“15 minutes responded similarly to those who received the 3â€“5-mg IV

boluses, but those patients receiving boluses experienced significant dose-limiting nausea and vomiting.[49]

Role in Overdoses with Î²-Adrenergic Antagonists

Overdoses with Î²-adrenergic antagonists are particularly dangerous and are manifested by hypotension, bradycardia, prolonged atrioventricular conduction times, depressed cardiac output and cardiac failure. Other noncardiovascular effects include

alterations in consciousness, seizures, and, rarely, hypoglycemia.[1,11,14,16,22,66] Management is often complicated and many drugs, including atropine, isoproterenol, epinephrine, norepinephrine, dopamine, dobutamine, and various combinations, are used with variable success.[15] Animal studies document the ability of glucagon to increase contractility, restore the sinus node function after sinus node arrest, increase atrioventricular (AV) conduction, and improve survival.[38,48,56] Glucagon has successfully reversed bradydysrhythmias and hypotension in patients unresponsive to the aforementioned drugs, and should be administered early in the management of patients with severe overdoses.[9,11,14,30,55,64] By increasing myocardial cAMP concentrations independent of the Î² receptor,[34,42] glucagon is able to increase the inotropic[2,17,40,48] and the chronotropic[2,17,30,40,48,68] activity of the heart.

Glucagon successfully reversed the bradycardia, low-output heart failure, and hypotension that developed in a premature newborn, presumably as a result of an inappropriately large prenatal dose of labetalol given to the mother. This neonate, delivered at 32 weeks gestation and weighing 1.8 kg, received 0.3 mg/kg glucagon intravenously initially and 5 additional doses of 0.3â€“0.6 mg/kg over the next 5 hours, with improvement in heart rate, blood pressure, and perfusion. Epinephrine and diuretics were also used.[60]

Combined Effects with Phosphodiesterase Inhibitors and Calcium

Strategies for enhancing the beneficial effects of glucagon have involved combining it with the phosphodiesterase III inhibitor (PDI III) amrinone (inamrinone) and its derivative milrinone and most recently rolipram (PDI IV). In a canine model of propranolol

toxicity, both amrinone (inamrinone) and milrinone alone were comparable to glucagon,[38,57] but the combination of amrinone and glucagon resulted in a decrease in mean arterial pressure. A tachycardia occurred when milrinone was used with glucagon.[37,56] In an ex vivo model using strips of rat ventricular heart, rolipram enhanced the inotropic effect of glucagon and limited glucagon tachyphylaxis.[27]

The relationship between calcium and the chronotropic effects of glucagon was demonstrated in rats.[6] Maximal chronotropic effects of glucagon are dependent on a normal circulating ionized calcium. Both hypocalcemia and hypercalcemia blunt the maximal chronotropic response.[5,6]

Role in Calcium Channel Blocker Overdose

Calcium channel blocker overdoses produce a constellation of clinical findings similar to those recognized with Î²-adrenergic antagonist overdoses, including hypotension, bradycardia, heart block, and myocardial depression. Animal studies[26,54,61,62,72,73] demonstrate the ability of glucagon to reverse the myocardial depression produced by nifedipine, diltiazem, and verapamil. Human case reports demonstrate similar benefit.[10,12,43,46,47,63] Some authors suggest that the addition of amrinone to glucagon therapy is beneficial.[69]

Reversal of Hypoglycemia

Glucagon was once proposed as part of the initial treatment for all comatose patients.[52] Glucagon stimulates the breakdown of glycogen to glucose in the liver by interacting with G_S. The theoretical rationale for this approach is only partially sound: Hypoglycemic patients may present in coma or with an altered mental status and hypoglycemia can be present concomitantly with

a drug overdose. Immediately restoring the patient's blood glucose level may be lifesaving. Glucagon, however, requires time to act and may be ineffective in a patient with depleted glycogen stores. Patients with type 2 diabetes are more likely to respond than are patients with type 1 diabetes. The intravenous administration of 0.5â€“1.0 g/kg of 50% dextrose in adults rapidly reverses hypoglycemia and does not rely on glycogen stores for its effect. Intravenous dextrose, therefore, is preferred over glucagon as the initial substrate to be given to all patients with an altered mental status presumed to be related to hypoglycemia (see Antidotes in Depth: Dextrose). Glucagon retains a role as a temporizing measure, until medical help can be obtained, in settings such as in the home, where IV dextrose is not an option.

In patients with insulinoma, glucagon may actually worsen hypoglycemia, after an initial hyperglycemic response, as the result of a feedback rise in insulin.

Adverse Effects and Safety Issues

Side effects associated with glucagon include dose-dependent nausea, vomiting,[41] hyperglycemia, hypoglycemia, and hypokalemia; relaxation of the smooth muscle of the stomach, duodenum, small bowel, and colon; and, rarely, urticaria, respiratory distress, and hypotension.[18] The hyperglycemia is followed by an immediate rise in insulin, which causes an intracellular shift in potassium, resulting in hypokalemia.[23,41,48] It is unclear whether stimulation of the Na^+-K^+-adenosine triphosphatase (ATPase) in skeletal muscle also contributes to the hypokalemia as occurs with Î²-adrenergic agonists.[31,51]

Glucagon can also increase the release of catecholamines in a patient with a pheochromocytoma, resulting in a hypertensive crisis,[23] which can be treated with phentolamine.[18] Continuous prolonged treatment with glucagon might lead to a dilated cardiomyopathy, as was reported in a patient with a

glucagonoma.[4] Glucagon is a pregnancy category B drug.

Dosing

An initial IV bolus of 50 Âµg/kg, infused over 1â€“2 minutes, is recommended (3â€“5 mg in a 70-kg person).[16] If clinically acceptable, a longer duration of infusion may be used to limit vomiting. Higher doses may be necessary if the initial bolus is ineffective, and up to 10 mg can be used in an adult.[25] Using too small a dose can potentially decrease systemic vascular resistance.[49] In many cases,

the bolus dose has been followed by a continuous infusion of 2â€“5 mg/h (up to 10 mg/h) in 5% dextrose in water, which can be tapered as the patient improves.[1,24,25,50,55,66] This dosing regimen has never been studied and is based on case reports. Experimental heart preparations clearly demonstrate tachyphylaxis with continuous administration. Whether this occurs in humans is unclear, but might plead for repeated bolus infusions over 1â€“5 minutes rather than continuous infusion.[27,71]

Availability

Glucagon (rDNA origin) by Eli Lilly and Company is available as a 1-mg (1-unit) lyophilized powder for injection, with an accompanying 1 mL of diluent in a disposable syringe.[18] The diluent contains 12 mg/mL of glycerin water for injection, and hydrochloric acid, if needed, for pH adjustment. Glucagon (rDNA origin) as GlucaGen by Novo Nordisk A/S is available as a 1-mg (1-unit) lyophilized powder for injection. It should be reconstituted with 1 mL of sterile water for injection. Concentrations greater than 1 mg/1 mL should not be used. An adequate supply of glucagon in the emergency department is at least twenty 1-mg vials, with assurance of another 30 mg in the pharmacy.[7,39]

Summary

Glucagon can produce positive inotropic and chronotropic effects despite Î²-adrenergic and calcium channel antagonism. Glucagon is beneficial in the treatment of patients with severe overdoses of Î²-adrenergic antagonists and calcium channel blockers. The effects of glucagon may not persist and other therapies, such as insulin and dextrose, should also be considered (Chaps. 58 and 59). The relatively benign character of an IV bolus of glucagon in the patient with a serious overdose of a Î²-adrenergic antagonist or calcium channel blocker should lead the clinician to use glucagon early in patient management. Clinicians should be prepared for vomiting and the attendant risk for aspiration.

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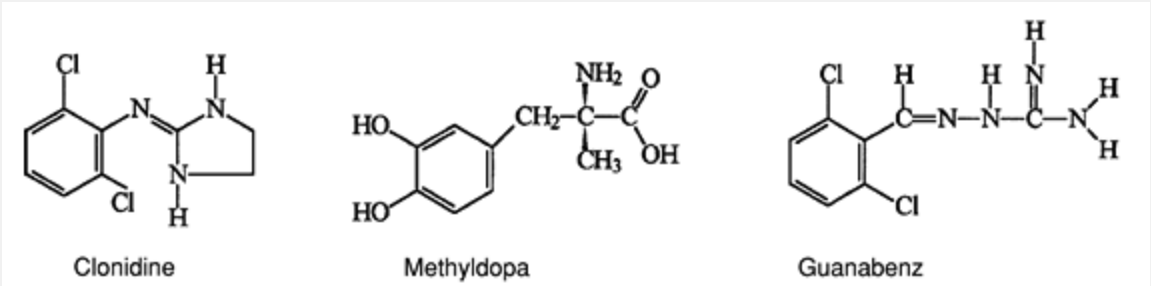
Chapter 60
Other Antihypertensives

Francis DeRoos



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Case 1 A 2-year-old boy was brought to the emergency department because of lethargy. The patient had no medical history, but shortly before this event he was playing with a bottle

of clonidine tablets. Physical examination revealed a lethargic but well-developed child whose initial vital signs were: blood pressure, 110/70 mm Hg; heart rate, 55 beats/min at rest and 80 beats/min with stimulation; respiratory rate, 16â€“20 breaths/min, with intermittent deep, sighing respirations; temperature, 97.9Â°F (36.6Â°C). The head and neck examination was significant for 2-mm pupils that were slightly reactive to light. Lung and abdominal examinations were normal. Heart examination was notable for a regular bradycardia. Neurologic evaluation revealed a somnolent child with poor muscle tone and slight hyporeflexia. The gag reflex was intact. Of note, the patient became much more active, and at times agitated, with tactile stimulation, and he had strong, purposeful movements when intravenous access was initiated.

Supplemental oxygen and an initial intravenous dose of 0.5 mg of naloxone, followed by a second dose of 1.5 mg, were administered without clinical response. Activated charcoal (12.5 g) was given via nasogastric tube. An electrocardiogram (ECG) revealed sinus bradycardia at a rate of 60 beats/min with no conduction abnormalities. Laboratory tests included an arterial blood gas with a PH 7.36, PCO_2 of 42 mm Hg, and PO_2 of 113 mm Hg. The patient was admitted to the pediatric intensive care unit for close observation and cardiac monitoring. Over the next 16 hours the patient's blood pressure remained stable, his heart rate increased to 90 beats/min, and his mental status returned to normal.

As our understanding of the medical complications of chronic hypertension have grown along with the evidence supporting the conclusion that its treatment improves long-term morbidity and mortality, more and more antihypertensive drugs have become available. Two of the most popular classes of antihypertensives, calcium channel blockers and Î²-adrenergic antagonists, were discussed in Chaps. 58 and 59, but numerous other drugs are also marketed in the United States and are discussed here.

Although overdoses involving these drugs are rarely reported,

either because of limited use (eg, the older agents such as reserpine, trimethaphan, and methyldopa) or limited toxicity (eg, diuretics and angiotensin II receptor antagonists), poisoning does occur. Most of the adverse effects and toxicity in overdose are exaggerated pharmacologic effects.

Clonidine and other Centrally Acting Antihypertensives

Clonidine is an imidazoline compound that was synthesized in the early 1960s. Because of its potent peripheral Î±$_2$-adrenergic agonist effects, it was initially studied as a potential topical nasal decongestant. However, hypotension was a common side effect, which redirected its consideration for other therapeutic applications.[87] Clonidine is the best understood and the most commonly used of all the centrally acting antihypertensives, a group that includes methyldopa, guanfacine, and guanabenz. Although these drugs differ chemically and structurally, they all decrease blood pressure in a similar mannerâ€"by reducing the sympathetic outflow from the central nervous system. The imidazoline compounds, oxymetazoline and tetrahydrozoline, which are used as ocular topical vasoconstrictors and nasal decongestants, produce similar systemic effects when ingested[87] (Chap. 50).

Since 1985, the increased efficacy and improved side-effect profiles of the newer antihypertensives have diminished the use of the Î±$_2$-adrenergic agonists in routine hypertension management. However, clonidine use is increasing as a result of a wide variety of applications, including attention deficit hyperactivity disorder (ADHD), peripheral nerve and spinal anesthesia, and as an adjunct in the management of opioid, ethanol, and nicotine withdrawal.[94,107,113,116,194] In addition, abuse of clonidine may be a growing problem in opioid-dependant patients and it has been

used in criminal acts of chemical submission.[17,129]

Although clonidine exposure is relatively uncommon, it may cause significant toxicity, particularly in children. One report from 2 large pediatric hospitals identified 47 children requiring hospitalization for unintentional clonidine ingestions over a 5-year period.[234] Significant clonidine poisoning resulting from formulation and dosing errors are also reported.[181,210]

Pharmacology and Pharmacokinetics

Clonidine is well absorbed from the gastrointestinal tract (approximately 75%) with an onset of action within 30â€“60 minutes. The plasma concentration occurs at 2â€“3 hours and lasts as long as 8 hours.[48] Clonidine has 20â€“40% protein binding and an apparent volume of distribution of 3.2â€–5.6 L/kg.[127] The majority of clonidine is eliminated unchanged via the kidneys.[127]

Guanabenz and guanfacine are structurally and pharmacologically very similar to each other. They are well absorbed orally, achieving peak levels within 3â€–5 hours, and both have large volumes of distribution (4â€–6 L/kg for guanfacine, 7â€–17 L/kg for guanabenz).[92,204] Guanabenz is metabolized predominantly in the liver and undergoes extensive first-pass effect, whereas guanfacine is eliminated equally by the liver and kidney.[92,204] Neither drug has significant active metabolites.

Whereas clonidine, guanabenz, and guanfacine are all active drugs, with direct Î±$_2$-adrenergic agonist effects, methyldopa is a prodrug. It enters the CNS, probably by an active transport mechanism, before it is converted into its pharmacologically active degradation products.[19] Î±-Methylnorepinephrine is the most significant of its metabolites, although Î±-methyldopamine and Î±-methylepinephrine may also be important.[58,84,180] These metabolites are direct Î±$_2$-adrenergic agonists and impart their hypotensive effect just like the other centrally acting

antihypertensives. Approximately 50% of an oral dose of methyldopa is absorbed and peak plasma concentrations are achieved in 2â€“3 hours.[148] However, because methyldopa requires metabolism into its active form, these concentrations have little correlation with its clinical effects. Methyldopa has a small volume of distribution (0.24 L/kg), with little protein binding (15%).[148] It is eliminated in the urine, both as parent compound and after hepatic sulfation.[154]

Clonidine is available in both oral and patch form. The patch, referred to as the clonidine transdermal therapeutic system (TTS), allows slow, continuous delivery of drug over a prolonged period of time, typically 1 week. Similar delivery systems are effective in management of chronic pain with fentanyl and in the cessation of smoking tobacco with nicotine. This formulation, however, offers new clinical challenges. Each patch contains significantly more drug than is typically delivered during the prescribed duration of use. For example, a patch that delivers 0.1 mg/d of clonidine contains 2.5 mg total, whereas the 0.3 mg/d product contains 7.5 mg.[28] Even after 1 week of use, between 35 and 50% and, in some instances, as much as 70%, of the drug remains in the patch.[28,80] Puncturing the outer membrane layer or backing opens the drug reservoir and allows a significant amount of the drug to be released rapidly. In addition, patients do not perceive this delivery system as a medication, and may not exercise appropriate precautions. For example, discarding a used patch in an open wastebasket provides toddlers, who often are fascinated with stickers and other adhesive objects, an opportunity to remove the patch and apply, taste, or ingest it. Numerous reports of toxicity in both adults and children have resulted from dermal exposure, mouthing, or ingesting one clonidine patch, emphasizing this concern.[28,38,80,85,110,174,175]

Pathophysiology

Clonidine and the other centrally acting antihypertensives exert their hypotensive effects primarily via stimulation of presynaptic Î±$_2$-adrenergic receptors in the brain.[167,187,225] This central Î±$_2$-adrenergic receptor agonism enhances the activity of inhibitory neurons in the vasoregulatory regions of the CNS, notably the nucleus tractus solitarius in the medulla, resulting in decreased norepinephrine release. This results in decreased sympathetic outflow from the intermediolateral cell columns of the thoracolumbar spinal tracts into the periphery[1,224] and reduces heart rate, vascular tone, and, ultimately, arterial blood pressure.[168,236] This centrally mediated sympatholytic effect is modulated by nitric oxide and Î³-aminobutyric acid (GABA), which may explain some of the clinical variability that occurs among patients who have overdosed with clonidine.[29,69,202,229]

In therapeutic oral dosing, clonidine and the other centrally acting antihypertensives have little effect on the peripheral Î±$_2$ receptors, the peripheral sympathetic nervous system, or the normal circulatory responses that occur with exercise or the Valsalva maneuver.[147,158] However, when serum concentrations rise above 2 ng/mL, as in the setting of intravenous administration or oral overdose, peripheral postsynaptic Î±$_2$-adrenergic stimulation can occur, causing increased norepinephrine release and producing vasoconstriction and hypertension.[36,42,150,212] This hypertension is short-lived, however, as the potent centrally mediated sympathetic inhibition becomes the predominant effect and hypotension ensues.[4,47,121,134,192]

Imidazoline-specific binding sites are identified both in the ventrolateral medulla of the brain and in other tissues, and may be important in the clinical effects of these agents.[192,217] Direct stimulation of these receptors appears to lower blood pressure, independent of central Î±$_2$-adrenergic effects.[20] Therefore, although their precise physiologic relationship has not been clearly elucidated, more evidence supports the concept that both imidazoline and Î±$_2$-adrenergic receptors modulate the ability of

clonidine, and presumably other centrally acting antihypertensives, to inhibit central norepinephrine release and the cardiovascular effects.[21,81,143]

Clinical Manifestations

Although the majority of the published cases involve clonidine, the signs and symptoms of poisoning with any centrally acting antihypertensive are similar. The central nervous system (CNS) and cardiovascular toxicity reflect an exaggeration of their pharmacologic action. Common signs include CNS depression, bradycardia, hypotension, and, occasionally, hypothermia.[6,165,197,221] Most patients who ingest clonidine, or the other similarly acting drugs, will manifest symptoms rapidly, typically within 30â€“90 minutes.[234] The exception may be methyldopa, which requires metabolism to be activated, possibly delaying toxicity for hours.[197,238]

CNS depression is the most frequent clinical finding and can vary from mild lethargy to coma.[38,74,132,134,144,146,152,157,173] In addition,

severely obtunded patients may suffer from decreased ventilatory effort and hypoxia.[4] Respirations may be slow and shallow, with intermittent deep sighing breaths. Various other terms are used to describe this phenomenon, including gasping, Cheyne-Stokes respirations, and periodic apnea.[6,10,110,134,135] This hypoventilation is typically responsive to tactile stimuli alone, although mechanical ventilation may be required in severe cases.[4,6,86,110,144] The associated CNS depression typically resolves over 12â€“36 hours,[10,82,157] although prolonged coma is rarely reported.[164] Other manifestations of this CNS depression include hypotonia, hyporeflexia, and irritability.[36,134,207] The cranial nerve examination often demonstrates miotic pupils that may remain reactive to light.[4,6,160,214] Two unusual case reports

describe seizures in the setting of clonidine poisoning,[95,130] the mechanism of which is unclear.

Hypothermia is associated with overdoses involving centrally acting antihypertensives.[6,134,135,165] This is thought to be a consequence of Î±-adrenergic effects within the thermoregulatory center, although others suggest that these drugs activate central serotonergic pathways that alter normal thermoregulation.[122,142] Although this phenomenon may last several hours, it rarely requires treatment and responds well to passive rewarming.[36,165]

Sinus bradycardia may occur in up to 50% of patients who ingest clonidine.[207,234] Although usually associated with hypotension, it can be an isolated finding. Plausible explanations for this bradycardia include an exaggerated centrally mediated sympatholytic effect, a centrally mediated increase in vagal tone, or a direct stimulation of $Î±_2$-adrenergic receptors on the myocardium.[44,118,224,235]

Other conduction abnormalities, including first-degree heart block, Wenckebach block, 2:1 atrioventricular block, and complete heart block, are described both in overdose and after therapeutic dosing.[68,109,157,189,191,222,235] It appears that very young patients and patients who have underlying sinus node dysfunction, concurrent sympatholytic drug therapy, or renal insufficiency are at greatest risk of developing bradydysrhythmias after central antihypertensive agent ingestion.[24,207,216]

Hypotension is the major cardiovascular manifestation of central antihypertensive toxicity.[6,28,144,157,207,234] This typically occurs within the first few hours after exposure.[61] Paradoxically, severe hypertension may be noted early in dosing, particularly during intravenous administration, or in massive overdoses.[4,42,47,95,121,134,212] This is the result of peripheral $Î±_2$-adrenergic agonism. Typically, as the central sympatholytic effects become predominant, the hypertensive effect is short-lived.[95] However, in patients with massive ingestions, hypertension may be

protracted and require pharmacologic intervention.[4,47,134,207]

There is no clear association between the amount of any centrally acting antihypertensive ingested and the clinical manifestations. In children, clonidine ingestions as small as 0.2 mg have resulted in clinically severe poisoning.[157] Fatalities from any of these agents are rare with few published reports within the Toxic Exposure Surveillance System (TESS) database (Chap 130).[197] This may be because these drugs effectively block all sympathetic outflow from the CNS and this physiologic effect is not essential for life. The CNS depression resulting in hypoventilation, hypoxia, and poor airway protection may be more pronounced in fatalities.

As a result of Food and Drug Administration postmarketing surveillance and a case report that identified 4 deaths of children who received clonidine, a question was raised about whether there was an association between patients with ADHD who were being treated with combination clonidine-methylphenidate therapy and sudden death.[27,56] However, close scrutiny of these cases revealed significant confounders and an investigation by the Food and Drug Administration concluded that there was inadequate evidence to confirm this association.[56,171,211,233]

Withdrawal

Abrupt cessation of central antihypertensive therapy may result in withdrawal that is characterized by excessive sympathetic activity. Symptoms include agitation, insomnia, tremor, palpitations, and hypertension that begins between 16 and 48 hours after cessation of therapy.[79,176,209] Ventricular tachycardia and myocardial infarction may occur in patients with clonidine withdrawal.[16,149,166] The frequency and severity of symptoms appear to be greater in patients treated with higher doses for several months and in those with the most severe pretreatment hypertension.[176] However, cases occur even when the dosing is gradually reduced.[25,226] Although this phenomenon is associated

with all centrally acting Î±$_2$-agonists, it appears to be most prominent in the shorter-acting drugs such as clonidine and guanbenz.[1,23,64,172,237] The mechanism for this hyperadrenergic phenomenon appears to involve an increase in CNS noradrenergic activity in the setting of decreased Î±$_2$-receptor sensitivity.[52] Reasonable treatment strategies include administering clonidine, via either the oral or intravenous route, followed by a closely monitored tapering of the dosing over several weeks, or benzodiazepines. Animal and human data suggest that Î²-adrenergic antagonists, including labetalol, are harmful in the setting of clonidine withdrawal and their use is contraindicated.[9,104]

Diagnostic Testing

Clonidine and other centrally acting antihypertensives are not routinely included in serum or urine toxicologic assays. Consequently, management decisions should be based on clinical parameters. No electrolyte or hematologic abnormalities are associated with this exposure. Because of the potential for bradydysrhythmias and hypoventilation, a 12-lead ECG and continuous cardiac and pulse oximetry monitoring are strongly recommended during the assessment.

Management

Appropriate therapy begins with particular focus on the patient's respiratory and hemodynamic status. Administration of activated charcoal is the primary mode of gastrointestinal decontamination in most ingestions. However, as in the initial case, in patients manifesting significant toxicity, the risks of placing a nasogastric tube and instilling activated charcoal may not exceed the potential benefits. Induction of emesis is contraindicated because of the possibility of rapid deterioration in mental status. Orogastric lavage has limited utility, because these drugs are rapidly

absorbed. Patients often present following the onset of symptoms rather than immediately after ingestion, and patients respond well to supportive care. In cases involving clonidine patch ingestions, whole-bowel irrigation appears to be an effective intervention.[85]

All patients with CNS depression should be evaluated for hypoxia and hypoglycemia. Respiratory compromise, including apnea, often responds well to simple auditory or tactile stimulation.[4,6,86,110] Significant arousal during preparation for intubation often precludes the need for mechanical ventilation.[4] Endotracheal intubation may be required, however, for the most severely poisoned patients.

Isolated hypotension should initially be treated with intravenous boluses of crystalloid. Bradycardia is typically mild and

usually does not require any therapy if adequate peripheral perfusion exists. If the bradycardia is severe, however, standard doses of atropine are often effective, but redosing may be required.[4,6,132,207] Dopamine may be beneficial in patients with recalcitrant bradycardia or hypotension.[4,6,28,70,132]

Naloxone was probably first used in clonidine poisoning because of the similarity of its clinical findings to those of opioid toxicity, namely CNS and respiratory depression and miosis. Several clonidine-poisoned patients have had significant arousal after naloxone administration, as well as increased respiratory effort, heart rate, and blood pressure.[10,114,214] However, the exact reason for this physiologic response remains unclear. Animal models suggest that endogenous CNS opioids may modulate sympathetic outflow.[54,103,192]

This concept is supported by a clinical study in which clonidine was administered to hypertensive patients for 3 days resulting in a significant decrease in blood pressure. Subsequent administration of 0.4 mg naloxone parenterally reversed the decrease in blood pressure and heart rate in almost 60% of the patients.[55] Because

of the short duration of effects of naloxone (20â€“60 minutes), redosing or continuous infusion may be required. As with some synthetic opioids, such as propoxyphene and fentanyl, clinical improvement may occur only after high doses (4â€“10 mg) of naloxone,[110,133] and some patients have no response regardless of dosing.[11,132,234] If, in fact, naloxone acts as a nonspecific sympatholytic agent, it may also be beneficial in poisoning involving other Î±-adrenergic agents; however, there is a paucity of published clinical experience. In 1 adult with severe guanabenz poisoning, 7 mg of naloxone failed to improve her clinical status.[165] Rarely, naloxone administration in the setting of clonidine overdose can precipitate significant hypertension, so continuous hemodynamic monitoring is indicated.[110,234]

The use of Î±-adrenergic antagonists such as tolazoline and yohimbine, as specific antidotes for patients with Î±-adrenergic agonist overdoses, is controversial. Although some patients have had significant clinical improvements,[144,157,178,188] tolazoline was ineffective in other patients.[4,207] The adult dose is 5â€“10 mg intravenous infusion every 15 minutes, up to a total maximum of 40 mg.[36] Given that tolazoline treatment is variably successful and that most physicians are unfamiliar with it, it cannot be recommended in the primary management strategy for centrally acting antihypertensive poisoning.

The early onset hypertension is typically self-limited, and therapy should be cautiously undertaken, with the expectation that the hypertension will be self-limited. If hypertension is severe or prolonged, treatment with an infusion of sodium nitroprusside is appropriate.[134] Other short-acting antihypertensives, such as esmolol, may exacerbate this paradoxical hypertension in a manner similar to that which occurs when these drugs are used in cocaine toxicity, by inducing unopposed $\hat{I}\pm_1$-receptor stimulation (Chap. 74). Although oral nifedipine has been used,[47] its lack of titratability and its unpredictable efficacy make its use inappropriate as well.

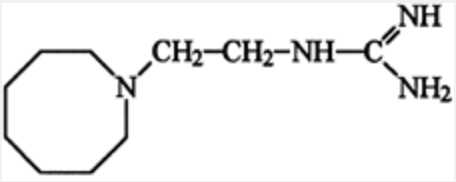
Other Sympatholytic Antihypertensives

Several other drugs also exert their antihypertensive effect by decreasing the effects of the sympathetic nervous system. Often termed *sympatholytics*, they can be classified as either ganglionic blocking agents, presynaptic adrenergic blocking agents, or Î±$_1$-adrenergic antagonists, depending on their mechanism of action. These drugs are rarely used clinically and little is known about their effects in overdose.

Ganglionic Blockers

Ganglionic blockers such as trimethaphan inhibit impulse transmission down both the postganglionic sympathetic and parasympathetic nerves, decreasing vascular tone, cardiac output, and blood pressure. These drugs were used more frequently in the 1950s and 1960s in Europe, but because of their significant side effects, they were quickly replaced with other drugs. Side effects stem from the unpredictable degree of sympathetic, as well as additional parasympathetic, blockade and include paralytic ileus, constipation, urinary retention, impotence, dry mouth, and blurred vision.[154] Trimethaphan is the only ganglionic blocker available in the United States and it is administered intravenously. Although there are no cases of intentional overdose reported, there are cases of cardiopulmonary arrest associated with administration of continuous doses and with a 10-fold pediatric dosing error while treating hypertensive crisis.[41,78] In overdose, the exaggerated hypotensive response should respond well to intravenous crystalloid boluses and, if needed, a direct-acting vasopressor such as norepinephrine.

Presynaptic Adrenergic Antagonists



Guanethidine

These drugs exert their sympatholytic action by decreasing norepinephrine release from presynaptic nerve terminals. Guanethidine and guanadrel interfere with the action potential that triggers norepinephrine release,[194] whereas reserpine depletes norepinephrine and other catecholamines from the presynpatic nerve terminals, probably by direct binding and inactivation of catecholamine storage vesicles.[65] Adverse effects of these drugs limit their clinical usefulness. These effects include a high incidence of orthostatic and exercise-induced hypotension, diarrhea, increased gastric secretions, and impotence.[154] In addition, this hypotensive effect may be prolonged for as long as 1 week.[106,195] Because of its ability to cross the bloodâ€“brain barrier, reserpine may also deplete central catecholamines and produce drowsiness, extrapyramidal symptoms, hallucinations, or depression.[126] In overdose, an extension of their pharmacologic effects is expected. Severe orthostatic hypotension should be anticipated and treated with intravenous crystalloid boluses and a direct acting vasopressor. If reserpine is involved, significant CNS depression should also be anticipated.[126]

Peripheral Î±$_1$-Adrenergic Antagonists

The fourth group of sympatholytic agents is the selective Î±$_1$-adrenergic antagonists, which include prazosin, terazosin, and doxazosin. The Î±$_1$ receptor is a postsynaptic receptor primarily located on vascular smooth muscle, although they are also found in the eye and in the gastrointestinal and genitourinary tracts.[39] In fact, this class of drugs provides first-line pharmacologic therapy for patients with urinary dysfunction secondary to benign prostatic hyperplasia. These drugs produce arterial smooth muscle relaxation, vasodilation, and lowering of the blood pressure. Although better tolerated than ganglionic blockers and peripheral adrenergic neuron blockers, these drugs may still produce significant symptoms of

postural hypotension, including lightheadedness, syncope, or palpitations, particularly after the first dose or if the dosing is rapidly increased.[15] Hypotension and CNS depression ranging from lethargy to coma are reported in overdose cases.[120,124,186] In addition, priapism can occur.[124,177] Treatment with supportive care, including intravenous fluid boluses and a vasopressor such as dopamine, was effective in the few overdose cases reported.[120,124,137]

Direct Vasodilators

Nitroprusside

Hydralazine, Minoxidil, Diazoxide

Early work established that these drugs produce vascular smooth muscle relaxation independent of innervation or known pharmacologic receptors.[49,111,112] More recently, this vasodilatory effect has been attributed to stimulation of nitric oxide release from vascular endothelial. The nitric oxide then diffuses into the underlying smooth muscle cells, stimulating guanylyl cyclase to produce cyclic guanosine monophosphate (cGMP). This second messenger indirectly inhibits calcium entry into the smooth muscle cells, producing vasodilation.[185] As this vasodilation occurs, the baroreceptor reflexes, which remain intact, produce an increased sympathetic outflow to the myocardium, resulting in an increase in heart rate and contractile force. Typically, these drugs are used therapeutically in patients with severe, refractory hypertension and in conjunction with a Î²-adrenergic antagonist to diminish the reflex tachycardia. Hydralazine, minoxidil, and diazoxide are effective orally, whereas sodium nitroprusside is only used intravenously. Minoxidil is also used topically, in a 2% solution, to promote hair growth, and significant poisoning has occurred in

suicidal adults who have ingested this formulation.[141] Diazoxide, although previously used to rapidly reduce blood pressure in hypertensive emergencies, is rarely used for this indication now as a consequence of its poor titratability and its variable, and occasionally profound, hypotensive effect.[111]

Adverse effects associated with daily hydralazine use include several immunologic phenomenon such as hemolytic anemia, vasculitis, acute glomerulonephritis, and, most notably, a lupuslike syndrome.[169] Minoxidil may cause electrocardiographic changes, both in therapeutic doses and in overdose. Sinus tachycardia, ST segment depressions, and T-wave inversions are reported.[77,170,201] The significance of these changes is unknown; they typically resolve with either continued therapy or as other toxic manifestations resolve.[77,201]

The common toxic manifestations of these drugs are an extension of their pharmacologic action. Symptoms can include lightheadedness, syncope, palpitations, and nausea.[3,131] Signs may be isolated to tachycardia alone,[96,170,201] flushing, or alterations in mental status, which is related to the degree of hypotension.[141] Based on American Association of Poison Control Centers annual poison data, it appears that in recent years, the majority of reported exposures to this class of drugs involve the topical formulation of minoxidil (Chap. 130).[53]

After appropriate gastrointestinal decontamination, routine supportive care should be performed, with special consideration to maintaining adequate mean arterial pressure. If intravenous crystalloid boluses are insufficient, a peripherally acting Î±-adrenergic agonist vasopressor such as norepinephrine or phenylephrine, is an appropriate next therapy. Dopamine and epinephrine should be avoided, to prevent an exaggerated myocardial response and tachycardia from Î²-adrenergic stimulation.

Nitroprusside

Sodium nitroprusside exerts its vasodilatory effects after spontaneously releasing into the blood the vasodilator nitric oxide. The nitroprusside molecule also contains 5 cyanide radicals that, although gradually released, on occasion produce cyanide toxicity.[153,190] Physiologic methemoglobin can bind the liberated cyanide. The binding capacity of physiologic methemoglobin is about 175 Âµg/kg of cyanide, corresponding to a little less than 500 Âµg/kg of infused sodium nitroprusside. These cyanide moieties are rapidly cleared, both by interacting with various sulfhydryl groups in the surrounding tissues and blood, and enzymatically in the liver by rhodanese, which couples them to thiosulfate-producing thiocyanate.[59] This cyanide detoxification process in healthy adults occurs at a rate of about 1 Âµg/kg/min, which corresponds to a sodium nitroprusside infusion rate of 2 Âµg/kg/min.[40,190] It is limited by the sulfur donor availability, so factors that reduce these stores, such as poor nutrition in infants and toddlers, critical illness, surgery, and diuretic use, place patients at risk for developing cyanide toxicity.[40,99] Therefore, depending on the balance of cyanide release (eg, the rate of sodium nitroprusside infusion) and the rate of cyanide detoxification (eg, the sulfur donor stores), cyanide toxicity can develop within hours. Infusion of nitroprusside at a rate of more than 1.5 mg/kg, administered over a few hours, or more than 4 Âµg/kg/min, for more than 12 hours, may overwhelm the capacity of rhodanese for detoxifying cyanide. Signs and symptoms of cyanide toxicity include alteration in mental status, anion gap metabolic acidosis, and, in late stages, hemodynamic instability. (Chapter 121 has a complete discussion of cyanide.)

One method of preventing cyanide toxicity from sodium nitroprusside is to expand the thiosulfate pool available for detoxification by the concomitant administration of sodium thiosulfate.[35,40,75,99,190] Recommendations include infusing 500

mg sodium thiosulfate (the standard 50-mL bottle of 25% sodium thiosulfate found in the Cyanide Antidote kit). Unfortunately, the thiocyanate that is formed may accumulate, particularly in patients with renal insufficiency, and produce thiocyanate toxicity.[59,99]

Thiocyanate is almost exclusively renally eliminated with an elimination half-life of 3â€“7 days. It is postulated that a continuous sodium nitroprusside infusion of 2.5 Âµg/kg/min in patients with normal renal function could produce thiocyanate toxicity within 7â€“14 days, although it may be as short as 3â€“6 days or as little as 1 Âµg/kg/min in patients with chronic renal insufficiency who are not receiving hemodialysis.[190] The symptoms of thiocyanate toxicity begin to appear at serum concentrations of 1 mmol/L (60 Âµg/mL), are very nonspecific, and may include nausea, vomiting, fatigue, dizziness, confusion, delirium, and seizures.[59] Thiocyanate toxicity may produce life-threatening effects, such as hemodynamic and intracranial pressure elevation, when serum concentrations are above 200 Âµg/mL.[40,59,75,218] An anion gap metabolic acidosis or hemodynamic instability does not occur with thiocyanate toxicity. Although cyanide or thiocyanate concentrations are not typically useful in the management of cyanide toxicity, they may be beneficial for

monitoring critically ill patients who are at risk of thiocyanate poisoning. Hemodialysis is the treatment of choice for patient with severe clinical manifestations of thiocyanate toxicity.

Diuretics

Diuretics can be divided into three main groups: (a) the thiazides and related compounds, including hydrochlorothiazide and chlorthalidone; (b) the loop diuretics, including furosemide, bumetanide, and ethacrynic acid; and (c) the potassium-sparing diuretics, including amiloride, triamterene, and spironolactone. Two other groups of diureticsâ€”the carbonic anhydrase inhibitors,

such as acetazolamide, and osmotic diuretics, such as mannitolâ€”are not used as antihypertensive agents.

The thiazides produce their diuretic effect by inhibition of sodium and chloride reabsorption in the distal convoluted tubule. Loop diuretics, in contrast, inhibit the coupled transport of sodium, potassium, and chloride in the thick ascending limb of the loop of Henle. Although their exact antihypertensive mechanism is unclear, an increased urinary excretion of sodium, potassium, and magnesium results from the use of loop diuretics. Potassium-sparing diuretics act either as aldosterone antagonists, such as spironolactone, or as renal epithelial sodium channel antagonists, such as triamterene, in the late distal tubule and collecting duct.[100]

The majority of toxicity associated with diuretics is metabolic and occurs during chronic therapy or overuse.[232] Hyponatremia develops within the first 2 weeks of initiation of therapy in more than 67% of susceptible patients.[203] Patients who are elderly, female, malnourished, or taking thiazides are at greatest risk.[8] With severe hyponatremia (<120 mEq/L), symptoms can include headache, nausea, vomiting, confusion, seizures, or coma. Pontine demyelination has been reported during rapid correction of severe hyponatremia secondary to diuretic abuse (Chap. 17).[37]

Other electrolyte abnormalities associated with diuretic use include hypokalemia and hypomagnesemia, which may precipitate ventricular dysrhythmias and sudden death. This is an extremely controversial topic, with several excellent studies providing conflicting results.[18,60,161,198,199] Although it is unclear how great a risk, if any, diuretic use may be, it remains prudent to monitor and correct the patient's potassium levels.[91,198,231] This is particularly important in elderly patients, and for those patients who concomitantly use digoxin, in which setting hypokalemia is clearly associated with dysrhythmias (Chap. 62).[22,208] Potassium-sparing diuretics can cause hyperkalemia, particularly in the

setting of renal insufficiency or when combined with other hyperkalemia-producing drugs such as angiotensin-converting enzyme inhibitors (ACEIs).[105]

Thiazide diuretics are associated with inducing hyperglycemia, particularly in patients with diabetes mellitus. This is a result of depletion of total-body potassium stores. Because insulin secretion is dependant on transmembrane potassium fluxes, this decrease in potassium concentration reduces the amount of insulin secreted.[128] This effect is dose dependant and reversible either by potassium supplementation, or discontinuation of the thiazide diuretic.[31,83] However, a recent prospective study was unable to identify an increased risk of developing diabetes mellitus in patients treated with thiazide diuretics.[72]

Thiazide diuretics are also associated with inducing hyperuricemia, uric acid, renal calculi, and gout. Uric acid is the end product of purine metabolism and its renal elimination is significantly dependant on intravascular and urinary volume. Diuretic-induced volume depletion decreases uric acid filtration and increases its reabsorption in the proximal tubule.[196,206] Several studies support the association with hyperuricemia and the development of gout.[26,76] One study found a link between thiazide diuretic use and the likelihood of the need for subsequent antigout therapy.[73]

Several unusual reactions are associated with thiazide diuretic use, including pancreatitis, cholecystitis, and hematologic abnormalities such as hypercoagulability, thrombocytopenia, and hemolytic anemia.[50,51,182,184,220,230]

Despite the widespread use of these drugs, acute overdoses are distinctly rare.[123] Major signs and symptoms include gastrointestinal distress, brisk diuresis, possible hypovolemia and electrolyte abnormalities, and altered mental status.[123] Typically, the diuresis is short lived because of the limited duration of effect and the rapid clearance of the majority of diuretics. Assessment should focus on fluid and electrolyte status, which should be

corrected as needed. If hyperkalemia is unexpectedly discovered, either the ingestion of a potassium-sparing agent should be considered or, more likely, an overdose of potassium supplements, which are frequently prescribed in conjunction with thiazide and loop diuretics.[93,97] Altered mental status, including coma, may result from diuretic overdose, without evidence of any fluid or electrolyte abnormalities.[14,123,183] Postulated mechanisms include a direct drug effect and induction of transient cerebral ischemia.[155]

Case 2 A 56-year-old man presents to the hospital complaining of progressive lip and tongue swelling. The patient had a history of nonâ€“insulin-dependent diabetes mellitus and hypertension. His medications include aspirin, glyburide, and hydrochlorothiazide, and a new antihypertensive which he began three weeks earlier. Physical examination revealed a well-appearing male in mild distress with obvious swelling of lips, face, and tongue. Initial vital signs were: blood pressure, 154/88 mm Hg; heart rate, 90 beats/min; respiratory rate, 18 breaths/min; temperature, 97.8Â°F (36.6Â°C). Head and neck examination was remarkable for marked swelling of lips, slight protrusion of tongue forcing the mouth open at rest, and left cheek swelling. Lung examination revealed no wheezes or rhonchi, with good air movement. No stridor was noted, although his voice was muffled. Heart, abdominal, and neurologic examinations were unremarkable. A diagnosis of angiotensin-converting enzyme inhibitor-induced angioedema was made and a nasopharyngeal airway was immediately placed. Diphenhydramine (50 mg IV) and methylprednisolone (125 mg IV) were administered, without significant improvement. Although the patient's upper airway was patent, the rapidity of the onset of such significant oropharyngeal swelling threatened his respiratory status. Topical anesthetics and systemic anxiolytics were used, and direct fiberoptic nasopharyngeal intubation was performed. The patient remained intubated for 36 hours. After the swelling had decreased, the patient tolerated extubation without difficulty. He

was discharged from the hospital with specific instructions to discontinue his new antihypertensive, enalapril, and instead to use verapamil.

Angiotensin-Converting Enzyme Inhibitors

ACEIs are among the most widely prescribed antihypertensive drugs. At the time of this writing there were 10 ACEIs approved by the US Food and Drug Administration for the treatment of hypertension (Table 60-1). In general, these drugs are well absorbed

from the gastrointestinal tract, reaching peak plasma levels within 1â€“4 hours. Enalapril and ramipril are prodrugs and require hepatic metabolism to produce their active forms. These drugs are primarily eliminated via the kidneys.

TABLE 60-1. Classification of Antihypertensives Available in the United States

Î²-Adrenergic antagonists (Chap. 59)
Calcium channel blockers (Chap. 58)
Sympatholytics
  Central α_2-adrenergic agonists
    Clonidine, guanabenz, guanfacine, methyldopa
  Ganglionic blocking agents
    Trimethaphan
  Peripheral adrenergic neuron antagonists
    Guanethidine, guanadrel, metyrosine, reserpine
  Peripheral α_1-adrenergic antagonists
    Prazosin, terazosin, doxazosin

Diuretics

Thiazide

Bendroflumethiazide, chlorthalidone, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, indapamide, methyclothiazide, metolazone, polythiazide, trichlormethiazide

Loop diuretics

Bumetanide, ethacrynic acid, furosemide, torsemide

Potassium sparing

Amiloride, eplerenone, spironolactone, triamterene

Vasodilators

Hydralazine, minoxidil, diazoxide, nitroprusside

Angiotensin-converting enzyme inhibitors

Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril

Angiotensin II receptor blockers

Candesartan cilexetil, eprosartan, irbesartan, losartan, telmisartan, valsartan

All ACEIs have a common core structure of a 2-methylpropanolol-L-proline moiety.[63] This structure binds directly to the active site of angiotensin-converting enzyme, which is found in the lung and vascular endothelium, preventing the conversion of angiotension I to angiotensin II. Because angiotensin II is a potent vasoconstrictor and stimulant of aldosterone secretion, vasodilation, decreased peripheral vascular resistance, decreased blood pressure, increased cardiac output, and a relative increase in renal, cerebral, and coronary blood flow occur.[63] This hypotensive response may be severe in select patients after their initial dose, resulting in syncope and cardiac ischemia.[33,88] Patients with renovascular-induced hypertension and patients who are hypovolemic from concomitant diuretic use appear to be at greatest risk.[88] Overall, however, these drugs are well tolerated and have a very low incidence of side effects. Some reported

adverse effects include rash, dysgeusia, neutropenia, hyperkalemia, chronic cough, and angioedema.[46,63,215] Because of their interference with the reninâ€“angiotensin system, ACEIs are potential teratogens and should never be used by a pregnant woman or a woman who intends to become pregnant.[13]

ACEI-Induced Angioedema

Angioedema is an inflammatory reaction in which there is increased capillary blood flow and permeability, resulting in an increase in interstitial fluid. If this process is confined to the superficial dermis, urticaria develops, whereas, if the deeper layers of the dermis or subcutaneous tissue are involved, angioedema results. Angioedema most commonly involves the periorbital, perioral, or oropharyngeal tissues.[179] This swelling may progress rapidly over minutes and result in complete airway obstruction and death.[62,66,193] The pathogenesis of acquired angioedema involves multiple vasoactive substances, including histamine, prostaglandin D_2, leukotrienes, and bradykinin. Because angiotension-converting enzyme (ACE) also inactivates bradykinin and substance P, ACE inhibition results in elevations in bradykinin concentrations that appear to be the primary cause of both ACEI-induced angioedema and cough (Fig. 60-1).[5,98] There is no evidence that the ACEI-induced angioedema phenomenon is IgE-mediated.[5]

Although the literature is replete with reports of ACEI-induced angioedema, the overall incidence is only approximately 0.1%.[57,98,102,200] One-third of these reactions occur within hours of the first dose and another third within the first week.[200] It is important to remember that the remaining one-third of cases can occur at any time during therapy, even after years.[32] Patients with a history of idiopathic angioedema, and possibly atopy, may be at greater risk.[159] There does not appear to be any doseâ€“response relationship.

Treatment varies depending on the severity and rapidity of the swelling. Because of its propensity to involve the tongue, face, and oropharynx, the airway must remain the primary focus of management. A nasopharygeal airway is often helpful. If there is any potential for, or suggestion of, airway compromise, endotracheal intubation should be performed. Severe tongue and oropharyngeal swelling may make orotracheal or nasotracheal intubation extremely difficult, if not impossible. If this is a concern, fiberoptic nasal intubation may be an attractive option, provided that the resources are available. Other techniques, including retrograde intubation over a guidewire that was passed through the cricothyroid membrane, and emergent cricothyrotomy, should also be considered.[179] The most important aspect of airway management in patients suffering from ACEI-induced angioedema, however, is early risk assessment for airway obstruction and rapid intervention prior to the development of severe, obstructive swelling.

Because of the potential for rapid, life-threatening airway obstruction, pharmacologic therapy for ACEI-induced angioedema should be aggressive and include standard agents used for anaphylaxis, such as subcutaneous epinephrine, intravenous diphenhydramine, and corticosteroids. However, because ACEI-induced angioedema is not an antibody-mediated allergic phenomenon, these

interventions will probably be ineffective, so their efficacy should not be assumed or relied on, to avoid definitive airway protection.

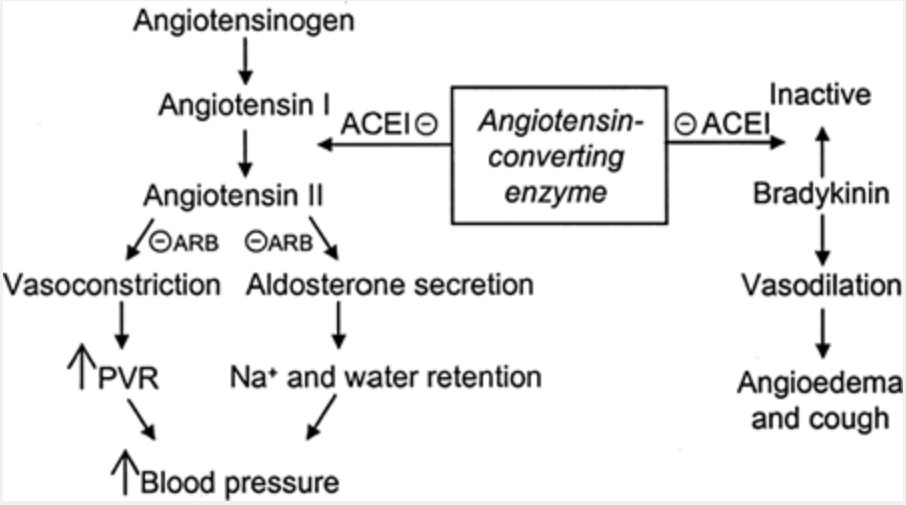


Figure 60-1. An overview of the normal function of angiotensin II and the mechanisms of action of angiotensin-converting enzyme inhibitors and the angiotensin II receptor antagonists. PVR = peripheral vascular resistance.

All patients with mild or quickly resolving angioedema should be observed for several hours to assure that the swelling does not progress or return. Outpatient therapy with a short course of oral antihistamines and corticosteroids is appropriate. Such patients should be instructed to discontinue ACEI therapy permanently and to consult their primary care physician about other antihypertensive options. Because this is a mechanistic and not allergic adverse effect, the use of any other ACEIs is contraindicated.

ACEI Overdose

The toxicity of ACEIs in overdose appears to be limited.[34,90,125,205] Althought several reports of overdoses involving ACEIs have been published, the majority of the cases reported manifested toxicity of a coingestant.[43,71,101,219,231]

Hypotension can occur in select patients,[12,117] but deaths are rarely reported in isolated ACEI ingestions.[162,228] Other patients may remain asymptomatic despite high serum drug concentrations.[119] Two studies suggest that clinical effects are uncommon in children with unintentional exposures to adult therapeutic doses.[90,205]

Treatment should focus on supportive care and on identifying any coingestants that may be more toxic, particularly other antihypertensives such as Î²-adrenergic antagonists and calcium channel blockers. In most cases, activated charcoal alone is sufficient gastrointestinal decontamination. Intravenous crystalloid boluses are often effective in correcting hypotension, although in rare cases, catecholamines may be required.[7]

Naloxone may also be effective in reversing the hypotensive effects of ACEIs. ACEIs may inhibit the metabolism of enkephalins and potentiate their opioid effects, which include lowering blood pressure.[45,145] In a controlled human volunteer study, continuous naloxone infusion effectively blunted the hypotensive response of captopril.[2] In one case report, naloxone appeared to be effective in reversing symptomatic hypotension secondary to a captopril overdose.[227] In another published case, naloxone was ineffective.[12] Although its role in the setting of ACEI overdose remains unclear, naloxone may obviate the need for large quantities of crystalloid or vasopressors and should therefore be considered.

Angiotensin II Receptor Blockers

Angiotensin II receptor blockers (ARBs) were first introduced in 1995 and currently 6 members of this class are marketed in the United States. These drugs are rapidly absorbed from the gastrointestinal tract, reaching peak plasma concentrations in 1â€“4 hours, and then are either eliminated unchanged in the feces, or, after undergoing hepatic metabolism via the mixed

function oxidase system, eliminated in the bile.[136,138,139 and 140,156]

Although these drugs are similar to ACEIs, in that they decrease the effects of angiotensin II rather than decrease the formation of angiotensin II, they act by antagonizing angiotensin II at the type 1 angiotensin (AT-1) receptor (Fig. 60-1).[108] This allows the drugs to inhibit the vasoconstrictive- and aldosterone-promoting effects of angiotensin II without interfering with bradykinin degradation,[136] significantly reducing or eliminating the risk of adverse effects, such as cough or angioedema, compared to ACEI therapy.[115,163,213] However, rare cases of angioedema associated with ARB therapy are reported.[30,223]

Like ACEIs, ARBs should never be used by a pregnant patient because of their teratogenic potential.[13] In addition, 0.5â€“1% of patients develop first-dose orthostatic hypotension.[67]

There are no published reports of overdoses involving these drugs, but hypotension should be anticipated and treated with intravenous crystalloid therapy and traditional catecholamines.

Summary

Numerous medications are currently marketed for the treatment of chronic hypertension, including centrally acting drugs, other sympatholytics, direct vasodilators, diuretics, ACEIs, and ARBs. Although these drugs are not typically associated with severe poisonings, either because of limited use, as with many of the sympatholytics and direct vasodilators, or because of limited toxicity, as with diuretics, ACEIs, and ARBs, severe poisonings have occurred and will probably continue to occur. Although centrally acting drugs, such as clonidine, may produce significant CNS depression and bradycardia, most of these drugs only produce hypotension in overdose. Management of ingestions involving these antihypertensives should focus on appropriate

gastrointestinal decontamination, typically oral activated charcoal, and hemodynamic monitoring and support with intravenous crystalloids and catecholamines. Naloxone may be used in clonidine- or ACEI-poisoned patients, but its efficacy is variable. Sodium nitroprusside use can result in cyanide toxicity if the infusion rate exceeds the body's thiosulfate stores. Although cyanide toxicity can be prevented with concomitant infusion of sodium thiosulfate, thiocyanate toxicity may develop, particularly in patients with renal dysfunction.

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Chapter 61
Antidysrhythmics

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A 27-year-old man presented to the emergency department after attempt bottle of his prescription disopyramide that was prescribed for paroxysma awake but lethargic on arrival and had the following vital signs: blood pre pulse, 140 beats/min; respirations, 26 breaths/min; temperature, 98.6Â°F exact nature of his overdose was unclear, he was intubated for airway pr glucose determination was 70 mg/dL. His electrocardiogram revealed a sir complex duration of 140 msec.

On physical examination the patient was intubated and sedated. His skin prominently on his face, and there was no moisture in his axilla. The pupi and minimally reactive to light. His heart sounds were normal though rap examination were normal. Laboratory evaluation, including a serum ace were normal.

He received sodium bicarbonate 100 mEq by rapid intravenous infusion, of his QRS complex duration to 90 msec; his blood pressure remained no placed and aspiration of 300 mL of gastric contents was performed prior t of activated charcoal. A sodium bicarbonate infusion was initiated at a rate

continued for 16 hours. On discontinuation of the infusion, the QRS comp patient was extubated on the second hospital day and made an uneventfu was transferred to the care of the inpatient psychiatry service.

The term *dysrhythmia* encompasses an array of abnormal cardiac rhythms significance from merely annoying to instantly life-threatening. Antidysrhy that are used to treat any of the various dysrhythmias. The importance in the modern practice of medicine cannot be overstated, as dysrhythmias common causes of preventable sudden cardiac death.[38 , 60] However, des understanding of the underlying mechanisms of dysrhythmia formation, a antidysrhythmics have been developed, each attempting to alter specific components of the cardiac impulse generating or conducting system. In a mechanism-based adverse effect of each agent, unique and often unantic Experience with overdose of many of these drugs is limited, and manager the underlying pharmacologic principles, existing case reports, and the

History and Epidemiology

Until recently, antidysrhythmics were considered among the most rational medications. This well-earned reputation related to their high efficacy at malignant dysrhythmias. Similarly, they are effective at controlling nuisa However, this approach changed dramatically following publication of the Suppression Trials (CAST and CAST II)[37 , 62 , 63] and, more recently, with interventions, such as ablation therapy and implantable defibrillators. CAS antidysrhythmic agents to suppress asymptomatic ventricular dysrhythmias of malignant dysrhythmias. The original CAST study was discontinued pre was noted that encainide and flecainide, 2 of the examined drugs, not on death but actually increased overall mortality. The CAST II trial noted sir moricizine.[63] It has since become clear that the enhanced mortality asso antidysrhythmics is a result of their prodysrhythmogenic effects, and that group carry such risk.[110]

This chapter focuses on the drugs that serve their primary clinical role a the exception of lidocaine, have few other medicinal indications. Chapter description of the various dysrhythmias and a discussion of their genesis. channel blockers and Î²-adrenergic antagonists, also used as antidysrhyt

separately in Chaps. 58 and 59 .

Classification of Antidysrhythmic Agents

Antidysrhythmic agents modify impulse generation and conduction by inte membrane sodium, potassium, and calcium ion channels. Generally, anti electrophysiologic effects either through blockade of the channel pore or, modification of its gating mechanism (described in Fig. 61-1).[66] Unfortuna complex mechanisms of action of the antidysrhythmics, the descriptive

terms used to explain their molecular selectivities are not always comple the description of an antidysrhythmic as a specific â€œchannel blockerâ€ opener,â€• although representative of a specific action of that drug, is many of these drugs are active at other channels or on other cells. Nonsp membrane ion channel may modify several different proteins within the b anticipated target.

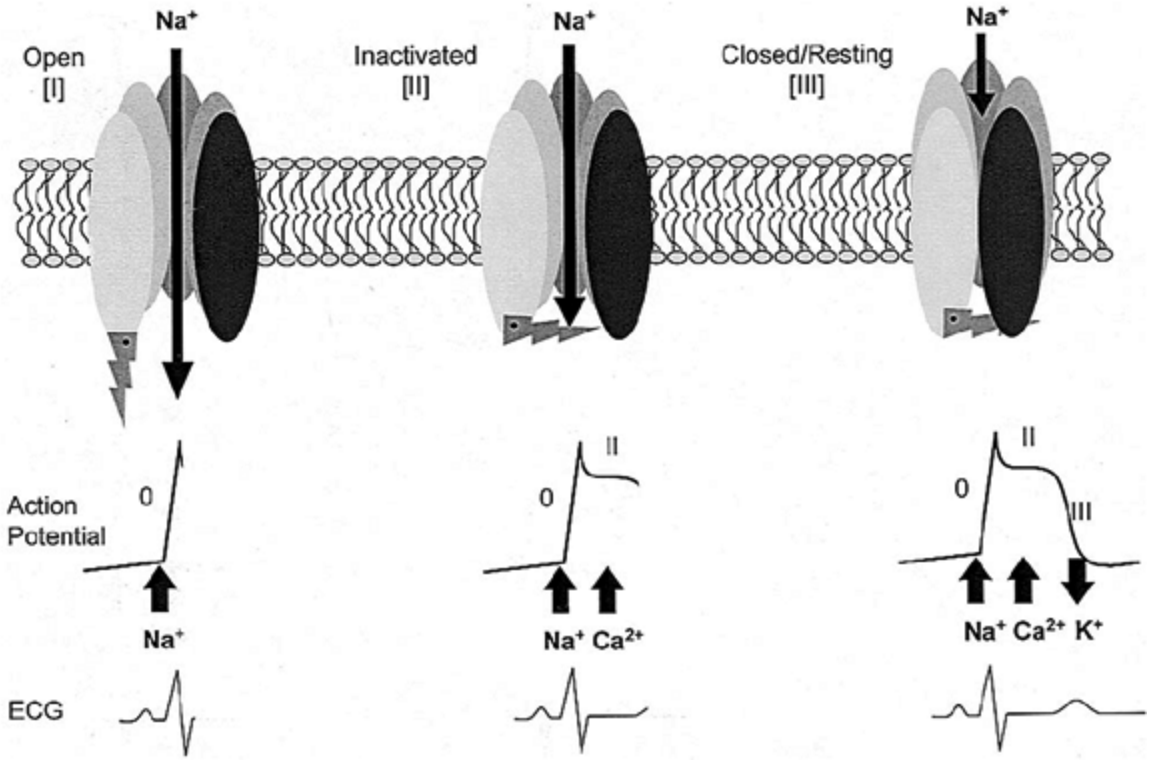

Figure 61-1. Sodium channel blockade. On appropriate signal, sodium c

which time the sodium channel converts from the resting [III] state to th sodium ion influx to initiate phase 0 of the action potential, or cellular d channels subsequently assume the inactivated state by closure of an inact voltage-dependent phenomena and occurs concomitantly with, although m activation. Cellular depolarization is maintained for a period of time by ot the plateau of the action potential. Prior to reactivating, sodium channels resting state, which also occurs in a voltage-dependent fashion. Many ar inactivated state of the channel and, by slowing conversion to the resting reopening, reducing the excitability of the cell. As this is a population ph dependent effects on channel blockade; thus, more drug interferes with certain xenobiotics, such as ciguatoxin and aconitine, stabilize the open s and produce persistent depolarization.

The Vaughan-Williams classification of antidysrhythmics by electrophysio the connection between the basic electrophysiologic actions and the anti Although initially proposed as a descriptive model for electrophysiologic a effects, the Vaughan-Williams classification is commonly invoked as a us therapy. In 1991, a competing system known as â€œthe Sicilian Gambitâ task force of European cardiologists based on the mechanisms by which dysrhythmogenic mechanisms. Although perhaps more contemporary in th classification system is complex and is therefore not widely implemented. classification would match the electrophysiologic effects of the antidysrhy interactions on different regions of the various ion channels, such as char conductance.[66]

This discussion of antidysrhythmics uses the Vaughan Williams classificat shortcomings delineated above.[131]

Class I Antidysrhythmics

All antidysrhythmics in Vaughan-Williams class I (A, B, and C) alter Na^+ voltage-gated, fast inward Na^+ channels (Table 61-1). These agents bind slow their recovery from the open or inactivated state to the resting state conversion must occur before the channel can reopen and participate in Consequently, as the proportion of drug-bound Na^+ channels increases, f

capable of reactivation on the arrival of the next depolarizing impulse. As excitability of the myocardium, abnormal rhythms are both prevented an

Blockade of these sodium channels slows the rise of phase 0 of the cellu correlates with a reduction in the rate of depolarization of the myocardial conduction through the myocardium is slowed, producing a measurable pr complex on the surface electrocardiogram. Correspondingly, slowed intra associated with reduced contractility, manifesting as negative inotropy. M results from effects of reduced intracellular Na^+ on Na^+ -Ca^{2+} exchange.[intracellular Ca^{2+} concentrations, normal levels of which are required for

The differences among class I drugs are directly related to their pharma Na^+ channel. However, it is noteworthy that the original subdivision of cla clinical observations, not current pharmacologic awareness, accounting fo ordering of the class I subdivisions.[131] Type IB drugs have their highest are in the inactivated state. This occurs at the end of depolarization, dur during periods of myocardial ischemia, all situations in which the myocar These drugs also have rapid â€œon-offâ€• binding kinetics and are thus late systole, the period during which the Na^+ channels are predominantly They are almost exclusively unbound during diastole, which is the major at normal heart rates. However, the degree of binding increases as the h because the duration of diastole decreases and the relative proportion of increases; this is termed *use dependence* (Chap. 23). Because they do r channels, class IB drugs do not affect the rate of rise of phase 0 of the a have no effect on the electrocardiogram in therapeutic doses.[130] Alternativ either prefer activated Na^+ channels or they release from the Na^+ channe still bound during the next cardiac cycle.[130] This prolonged channel block reactivation results in greater pharmacologic effects and toxicity, even at these drugs reduce V_{max} and prolong the QRS complex on the electrocard between the other two subclasses.

Although by the Vaughan-Williams classification class I drugs are conside channel blockers, many of the represented drugs, particularly those in cla effects on cardiac potassium channels. These channels are critical to mai action potential and repolarization of the myocardial cell. Slowing of pota the duration of the action potential and accounts for the persistence of r

during which the cell is incapable of re-depolarization. This effect produce

surface electrocardiogram, and predisposes to the triggering of polymorp tachycardia.[111] Because they have no effect on myocardial potassium cha alter refractoriness or the QTc interval. In fact, class IB drugs often redu duration, shortening refractoriness. Further discussion of potassium chann Chap. 23 and below in the discussion of class III antidysrhythmics.

Disopyramide
PO
Liver, kidney
Class IA
Na^+ , K^+ , Ca^{2+}
Congestive heart failure, negative inotropic effects, anticholinergic, torsad hypoglycemia
0.59 Â± 0.15
35â€“95 depending on plasma concentration
Procainamide
IV, PO
50â€“60% unchanged in kidney, liver, active metabolite
Class IA
Na^+ , K^+
Hypotension, QRS widening, fever, SLE like syndrome, torsades de pointe
1.9 Â± 0.3
16 Â± 9
Quinidine
PO
Liver, kidney, 10â€“20% unchanged
Class IA
Na^+ , K^+ , Ca^{2+}
Heart block, severe sinus node dysfunction, prolonged QT syndrome, hy torsades de pointes, thrombocytopenia, â†‘ digoxin levels
2.7 Â± 1.2

87 Â± 3
Lidocaine
SC, IV, PO
Liver, active metabolite
Class IB
Na^+
Fatigue, agitation, paresthesias, seizures, hallucinations, rarely bundle br
1.1 Â± 0.4
70 Â± 5
Mexiletine
IV, PO
Liver
Class IB
Na^+
See lidocaine
4.9 Â± 0.5
63 Â± 3
Moricizine
PO
Liver
Class IB
Na^+
â†‘ Mortality after myocardial infarction, bradycardia, CHF, ventricular fi
tachycardia
?
95
Phenytoin
IV, PO
Liver
Class IB
Na^+
Hypotension and asystole related to IV propylene glycol infusion, nystagr
0.64 Â± 0.04
89 Â± 23

Tocainide
IV, PO
Kidney, liver
Class IB
Na^+
See lidocaine , aplastic anemia, interstitial pneumonia
3.0 Â± 0.2
10 Â± 15
Flecainide
IV, PO
Liver 75%, kidney 25%
Class IC
Na^+ , Ca^{2+} , K^+
Negative inotropic effects, bradycardia, heart block, ventricular fibrillatio neutropenia
4.9 Â± 0.4
61 Â± 10
Propafenone
IV, PO
Liver
Class IC
Na^+ , K^+
Asthma, congestive heart failure, hypoglycemia, AV block, QRS prolonga fibrillation, ventricular tachycardia
3.6 Â± 2.1
85 Â± 95
Î²-Adrenergic antagonists
IV, PO
Liver
Class II
Î²-adrenergic receptor
Congestive heart failure, asthma, hypoglycemia, Raynaud disease

Amiodarone

IV, PO
Liver
Class III
Na^+ , Ca^{2+}
Negative inotropic effects, pulmonary fibrosis, corneal microdeposits, thy
photosensitivity, â†‘ diltiazem, quinidine, procainamide, flecainide, digoxi
66 Â± 44
99.98 Â± 0.01
Bretylium
IV, IM
Kidney
Class III
K^+
Hypertension followed by hypotension, nausea, and vomiting
5.9 Â± 0.8
(0â€“8)
Dofetilide
IV, PO
Kidney
Class III
K^+
Torsades de pointes
3.6 Â± 0.8
64
Ibutilide
IV
Kidney
Class III
K^+ , Na^+ opener
Torsades de pointes, heart block
11
40
Calcium channel blockers
IV, PO

Liver
Class IV
Ca^{2+}
Asystole (if used IV with IV Î²-adrenergic receptor antagonists), AV bloc heart failure, constipation, â†‘ digoxin levels

Adenosine
IV
All cells (adenosine deaminase)
Not classified
Nucleoside-specific G protein-coupled adenosine receptors, â†‘Ca^{2+} curre K^{+} current
Transient asystole <5 s, chest pain, dyspnea, atrial fibrillation, â†“ BP, e dipyridamole and in heart transplant patients, â†‘ dose needed with met

Drug	Route	Primary Route of Elimination	Vaughan-Williams Classification	Channel Blockade	Adverse Effects and Complicatir Factors

TABLE 61-1. Antidysrhythmics: Pharmacology, Pharmacokinetics,

Class IA Antidysrhythmics: Procainamide, Disopyramide

Procainamide

Procainamide (Fig. 61-2) can be used to suppress either atrial or ventr Although absorption from the GI tract is rapid and relatively complete fol (75â€“95%), it may be delayed in overdose situations. A sustained-relea Importantly, procainamide undergoes hepatic biotransformation by acetyl acetylprocainamide (NAPA), the rate of which is genetically determined. A

channel-blocking activity of procainamide, it prolongs the action potential of the K^+ rectifier currents, and for this reason is classified as a class II acecainide.[55] Both procainamide and NAPA are renally eliminated and ma with renal insufficiency.[35, 83] However, NAPA's main advantage over proc propensity to produce a drug-induced lupuslike syndrome caused by the antibodies.[55]

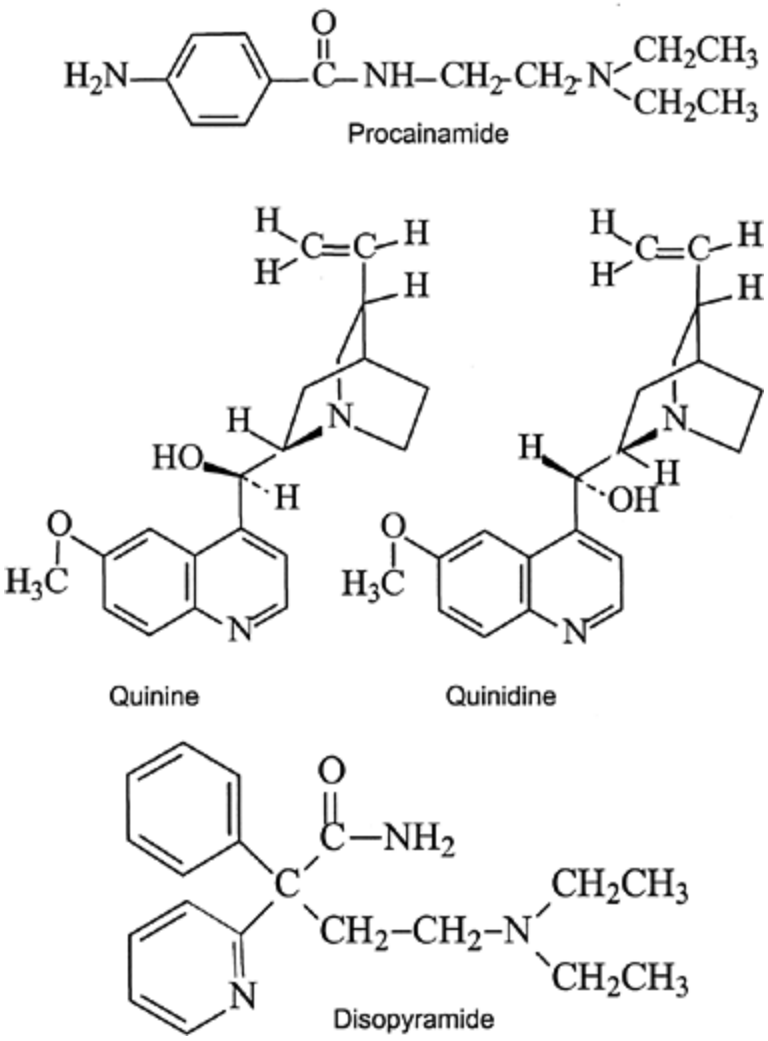

Figure 61-2. Structures of class IA antidysrhythmics and quinine.

Rapid intravenous dosing of procainamide is potentially dangerous because distribution is smaller than its final volume of distribution. Because this the heart, myocardial effects may be unexpectedly pronounced. Thus, to

infusion, the intravenous loading dose should be administered by slow int electrocardiogram monitoring. Although the chronic use of procainamide i the development of antinuclear antibodies or drug-induced systemic lupu syndrome is not associated with acute poisoning. Other reported adverse antimuscarinic effects with acute overdose[133] and myopathic pain, throm agranulocytosis following long-term use.

Both procainamide and NAPA serum concentrations should be determined therapeutic serum concentrations (5â€“20 Âµg/mL) and in patients with Because the elimination half-life of procainamide is 3â€“4 hours, which is that of NAPA (6â€“10 hours), chronic overdosing typically results in NAPA the QTc interval, a reflection of K^+ channel blockade, correlates directly, correlates inversely, with the degree of poisoning. Severe effects usually (procainamide plus NAPA) serum concentrations are greater than 60 Âµg/ structural similarity with amphetamine (Fig. 61-3), patients with procain false-positive urine enzyme-multiplied immunoassay test (EMIT) for amp

Quinidine

Quinidine (Fig. 61-2), the *d* -isomer of quinine, is derived from the bark Because it is a weak base, it is typically formulated as the sulfate or gluc management of atrial or ventricular dysrhythmias. Quinidine undergoes h and both active and inactive metabolites are renally eliminated. Thus, th ($t_{1/2}$) of approximately 6â€“8 hours is prolonged by both liver disease (t failure (to 9â€“12 hours).

Quinidine has substantial acute cardiotoxicity following overdose that in conduction abnormalities and an increased QTc interval. â€œQuinidine sy on therapeutic doses of quinidine experience paroxysmal, transient loss o frequently a result of torsades de pointes.[40 , 64 , 124] Many of the ECG ch hypokalemia.

Because quinidine shares many pharmacologic properties with quinine (Ch that patients may occasionally suffer from cinchonism following either chr overdose. This syndrome includes abdominal symptoms, tinnitus, and alte Quinidine also produces peripheral and cardiac antimuscarinic effects, wh the atrioventricular (AV) node. Thus, quinidine may actually exacerbate t

atrial flutter, explaining the need for rate control prior to chemical cardio quinidine.[61] Furthermore, as with quinine, quinidine-induced blockade of islet cells may cause uncontrolled insulin release, leading to hypoglycemi

Serum quinidine concentrations greater than 14 Âµg/mL are associated evidenced by a 50% increase in either the QRS or QTc interval. However, procainamide, quinidine is associated with an increased QTc at both sub serum concentrations.[40]

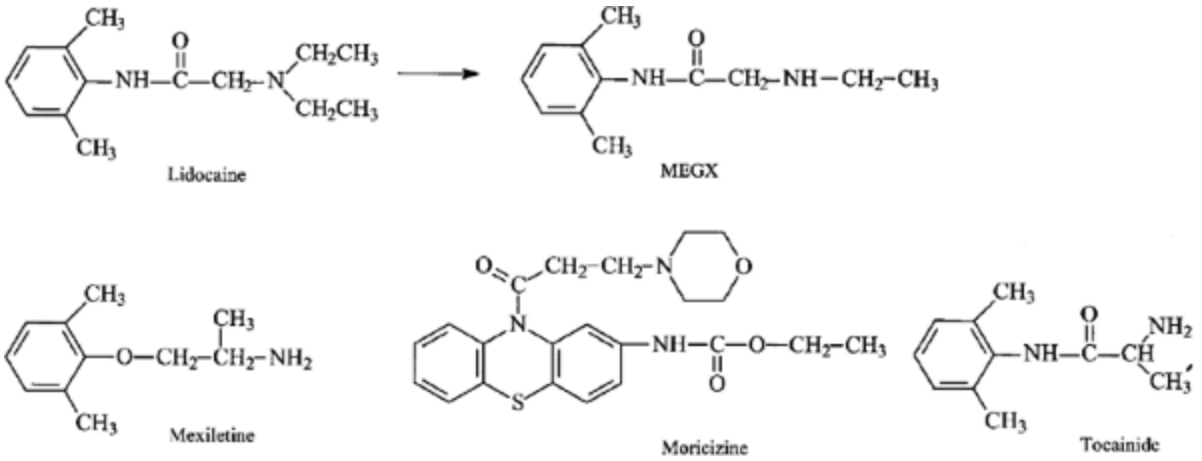

Figure 61-3. Structures of the class IB antidysrhythmic agents lidocaine tocainide, mexiletine, and moricizine.

Disopyramide

Disopyramide (Fig. 61-2) is more likely than the other class IA antidysr inotropy and congestive heart failure. This effect may be noted both in p dosing,[125] and in those who overdose. This propensity may relate in part block myocardial calcium channels.[59] Disopyramide's mono-*N* -dealkylated most pronounced anticholinergic effects of the class, accounting for the o disopyramide to treat neurocardiogenic syncope.[19]

Electrophysiologic abnormalities similar to those associated with poisoning can occur, including atrioventricular and intraventricular conduction abno pointes, and other ventricular dysrhythmias. Disopyramide frequently ca

hypoglycemia through its antagonism of K^+ channels in the pancreatic isl

Patients who overdose on disopyramide frequently develop classic antic including mydriasis, urinary retention, and gastrointestinal stasis.[105, 11(hallucinations may be prominent.

Class IA Management

Management centers on assessment and correction of cardiovascular dys evaluation and intravenous line placement, the 12-lead ECG and continuo paramount importance. Appropriate gastrointestinal decontamination is re patient is stabilized and should include whole-bowel irrigation if a sustai involved.

For patients with widening of the QRS complex duration, bolus administra hypertonic sodium bicarbonate is indicated. Depolarization is accelerated a duration is reduced, by enhancing rapid sodium ion influx through the m However, hypokalemia from the use of sodium bicarbonate may further p requiring careful monitoring of the serum K^+ and ECG. Class IA antidys is treated primarily with rapid 0.9% NaCL infusion, in order to expand th volume and to simultaneously increase myocardial contractility (ie, enhar Hypotension in the setting of QRS complex duration prolongation may res hypertonic sodium bicarbonate, which enhances inotropy by both acceler raising intravascular volume. Dopamine, dobutamine, isoproterenol, nore balloon pump insertion may also be required, but their use has not beer Because disopyramide also blocks calcium channels, calcium administratio although evidence to support this antidotal effect is lacking. Glucagon e depression in canine models, but it has not been evaluated in humans.[95]

Patients with stable ventricular dysrhythmias occurring in the setting of poisoning are usually treated with hypertonic sodium bicarbonate or lidoca counterintuitive to administer another class I antidysrhythmic to a patient class I antidysrhythmic, there is sound theoretical and experimental litera practice.[135] That is, because lidocaine is a class IB drug with rapid on-of displace the â€œslowerâ€• class IA drug from the sodium channel, effe blockade. Sodium bicarbonate enhances conduction through the myocard termination of the ventricular dysrhythmia. Magnesium sulfate and overdri

treating torsade de pointes.[72] Drugs that must be avoided in treating pa associated with class IA poisoning include other class IA and IC drugs, as antagonists and calcium channel blockers, all of which may exacerbate

The roles of activated charcoal hemoperfusion, hemofiltration, and conti hemodiafiltration are inadequately defined, but may be most beneficial fo [83] There is no clinical evidence to support the use of hemodialysis or he disopyramide poisoning.

Class IB Antidysrhythmics: Lidocaine, Toca Mexiletine, and Moricizine

Lidocaine

Lidocaine (Fig. 61-3), known internationally as lignocaine, is an aminoacy derivative of cocaine. Its predominant clinical uses are as a local anesthe

and, for mechanistically similar reasons, as a drug to control ventricular may prevent myocardial reentry by preferentially suppressing conduction Following an intravenous bolus, lidocaine rapidly enters the central nervou redistributes into the peripheral tissue with a distribution half-life of app Lidocaine is 95% dealkylated by hepatic cytochrome P450 (CYP) 3A4 to a monoethylglycylxylidide (MEGX) and, subsequently, to the inactive glycine further metabolized to monoethylglycine and xylidide.[123] MEGX, although channel blocker than the parent drug,[13] may bioaccumulate because of it life.

Patients with lidocaine toxicity develop both central nervous system and generally in that order. Because of its rapid entry into the brain, acute l produces central nervous system dysfunction, particularly seizures, as its Concomitant respiratory arrest generally occurs. Shortly following the cer depression in the intrinsic cardiac pacemakers leads to sinus arrest, AV conduction delay, hypotension, and/or cardiac arrest.[6] If the patient is s the drug distributes from the heart, and spontaneous cardiac function re

Nonmassive acute lidocaine toxicity is generally related to excessive or

dosing. Common settings include intravenous administration when the int subcutaneous, inadvertent excessive subcutaneous administration during swallowing of viscous oral lidocaine. The typical CNS manifestations of n poisoning include drowsiness, weakness, a sensation of â€œdrifting awa diplopia, decreased hearing, paresthesias, muscle fasciculations, and seizu these effects develop when serum lidocaine concentrations exceed 5 Âµg/ by paresthesias or somnolence. Any of these symptoms should, therefore, examine the patient's medication administration history or drug-infusion r well as hypotonia in neonates, are reported to result from lidocaine toxicit serum concentrations.[108]

Chronic lidocaine toxicity most commonly occurs as a therapeutic misadve therapeutic infusions, generally in a critical care unit. Hepatic blood flow influence the rate of lidocaine metabolism, and only a small percentage is kidney. Consequently, toxicity following appropriate therapeutic dosing is patients with congestive heart failure, shock, liver disease, or concomitan inhibitors such as cimetidine.[91 , 127] Adverse reactions to lidocaine also i decreasing body weight, and increasing infusion rate.[33] Lidocaine toxicity patients receiving infusions at 3 mg/min.[117] Partly for this reason, lidocai used to prevent dysrhythmias in the immediate postmyocardial infarction

When used as an antidysrhythmic, lidocaine must be administered parent first-pass hepatic metabolism associated with oral ingestion. However, n unequivocally demonstrate the toxicity associated with orally administere gastrointestinal tract absorption only one-third of the drug is bioavailable primary metabolite, MEGX, is nearly as toxic as lidocaine itself, substantia following ingestion. Because of their small size and the relatively high co lidocaine (typically 4%), children seem overrepresented in reports of oral little as 15 mL of 2% viscous lidocaine in a 3-year-old child (estimate, 30 may cause seizures.[57 , 114]

It should be noted that when lidocaine is absorbed from the oropharynx surfaces, skin, or subcutaneous tissues, hepatic metabolism is bypassed, systemic bioavailability of the parent compound. Thus, seizures are repor application of lidocaine used for bronchoscopy,[138] as well as intrauretera ureteroscopic stone extraction.[99] Furthermore, deaths related to tumesce

reported.[107] In this technique, a large volume of dilute lidocaine is used prior to liposuction. Although in some reports the cause of death was co lidocaine concentrations were commonly elevated, and it is likely that lid involved in the adverse events.[68, 107] Interestingly, proponents of this p lidocaine doses up to a maximum of 55 mg/kg are safe,[97] whereas the c limit for subcutaneous lidocaine with epinephrine is 5â€“7 mg/kg. Of sign recommended doses used for liposuction procedures do not consider the saturate the CYP3A4 hepatic microsomal enzymes. When saturation occur absorption and lidocaine toxicity may result.

The high frequency of lidocaine-related medication errors relates in part t diverse â€œampsâ€• of lidocaine designed for varying indications includ preparation of infusions, and local anesthesia.[67] With the reduced emphas current advanced cardiac life support (ACLS) protocols, one important set poisoning may be eliminated.[27]

Tocainide

Tocainide (Fig. 61-3) is indicated for the treatment of ventricular dysrhy for oral administration. Although a lidocaine analog, it does not undergo therefore almost 100% orally bioavailable.[77] Tocainide has pharmacologic identical to lidocaine.[77, 112] Both renal failure and congestive heart failu considerably. The few overdoses reported with tocainide are associated w complications similar to those that occur with lidocaine overdose.[10, 34, associated with hepatotoxicity and blood dyscrasias, which, although rare, widespread use.

Mexiletine

Mexiletine (Fig. 61-3), originally developed as an anorectic agent, was fo antidysrhythmic, local anesthetic, and anticonvulsant activity.[23] It is curr for the management of ventricular dysrhythmias. Its chemical structure properties are similar to those of lidocaine. Mexiletine, a base, is absorbe therefore, its absorption is increased when the gastric contents are alkal failure and cirrhosis, as well as therapy with cimetidine or disulfiram, dec mexiletine.[76] Its metabolism, predominantly through CYP2D6, is accelerat

phenobarbital, rifampin, and phenytoin.[76]

Adverse therapeutic effects are primarily neurologic and are similar to tho lidocaine. The few reported cases of mexiletine overdose describe promi

such as complete heart block, torsades de pointes, and asystole.[31, 47] Ne overdose includes self-limited seizures, generally in the setting of cardiot case report described a patient with mexiletine poisoning who experience any hemodynamic or electrocardiographic abnormalities.[93] The use of oth antidysrhythmics, such as lidocaine or tocainide, may potentiate the neu Mexiletine may produce a false-positive result on the amphetamine immu

Moricizine

Moricizine (Fig. 61-3) is a phenothiazine derivative that possesses the g drugs, but is difficult to specifically subclassify. It depresses Na^+ current the other class IA drugs,[30] but has other properties that more appropriate or IC. It is historically discussed as a class IB drug, as it is here. The pa extensive and rapid metabolism. Dose-related increases in PR and QRS in hemiblocks, bundle-branch blocks, and sustained ventricular tachydysrhyt drug during the CAST II trial, in the setting of myocardial infarction, sugg prodysrhythmic.[63] Clinical experience with overdose of this drug is limited similar to other class I antidysrhythmics.

Class IB Management

The focus of the initial management for intravenous lidocaine-induced car cardiopulmonary resuscitation to allow lidocaine to redistribute away from setting, management of hemodynamic compromise includes fluid replacem strategies. Resistant hypotension may require dopamine or norepinephrin insertion of an intraaortic balloon assist pump.[50] Bradydysrhythmias typica atropine, requiring the administration of dopamine, norepinephrine, or is or insertion of a transvenous pacemaker may be useful,[94] but the myocar electrical capture. Lidocaine-induced seizures, and those related to lidoca brief in nature and do not require specific therapy. For patients requiring benzodiazepine generally suffices; rarely, a barbiturate is required.

Following oral poisoning by a class IB drug, administration of activated c
Enhanced elimination techniques are limited following intravenous poisonin
time course of poisoning. Cardiopulmonary bypass, which does not direct
maintains hepatic perfusion, thereby allowing the lidocaine to be metabo
may rarely be warranted following lidocaine overdose if liver failure or ci
use of other treatment modalities to be used. Hemoperfusion or hemodial
clearance of tocainide, but its indications remain unclear.[134] Mexiletine's
its rapid metabolism make it a poor candidate for extracorporeal drug re

Class IC Antidysrhythmics: Flecainide and

Flecainide

Flecainide, a fluorobenzamide derivative of procainamide, is used orally t
and ventricular dysrhythmias, particularly atrial fibrillation.[2 , 71] Seventy-
metabolized hepatically by CYP2D6 to two major metabolites, one active a
remaining 25% is excreted renally.[12] Thus, renal insufficiency, drug inter
heart failure all decrease its clearance. Additionally, alkaluria reduces its
through enhanced tubular reuptake of nonionized drug. Patients using the
left ventricular dysfunction with worsening congestive heart failure. This is
flecainide's negative inotropic effect, which itself may relate to its antago
channels. Furthermore, sudden dysrhythmic death may occur, particularly
ischemic heart disease.[136]

Reported overdose experience is limited to case reports that uniformly i
overdose. A 50% increase in QRS duration, a 30% prolongation of the PR
in the QTc interval occurs with flecainide toxicity.[88] The expected consequ
electrophysiologic disturbances include bradycardia, premature ventricular
ventricular fibrillation.[5] The combination of marked QRS and PR interval
minimal QTc interval prolongation, is characteristic of flecainide toxicity a
described with other antidysrhythmic agents.[29]

Propafenone

Propafenone bears a structural resemblance to propranolol,[51] as well as

quantitative, electrophysiologic properties.[87] Propafenone blocks fast inwa weak Î²-adrenergic antagonist, and is an L-type calcium channel blocker. result of first-pass metabolism by CYP2D6 to 5-OH-propafenone, the prir The long half-life allows the accumulation of parent compound, particularly metabolizer pharmacogenetic variant of CYP2D6, which may cause exces antagonism.[78 , 119] The activity of a second metabolite, *N* -depropylpropa Propafenone overdose produces sinus bradycardia, as well as ventricular inotropy.[45]

Acute overdose typically produces wide complex tachycardia, right bundl AV block, and prolongation of the QTc interval, as well as generalized se administration of phenytoin to a child with propafenone poisoning was as prolongation of the QRS interval, which initially responded to sodium bica subsequently developed bradyasystolic arrest.[86] Massive overdose in a yc the subsequent development of a mild cardiomyopathy and a left bundle-

Class IC Management

Initial stabilization should include standard management strategies for hy Additionally, therapy for hypotension, and for the electrocardiographic ma poisoning, includes intravenous hypertonic sodium bicarbonate to overcom blockade.[70] An animal study documents the beneficial effects of hyperton flecainide-induced ventricular dysrhythmias, and 3 reports of human over narrowing in response to hypertonic sodium bicarbonate administration.[18 loading with hypertonic saline may be similarly effective, it remains unpr of flecainide is reduced by urinary alkalinization, suggesting that sodium may ultimately prove superior to sodium bicarbonate.[89] The administration antidysrhythmics is clearly contraindicated because of their additive blocka However, amiodarone has been successful in the setting of ventricular fil therapy.[120] The efficacy of an external or internal pacemaker may

be limited because of the drug-induced increased electrical pacing thresho therapy with cardiopulmonary bypass[32] or extracorporeal membrane oxy and should be considered if readily available.

Extracorporeal removal is not expected to be beneficial for patients with

fact, has been unsuccessful. Although hemodialysis was successful in rer overdose, additional studies are needed to determine its clinical benefit.[2]

Class III Antidysrhythmics

Amiodarone, Dofetilide, and Ibutilide

The class III antidysrhythmics prevent and terminate reentrant dysrhythm potential duration and effective refractory period without slowing conducti or 1 of the action potential. This drug-induced effect on the action potent blockade of the rapidly activating component of the delayed rectifier pota responsible for repolarization.

The class III antidysrhythmics in use today prolong repolarization of both Thus, common electrocardiographic effects of the class III drugs at thera prolongation of the PR and QTc intervals and abnormal T and U waves. Ch discussion of the pharmacologic mechanisms of this class. Chapters 23 ar

Amiodarone

Amiodarone (Fig. 61-4) is an iodinated benzofuran derivative that is stru thyroxine, and procainamide. Forty percent of its molecular weight is ioc of patients with out-of-hospital cardiac arrests, caused by refractory ver resulted in a higher rate of survival until hospital admission.[36] Furthermor the ACLS guidelines places tremendous emphasis on the early intravenou amiodarone.[27] This, along with its ability to terminate or prevent atrial increased use of this drug despite its association with potentially severe few reported cases of amiodarone overdose.[52]

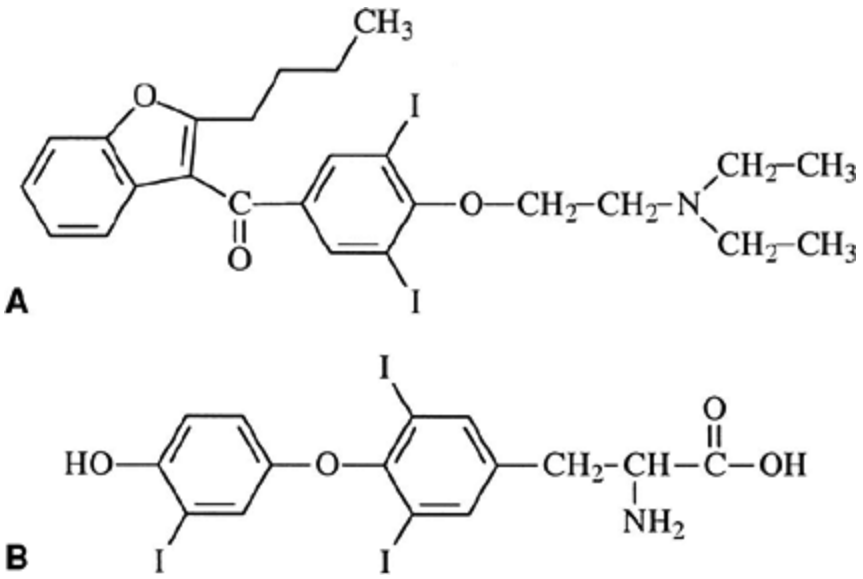

Figure 61-4. Structures of amiodarone (A) compared with triiodothyroni amiodarone is nearly 40% iodine by weight.

Although amiodarone has multiple pharmacologic effects, its efficacy as a primarily a result of its class III antidysrhythmic effects. It also has weak antagonist activity and can block both L-type calcium channels and inact Amiodarone is slowly absorbed by the oral route and concentrates in the tissue. Its oral bioavailability is extremely variable among individuals, as of approximately 66 L/kg.[28] Steady-state pharmacokinetics may not occur and the elimination half-life is 2 months. Amiodarone is metabolized via desethylamiodarone, which has comparable activity to the parent compou biliary excretion and virtually none is renally cleared.

The electrocardiographic effects of amiodarone differ, based on the route Therapeutic oral doses prolong PR and QTc intervals but not the QRS co may produce a prolongation of the PR interval, but has few other electr Ventricular dysrhythmias and sinus bradycardia are the most serious card therapeutic doses of amiodarone.[137] Prodysrhythmic monomorphic and p tachycardias resistant to cardioversion and pharmacologic interventions a surprisingly uncommon, given the frequency and extent to which QTc int Amiodarone's ability to compete for P-glycoprotein is responsible for sev effects, including elevated digoxin and cyclosporin levels and enhanced

of warfarin.[141]

The diverse complications associated with long-term therapy do not occu intravenous use. Chronic therapy with oral amiodarone is associated with thyroid, corneal, hepatic, and cutaneous toxicity, organs in which it bioa effects appear to be dose related, but because of the wide range of bioa patterns among different patients, as well as the overlap between therape concentrations, therapeutic drug monitoring is of limited benefit. Pneumo consequential extracardiac adverse effect, effects up to 5% of patients ta therapeutically. Amiodarone pneumonitis may develop within days of init typically occurs following years of therapy. Its occurrence may be dose re in those taking <200 mg daily) and the recent focus on using the minima the incidence of pneumonitis.[98] Oxygen supplementation may speed the which may explain the initial belief that patients with chronic lung disease amiodarone pneumonitis. Manifestations of pneumonitis include dyspnea, hypoxia, and radiographic changes.[24] CT scan is the most helpful initial pneumonitis, but is not used for monitoring purposes (this is often done CO).[54] Bronchoalveolar lavage typically reveals interstitial pneumonitis wit characteristic finely vacuolated foamy cytoplasm, but confirmation of the lung biopsy.

Thyroid dysfunction, either amiodarone-induced thyrotoxicosis (AIT) or hypothyroidism (AIH), occurs in approximately 4% of patients.[25] AIH is r iodine intake is sufficient.[84] AIH is likely caused by an exaggerated Wolf iodine, in this case from amiodarone, inhibits the organification and relea appears to exist in two distinct forms: type I AIT, which occurs in patien glands and iodine-induced excessive thyroid hormone synthesis and relea

type II AIT, in which destructive thyroiditis leads to release of thyroid ho follicular cells. The relative prevalence of the two forms of AIT is unknown ambient iodine intake. Amiodarone may also reduce the effect of thyroid tissue.[46] The diagnosis is confirmed with standard thyroid function testin

Corneal microdeposits are extremely common during chronic therapy and Abnormal elevation of hepatic enzymes occurs in more than 30% of those hepatotoxicity may be associated with progression to cirrhosis. Periodic

aminotransferases is typically recommended.[104] Slate gray or bluish disco common, particularly in sun-exposed portions of the body.[113]

Dofetilide

Dofetilide is a newer class III antidysrhythmic that is FDA approved for c or atrial flutter to a normal sinus rhythm. Dofetilide increases the effecti substantially in atrial tissue than in ventricular fibers, accounting for this many of the other antidysrhythmics, it may reduce the morbidity of atria congestive heart failure, and is still used despite the move from rhythm t fibrillation.[41 , 132] Dofetilide has no known effect on calcium or sodium ch Î²-adrenergic antagonism. Dofetilide increases the QTc intervals, but does interval or QRS complex in humans. Heart rate and blood pressure are a

Although limited data are available, the expected and reported adverse c ventricular tachycardia, particularly torsade de pointes.[41 , 137] The appro de pointes in patients receiving high therapeutic doses of the drug is 3%. and Drug Administration has in place strict requirements for the use of c

Overdose data reported by the manufacturer include 2 cases. One patien capsules and experienced no events, whereas a second patient inadverter supratherapeutic doses 1 hour apart and experienced fatal ventricular fib dose.[100]

Ibutilide

Ibutilide is an antidysrhythmic with predominant class III activity. It is m conversion of atrial fibrillation and flutter to normal sinus rhythm. Becaus metabolism, ibutilide can only be administered parenterally. Its metabolic understood, but they do not involve the isoenzymes CYP3A4 or CYP2D6. far do not indicate that age, sex, hepatic, or renal dysfunction necessitat recommended dosage. In addition to its effects on the delayed rectifier c concentrations, ibutilide activates a slow inward sodium current that is u channel blockers.[90]

Ibutilide can increase the QTc interval and cause torsade de pointes, esp congenital long-QT syndrome (Chap. 23). Although ibutilide can enhance

cardioversion for atrial fibrillation, its use in patients with ejection fractio with a increased incidence of sustained polymorphic ventricular tachycard failure, including biopsy-identified crystals, is reported in association with causal relationship is not yet definitive.[48] Acute overdose information, onl through the manufacturer, suggests that ventricular dysrhythmias and hi abnormalities should be expected.[101]

Class III Management

Treatment experience with class III drug overdose is limited. Isoproteren successfully treated amiodarone-induced torsades de pointes.[118] Administ antidysrhythmics or propranolol for the control of monomorphic ventricul reported, cannot be recommended on theoretical grounds. Paradoxically, â€œtorsadogenicâ€• effects of the other class III antidysrhythmics.[121] T by the beneficial effects of amiodarone on the dispersion of myocardial r channel-blocking activity (Chap. 23).

Hemodialysis is not expected to be beneficial in general, either because or because of large volumes of distribution. Multiple-dose activated charc hemoperfusion may be helpful if used immediately following overdose, bu been studied in humans.

Unclassified: Adenosine

Adenosine, a nucleoside found in all cells, is released from myocardial ce pathophysiologic conditions. It is administered as a rapid IV bolus to ter supraventricular tachycardia.[8] The effects of adenosine are mediated by protein-coupled adenosine (A_1) receptors that activate acetylcholine-sens the atrium, sinus nodes, and AV nodes. The resultant hyperpolarization re firing. Adenosine also reduces the Ca^{2+} currents, and its antidysrhythmic effect in increasing AV nodal refractoriness and from inhibiting delayed by sympathetic stimulation.[79]

Adverse effects of adenosine administration are very common and includ dyspnea, chest tightness, flushing, hypotension, and atrial fibrillation. Al following intrapulmonary administration, it is not reported following intrav

probably chest tightness, is related to stimulation by adenosine of the pu Fortunately, most of the adverse effects of adenosine are transitory becau to inosine by both extracellular and intracellular deaminases. The clinical dipyridamole, an adenosine uptake inhibitor, and by denervation hyperse recipients. Methylxanthines may produce adenosine receptor blockade. In larger-than-usual doses of adenosine are required to produce an antidysr adenosine is not reported. Treatment is supportive because of the rapid e

Summary

There are many antidysrhythmics presently in clinical use. In the overdos B, and class C drugs are associated with sodium channel blockade, which dysrhythmias and morbidity if not treated judiciously. The class IC drugs than the other class I drugs, although even the class IB drugs may be le

The class III antidysrhythmics in overdose can cause malignant dysrhyth de pointes. Amiodarone has may noncardiac effects, particularly pneumon limit its therapeutic usefulness. The clinical effects following overdose are class III drugs, but will likely manifest as an exaggeration of the therap It is only by understanding the pharmacokinetics and toxicokinetics of the management can be accomplished.

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Chapter 62
Cardioactive Steroids

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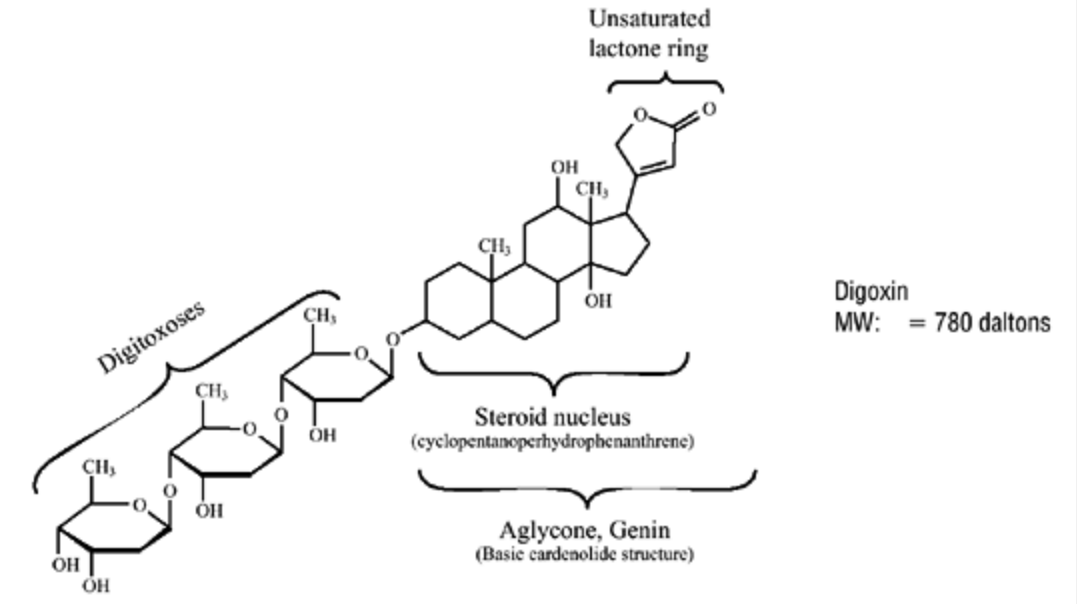

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A 92-year-old woman was brought to the hospital by her grandson. The grandson stated that she had lost her appetite for several days, refused her medications for 2 days, and had begun to vomit on the day of admission. The woman complained of being weak and having no appetite because of her constant nausea. Her past medical history was significant for congestive heart failure and hypertension, for which she was chronically treated with digoxin, furosemide, and enteric-coated aspirin. Her grandson reported that 5 days prior to admission, she had initiated a course of clarithromycin for sinusitis.

On presentation to the emergency department (ED), the patient was not in acute distress, and was alert and oriented to place and person but not to time. Her vital signs were: blood pressure, 140/95 mm Hg; pulse, 50 beats/min and regular; respiratory rate, 16 breaths/min; and rectal temperature, 98.8Â°F (37.1Â°C). The woman weighed 121 lbs (55 kg). Her neck was supple with no jugular venous distension or carotid bruits appreciated. Auscultation of the lungs revealed bibasilar crackles. Cardiac auscultation revealed a normal S_1, S_2, and an S_3 gallop, with no audible murmurs. Abdominal examination revealed a soft abdomen with increased bowel sounds and without masses or bruit. Examination of the patient's lower extremities revealed 1+ pitting edema without clubbing or cyanosis, and all pulses were 2+. Neurologic examination was nonfocal.

The patient was attached to a cardiac monitor with continuous pulse oximetry. An IV line was inserted, and blood samples were obtained for complete blood count (CBC); electrolytes, including calcium and magnesium; blood urea nitrogen (BUN); creatinine; glucose; liver enzymes; lipase; digoxin; and salicylate levels. The electrocardiogram (ECG) revealed high-degree heart block with a ventricular rate of 30â€“50 beats/min (Fig. 62-1), which then converted spontaneously to atrial flutter with variable block and a

ventricular response rate of 30â€“40 beats/min (Fig. 62-2). Transcutaneous pacer pads were placed on the patient in standby mode, while 5 vials of digoxin-specific Fab were requested. Stat laboratory results revealed serum sodium, 142 mEq/L; chloride, 114 mEq/L; potassium, 3.6 mEq/L; bicarbonate, 24 mEq/L; BUN, 12 mg/dL; creatinine, 1.4 mg/dL; glucose, 98 mg/dL; calcium, 9.8 mg/dL; magnesium, 2.0 mEq/L. Liver enzymes, lipase, and CBC were all normal. A serum digoxin concentration was pending.

Fifteen minutes after the examination was completed, the patient vomited. Although her heart rate decreased to 30 beats/min, her blood pressure remained at 130/80 mm Hg. Atropine 1 mg IV was

administered for the bradycardia but did not increase heart rate; subsequently, 5 vials of digoxin-specific Fab IV were administered over 15 minutes. Within 20 minutes of the infusion, her heart rate had increased to 86 beats/min. The initial serum digoxin concentration was 3.8 ng/mL (therapeutic range: 0.5â€“2.0 ng/mL).

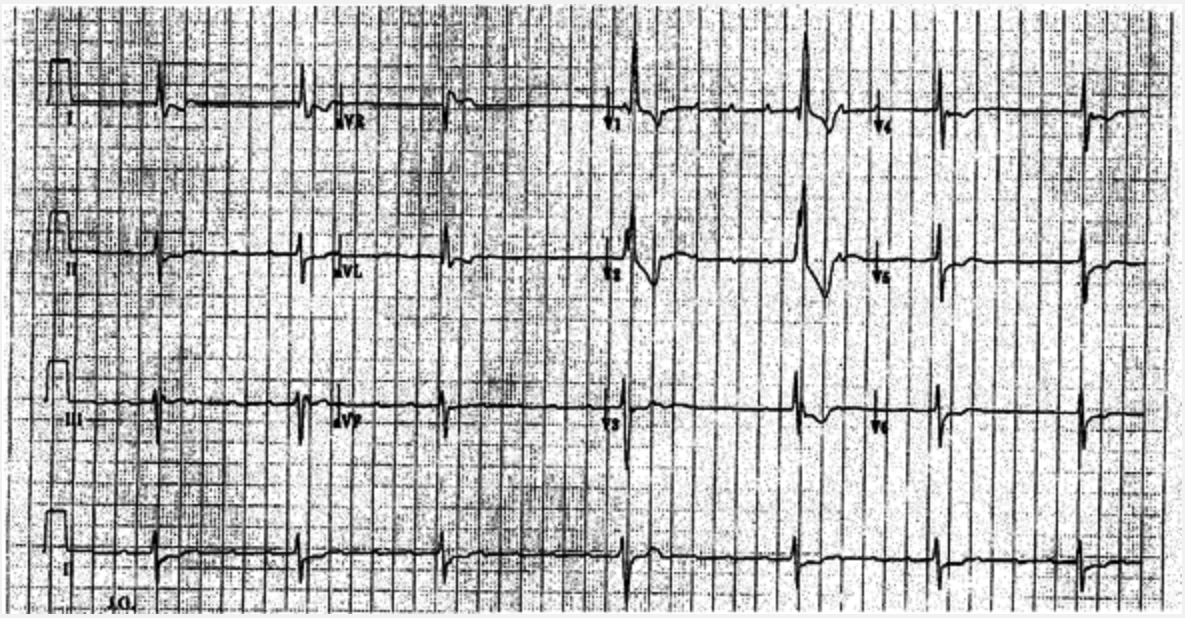

Figure 62-1. Electrocardiograph of a 92-year-old woman

demonstrating a high-degree heart block with a ventricular rate of 30â€“50 beats/min.

History and Epidemiology

Although there is evidence in the *Ebers Papyrus* (Papyrus Smith) that the Egyptians used plants containing cardioactive steroids at least 3000 years ago, it was not until 1785, when William Withering wrote the first organized account about the effects of the foxglove plant, that the use of cardioactive steroids was more widely accepted into the Western apothecary. The discussion and case reports of the 163 patients for whom Withering prescribed foxglove and his correspondence with other physicians on the subject, comprise the first work related to the medical use of cardioactive steroids. Foxglove was initially used as a diuretic and for the treatment of â€œdropsyâ€• (edema), and Withering eloquently described its â€œpower over the motion of the heart, to a degree yet unobserved in any other medicine.â€• [122]

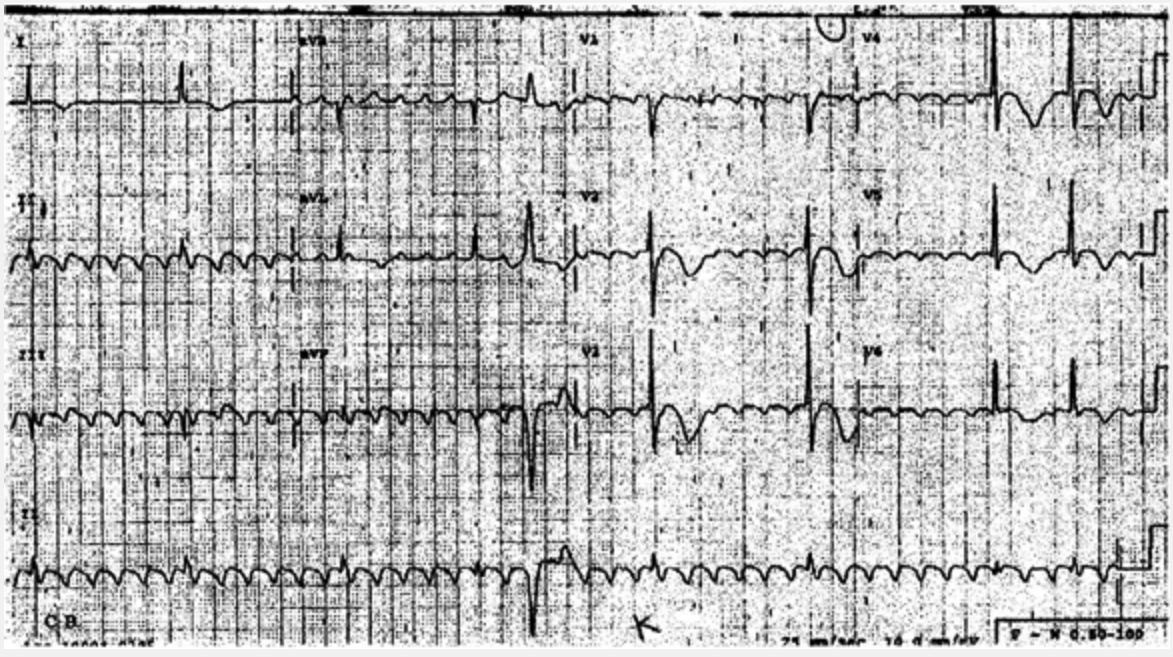

Figure 62-2. Electrocardiograph of the patient in Figure 62-1 after subsequently converted to atrial flutter with variable block and a ventricular rate of 30â€“40 beats/min.

Subsequent to these reports, cardioactive steroids became the mainstay of treatment for congestive heart failure, and to control the ventricular response rate in atrial tachydysrhythmias. Because of their narrow therapeutic index and widespread use both acute toxicity and chronic toxicity remain important problems.[82] According to the American Association of Poison Control Centers data, between the years 1999 and 2003 there were approximately 10,800 exposures to cardioactive steroid-containing plants with no attributable deaths, and 13,900 exposures to cardioactive steroid containing pharmaceuticals resulting in 73 deaths (Chap. 130).

Toxicity is typically encountered in the very young or the very old. In children, most acute overdoses are unintentional, resulting from dosing errors, often a decimal point error resulting in 10 times the appropriate dose. Adult patients more often have acute

exposures related to intentional ingestions. Older adults are at particular risk for toxicity, either from interactions of the cardioactive steroids with their chronic regimen of other medications, or indirectly, as a consequence of an alteration in the absorption or elimination kinetics of their therapeutic cardioactive steroid. Drugâ€“drug interactions may change cardioactive steroid clearance in the liver or kidney, may alter protein binding, or may result in increased bioavailability.

The most commonly prescribed cardioactive steroid in the United States is digoxin; other, internationally available but much less commonly used preparations are digitoxin, ouabain, lanatoside C, deslanoside, and gitalin. Cardioactive steroid toxicity may also result

from exposure to certain plants or animals. Documented plant sources of cardioactive steroids include oleander (*Nerium oleander*); yellow oleander (*Thevetia peruviana*), which has been implicated in the suicidal deaths of thousands of patients in Southeast Asia;[24] foxglove (*Digitalis* spp); lily of the valley (*Convallaria majalis*); dogbane (*Apocynum cannabinum*); and red squill (*Urginea maritima*). Cardioactive steroid poisoning may result from plant branches (oleander); teas containing seeds of these plants; and water and herbal products contaminated with plant cardioactive steroids (Chap. 43).[15,18,50,77,88,95,114] Toxicity also results from ingestion, instead of the intended topical application, of a purported aphrodisiac derived from the dried secretion of the *Bufo marinus* toad, which contains a bufadienolide-class cardioactive steroid.[9,11,12] Although there are no reported human exposures, fireflies of the *Photinus* species (*P. ignitus*, *P. marginellus*, and *P. pyralis)* contain a cardioactive steroid designated lucibufagin that is similar in structure to the bufadienolides.[29,63]

Chemistry

Cardioactive steroids all contain an aglycone or â€œgeninâ€• nucleus structure with a steroid core, and an unsaturated lactone ring attached at C-17. Cardiac glycosides contain additional sugar groups attached to C-3 (see illustration at beginning of chapter). Cardenolides are plant-derived aglycones with a 5-member unsaturated lactone ring. The bufadienolide and lucibufagin groups of cardioactive steroid molecules are mainly animal derived (with such notable exceptions as scillaren from red squill) and contain a 6-member unsaturated lactone ring. When the aglycone digoxigenin is linked to 1 or more hydrophilic sugar (digitoxoses) residues at C-3, it forms digoxin, a cardiac glycoside. The sugar residues confer increased water solubility and enhance the ability of the molecule to enter cells. Digitoxin's aglycone differs from digoxin's by the lack of a hydroxyl group on C-12, and ouabain differs from digoxin by both the absence of a hydroxyl group on C-12 and the addition of hydroxyl

groups on C-1, -5, -10, and -11. The cardioactive components in toad venom are genins, and lack sugar moieties.

Pharmacokinetics

The correlation between clinical effects and serum concentrations is based on steady-state concentrations, which are dependent on many absorption, distribution, and elimination factors (Table 62-1). Although not proven with other cardioactive steroids, they likely follow the distribution pattern of digoxin or digitalis in that obtaining a serum concentration before 6 hours after an ingestion (the time at which the tissue concentration has peaked) gives a misleadingly high serum concentration, resulting from its biphasic distribution. After therapeutic dosing, the intravascular distribution and elimination of digoxin from the plasma are best described using a two-compartment model that is achieved over approximately 36â€“48 hours in patients with normal renal function. The distribution or Î± phase represents the rapid rise of drug concentration intravascularly, which is dependent on whether the method of administration is intravenous or oral. An exponential decline occurs as the drug is rapidly distributed from the blood to the peripheral tissues with a 30-minute distribution half-life. During the distribution phase, most of the intravascular cardioactive steroid leaves the blood and is found in the tissues, resulting in a large volume of distribution (Vd) (eg, digoxin's Vd is 5.0 L/kg with therapeutic use). The Î² or elimination phase with a half-life of approximately 36 hours represents the drug's total-body clearance, which for digoxin is achieved primarily by the kidneys (70% in a person with normal renal function).[16,44] After a massive acute digoxin overdose, the half-life may be shortened to as little as 13â€“15 hours because of elevated serum concentrations, resulting in greater renal clearance prior to distribution to the tissues.[49,109] Even with therapeutic administration of cardioactive steroids, adjustments to the dosing regimen must be made for physiologic changes associated with age, hypothyroidism, hepatic disease, and renal diseases if the physiologic changes are associated with a

decreased creatinine clearance, alkalosis, chronic hypoxemia, myocardial disease, and cor pulmonale, and for electrolyte abnormalities, including hypomagnesemia, hypercalcemia, hypernatremia, and, commonly, hypokalemia, to avoid toxicity. Hypokalemia resulting from a variety of mechanisms, such as the use of loop diuretics, poor dietary intake, diarrhea, and the administration of potassium-binding resins, enhances the effects of cardioactive steroids on the myocardium and is associated with dysrhythmias at lower serum cardioactive steroid concentrations. Chronic hypokalemia reduces the number

of Na^+-K^+-adenosine triphosphatase (ATPase) units in skeletal muscle, thereby potentially decreasing the volume of drug distribution.[2,61]

TABLE 62-1. Pharmacology of Selected Cardioactive Steroids

Pharmacology	Digoxin	Digitoxin
Onset of Action		
Oral	1.5â€“6 h	3â€“6 h
IV	5â€“30 min	30 minâ€“2 h
Maximal effect		
Oral	4â€“6 h	6â€“12 h
IV	1.5â€“3 h	4â€–8 h

Intestinal absorption	40â€“90% (mean 75%)	>95%
Plasma protein binding	25%	97%
Volume of distribution	6â€“7 L/kg (adults) 16 L/kg (infants) 10 L/kg (neonates) 4â€“5 L/kg (adults with renal failure)	0.6 L/kg (adults)
Elimination half-life	1.6 days	6â€“7 days
Route of elimination	Renal (60â€“80%), with limited hepatic metabolism	Hepatic metabolism (80%)
Enterohepatic circulation	7%	26%

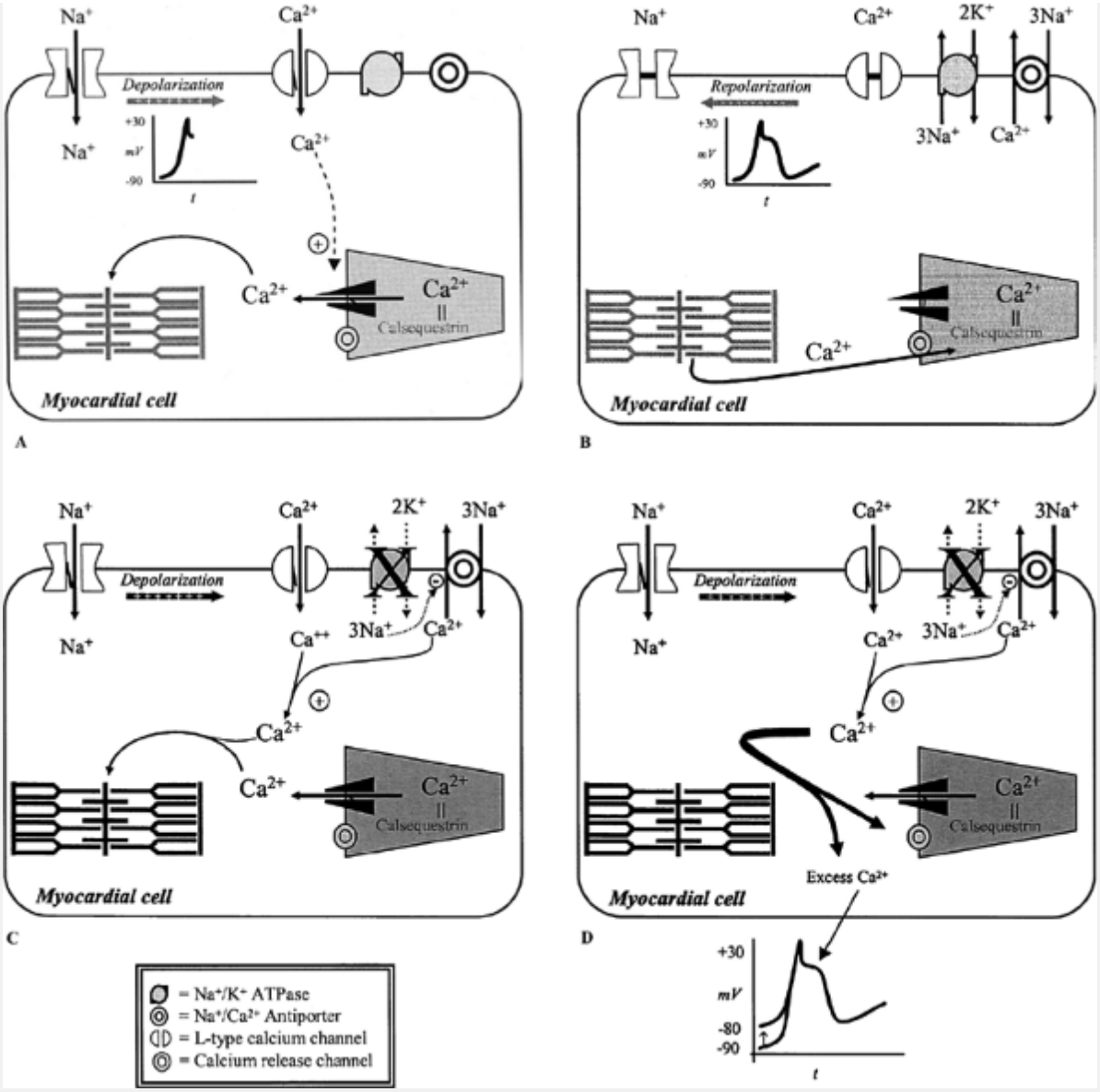

Figure 62-3. A. Normal depolarization. Depolarization occurs following the opening of fast Na^+ channels; the rise in intracellular potential opens voltage-dependent Ca^{2+} channels; and the influx of Ca^{2+} induces the massive release of Ca^{2+} from the sarcoplasmic reticulum, producing contraction. B. Normal repolarization. Repolarization begins with active expulsion of Na^+ ions in exchange for K^+ using an ATPase. This electrogenic (3 Na^+ for 2 K^+) pump creates an Na^+ gradient that is used to

expel Ca^{2+} via an antiporter. The sarcoplasmic reticulum resequesters its Ca^{2+} load via a separate ATPase. C. Pharmacologic cardioactive steroids. Digitalis inhibition of the Na^{+}-K^{+}-ATPase raises the intracellular Na^{+} content, preventing the antiporter from expelling Ca^{2+} in exchange for Na^{+}. The net result is an elevated intracellular Ca^{2+}, resulting in enhanced inotropy. D. Toxic cardioactive steroids. Excessive elevation of the intracellular Ca^{2+} elevates the resting potential, producing myocardial sensitization, and predisposes to dysrhythmias. The addition of exogenous Ca^{2+} may overwhelm the capacity of the sarcoplasmic reticulum to sequester this ion, resulting in systolic arrest. X = cardioactive steroid.

Drug interactions between digoxin and quinidine, verapamil, diltiazem, carvedilol, amiodarone, and spironolactone are common.[19,22,43,66,91] These interactions occur because of a reduction of the protein binding of the cardioactive steroids, increasing their availability to the tissues; a reduction in excretion as a consequence of a decrease in renal perfusion; or as a result of interference with their secretion by the kidneys and intestines because of inactivation of P-glycoproteins. In approximately 10â€“15% of those patients receiving digoxin, a significant amount of digoxin is inactivated in the gastrointestinal tract by enteric bacterium, primarily *Eubacterium lentum.* Inhibition of this inactivation by the alteration of the gastrointestinal flora by many antibiotics, particularly the macrolide antibiotics, may result in increased bioavailability.[71] Indeed, the use of certain antibiotics may produce as much as a 2-fold increase in serum cardioactive steroid concentration.[90]

Mechanisms of Action and Pathophysiology

Electrophysiologic Effects on Inotropy

The cardioactive steroids increase the force of contraction of the heart (positive inotropic effect) by increasing cytosolic Ca^{2+} during systole. Both Na^{+} and Ca^{2+} ions enter and exit cardiac muscle cells during each depolarization and contraction. Sodium entry heralds the start of the action potential (phase 0) and carries the inward, depolarizing positive charge. Calcium subsequently enters the cardiac myocyte through L-type calcium channels during the plateau phase of the action potential, and this Ca^{2+} triggers the release of more Ca^{2+} into the cytosol from the sarcoplasmic reticulum. During repolarization and relaxation (diastole), Ca^{2+} is both pumped back into the sarcoplasmic reticulum by a local Ca^{2+}-ATPase and is pumped extracellularly by an Na^{+}-Ca^{2+} antiporter and a sarcolemmal Ca^{2+}-ATPase (Fig. 62-3; Chap. 23).[76]

Cardioactive steroids inhibit active transport of Na^{+} and K^{+} across the cell membrane during repolarization by binding to a specific site on the extracytoplasmic face of the a subunit of the membrane Na^{+}-K^{+}-ATPase. This inhibits the cellular Na^{+} pump activity, which decreases Na^{+} extrusion and increases Na^{+} in the cytosol, thereby decreasing the transmembrane Na^{+} gradient. Because the Na^{+}-Ca^{2+} antiporter derives its power not from adenosine triphosphate (ATP) but rather from the Na^{+} gradient generated by the Na^{+}-K^{+} transport mechanism,[28] the dysfunction of the Na^{+}-K^{+}-ATPase pump reduces Ca^{2+} extrusion from the cell. The additional cytoplasmic Ca^{2+} enhances the Ca^{2+}-induced Ca^{2+} release from the sarcoplasmic reticulum during systole and by this mechanism increases the force of contraction of the cardiac muscle.

Effects on Cardiac Conduction

At therapeutic serum concentrations, cardioactive steroids also increase automaticity and shorten the repolarization intervals of the atria and ventricles (Table 62-2). There is a concurrent decrease in the rate of depolarization and conduction through the sinoatrial (SA)

and (atrioventricular) AV nodes, respectively. This is mediated both indirectly via an enhancement in vagally mediated parasympathetic tone, and directly by depression of this tissue. These changes in nodal conduction are reflected on the ECG by a decrease in ventricular response rate to suprajunctional rhythms and by PR interval prolongation (part of â€œdigitalis effectâ€•). The effects of cardioactive steroids on ventricular repolarization are related to the elevated intracellular resting potential caused by the enhanced availability of Ca^{2+}, and manifest on the ECG as QTc interval shortening and ST segment and T-wave forces opposite in direction to the major QRS forces. The last effect results in the characteristic scooping of the ST segments (the second part of which is referred to as *digitalis effect*) (Fig 62-4). Excessive increases in intracellular Ca^{2+}, caused by excessive cardioactive steroid effects, result in delayed afterdepolarizations. These are fluxes in membrane potential caused by spontaneous Ca^{2+}-induced Ca^{2+} release, which is caused by the excess Ca^{2+}, and appear on the ECG as U waves. Occasionally, these may initiate a cellular depolarization that manifests as a premature ventricular contraction (Chap. 23).[27,58]

TABLE 62-2. Electrophysiologic Effects of Cardioactive Steroids on the Myocardium

	Atria and Ventricles	AV Node	ECG
Excitability	â†‘	â€”	Extrasystoles, tachydysrhythmias
Automaticity	â†‘	â€”	Extrasystoles, tachydysrhythmias
Conduction velocity	â†“	â†“	â†‘ PR interval, AV block
Refractoriness	â†“	â†‘	â†‘ PR interval, AV block, decreased QTc interval

Hypokalemia inhibits Na^+-K^+-ATPase activity and contributes to the pump inhibition induced by cardioactive steroids, enhances myocardial automaticity, and, as a consequence, increases myocardial susceptibility to cardioactive steroid-related dysrhythmias. This may be partly a result of decreased competitive inhibition between the cardioactive steroid and potassium at the Na^+-K^+-ATPase exchanger.[93] Severe hypokalemia (<2.5 mEq/L) reduces the rate of sodium pump function, slowing the pump and exacerbating concomitant sodium pump inhibition, because of cardioactive steroids.[58]

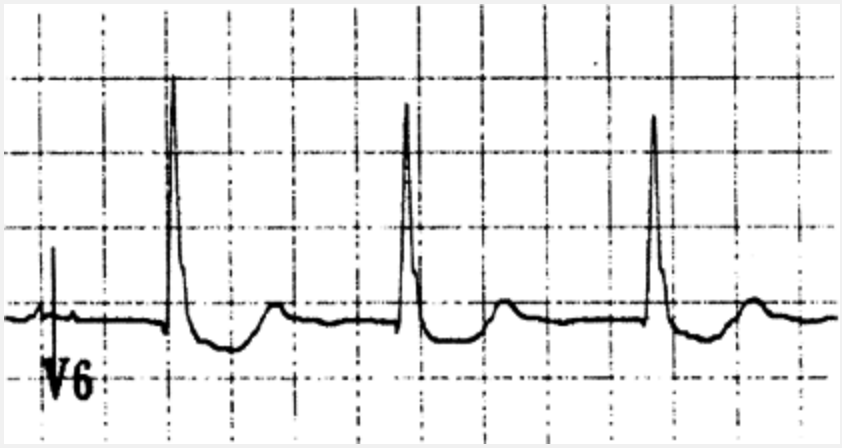

Figure 62-4. Digitalis effect noted in the lateral precordial lead, V6. Note the prolonged PR interval and the repolarization abnormality (scooping of the ST segment).

Effects of Cardioactive Steroids on the Autonomic Nervous System

Cardioactive steroids affect the parasympathetic system by increasing the release of acetylcholine from vagal fibers,[73,112] possibly through augmentation of intracellular calcium. Cardioactive steroids affect the sympathetic system by increasing efferent sympathetic discharge,[83,107] which, in turn, may exacerbate dysrhythmias.

Clinical Manifestations

Both adults and children with acute cardioactive steroid poisoning present in a similar manner, as do adults and children with chronic poisoning. However, the clinical manifestations in both adults and children vary based on the chronicity of the exposure.

Noncardiac Manifestations

Acute Toxicity

An asymptomatic period of several minutes to several hours may follow a single, orally administered, toxic dose of cardioactive steroid. The first symptom is typically nausea, vomiting, or abdominal pain. Central nervous system effects of acute toxicity can include lethargy, confusion, and weakness that are not caused by hemodynamic changes.[15]

Chronic Toxicity

Chronic toxicity is often difficult to diagnose as a result of its insidious development and protean manifestations. Symptoms may include those that occur with acute poisonings; however, they are often less obvious. Gastrointestinal symptoms include anorexia, nausea, vomiting, abdominal pain, and weight loss. Neuropsychiatric disorders include delirium, confusion, disorientation, drowsiness, headache, hallucinations, or rarely, seizures.[15,36,37] Visual disturbances include transient amblyopia, photophobia, blurring, scotomata, photopsia, decreased visual activity, and aberrations of color vision (chromatopsia), such as yellow halos (xanthopsia) around lights.[67,68]

Electrolyte Abnormalities

Elevated serum potassium concentrations frequently occur in patients with acute cardioactive steroid poisoning.[58,61] Hyperkalemia has important prognostic implications, as the serum potassium concentration is a better predictor of lethality than either the initial ECG changes or the serum cardioactive steroid concentration.[4,5] In a study of 91 acutely digitoxin-poisoned patients, conducted before digoxin-specific Fab was available, approximately 50% of the patients with serum potassium concentrations of 5.0â€“5.5 mEq/L

died. Although a serum potassium concentration lower than 5.0 mEq/L was associated with no deaths, all of the 10 patients with serum potassium concentration above 5.5 mEq/L died.[4] This hyperkalemia causes further hyperpolarization of myocardial conduction tissue, in particular, increasing AV nodal block, thereby exacerbating cardioactive steroid-induced bradydysrhythmias and conduction delays.[58] However, correction of the hyperkalemia alone does not increase patient survival,[4] as it is a marker of, not the cause of, the morbidity and mortality associated with cardioactive steroid poisoning. Elevation of the serum potassium concentration after administration of cardioactive steroids is a result of cardioactive steroid inhibition of the Na^+-K^+-ATPase pump, which results in the inhibition of potassium uptake in exchange for Na^+ by skeletal muscle (the largest potassium reservoir). The interrelationships between intracellular and extracellular potassium and cardioactive steroid therapy are complex and incompletely understood.

Cardiac Manifestations

The alterations in cardiac rate and rhythm occurring with cardioactive steroid poisoning can produce almost every known type of dysrhythmia with the exception of the rapidly conducted supraventricular tachydysrhythmias. In 10â€“15% of cases, the appearance of an ectopic ventricular rhythm is the first sign of toxicity, and this is the most frequent rhythm disturbance noted.[92] Although no dysrhythmia is pathognomic of cardioactive steroid toxicity, toxicity should be suspected when there is evidence of increased automaticity in combination with depressed conduction through the SA and AV nodes.[58] Bidirectional ventricular tachycardia is nearly diagnostic, although it can also occur with poisoning by aconitine and a few other uncommon xenobiotics[103] (Fig. 5-13). These dysrhythmias result from the complex electrophysiologic influences on both the myocardium and conduction system of the heart resulting from direct, vagotonic, and other autonomic actions

of the cardioactive steroids. The effects of digoxin vary with the dose, and differ, depending on the type of cardiac tissue involved. The atrial and ventricular myocardial tissues exhibit increased automaticity and excitability, resulting in extrasystoles and tachydysrhythmias. Conduction velocity is reduced in both the atrial conducting system and nodal tissue, resulting in an increased PR interval and AV nodal block. Indeed, AV junctional blocks of varying degrees, associated with increased ventricular automaticity, are the most common manifestations, occurring in 30â€“40%, of patients with cardioactive steroid toxicity.[74] Atrioventricular dissociation can result from suppression of the dominant pacemaker with escape of a secondary pacemaker, or from inappropriate acceleration of a ventricular pacemaker. Hypotension, shock, and cardiovascular collapse can ensue. Table 62-3 summarizes these phenomena.

Acute Toxicity

The initial increased vagal tone at the SA and AV nodes results in an atropine-responsive bradydysrhythmia. There are a multitude of cardiac dysrhythmias associated with cardioactive steroid toxicity unified by a sensitized myocardium and a depressed AV node (Table 62-3).

TABLE 62-3. Cardiac Dysrhythmias Associated with Cardioactive Steroid Poisoning

Myocardial irritability
- Atrial flutter and atrial fibrillation with block
- Nonparoxysmal atrial tachydysrhythmias with block
- Premature ventricular contractions
- Nonsustained ventricular tachycardia
- Delayed afterdepolarizations
- Bidirectional ventricular tachycardia
- Ventricular bigeminy
- Ventricular fibrillation

Conduction system dysfunction
- AV dissociation
- Exit blocks
- High-degree AV block
- His-Purkinje dysfunction
- Junctional tachycardia
- SA nodal arrest
- Sinus bradycardia

Chronic Toxicity

Bradydysrhythmias that appear later in acute poisonings, and those that occur in patients with chronic cardioactive steroid toxicity, occur by direct actions of the drug on the heart and often are minimally responsive to, or cannot be corrected by, atropine administration. Ventricular tachydysrhythmias are more common in patients with chronic or late acute poisoning than in patients with early acute poisoning.

Diagnostic Testing

Properly obtained and interpreted serum digoxin concentrations significantly aid in the management of patients with suspected

digoxin toxicity, as well as in the management of patients poisoned by several other cardioactive steroids. Although most institutions report a therapeutic range for serum digoxin concentration from 0.5â€“2.0 ng/mL (SI units: 1â€“2.6 nmol/mL), current research suggests lowering the upper limit to 1.0 ng/mL to maintain benefit while lowering the risk of toxicity.[96,105] Regardless of the therapeutic serum concentration range used, it must be interpreted in relation to the clinical condition of the patient; the relationship of the time of obtaining the blood sample to that of the last dose; and to other metabolic abnormalities and medications, including hypokalemia, hypomagnesemia, hypercalcemia, hypernatremia, alkalosis, hypothyroidism, hypoxemia, and catecholamines, and the use of calcium channel blockers, quinidine, amiodarone, or diuretics.

Although cardioactive steroid poisoning is multifactorial, resulting from the interactions of the many diverse factors previously mentioned, there is a significant correlation between the clinical condition and the serum concentration. In general, patients with pharmaceutical cardioactive steroid toxicity have mean serum concentrations above 2 ng/mL, measured at least 6 hours postingestion for digoxin, and above 40 ng/mL for digitoxin.[57] The significance of these concentrations depends on when the value is obtained in relation to an acute ingestion and the distribution phase of the drug (as discussed above). A value of 15 ng/mL of digoxin is, therefore, more ominous 6 hours after an ingestion than 1 hour after an ingestion. Because there are multiple determinants of digoxin toxicity, there is an overlap in serum digoxin concentrations between toxic and nontoxic patients, and it may be inaccurate to use the therapeutic range of digoxin of 0.5â€“2.0 ng/mL as the sole indicator of toxicity.[99]

In most hospitals, â€œdigoxin levelsâ€• are the only estimation available to physicians in the acute setting when evaluating a patient for presumed cardioactive steroid poisoning. The polyclonal assays typically used in most institutions frequently, but unpredictably, cross-react with other plant- or animal-derived cardioactive steroids.

Although only digoxin is accurately detected by monoclonal digoxin immunoassay, an elevated serum digoxin concentration in the correct clinical setting may qualitatively assist in making a presumptive diagnosis of nondigoxin cardioactive steroid poisoning (Chaps. 43 and 114).[13,86] For example â€œdigoxinâ€• concentrations are recorded from serum spiked with oleandrin and oleandrigenin from *Nerium oleander*, from patients after exposure to *Thevetia peruviana* (yellow oleander) or toad secreted bufadienolides, using various techniques including high-performance liquid chromatography (HPLC) and monoclonal and polyclonal antibody analysis.[9,25,52] With the use of more specific analytic technology, patients with cardioactive steroid poisoning from plant- or animal-derived cardioactive steroids may have low or nonexistent digoxin concentration (Chaps. 43 and 114).

Serum concentrations of digoxin are measured in one of two ways: free digoxin and total digoxin. The most common method of quantifying total digoxin in the serum is by fluorescence polarization immunoassay (FPIA). Under normal circumstances, measuring total digoxin in the serum is sufficient, as serum concentrations are predictive of cardiac concentrations.[23] However, after the use of digoxin-specific Fab (which remains almost entirely within the intravascular space [Vd of 0.40 L/kg]), there is a large elevation in total cardioactive steroid concentrations because the cardioactive steroid is drawn from the tissues and complexes with the antibody fragment, thus trapping the cardioactive steroid in the intravascular space. When this bulk movement is reversed by binding with Fab fragments, a tremendous increase, often approaching an order of magnitude, in total serum digoxin concentrations, occurs. In this situation, methods that detect only unbound digoxin, including treatment with Fab denaturing agents, ultrafiltration, and equilibrium dialysis, allow the quantification of free digoxin in the serum.[34] Paradoxically, excess digoxin antibody can cause a false elevation in the apparent â€œdigoxin concentrationâ€• (Chap. 7).

Endogenous Digoxinlike Immunoreactive Substance

Some patients who are not receiving a cardioactive steroid may have a positive digoxin assay as a result of an endogenous substance that is structurally and functionally similar to the prescribed cardioactive steroids.[43] This finding is described in patients with increased inotropic need or reduced renal clearance, including neonates;[115] and patients with renal insufficiency,[10,38,51] liver disease,[79] subarachnoid hemorrhage,[121] congestive heart failure,[40,100] insulin-dependent diabetes,[33] stress,[37,116] acromegaly,[24] hypothermia;[115] after strenuous exercise;[116] and in pregnancy.[31,39,48] An endogenous Na^+-K^+-ATPase inhibiting dihydropyrone-substituted bufenolide cardioactive steroid has been isolated from human placenta. It differs from the toad bufadienolides solely by a single double-bond pyrone ring. Because bufenolides are not normally found in either healthy humans or edible plants, a synthetic pathway to produce dihydropyrone-substituted steroids in humans may be responsible for this endogenous digoxinlike immunoreactive substance (EDLIS). Further research is necessary to confirm this pathway.[48] The use of ultrafiltration techniques, while altering incubation time and temperature at which the digoxin assay is performed, can eliminate the contribution of EDLIS.[32] The clinician suspecting this problem should consult the clinical laboratory. Clinical observations indicate that the serum digoxin concentration contributed by endogenous digoxinlike immunoreactive substances is usually less than 2 ng/mL. Other endogenous substances, such as bilirubin,[79] and exogenous substances, such as spironolactone,[101] can cross-react with the digoxin assay and cause a false-positive result.

Therapy

Management Overview

Initial treatment of a patient with acute cardioactive steroid poisoning includes providing general supportive care, discontinuing cardioactive steroid therapy, preventing further exposure, preventing further gastrointestinal (GI) absorption, monitoring for

dysrhythmias, determining electrolyte and digoxin concentrations, administering digoxin-specific antibody fragments, and treating specific complications such as dysrhythmias and electrolyte abnormalities.

Gastrointestinal Decontamination

Initial treatment should be directed toward prevention of further GI absorption. Emesis or lavage may be considered only rarely, because efficacy is limited, secondary to rapid absorption from the gut and to the emetic effects of the drug itself. Patients with chronic ingestion do not usually benefit from these GI decontamination techniques, because of the limited availability of drug in the gastrointestinal tract for removal. Because many cardioactive steroids, such as digitoxin and digoxin, are recirculated enterohepatically and enteroenterically, both late and repeated activated charcoal administration (1 g/kg of body weight every 2â€“4 hours for up to 4 doses) may be beneficial in reducing serum concentrations.[16,65,69,84,119] Steroid-binding resins such as cholestyramine and colestipol,[47,89] like activated charcoal,[20] can prevent reabsorption of cardioactive steroids from the GI tract and reduce the serum half-life by interrupting both enteroenteric and enterohepatic circulation, and may be used in cases where digoxin-specific Fab is not immediately available, or when renal function is inadequate.[20,47]

Advanced Management

Digoxin-Specific Antibody Fragments

The standard of care for patients with life-threatening cardioactive steroid toxicity is the use of digoxin-specific antibody fragments.[1,32,34,85,88,95,104,110,123] Purified digoxin-specific Fab causes a sharp decrease in free serum digoxin concentrations, a concomitant, but clinically unimportant, massive increase in total serum digoxin, an increase in renal clearance of cardioactive steroid, and a decrease in the serum potassium level.[1] In addition, the administration of digoxin-specific Fab is pharmacoeconomically sound.[21] Although the drug itself is expensive, its expense is far outweighed by obviating the need, risk, and expense of long-term ICU stays, and of repetitive evaluation of potassium and digoxin levels. Table 62-4 lists the indications for administering digoxin-specific Fab. Extensive discussion is found in Antidotes in Depth: Digoxin-Specific Antibody Fragments (Fab).

Additional Cardiac Therapies

In the event that digoxin-specific fragments are not immediately available, the secondary drugs for the management of ventricular irritability include phenytoin and lidocaine. These drugs depress the enhanced ventricular automaticity without significantly slowing, and perhaps enhancing, AV nodal conduction.[94] In fact, phenytoin may reverse digitalis-induced prolongation of AV nodal conduction while suppressing digitalis-induced ectopic tachydysrhythmia, without diminishing myocardial contractile forces.[46] In addition, phenytoin can terminate supraventricular dysrhythmias induced by digitalis more effectively than lidocaine.[94] Underlying atrial fibrillation and flutter typically do not convert to a normal sinus rhythm with administration of phenytoin or lidocaine. When used, phenytoin should be infused slowly intravenously (~50 mg/min) or in boluses of 100 mg repeated every 5 minutes until control of the dysrhythmias is achieved or a maximum of 1000 mg has been given in an adult, or 15â€“20 mg/kg in a child.[8,78] Fosphenytoin has not been evaluated

in this setting. Maintenance oral doses of phenytoin 300â€“400 mg/d in an adult, and 6â€“10 mg/kg/d in a child, should be continued until digoxin toxicity is resolved. Lidocaine is given as a 1.0â€–1.5-mg/kg IV bolus followed by continuous infusion at 1â€–4 mg/min in an adult, or as a 1.0â€–1.5-mg/kg IV bolus followed by 30â€–50 Âµg/kg/min in a child, as required to control the rhythm disturbance. (Chap. 61).

TABLE 62-4. Indications for Administration of Digoxin-Specific Antibody Fragments

Any potential digoxin-related life-threatening dysrhythmia
Potassium concentration >5.0 mEq/L in setting of acute digoxin poisoning
Chronic digoxin poisoning with dysrhythmias, significant gastrointestinal symptoms, or acute onset of significantly altered mental status, or renal insufficiency
Serum digoxin concentration (SDC) â‰¥15 ng/mL at any time, or â‰¥10 ng/mL 6 h postingestion
Ingestion of 10 mg in adult
Ingestion of 4 mg in a child
To aid in treatment of suspected cardioactive steroid poisoning without a confirmatory level
Poisoning by nondigoxin cardioactive steroid
Digoxin-specific Fab dosing (round up vial calculation)

$$\text{No. of vials} = \frac{\text{SDC (ng/mL)} \times \text{Pt Wt (kg)}}{100}$$

$$\text{No. of vials} = \frac{\text{Amount ingested (mg)}}{0.5\ \text{(mg/vial)}} = 80\%\ \text{bioavailability}$$

Empiric therapy for acute poisoning:
10â€–20 vials (adult or pediatric)
Empiric therapy for chronic poisoning:

Adultâ€”3â€“6 vials
Pediatricâ€”1â€“2 vials

Class IA antidysrhythmics are contraindicated in the setting of cardioactive steroid poisoning because they may induce or worsen AV nodal block and decrease His-Purkinje conduction at slow heart rates, and because of their Î±-adrenergic receptor blockade and vagal inhibition significant hypotension and tachycardia may occur. Class IA antidysrhythmics are also prodysrhythmogenic and their safety in the setting of cardioactive steroid poisoning is unstudied. Additionally, quinidine reduces renal clearance of digoxin and digitoxin.

In patients with symptomatic supraventricular bradydysrhythmias or high degrees of AV block, atropine 0.5 mg should be administered intravenously to an adult, or 0.02 mg/kg with a minimum of 0.1 mg to a child. Atropine should be titrated to block the vagotonic effects of the cardioactive steroid. The dose may be repeated at 5-minute intervals if necessary. Therapeutic success is unpredictable, because the depressant actions of cardioactive steroids are mediated only in part through the vagus nerve. The use of isoproterenol should be avoided in cardioactive steroid-induced conduction disturbances, as there may be an increased incidence of ventricular ectopic activity in the presence of toxic levels of cardioactive steroids.

Pacemakers and Cardioversion

External or transvenous pacemakers have limited indications in the management of cardioactive steroid poisoning since digoxin-specific Fab became available. In one retrospective study of 92

digitalis-poisoned patients, 51 patients were treated with cardiac pacing and/or digoxin-specific Fab, and the overall mortality rate was 13%.[111] Prevention of life-threatening dysrhythmias failed in 8% of

patients treated with immunotherapy and in 23% of patients treated with internal pacemakers. The main reasons for failure of digoxin-specific Fab was pacing-induced dysrhythmias and delayed or insufficient doses of digoxin-specific Fab. Iatrogenic complications of pacing occurred in 36% of patients. Thus, overdrive suppression with a temporary transvenous pacemaker should not be used to abolish ventricular tachydysrhythmias in the presence of cardioactive steroid poisoning.[5,111] Pacemakers have limited utility and substantial risks in patients with cardioactive steroid toxicity making the use of digoxin-specific Fab first-line therapy.[111]

Transthoracic electrical cardioversion for atrial tachydysrhythmias, in the setting of digoxin poisoning, is both clinically and experimentally associated with the development of potentially lethal ventricular dysrhythmias. The dysrhythmias are similar to digoxin toxic rhythms,[97] and related to the degree of toxicity, and the amount of administered current in cardioversion.[97] In cardioactive steroid-poisoned patients with unstable rhythms, such as hemodynamically unstable ventricular tachycardia and ventricular fibrillation, cardioversion and defibrillation, respectively, are indicated.

Electrolyte Therapy

Potassium

Hypokalemia and hyperkalemia can exacerbate cardioactive steroid cardiotoxicity. When hypokalemia is noted in conjunction with tachydysrhythmias or bradydysrhythmias, potassium replacement should be administered with serial monitoring of serum potassium, because iatrogenic hyperkalemia is detrimental. In this setting, digoxin-specific Fab administration generally should not be used until the hypokalemia is corrected because the reinstitution of Na^+-K^+-ATPase function may cause profound hypokalemia.

In the presence of acute cardioactive steroid toxicity, when potassium exceeds 5.0 mEq/L, digoxin-specific antibodies are

indicated. When marked hyperkalemia develops in conjunction with ECG evidence of hyperkalemia, and if digoxin-specific Fab is not available immediately, an attempt should be made to lower the serum potassium with IV insulin, dextrose, sodium bicarbonate, and oral administration of the ion-exchange resin sodium polystyrene sulfonate. Similar caution, as stated above, should be applied to the subsequent administration of digoxin-specific Fab because of concern for profound hypokalemia. Calcium chloride is beneficial in most hyperkalemic patients, but in the presence of cardioactive steroid, poisoning by calcium salts may be disastrous, as intracellular hypercalcemia is already present. Although a 2004 study was unable to show an adverse effect,[41] a number of experimental studies cite the additive or synergistic actions of calcium and cardioactive steroids on the heart, resulting in dysrhythmias,[35,81,102] cardiac dysfunction[59] (eg, hypercontractility, or the so-called stone heart, hypocontractility), and cardiac arrest.[70,102,117] Furthermore, 3 case reports[7,62] of deaths in cardioactive steroid-poisoned patients following calcium administration support the withholding of calcium administration in the setting of hyperkalemia. The purported mechanism is augmented intracellular cytoplasmic Ca^{2+}, which results from an increased transmembrane concentration gradient that further inhibits calcium extrusion through the Na^{+}-Ca^{2+} exchange and/or increased intracytoplasmic stores.[57] This additional cytoplasmic calcium may result in altered contraction of myofibril organelles,[59] less negative intracellular resting potential that allows delayed afterdepolarizations to reach firing threshold,[45,57,81] altered function of the sarcoplasmic reticulum,[59,93] or increased calcium interfering with myocardial mitochondrial function (see Chap. 23).[59] Although some investigators suspect that the rate of administration of the calcium may be a factor in the subsequent cardiac toxicity,[70,81] calcium administration should be avoided, as there are better, safer, alternative treatments available for cardioactive steroid-induced hyperkalemia (eg, digoxin-specific Fab, insulin and sodium bicarbonate).[7,35,62,81,102]

Magnesium

Hypomagnesemia may also occur in cardioactive steroid-poisoned patients, secondary to the contributory factors mentioned with hypokalemia, such as long-term diuretic use to treat congestive heart failure. Concomitant hypomagnesemia may result in refractory hypokalemia, despite potassium replacement.[120] The theoretical benefits of magnesium therapy include blockade of the transient inward calcium current, antagonism of calcium at intracellular binding sites, decreased cardioactive steroid-related ventricular irritability, and blockade of potassium egress from cardioactive steroid-poisoned cells.[3,30,53,87,98,108,120] Although hypomagnesemia increases myocardial digoxin uptake and decreases cellular Na^+-K^+-ATPase activity, there is conflicting evidence on whether magnesium â€œreactivatesâ€• the cardioactive steroid-bound Na^+-K^+-ATPase activity.[79,98,108]

The successful use of intravenous magnesium sulfate in the treatment of ventricular tachydysrhythmias, caused by digoxin toxicity, is reported, even in the presence of elevated serum magnesium levels.[60] The mechanism of efficacy of magnesium may be its ability to suppress delayed afterdepolarizations, prolong refractory period by decreasing calcium uptake and potassium efflux,[108] activate Na^+-K^+-ATPase as an essential metallo-coenzyme, or antagonize digoxin at the sarcolemma Na^+-K^+-ATPase pump. However, this treatment is only temporizing, until digoxin-specific Fab is available for definitive therapy, and is not advocated as first-line therapy. The precise dosing of magnesium sulfate in cardioactive steroid-poisoned patients is not established.[3,30,53,60,87,98,120] A common regimen uses 2 g of magnesium sulfate IV over 20 minutes in an adult (25â€“50 mg/kg/dose to a maximum of 2 g in a child). Following stabilization, an adult patient with severe hypomagnesemia may require a magnesium infusion of 1â€“2 g/h (25â€“50 mg/kg/h to a maximum of 2 g in a child), with serial monitoring of serum magnesium levels, telemetry, respiratory rate (observing for

bradypnea), deep-tendon reflexes (observing for hyporeflexia), and monitoring of blood pressure. Magnesium is contraindicated in the setting of bradycardia or atrioventricular block, preexisting hypermagnesemia, and renal insufficiency or failure.

Extracorporal Removal

Forced diuresis,[64] hemoperfusion,[75,118] and hemodialysis[118] are ineffective in enhancing the elimination of digoxin because of its large volume of distribution (4â€“10 L/kg), which makes it relatively inaccessible to these techniques. Because of its high affinity for tissue proteins, approximately 10 times less digoxin is found in the serum than is found at the tissue level, and of that amount, approximately 20â€“40% is protein-bound.[55]

Various investigations into new methods of extracorporal removal are under investigation. Plasmapheresis may have a role for removing retained Fab-digoxin complexes to prevent rebound toxicity after digoxin overdose treatment in anuric patients, but its usefulness has not been clearly defined.[14,85] Additionally, there is a suggestion that hemoperfusion through a Î²$_2$-microglobulin adsorptive column might be useful for treating acute digoxin toxicity.[53,113]

Summary

Digoxin and digitoxin are the most commonly prescribed members of the drugs classified as cardioactive steroids, which share common structural similarities and functions at the cellular level. Cardioactive steroids have a narrow therapeutic index. Signs and symptoms of cardioactive steroid toxicity range from subtle to profound. Both cardiac and noncardiac effects follow cardioactive steroid poisoning. Patients with acute toxicity often have a higher serum concentration of the drug and may present with profound nausea, vomiting, bradycardia, atrial and ventricular ectopy with block, or

hyperkalemia. Patients with chronic toxicity often have a lower serum concentration of cardioactive steroids and may present similarly, but more often the symptoms are more proteanâ€”loss of appetite, headache, weakness, nausea, alteration in mental statusâ€”all of which may be combined with similar ectopic rhythms as with acute toxicity. In addition to overt overdose, an elevation in the serum cardioactive steroid concentrations and an exacerbation of the clinical drug effect leading to toxicity may occur from drug interactions or from deterioriating metabolic processes such as with declining renal function, or from electrolyte abnormalities such as hypokalemia, and hypomagnesemia. A systematic approach toward treating patients using basic supportive and decontamination management techniques, supplemented by the early administration of digoxin-specific Fab immunotherapy can significantly reduce morbidity and mortality in these high-risk patients.

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Antidotes in Depth

Digoxin-Specific Antibody Fragments (Fab)

Mary Ann Howland

Digoxin-specific antibody fragments are indicated for the management of patients with toxicity related to digoxin, digitoxin, and all natural cardioactive steroids, such as oleander, squill, and toad venom. Digoxin-specific antibody fragments have an excellent record of efficacy and safety, and should be administered early in both established and suspected cardioactive steroid poisoning.

History

The production of antibody fragments to treat patients poisoned with digoxin followed the development of digoxin antibodies for measuring serum digoxin concentrations by radioimmunoassay (RIA).[11] The RIA technique permitted the correlation between serum digoxin concentration and clinical digoxin toxicity.

In 1967, Butler and Chen suggested that purified antidigoxin

antibodies with a high affinity and specificity should be developed to treat digoxin toxicity in humans.[11] The digoxin molecule alone, with a molecular weight of 780 daltons, was too small to be immunogenic. But digoxin could function as a hapten when joined to an immunogenic protein carrier such as albumin. These investigators immunized sheep with this conjugate to generate antibodies. The immunized sheep subsequently produced a mixture of antibodies that included antialbumin antibodies and antidigoxin antibodies. The antibodies were separated and highly purified to retain the digoxin antibodies, while removing the antibodies to the albumin and all other extraneous proteins. The antibodies that were developed have a high affinity for digoxin, and sufficient cross-reactivity with digitoxin to be clinically useful for the treatment of both poisonings. On the other hand, the specificity is so high that endogenous steroids, which resemble digoxin structurally, are not affected by antibody administration.

Intact IgG antidigoxin antibodies reversed digoxin toxicity in dogs. Unfortunately, the urinary excretion of digoxin was delayed, and free digoxin was released after antibody degradation occurred. Furthermore, concern for hypersensitivity reactions also existed. To make these antibodies safe and effective in humans, whole IgG antidigoxin antibodies were cleaved with papain, yielding two antigen-binding fragments (Fab), with a molecular weight of 50,000 daltons each, and one Fc fragment.[12] The Fc fragment does not bind antigen, but it does increase the potential for hypersensitivity reactions and was eliminated. The advantages of digoxin-specific antibody fragments when compared to whole IgG antibodies include larger volume of distribution, more rapid onset of action, smaller risk of adverse immunologic effects, and more rapid elimination.[12,46,48] Ultimately, the first commercial product, Digibind, a relatively pure, very safe, and extremely effective Fab product, was produced. Another commercial product, DigiFab, is currently available.

Pharmacology

Immediately following IV administration, digoxin-specific antibody fragments bind intravascular free digoxin. Unbound antibodies then diffuse into the interstitial space, binding free digoxin there. A concentration gradient is then established, which facilitates movement of the free intracellular digoxin, and digoxin that is dissociated from its binding sites (the external surface of Na^+-K^+-adenosine triphosphatase [ATPase] enzyme) in the heart and in skeletal muscle, into the interstitial or intravascular spaces.[68] The dissociation rate constant of digoxin for Na^+-K^+-ATPase, therefore, affects the time course for binding to digoxin-specific antibody fragments and, consequently, the onset of action.[50,69]

The binding affinity of digoxin-specific antibody fragments for digoxin and digitoxin are about 10^9â€“10^{11} M^{-1} and 10^8â€“10^9 M^{-1}, and are greater than the affinity of digoxin or digitoxin for the Na^+-K^+-ATPase pump receptor.[21]

Pharmacokinetics

The pharmacokinetics of Digibind versus DigiFab (previously named DigiTAb) were compared in human volunteers.[85] Each subject received 1 mg of digoxin intravenously as a 5-minute bolus, followed 2 hours later by a 30-minute intravenous infusion of 76 mg (equimolar neutralizing dose) of Digibind or DigiFab. Free and total digoxin (free plus digoxin-specific antibody fragment bound) were assayed using an ultrafiltration method over 48 hours. At 30 minutes after infusion of either digoxin-specific antibody fragment, the free digoxin serum concentration was below the level of detection of the assay and remained so for several hours. A few patients had free digoxin concentrations rebound to peak concentrations of 0.5 ng/mL at approximately 18 hours. The area under the plasma drug concentration versus time curve (AUC) for 2â€“48 hours, for free digoxin, was similar for both treatment groups. The elimination half-life of total digoxin

averaged 19.5 hours. The distribution half life was 1 hour for each digoxin-specific antibody fragments, and the volumes of distribution were 0.3 L/kg for DigiFab versus 0.4 L/kg for Digibind.[21,22] The systemic clearance of DigiFab was higher than Digibind and accounted for the shorter elimination half life of DigiFab (15 hours versus 23 hours).[85] Urine sampling over the first 24 hours demonstrated mostly free digoxin and very little digoxin-specific antibody fragments. The authors postulate that during renal excretion, the digoxin-specific antibody fragments-digoxin complex is metabolized in the kidney by the proximal tubular cells, releasing free digoxin and unmeasured digoxin-specific antibody fragments metabolites.

Similar findings were described by Smith and associates in 1976, following the first clinical use of digoxin-specific antibody fragments in a patient who gave a history of ingesting 90 (0.25 mg) digoxin tablets.[75] Total serum digoxin concentration, which was 17.6 ng/mL before digoxin-specific antibody fragments were given, rose to 226 ng/mL one hour after the start of the digoxin-specific antibody fragments infusion and remained there for 11 hours, before falling over the next 44 hours, with a half-life of 20 hours.[75] Fab concentrations peaked at the end of the infusion and then apparently exhibited a biphasic or triphasic decline, probably reflecting distribution into different compartments, as well as excretion and catabolism. Free serum digoxin concentrations were undetectable for

the first 9 hours, then rose to a peak of 2 ng/mL at 16 hours, and fell to 1.5 ng/mL at both 36 hours and 56 hours at which time sampling stopped. An analysis of renal elimination based on an incomplete collection suggested that digoxin was excreted only in the bound form during the first 6 hours, but by 30 hours after Fab administration all digoxin in the urine was free digoxin.

In order to better match availability of digoxin-specific antibody fragments to liberated digoxin, one study compared a loading dose

of digoxin-specific antibody fragments followed by an infusion to the total digoxin-specific antibody fragments dose infused over a short amount of time.[65] The former strategy increased the ratio of digoxin bound to unbound digoxin-specific antibody fragments from 50 to 70%.[65] The authors hypothesized that too rapid an infusion regimen would permit digoxin-specific antibody fragments elimination to occur before they could optimally bind digoxin being redistributed from tissue sites.[65]

Digoxin takes several hours to distribute from the blood to the tissue compartment. As expected, a rodent model demonstrated that digoxin-specific antibody fragments were more effective when administered prior to complete distribution of digoxin.[62] Once distribution is complete, increasing the dose of digoxin-specific antibody fragments improved efficacy as measured by comparing the area under the time-versus-concentration curve (AUC) of digoxin to that of the Fab-digoxin complex.[62]

Pharmacokinetic studies in patients with renal failure demonstrate that the half-life of digoxin-specific antibody fragments is prolonged 10-fold, with no change in the apparent Vd.[79] Digoxin-specific antibody fragment serum concentrations remain detectable for 2â€“3 weeks. Total digoxin serum concentrations generally follow digoxin-specific antibody fragments. There is no evidence for dissociation of digoxin-specific antibody fragments-digoxin complex over time.[86] In contrast, case reports demonstrate that free digoxin levels reappear up to 10 days following administration of digoxin-specific antibody fragments to patients with severe renal dysfunction, as compared to 12â€“24 hours in patients with normal renal function.[27,41,52,53,71,73,79,80,81,86] In one series of patients with end-stage renal disease, the maximum average concentration of free digoxin was 1.30 Â± 0.7 ng/mL and occurred at 127 Â± 40 hours.[81] The mechanism for this rebound is unclear. Following the peak, there is a slow decline that parallels the elimination of digoxin-specific antibody fragments.

Efficacy

A large study evaluating adults and children with acute and chronic digoxin toxicity established the efficacy of digoxin-specific antibody fragments.[1] Of the 150 patients treated, 148 were evaluated pretreatment for cardiovascular manifestations of toxicity: 79 patients (55%) had high-grade atrioventricular (AV) block, 68 (46%) had refractory ventricular tachycardia, 49 (33%) had ventricular fibrillation, and 56 (37%) had hyperkalemia. Ninety percent of patients had a response to digoxin-specific Fab within minutes to several hours of Digibind administration. Complete resolution of all signs and symptoms of digoxin toxicity occurred in 80% of cases. A partial response was observed in 10% of patients, and of the 15 patients who did not respond, 14 were moribund or actually found not to be digoxin toxic. The spectacular success of digoxin-specific antibody fragments for patients with digoxin toxicity is demonstrated by the fact that of the 56 patients who had cardiac arrest caused by digoxin, 54% survived hospitalization, as compared with 100% mortality before the advent of these fragments.[1,5] Newborns, infants, and children have all been successfully treated with Digibind.[5,39,70]

Adverse Effects and Safety

Digoxin-specific antibody fragments are effective, as well as very safe. Reported adverse effects include hypokalemia as a consequence of reactivation of the Na^+-K^+-ATPase, withdrawal of the inotropic or atrioventricular nodal blocking effects of digoxin leading to congestive heart failure or a rapid ventricular rate in patients with atrial fibrillation, and, rarely, allergic reactions.[21,22] In the multicenter study of 150 patients, the only acute clinical manifestations were hypokalemia in 6 patients (4%), worsening of congestive heart failure in 4 patients (3%), and transient apnea in a several-hours-old neonate.[1] There were no other reactions reported in any of the patients in this series. In a postmarketing

surveillance study of Digibind that included 451 patients, 2 patients with a prior history of allergy to antibiotics reportedly developed rashes.[57] One of these patients developed a total body rash, facial swelling, and a flush during the infusion. The other experienced a pruritic rash. Two other adverse reactions (thrombocytopenia and rigors) were probably unrelated to the use of Digibind.[57] One patient received Digibind on 3 separate occasions over the course of 1 year for multiple suicide attempts, with no adverse effects.[8]

During the clinical trials with DigiFab, 1 patient developed pulmonary edema, bilateral pleural effusion, and renal failure, most likely caused by the loss of the inotropic and chronotropic digoxin effects.[22] Phlebitis and postural hypotension were related to the infusion of DigiFab in two healthy volunteers.

Both products warn that patients with allergies to papain, chymopapain, or other papaya extracts may be at risk for an allergic reaction because trace amounts of these residues may remain in the digoxin-specific antibody fragments.[22,48] Manufacturers of DigiFab state that because some literature suggests a resemblance between dust mite allergens and some latex allergens with the antigenic structures of papain, patients may exhibit cross-allergenicity. Patients with an allergy to sheep protein or those who have previously received ovine antibodies or ovine Fab may also be at risk for allergic reactions, although this is not reported.

Indications for Digoxin-Specific Fab

Digoxin-specific antibody fragments are indicated for life-threatening, or potentially life-threatening, digoxin, digitoxin, or other xenobiotic resulting in cardioactive steroid toxicity.[21] Patients with progressive bradydysrhythmias, including symptomatic sinus bradycardia, or second- or third-degree heart block unresponsive to atropine, and those patients with severe

ventricular dysrhythmias, such as ventricular tachycardia or ventricular fibrillation, should also be treated with digoxin-specific antibody fragments. Ventricular tachycardia with a fascicular block is likely to be a digoxin-toxic rhythm.[47] Any patient with a potassium concentration exceeding 5 mEq/L that is attributable to a cardioactive steroid in the presence of other manifestations of digoxin toxicity should also be treated. Acute ingestions greater than 4 mg in a healthy child (or more than 0.1 mg/kg), or 10 mg in a healthy adult, require digoxin-specific antibody fragments, with the threshold lower in patients with significant medical

illness. Serum digoxin concentrations are not representative of myocardial concentrations until tissue distribution takes place. Following ingestion, a time delay of 4â€“6 hours is usually required for digoxin to achieve distribution from the serum to the myocardium. Serum concentrations of â‰¥10 ng/mL, at steady state after an acute ingestion, are an indication for treatment with digoxin-specific antibody fragments. Because the elderly appear at greatest risk of lethality, the threshold for treating those older than 60 years of age should be lowered.[7] Before the advent of digoxin-specific antibody fragments, mortality in patients older than 60 years of age was 58%, as compared to 8% in patients younger than 40 years of age, and to 34% in patients between the ages of 40 and 50 years of age.[7] A rapid progression of clinical signs and symptoms, such as cardiac and gastrointestinal toxicity and an elevated or rising potassium level, in the presence of an acute overdose, suggests a potentially life-threatening ingestion and the need for digoxin-specific antibody fragments.

In a patient with an unknown ingestion who is clinically ill with characteristics suggestive of poisoning by a cardioactive steroid, a calcium channel-blocking agent, or a Î²-adrenergic antagonist, digoxin-specific antibody fragments should be administered early in the management, and always prior to calcium use. If digoxin or another cardioactive steroid is involved, the effects can be

reversed, obviating the need to administer calcium and avoiding the danger of giving calcium to a cardioactive steroid-toxic patient. Cardioactive steroid toxicity causes intracellular myocardial hypercalcemia, and the administration of exogenous calcium may further exacerbate conduction abnormalities and potentially result in cardiac arrest, unresponsive to further resuscitation. Also, when it is difficult to distinguish clinically between digoxin poisoning and intrinsic cardiac disease, the administration of digoxin-specific antibody fragments can help establish the diagnosis.

A recent computer-based simulation model compared the treatment of non-lifethreatening digoxin toxicity with standard therapy. The authors concluded that treatment with digoxin-specific antibody fragments could decrease length of hospitalization by 1.5 days.[20]

Onset of Response

In the multicenter study of 150 patients, the mean time to initial response from the completion of the digoxin-specific antibody fragments infusion (accomplished over 15 minutes to 2 hours) was 19 minutes (range, 0â€“60 minutes), and the time to complete response was 88 minutes (range, 30â€“360 minutes).[16] Time to response was not affected by age, concurrent cardiac disease, or presence of chronic or acute ingestion.[1]

Dosing

The dose of digoxin-specific antibody fragments depends on the total body load (TBL) of digoxin. Adult and pediatric patients receiving digoxin therapeutically who develop chronic digoxin toxicity require small doses of digoxin-specific antibody fragments because their total body burden of digoxin is smaller when toxicity develops. Children with acute overdoses require digoxin-specific

antibody fragments doses based on the amount of digoxin ingested, in a manner similar to adults with acute ingestions.

Estimates of digoxin TBL can be made in three ways: (a) estimate the quantity of digoxin acutely ingested and assume 80% bioavailability (mg ingested Ã— 0.8 = TBL); (b) obtain a serum digoxin concentration (SDC), and, using a pharmacokinetic formula, incorporate the apparent volume of distribution (Vd) of digoxin and the patient's body weight (in kg); or (c) use an empiric dose based on the average requirements for an acute or chronic overdose in an adult or child.

TABLE A19-1. Sample Calculation Based on History of Acute Digoxin Ingestion

Adult
Weight: 70 kg
Ingestion: Fifty (0.25-mg) digoxin tablets
Calculation:
0.25 mg Ã— 50 = 12.5 mg ingested dose
12.5 mg Ã— 0.80 (80% bioavailability) = 10 mg (absorbed dose)

$$\frac{10\ \text{mg}}{0.5\ \text{mg/vial}} = 20\ \text{vials}$$

Child
Weight: 10 kg
Ingestion: Fifty (0.25-mg) digoxin tablets
Calculation: Same as for adult. Child will require 20 vials

Each of these methods of estimating the dose of digoxin-specific antibody fragments has limitations. History of ingestion is often unreliable, and empiric doses based on averages may overestimate or underestimate Fab requirements. Using the pharmacokinetic

formula assumes a steady-state Vd of 5 L/kg. This is not accurate in the acute setting. In addition, the 5 L/kg Vd is a population average that varies both with each individual and in certain disease states, such as the decreases that occur in patients with renal disease and hypothyroidism.[87]

Sample calculations for each of these methods are shown in Tables A19-1, A19-2, and A19-3. Each vial of digoxin-specific antibody fragments contains 38 mg (Digibind) or 40 mg (DigiFab)

of purified digoxin-specific antibody fragments that will bind approximately 0.5 mg of digoxin or digitoxin. If the quantity of ingestion cannot be reliably estimated, it is safest to use the largest calculated estimate. Alternatively, the clinician should be prepared to increase dosing, should resolution be incomplete.

TABLE A19-2. Sample Calculations Based on the Serum Digoxin Concentration (SDC)

Adult

Weight: 70 kg

SDC = 10 ng/mL

Volume of distribution = 5 L/kg

Calculation[a]:

$$\text{No. of vials} = \frac{\text{Total body load (mg)}}{0.5\ \text{mg/vial}} = \frac{\text{SDC} \times V_d \times \text{Pt Wt (kg)}}{1000 \times 0.5\ \text{mg/vial}}$$

$$\text{No. of vials} = \frac{10\ \text{ng/mL} \times 5\ \text{L/kg} \times 70\ \text{kg}}{1000 \times 0.5\ \text{mg/vial}}\ \text{(Round up)}$$

No. of vials = 7

Child

Weight: 10 kg

Serum digoxin concentration: 10 ng/mL
Volume of distribution: 5 L/kg
Calculation[a]:

$$\text{No. of vials} = \frac{10\ \text{ng/mL} \times 5\ \text{L/kg} \times 10\ \text{kg}}{1000 \times 0.5\ \text{mg/vial}}\ \text{(Round up)}$$

No. of vials = 1

Quick Estimation (for Adults and Children)

$$\text{No. of vials} = \frac{\text{SDC (ng/mL)} \times \text{Pt Wt (kg)}}{100}\ \text{(Round up)}$$

[a] 1000 is a conversion factor to change ng/mL to mg/L.

TABLE A19-3. Empiric Dosing Recommendations

Acute Ingestion
Adult: 10â€“20 vials
Child[a]: 10â€“20 vials
Chronic Toxicity
Adult: 3â€“6 vials
Child[b]: 1â€“2 vials

[a]Monitor for volume overload in very small children.
[b]The prescribing information contains a table for infants and children, with corresponding serum concentrations.

Administration

According to the manufacturer, Digibind should be administered IV over 30 minutes via a 0.22-micron membrane filter.[21] The 38-mg

vial must be reconstituted with 4 mL of sterile water for IV injection, furnishing an isoosmotic solution. This preparation can be further diluted with sterile isotonic saline for injection (for small infants, addition of 34 mL to the 4 mL [for 38 mL total] achieves 1 mg/mL). After Digibind is reconstituted, it should be used immediately, or if refrigerated, it should be used within 4 hours.[21] Although slow IV infusion over 30 minutes is preferable, Digibind may be given by IV bolus to a critically ill patient.

Each vial of DigiFab should be reconstituted with 4 mL of sterile water for IV injection and gently mixed to provide a solution containing 10 mg/mL of digoxin-specific antibody fragments.[22] The reconstituted product should be used promptly or, if refrigerated, it should be used within 4 hours. This preparation can be further diluted with sterile isotonic saline for injection. DigiFab should be administered slowly as an intravenous infusion over at least 30 minutes unless the patient is critically ill, in which case the DigiFab can be given by IV bolus. If a rate-related infusion reaction occurs, the infusion should be stopped and restarted at a slower rate. For infants and small children, the manufacturer recommends diluting the 40-mg vial with 4 mL of sterile water for IV injection and administering the dose undiluted using a tuberculin syringe. For very small doses, this preparation can be further diluted with an additional 36 mL of sterile isotonic saline for injection (for a total of 40 mL) to achieve a 1 mg/mL concentration.

Availability

Digoxin-specific antibody fragments are available as Digibind or DigiFab. Vials contain 38 mg or 40 mg of purified lyophilized digoxin-immune ovine immunoglobulin fragments, respectively. Digibind is prepared using digoxin as the hapten. DigiFab is prepared using a digoxin derivative (digoxin-dicarboxymethoxylamine) as the hapten. Affinity chromatography is used to isolate and purify the digoxin-specific antibody

fragments following papain digestion.

Measurement of Digoxin Serum Concentration after Digoxin-Specific Antibody Fragments Administration

Many laboratories are not equipped to determine free serum digoxin concentrations. Therefore, after digoxin-specific antibody fragments are administered, total serum digoxin concentrations are no longer clinically useful, because they represent free plus bound digoxin.[21,31,36,44,77] The type of test employed can either result in falsely high or falsely low serum concentrations, depending on which phase (solid or supernatant) is sampled.[35,49] If the correct dose of digoxin-specific antibody fragments is administered, the free serum digoxin concentrations should be near zero. Free digoxin concentrations begin to reappear 5â€“24 hours or longer after Fab administration, depending on the antibody dose, infusion technique, and the patient's renal function. Newer commercial methods, employing ultrafiltration or immunoassays, make free digoxin measurements easier to perform and, therefore, more clinically useful, but they remain associated with errors in the underestimation or overestimation of the free digoxin level.[30,37,54,60,78,82] Free digoxin concentrations are particularly useful in patients with severe renal dysfunction. Independent of the availability of these data, the patient's cardiac status must be carefully monitored for signs of recurrent toxicity.

Other pitfalls in the measurement and utility of serum digoxin concentrations include endogenous and exogenous factors. Endogenous digoxinlike immunoreactive substances (EDLISs) have been described in infants, in women in the third trimester of pregnancy, and in patients with renal and hepatic failure.[29,32,33,38,40,50,83,84] When EDLISs are free or weakly bound, as in these circumstances, they are measurable by the

typical RIA and can account for factitiously high reported serum digoxin concentrations in the absence of digoxin treatment. The role of EDLIS in the body has not been fully elucidated, but it does have an effect on both the Na^+-K^+-ATPase pump and the cardioactive steroid receptor site.[33] EDLISs are implicated as a causative factor in hypertension and renal disease. Exogenous factors relate primarily to measurement techniques and interpretation.[42] Digoxin is metabolized to compounds with varying levels of cardioactivity.[45] Some metabolites cross-react and are measured by RIA, while others are not. The in vivo production of these metabolites varies in patients, and may depend on intestinal metabolism by gut flora as well as renal and liver clearance.

Role of Digoxin-Specific Antibody Fragments with other Cardioactive Steroids

Digoxin-specific antibody fragments were designed to have high-affinity binding for digoxin and digitoxin. There are structural similarities, however, between all cardioactive steroids. In fact, RIA-determined digoxin concentrations have been reported in patients following poisoning with nondigoxin cardioactive steroids,[27,47,61] suggesting that cross-reactivity exists between digoxin-specific antibody fragments and other cardioactive steroids. Thus, digoxin-specific antibody fragments may have some efficacy in all natural cardioactive steroid poisonings, including oleander, yellow oleander, squill, and toad venom.[3,9,10,14,26,28,63] In vitro studies also suggest the binding affinity of Digibind for cardioactive steroids.[18,19,58]

The successful reversal, by Digibind, of cardiotoxicity resulting from ingestion of *Nerium oleander* was reported.[72] This patient responded to 5 vials (200 mg) of Fab, but larger doses may be

required in other cardioactive steroid poisonings because of the lower affinity binding of Digibind for these toxins. DigiFab is expected to have similar affinity binding toward cardioactive steroids. Both products are polyclonal, contributing to their broad spectrum of affinity for nondigoxin cardioactive steroids. Treatment decisions should be based on empirical grounds, with initial therapy consisting of 10â€“20 vials. Subsequent doses can be based on clinical response.

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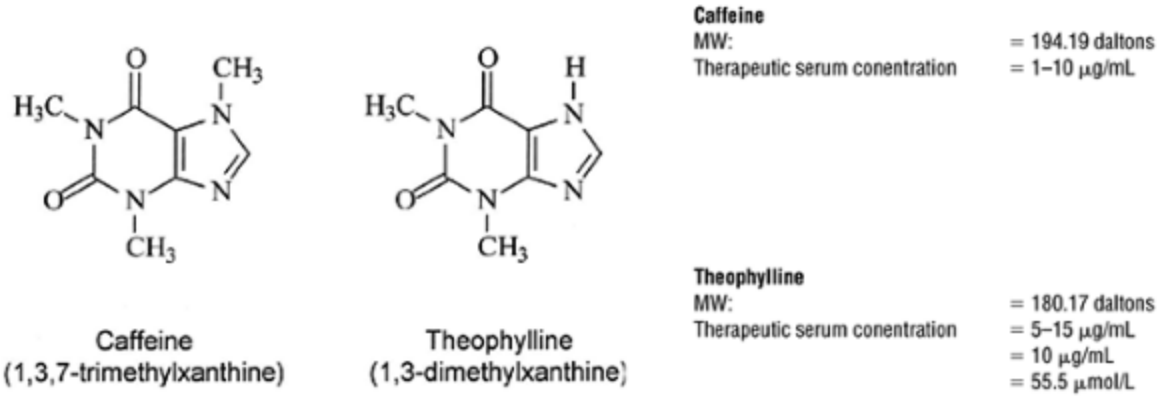
Chapter 63

Methylxanthines and Selective Î²2-Adrenergic Agonists

Robert J. Hoffman



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A 17-year-old girl presented to the emergency department reporting that she ingested thirty-five (200-mg) tablets of caffeine approximately 2 hours earlier. She complained of nausea,

vomiting, and palpitations. Her vital signs were: blood pressure, 115/66 mm Hg; pulse 142 beats/min; respiratory rate, 20 breaths/min; and temperature, 100.2Â°F (37.9Â°C). The patient was attached to a cardiac monitor. She was anxious, disoriented, and cooperative. Significant physical findings included mydriasis, tachycardia, tremor, and diaphoresis. A 12-lead ECG demonstrated a sinus tachycardia, with frequent unifocal premature ventricular contractions (PVCs). Fifty grams of activated charcoal with sorbitol was given orally, but she immediately vomited. Metoclopramide (10 mg IV) was administered, and 30 minutes later 50 g of activated charcoal with sorbitol was orally administered again, but vomiting recurred.

At admission the patient's serum electrolytes were: sodium, 140 mEq/L; potassium, 3.0 mEq/L; chloride, 107 mEq/L; bicarbonate, 16 mEq/L; BUN, 8 mg/dL; creatinine, 1 mg/dL; and glucose, 248 mg/dL. One liter of 0.9% NaCl solution was administered intravenously over 30 minutes, and potassium chloride (40 mEq IV) was administered twice by infusion over 1 hour. The patient's serum electrolytes 3 hours after admission and subsequent to potassium repletion were: sodium, 141 mEq/L; potassium, 2.8 mEq/L; chloride, 110 mEq/L; and bicarbonate, 17 mEq/L. The patient continued to have a sinus tachycardia with frequent unifocal PVCs, and the blood pressure decreased to 98/50 mm Hg. Two liters of lactated Ringer solution was administered by bolus over 1 hour, and the blood pressure increased to 108/56 mm Hg. Fifty grams of activated charcoal with sorbitol was orally administered again, this time without ensuing emesis. Approximately 4 hours after presentation

and 6 hours after ingestion, a serum sample for a quantitative caffeine concentration was obtained. The treating institution lacked the capability to determine a quantitative caffeine concentration, and the blood sample was sent to a reference laboratory. Serum electrolyte assays were repeated at

approximately 7 hours postingestion. Although the bicarbonate had increased to 20 mEq/L, the potassium was still 2.8 mEq/L. The patient again received potassium chloride (40 mEq IV) by infusion over 1 hour. The severity and persistence of hypotension and hypokalemia combined with a lack of intensive care capabilities necessitated transfer to the intensive care unit in a nearby children's hospital.

At the receiving institution, her vital signs had improved to blood pressure, 110/64 mm Hg; pulse, 110 beats/min; respiratory rate, 18 breaths/min; and temperature, 99.0Â°F (37.2Â°C). Fifty grams of activated charcoal without sorbitol was readministered. The patient experienced anxiety and agitation that responded to lorazepam (3 mg IV). She was awakened during the night to be reevaluated and to receive another dose of activated charcoal orally. Otherwise, the patient remained sedated through the night. She awoke in the morning with a normal mental status and reported feeling ill but much improved. Repeat electrolyte assays were normal except for a potassium of 3.1 mEq/L. Her serum caffeine concentration at that time, approximately 18 hours postingestion, was 88 Âµg/mL. Caffeine concentration assays were repeated twice that day, with results of 56 Âµg/mL and 40 Âµg/mL, at which time further assays were deemed unnecessary. Serum electrolyte assays repeated that evening, and at all subsequent times, were normal. The patient was discharged from intensive care and admitted to a psychiatric service. The serum sample for the 6-hour caffeine concentration drawn at the initial institution was later determined to be 149 Âµg/mL.

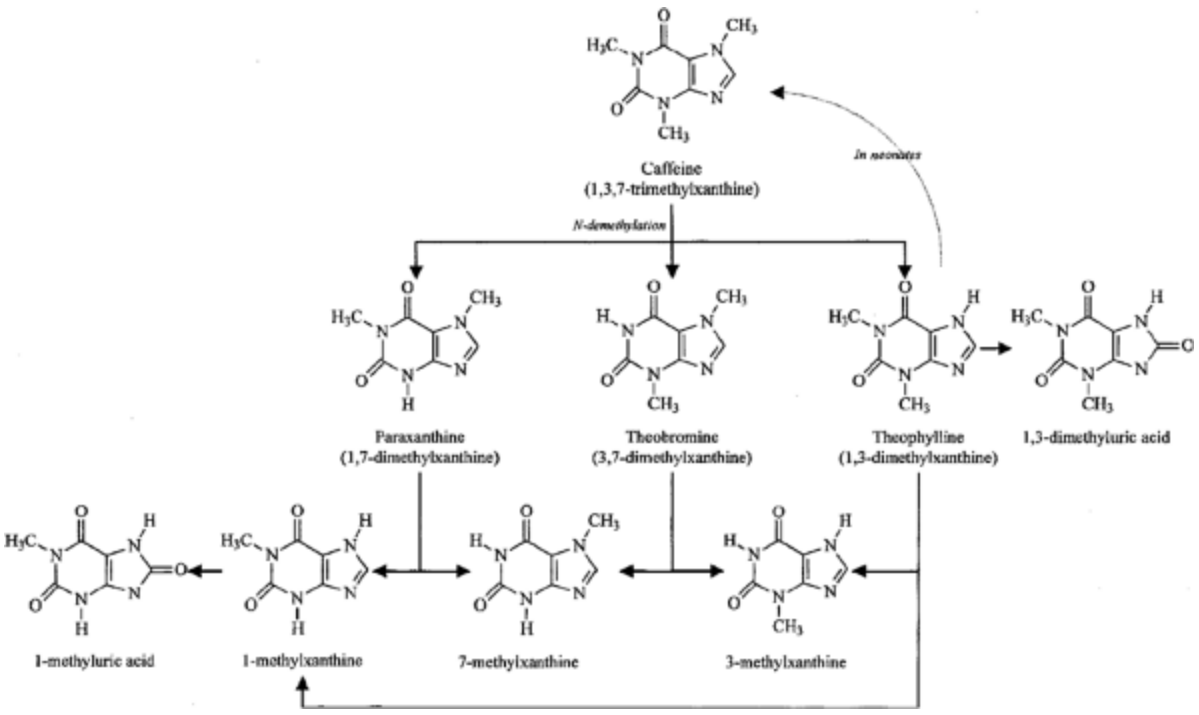

Figure 63-1. Metabolism of caffeine and other methylxanthines by the hepatic P450 enzyme system.

Methylxanthines, which include caffeine (1,3,7 trimethylxanthine), theobromine (3,7-dimethylxanthine), and theophylline (1,3-dimethylxanthine), are so named because they are methylated derivatives of xanthine (Fig. 63-1). Members of this group of plant-derived alkaloids have very similar pharmacologic properties and cause similar clinical effects. Methylxanthines are used ubiquitously throughout the world, most commonly in beverages imbibed for their stimulant, mood elevating, and fatigue abating effects. *Coffea arabica* and related species are used to make coffee, a beverage rich in caffeine. Cocoa and chocolate are derived from the seeds of *Theobroma cacao* , which contains theobromine and, to a lesser extent, caffeine. *Thea sinensis* , a bush native to China but now cultivated worldwide, produces leaves from which various teas, rich in caffeine and containing small amounts of theophylline and theobromine, are brewed.

Selective Î²2 -adrenergic agonists have been developed for the treatment of bronchoconstriction. Their selectivity has improved therapy for bronchoconstriction, allowing avoidance of the adverse effects of epinephrine, an Î±- and Î²-adrenergic agonist, as well as isoproterenol, a Î²1 - and Î²2 -adrenergic agonist. All Î²2 -adrenergic agonists have nearly identical clinical effects and the principal differences are their pharmacokinetics. This chapter does not examine each Î²2 -adrenergic agonist individually; rather, they are discussed as a class. The Î²2 -adrenergic agonists include albuterol, bitolterol, clenbuterol, formoterol, pirbuterol, salmeterol, terbutaline, and ritodrine.

Epidemiology

From 1998 to 2003, the American Association of Poison Control Centers (AAPCC) reported the following trends in methylxanthine exposures. Theophylline exposures decreased from 2609 involving 20 deaths in 1998 to 861 exposures and 10 deaths in 2003. Caffeine exposures decreased from 7390 exposures in 1998 to 6086 exposures of pharmaceutical and herbal caffeine in 2003, but increased from no deaths in 1998 to 5 deaths in 2003. The decrease in theophylline exposures presumably reflects continued decrease in use of theophylline as a therapeutic agent. The number of caffeine exposures, has essentially remained stable, reflecting steady use of caffeine, particularly caffeine in substances other than coffee, tea, and soft drinks.

There were 11,397 selective Î²2 -adrenergic agonists exposures and 1 death in 1998, and 10,501 exposures and 1 death in 2003. The number of selective Î²2 -adrenergic agonists exposures has remained stable, presumably from consistent use of these agents, but death remained uncommon. Chapter 130 discusses poison exposure data.

The overwhelming preponderance of caffeine consumed is in

beverages, and a lesser portion in foods and tablets or capsules. Users typically seek the stimulant and psychoactive effects of caffeine. Caffeine is also increasingly advocated for use as a weight-loss agent.[15, 72] The use of guarana, a plant with a very high caffeine content, for weight loss and athletic performance enhancement, has increased dramatically in recent years. With some scientific evidence demonstrating benefit in athletic performance, caffeine is advocated as a concentration[97, 156] and â€œenergyâ€• booster and as athletic performance enhancer.[33, 96] Despite the limited experience with overdose from these combination preparations, formulations containing caffeine/guarana combined with ephedrine/ma huang cause illnesses such as myocardial infarctions and death.[79] Formulations containing phenylpropanolamine and caffeine, also once marketed as an anorexiant diet aid, were removed from US markets because of adverse drug events, and a demonstrated lack of benefit from the inclusion of caffeine and a sympathomimetic agent for the purpose of appetite suppression.[82] (Chapter 39 discusses dietary supplements.)

Medicinally, caffeine is used to treat neonatal apnea and bradycardia syndrome; as an analgesic adjuvant, particularly when combined with relatively mild analgesics such as acetaminophen, aspirin, and ibuprofen; and as an adjuvant treatment for migraine headaches, as well as postlumbar puncture headaches.

Theophylline, or its water-soluble salt aminophylline, is rarely used to treat respiratory conditions. Theophylline was used to treat reversible bronchospastic airway disease, particularly asthma and chronic obstructive pulmonary disease. Theophylline was once the mainstay of therapy for such diseases, but more selective agents with fewer side effects, such as albuterol and other selective $\hat{I}^2_2$ -adrenergic agonists, are now more commonly used. However, because antiinflammatory and other beneficial effects of theophylline have been described, its role in the treatment of pulmonary disease may again expand.[102] In neonates,

theophylline and aminophylline are used similarly to caffeine to treat neonatal apnea and bradycardia syndrome. The result of such treatment is increased respiratory rate, decreased apnea, increased cardiac chronotropy and inotropy, and increased cardiac output.[31]

Caffeine and theophylline toxicity may result from either iatrogenic or self-administration, and acute or chronic toxicity can occur in either circumstance. Chronic toxicity from caffeine is most typically described as a result of the frequent self-administration of caffeine. A particular syndrome associated with chronic caffeine use consisting of headache, palpitations, tachycardia, insomnia, and delirium is termed *caffeinism* . Chronic theophylline toxicity results from the use of theophylline as a medicinal therapeutic agent. Neonates receiving caffeine therapy may develop either acute or chronic caffeine toxicity.[7 , 17]

Most reported cases of theobromine poisoning occur in animals and typically result from small animals ingesting cocoa or chocolate.[50 , 54 , 80] Theobromine has become an ingredient of numerous â€œenergyâ€• drinks used for stimulation and athletic enhancement. No reports of human toxicity exist, but it would not be unexpected if toxicity from these sources are soon reported.

Use of Î²2 -adrenergic agonists is widespread. Adverse effects are associated with both therapeutic dosing and overdose. Excessive use of Î²2 -adrenergic agonists can result in tachyphylaxis, a phenomenon in which downregulation of receptors occurs and the effects from this drug diminishes as a result of excessive use.[43 , 92] Consequently, patients may require higher doses to achieve the same clinical effect they previously experienced at lower doses, resulting in more profound systemic side effects. The most common manifestation of selective Î²2 -adrenergic agonist toxicity occurs in children who ingest oral albuterol. Toxicity of terbutaline and ritodrine are infrequent but well-reported.

Pharmacology

Methylxanthines

Methylxanthines cause the release of endogenous catecholamines, resulting in stimulation of Î²$_1$ and Î²$_2$ receptors. The resulting adrenergic agonism is important in both their therapeutic effects and in their toxicity.[179] Levels of endogenous catecholamines are extremely elevated in patients with acute methylxanthines poisoning.[21]

Methylxanthines are structural analogs of adenosine and also function pharmacologically as adenosine antagonists. Adenosine is believed to modulate histamine release and cause bronchoconstriction, which may explain the clinical efficacy of adenosine antagonists in the treatment of bronchospasm. Additionally, adenosine antagonism results in release of norepinephrine, and to a lesser extent epinephrine.

At supratherapeutic doses, methylxanthines also inhibit phosphodiesterase, the enzyme responsible for degradation of intracellular cyclic adenosine monophosphate (cAMP). Phosphodiesterase inhibition was long considered to be the primary therapeutic mechanism of the methylxanthines, but clinically significant elevations in cAMP levels are not achieved until serum methylxanthine levels are well above the therapeutic range. This likely occurs as a result of the structural similarity of cAMP and methylxanthines. cAMP is involved in the postsynaptic second messenger system of Î²-adrenergic stimulation. Thus, elevated cAMP levels cause clinical effects similar to adrenergic stimulation, including smooth muscle relaxation, peripheral vasodilation, myocardial stimulation, and CNS excitation.

Selective Î²$_2$ -Adrenergic Agonists

Selective Î²$_2$ -adrenergic agonists act quite specifically at Î²$_2$ -

adrenergic receptors, resulting in an increase in intracellular cAMP. The effects of $\hat{I}^2_2$ agonism include relaxation of vascular, bronchial, and uterine

smooth muscle, glycogenolysis in skeletal muscle, and hepatic glycogenolysis and gluconeogenesis. These receptors are located in other areas, such as type II alveolar cells, mast cells, and lymphocytes, but their significance is unknown. Selective $\hat{I}^2_2$ -adrenergic agonists are characterized as either directly activating the $\hat{I}^2_2$ receptor, such as albuterol, being taken up into a membrane depot, such as formoterol, or interacting with a receptor-specific auxiliary binding site, such as salmeterol. These differences do not appear to be relevant in acute toxicity.[95]

Pharmacokinetics and Toxicokinetics

Caffeine

Pharmacokinetics

Caffeine is bioavailable by oral, intravenous, subcutaneous, intramuscular, and rectal routes of administration. Oral administration, which is by far the most common route of exposure, results in nearly 100% bioavailability of the drug. The presence of food in the gut does little to affect peak concentration. However, food in the gut does delay time until the peak plasma concentration is reached, which is typically 30â€“60 minutes in the absence of food. Caffeine rapidly diffuses into the total body water and all tissues, and readily crosses the bloodâ€“brain barrier and the placenta. The volume of distribution is 0.6 L/kg, and 36% is protein bound. Caffeine is secreted in breast milk.[177]

Caffeine exhibits Michaelis-Menten kinetics and is metabolized via the microsomal cytochrome P450 (CYP) system, primarily by the isozyme CYP1A2. The major pathway involves demethylation to

1,7-dimethylxanthine (paraxanthine) followed by hydroxylation or repeated demethylation followed by hydroxylation. To a lesser extent, caffeine is also metabolized to 3,7-dimethylxanthine (theobromine) and 1,3-dimethylxanthine (theophylline). Neonates demethylate caffeine, producing theophylline, and also possess the unique ability to convert theophylline to caffeine by methylation.[3,11,12,30,67] By approximately 4â€“7 months of age, infants metabolize and eliminate caffeine in a manner similar to adults.[10] All people metabolize some quantity of caffeine to active metabolites, including theophylline and theobromine. The degree to which this occurs is dependent on the age, cytochrome P450 enzyme induction status, and other factors. For this reason, there may be a role for assessment of serum theophylline concentration in the management of patients with suspected caffeine overdose, but such role is not clearly defined and obviously limited.

Less than 5% of caffeine is excreted in the urine unchanged. The half-life of caffeine is highly variable and dependent on several factors. Generally speaking, younger patients, particularly infants, as well as patients with cytochrome P450 inhibition, such as pregnant patients and patients with cirrhosis, have longer caffeine half-lives than the 4.5-hour half-life in healthy, adult, nonsmoking patients.[32,47,51,171]

Toxicokinetics

Caffeine toxicity is a dose-dependent phenomenon. Unfortunately, the range of toxicity reported in different references varies greatly, and no definite conclusions can be drawn regarding serum levels and symptomatology in overdose. Therapeutic dosing in adults is 100â€“200 mg orally every 4 hours; in neonates, a typical loading dose is 20 mg/kg, with daily maintenance dosing of 5 mg/kg. Based on case reports and series, lethal dosing in adults is estimated at 150â€“200 mg/kg, and death is associated with serum concentrations >80 Âµg/mL. Although numerous fatalities

occur with serum concentrations <200 Âµg/mL, survival of a patient with an acute caffeine overdose and a serum concentrations >400 Âµg/mL is also reported.[175] Infants survive toxicity with greater serum concentrations of caffeine than are tolerated by children and adults.

Theophylline

Pharmacokinetics

Theophylline is approximately 100% bioavailable by the oral route. Many of the available oral preparations are sustained-release, designed to provide stable serum concentrations over a prolonged period with less-frequent dosing. Peak absorption generally occurs 6â€“10 hours after ingestion. However, following overdose of sustained-release preparations, the time to peak absorption may take twice as long as that of the immediate release preparations.

Similar to caffeine, theophylline rapidly diffuses into the total body water and all tissues, readily crosses the bloodâ€“brain barrier and placenta, and is secreted into breast milk.[14 , 104 , 190 , 192] Theophylline's volume of distribution is 0.5 L/kg, and 56% of it is protein bound.

Theophylline is metabolized via the microsomal cytochrome P450 system, primarily by the isozyme CYP1A2. The major pathway is demethylation to 3-methylxanthine, in addition to being demethylated or oxidized to other metabolites. Less than 10% of theophylline is excreted in the urine unchanged.

Similar to caffeine, the half-life of theophylline is highly variable, and is dependent on several factors. In healthy, adult, nonsmoking patients, the half-life is 4.5 hours. Theophylline's half-life in infants and the elderly, as well as in patients with cytochrome P450 inhibition, pregnant patients, and patients with cirrhosis, is longer than in healthy children and adult nonsmoking patients.[88 ,

[117 , 170] Factors that induce cytochrome P450, such as cigarette smoking, and others that inhibit cytochrome P450, such as exposure to cimetidine, erythromycin, and oral contraceptives, can significantly alter theophylline clearance.[75 , 116 , 131 , 132 , 147 , 181] Decreased theophylline or caffeine metabolism or reversal of enzyme induction predisposes to the development of chronic toxicity.

Toxicokinetics

Like caffeine, theophylline exhibits Michaelis-Menten kinetics.[146] At higher doses and in overdose, it undergoes zero-order elimination, and only a fixed amount of the drug can be eliminated in a given time because of saturation of metabolic enzymes.[144]

Therapeutic serum concentrations of theophylline are 5â€“15 Âµg/mL; higher concentrations are considered toxic. Morbidity and mortality occur with relatively lower concentrations in chronic toxicity. Although morbidity and mortality are not always predictable based on serum concentrations, life-threatening toxicity, including seizures, ventricular dysrhythmias, and death, is associated with serum concentrations of 80â€“100 Âµg/mL in acute overdoses and serum concentrations of 40â€“60 Âµg/mL in chronic toxicity.

Theobromine

As is the case with the other methylxanthines, theobromine is well absorbed from the gut, and is 80% bioavailable when administered in solution. It is bioavailable orally, intravenously, and rectally. Theobromine has 21% protein binding, a volume of distribution of 0.62 L/kg, and a plasma half-life of 6â€“10 hours.[55 , 141] Theobromine undergoes hepatic metabolism by the CYP system similarly to

caffeine and theophylline.[29] Like the other methylxanthines,

theobromine is excreted in breast milk, and consumption of chocolate results in measurable concentrations in breast milk. Toxic concentrations of theobromine in animals are known, but comparable human data is lacking.

Selective Î²â‚‚ -Adrenergic Agonists

Pharmacokinetics

These agents are used inhalationally, orally, and parenterally. They are bioavailable by both the inhalational and enteral route, and much of â€œinhaledâ€• Î²â‚‚ -adrenergic agonists may actually be swallowed and absorbed from the GI tract. Absorption, distribution, and elimination vary among these agents. The half-life of albuterol is approximately 4 hours. Less than 5% crosses the bloodâ€“brain barrier. It is metabolized extensively in the liver, and excreted in urine and feces as albuterol and metabolites.[2]

Terbutaline is partially metabolized in the liver, mainly to inactive conjugates. With parenteral administration, 60% of a given dose is excreted in the urine unchanged.[1]

Toxicokinetics

Ingestion of Î²â‚‚ -adrenergic agonists, which happens predominantly in young children treated with oral albuterol preparations, can cause significant symptomatology.[101] For oral albuterol poisoning, 1 mg/kg appears to be the dose threshold for developing significant toxicity.[186]

Methylxanthine Pathophysiology

Caffeine, theobromine, and theophylline affect the same organ systems and cause qualitatively similar effects.

It should be noted, however, that there are distinct differences in the activity and effects of the various methylxanthines, particularly in therapeutic dose. The major clinical effects at both therapeutic doses and in overdose result from adenosine antagonism, release of endogenous norepinephrine and consequent Î²-adrenergic receptor stimulation, and phosphodiesterase inhibition. Toxicity affects the gastrointestinal, cardiovascular, central nervous, and musculoskeletal systems, in addition to causing a constellation of metabolic derangements. Polypharmacy poisoning with methylxanthines and other agents that result in adrenergic stimulation, such as ephedrine, amphetamines, or cocaine, may be particularly severe.[52 , 184]

Theobromine toxicity is exceedingly rare. There are limited human data, and most published cases are actually veterinary. Animals with theobromine poisoning may experience emesis, incontinence, restlessness, excitement, tachycardia, seizures, coma and death. These characteristic symptoms, as well the pharmacologic similarity between theobromine and other methylxanthines, dictates that management principles for caffeine and theophylline be applied in cases of theobromine toxicity.

Toxicity

Gastrointestinal

In overdose, methylxanthines cause nausea, and most significant acute overdoses result in severe and protracted emesis. Emesis occurs in 75% of cases of acute theophylline poisoning, whereas only 30% of cases of chronic poisoning are characterized by emesis.[163] This emesis is often quite severe and may be difficult to control despite the use of potent antiemetics. This is especially evident with sustained-release theophylline preparations.[5]

Methylxanthines cause an increase in gastric acid secretion and smooth muscle relaxation. These factors contribute to the gastritis

and esophagitis reported in chronic methylxanthine users.[42] Gastritis is noted in drinkers of decaffeinated coffee, so some of the adverse gastric effects associated with coffee drinking may be a result of ingredients other than caffeine alone.

Cardiovascular

Methylxanthines are cardiac stimulants that result in positive inotropy and chronotropy. Dysrhythmias, particularly tachydysrhythmias, are common in methylxanthine overdose. As a result of their adenosine antagonism, supraventricular tachycardias (SVTs) commonly occur in overdose. Tachydysrhythmias, particularly ventricular extrasystoles, are uncommon following therapeutic doses, whereas they are common in overdose.[39 , 124 , 157] In the setting of acute poisoning, generally benign sinus tachycardia is nearly universal in patients without antecedent cardiac disease. In any patient, particularly a patient with underlying cardiac disease, a sinus tachycardia can degenerate to a more severe rhythm disturbance, which is the most common cause of fatality associated with methylxanthines poisoning. Both atrial and ventricular dysrhythmias including SVT, multifocal atrial tachycardia, atrial fibrillation, premature ventricular contractions, and ventricular tachycardia, can result from methylxanthine toxicity.[20 , 160] Electrolyte disturbances, particularly hypokalemia, may be a contributing factor in the development of dysrhythmias. Dysrhythmias occur more commonly and at lower serum concentrations in cases of chronic poisoning. Consequential dysrhythmias occur in 35% of chronic theophylline poisonings, but in only 10% of acute poisonings.[160] These dysrhythmias occur at serum levels of 40â€“80 Âµg/mL in chronic theophylline overdoses, and most commonly at serum levels greater than 80 Âµg/mL in acute overdose. Neonates born to mothers who consumed >500 mg/d of caffeine are more likely to have dysrhythmias than are neonates born to mothers who consumed <250 mg/d of caffeine.[76] Myocardial ischemia and

myocardial infarction may result from acute caffeine or theophylline poisoning.[61, 81, 119]

Tolerance to the pressor effects of methylxanthines develops after several days of use and rapidly disappears after relatively brief periods of abstinence.

At elevated serum concentrations, methylxanthines will result in peripheral vasodilation, causing a characteristic widened pulse pressure. One major mechanism by which hypotension occurs is $Î^2_2$ -adrenergic agonism. In cases of acute theophylline overdose, serum concentrations >100 Âµg/mL are usually associated with severe hypotension.

In therapeutic doses, methylxanthines cause cerebral vasoconstriction, which is a desirable effect when caffeine is used to treat a migraine headache. However, in overdose, this effect likely exacerbates CNS toxicity by diminishing cerebral perfusion.[119] Methylxanthines cause renal vasodilation, which, in addition to the increased cardiac output, results in a mild diuresis.[133]

It has been noted that dietary caffeine use is associated with a slight, but relevant, increase in blood pressure that may contribute to population levels of morbidity and mortality.[91]

Pulmonary

Methylxanthines stimulate the CNS respiratory center, causing an increase in respiratory rate. For this reason, caffeine and theophylline are used to treat neonatal apnea syndromes. Caffeine and theophylline overdose can cause hyperventilation, respiratory alkalosis, respiratory failure, respiratory arrest, and acute lung injury.

Neuropsychiatric

The stimulant and psychoactive properties of methylxanthines, particularly caffeine, elevate mood and improve performance of manual tasks.[24, 34, 90] These stimulant effects are typically considered desirable, and are one reason why caffeine is so widely used. CNS stimulation is an effect sought by users of coffee, tea, cocoa, and chocolate, but CNS stimulation resulting from therapeutic use of theophylline is generally considered to be an undesirable side effect. Caffeine is an effective analgesic adjuvant, possibly because of the stimulant properties of the drug.[123, 125, 154, 155]

Although at low doses methylxanthines improve cognitive performance and elevate mood, with increasing doses they result in adverse effects. Headache, anxiety, agitation, insomnia, tremor, irritability, hallucinations, and seizures can occur with caffeine or theophylline poisoning. In adults, caffeine doses of 50â€“200 mg result in increased alertness, decreased drowsiness, and lessened fatigue, and caffeine doses of 200â€“500 mg produce adverse effects. Children tend to develop CNS symptoms at lower serum theophylline concentrations than adults, and this excitation is a significant clinical disadvantage of theophylline use.

Seizures are a major complication of methylxanthine poisoning. The additional methyl group possessed by caffeine (1,3,7-trimethylxanthine) affords this agent greater CNS penetration relative to theophylline and theobromine, which are dimethylxanthines. Caffeine's ability to both promote and prolong seizures is well recognized, and caffeine has been used to prolong therapeutically induced seizures in electroconvulsive therapy.[49, 99] Seizures resulting from methylxanthines overdose tend to be severe and recurrent, and may be refractory to treatment. Antagonism of adenosine, the endogenous neurotransmitter responsible for halting seizures, contributes to the profound seizures associated with methylxanthine overdose.[56, 62, 161, 191]

When studied prospectively, chronic theophylline toxicity results in seizures in 14% of patients, whereas 5% of acutely poisoned patients experience seizures. In cases of chronic and acute-on-chronic toxicity, seizures are more likely to occur, and they typically occur at lower serum concentrations.[135] Patients at extremes of age, younger than 3 years and older than 60 years, are also more likely to experience seizures with overdose.

Musculoskeletal

Methylxanthines increase intracellular calcium content and increase striated muscle contractility, secondarily decreasing muscle fatigue. They also increase muscle oxygen consumption and increase the basal metabolic rate. These effects are sought by users of methylxanthines to enhance or improve athletic performance or lose weight.[9, 18, 41, 57, 71, 70] Theobromine has the most potent activity on the muscles, over 100 times that of caffeine, and theophylline has the least muscle-stimulating activity. All methylxanthines cause smooth muscle relaxation.

Tremor is the most common adverse effect from methylxanthines. Skeletal muscle excitation, which may include fasciculation, hypertonicity, myoclonus, or even rhabdomyolysis, can occur with methylxanthine overdose.[105, 115, 137, 149, 189] Mechanisms by which rhabdomyolysis may result include increased muscle activity, particularly from seizures, and direct cytotoxicity from excessive sequestered intracytoplasmic calcium. Interestingly, there are multiple case reports of compartment syndrome with rhabdomyolysis resulting from theophylline overdose.[114, 176]

Metabolic

Numerous metabolic derangements may result from acute methylxanthine toxicity, and are similar to other states of excess adrenergic agonism or increased metabolism.[75, 78, 153, 162]

Severe hypokalemia can result from Î²2 -adrenergic stimulation.[178] This results from influx of extracellular potassium into the intracellular compartment despite normal total body potassium content. Both electrocardiographic and neuromuscular complications of hypokalemia may develop. Other effects of Î²2 -adrenergic agonist poisoning include hypomagnesemia, hypophosphatemia.[28 , 101 , 183]

Transient hypokalemia resulting from Î²2 -adrenergic agonism occurs in 85% of patients with acute theophylline overdose, and typically the serum potassium concentration falls to approximately 3 mEq/L.[4 , 165] Stimulation of Na^+ -K^+ -adenosine triphosphatase (ATPase) results in a shift of serum potassium to the intracellular compartment of skeletal muscle. This hypokalemia is only a shift of potassium from the extracellular to the intracellular compartment, not a loss of potassium, and total body potassium stores are unchanged. The significance of hypokalemia in patients with methylxanthine overdose is unclear. Vomiting and renal losses do not contribute significantly to hypokalemia, but these may result in fluid loss. Hyperkalemia may result from overly aggressive repletion of potassium or from rhabdomyolysis.

Metabolic acidosis with increased serum lactate levels is commonly noted as a complication of theophylline overdose.[23 , 109] Tachypnea and respiratory alkalosis secondary to stimulation of the respiratory center may be contributory.

Hyperglycemia, with serum glucose of approximately 200 mg/dL, is common and occurs in 75% of acute theophylline overdoses. Hypophosphatemia, hypomagnesemia, hypocalcemia, hypercalcemia, and ketosis may also result from methylxanthines toxicity.[151] Hyperthermia caused by increased metabolic and muscle activity may result from caffeine and theophylline overdose. Leukocytosis, probably secondary to the high levels of circulating catecholamines, results from acute methylxanthine overdose. This phenomenon apparently lacks clinical significance.

In the absence of seizures or protracted emesis, chronic methylxanthine poisoning does not typically lead to metabolic derangements because such toxicity is an ongoing, compensated process.

Chronic Toxicity

The major difference between acute and chronic toxicity is the duration of exposure to the drug. Patients with chronic toxicity may manifest subtle signs such as anorexia, nausea, palpitations, or emesis, although they may also present with seizures or dysrhythmias.

The patient chronically receiving theophylline or caffeine has higher total body stores, and also often has underlying medical disorders, and may develop toxicity with a smaller amount of additional theophylline or caffeine. Chronic methylxanthine poisoning typically occurs in the setting of therapeutic use of theophylline, and may occur with iatrogenic administration of caffeine or from frequent, chronic consumption of caffeinated products. Patients often manifest subtle signs of illness, such as anorexia, nausea, palpitations, or emesis. However, the initial presentation in these patients, even with theophylline concentrations in the 40â€“60 Âµg/mL range, may be a seizure. In children chronically overdosed with theophylline, the peak serum theophylline concentration may fail to identify those who will progress to life-threatening toxicity. In the absence of protracted emesis or seizures, the initial electrolytes and blood gases are expected to be normal in patients with chronic methylxanthine toxicity.

Chronic Use

An inconclusive link to cancer, heart disease, osteoporosis, hyperlipidemia, and hypercholesterolemia are associated with

use.[60, 63, 74, 145, 187] Excessive consumption of caffeine-containing beverages can cause hypokalemia.[148]

Debate centers on the psychiatric and cognitive effects of chronic theophylline use, particularly in children.[113] To date, evidence suggests that although theophylline may acutely result in excessive CNS stimulation and hyperactivity, chronic use of methylxanthines does not adversely affect children's cognitive development.[19]

Caffeinism

Caffeinism is a syndrome of chronic toxicity resulting from excessive caffeine consumption. It may involve anxiety, palpitations, tremulousness, tachycardia, diuresis, headache, and diarrhea.[180] Patients suffering caffeinism also experience withdrawal symptoms upon abstinence. The chronic toxicity from excessive caffeine use, caffeinism, is a distinctly different entity from caffeine withdrawal.

Caffeine Withdrawal

Caffeine induces tolerance and a withdrawal syndrome, including headache, yawning, nausea, drowsiness, rhinorrhea, lethargy, irritability, nervousness, a disinclination to work, and depression, may result on abstinence.[173] Caffeine withdrawal symptoms are described in neonates born to mothers with consequential caffeine use.[121] The onset of caffeine withdrawal symptoms begins 12â€“24 hours after cessation of caffeine use, and lasts up to 1 week.[73] In a double-blind trial, 52% of adults with moderate caffeine intake developed a withdrawal syndrome on caffeine abstinence.[168]

Reproduction

Massive doses of methylxanthines are teratogenic, but the doses of typical use are not associated with birth defects. Decreased fecundity and adverse fetal outcome are noted in animals with chronic exposure to methylxanthines.[64, 68, 120] Human studies of fertility, fetal loss, and fetal outcome produce divergent results, and the effects of methylxanthines use during gestation are unclear.[87, 94, 126, 130]

Selective Î²2 -Adrenergic Agonist Pathophysiology

Gastrointestinal

Nausea and emesis are common adverse effects of selective Î²2 adrenergic agonist toxicity. Gastrointestinal symptoms of selective Î²2 -adrenergic agonist toxicity are not as severe as those resulting from methylxanthine toxicity and are not expected to require antiemetic therapy.

Cardiac

These drugs increase chronotropy and, in both therapeutic dose and overdose, result in tachycardia. Cardiac dysrhythmias, although described with Î²2 -adrenergic agonist poisoning, are usually supraventricular in origin and clinically inconsequential. Dysrhythmias other than sinus tachycardia should not be routinely attributed to Î²2 adrenergic agonist toxicity until other causes have been excluded.

Myocardial infarction is associated with both albuterol and isoproterenol.[58] Isoproterenol, once a common asthma therapy prior to widespread use of selective Î²2 -adrenergic agonists, has Î²1 - and Î²2 -adrenergic agonist activity and is a well-reported

cause of myocardial infarction. Given the frequency of use of selective Î²2 -adrenergic agonists, as well as toxicity and adverse effects, it seems that myocardial infarction is unlikely to occur with toxicity, but these reports clearly warrant caution about the possibility.

Elevation of the muscle fraction enzyme of creatine phosphokinase (CPK-MM) and of the myocardial band enzymes of creatine phosphokinase (CPK-MB) after large doses of Î²2 -adrenergic agonists, particularly terbutaline infusions and continuous albuterol nebulization, is well described.[44 , 45 , 174] The clinical significance of increased CPK-MB and cardiac troponin in patients receiving terbutaline infusions is unclear and has not been demonstrated to correlate clinically with adverse effects.[40]

Metabolic

Severe hypokalemia can result from Î²2 -adrenergic stimulation because of an influx of extracellular potassium into the intracellular compartment, despite normal total body potassium content. Both electrocardiographic and neuromuscular complications of hypokalemia may develop. This hypokalemia is only a shift of potassium from the extracellular to the intracellular compartment, not a loss of potassium, and total body potassium stores are unchanged. Other effects of Î²2 -adrenergic poisoning include hypomagnesemia and hypophosphatemia.

Diagnostic Testing

An ECG, serum electrolytes, and a serum caffeine or theophylline concentration, as appropriate, are indicated in cases of suspected methylxanthine toxicity. Because toxicity is dose related in acute overdose, serum concentrations of caffeine and theophylline may be loosely applied as a correlate with toxicity.

Some degree of methylation and demethylation of methylxanthines

may occur in patients of all ages, and one methylxanthine poisoning may result in a small elevation in the serum concentration of another methylxanthine metabolite. Overdose of caffeine may result in a spuriously elevated serum measurement for theophylline.[59 , 95] However, the utility of a serum theophylline concentration in cases of caffeine toxicity is undemonstrated; consequently, at this time, such concentrations should not be obtained.

Theophylline concentrations, and to a lesser extent caffeine concentrations, may be used to guide management of poisoning with the respective agents. For these concentrations to be maximally useful, it is important to know whether they reflect acute or chronic poisoning. In the setting of toxicity, serum methylxanthines concentrations should be obtained immediately and then serially every 1â€“2 hours until a downward trend is evident.

Unfortunately, serum caffeine concentrations are usually readily available only in institutions in which neonates are therapeutically treated with caffeine. Serum theophylline concentration is a more readily available laboratory assay, and the greater clinical experience with theophylline in therapeutic dose and in overdose provides a more established correlation between serum theophylline concentration and symptomatology.

Likewise, serum electrolytes, particularly potassium, should be monitored serially as long as the poisoned patient remains symptomatic and such values are in a range that may warrant treatment. Cardiac monitoring should continue until the patient is free of dysrhythmias other than sinus tachycardia, the patient has a decreasing serum methylxanthine level, and the patient is stable. In

patients with systemic illness, hyperthermia, or increased muscle tone, assessing serum creatine phosphokinase (CPK) and urinalysis

to detect rhabdomyolysis are also indicated.

Management

General Principles and Gastrointestinal Decontamination

After assuring adequacy of airway, breathing, and circulation, supportive care and maintenance of vital signs within acceptable limits are the mainstay of therapy for methylxanthine and selective Î²2 -adrenergic agonist toxicity. Decisions regarding gastrointestinal decontamination, including orogastric lavage, administration of activated charcoal, and whole-bowel irrigation, depend on the dosage and type of preparation involved, time since exposure, and the patient's physical condition. Activated charcoal is the only gastrointestinal decontamination that should be routinely considered for selective Î²2 -adrenergic agonist ingestions.

Emesis

Induced emesis is not indicated for selective Î²2 -adrenergic agonist ingestion and should only rarely be considered for minimally symptomatic patients whose methylxanthine ingestions occurred less than 1 hour earlier. A simulated overdose, controlled, volunteer study with sustained-release theophylline was unable to demonstrate reduction of absorption of theophylline in patients treated with syrup of ipecac.[130] Seizures are possible with any significant methylxanthine poisoning, and emesis in a patient experiencing a seizure is an obvious danger. Because the benefits of emetics are undemonstrated and emesis interferes with administration of activated charcoal, induced emesis is rarely considered for methylxanthine poisoning.[6 , 158]

Orogastric Lavage

Orogastric lavage may be considered for patients with potentially toxic methylxanthine ingestions and in patients who require endotracheal intubation. Orogastric lavage may not be effective in removing theophylline tablets, probably because of the large size of the tablets relative to the lumen of the orogastric tube. Selective Î²$_2$ -adrenergic agonist liquid ingestion that occurs within 1 hour prior to treatment may warrant aspiration through a nasogastric tube.

Ingestion of sustained-release theophylline tablets is associated with the formation of bezoars that may be difficult to remove or dislodge. Treatment in such cases has included endoscopic removal.[37]

Activated Charcoal

Activated charcoal may play an important role in the treatment of methylxanthine poisoning and selective Î²$_2$ -adrenergic agonists present in the GI tract prior to absorption, limiting the absorption of a given dose. Although multiple-dose activated charcoal (MDAC) is helpful in the management of methylxanthine toxicity, it is not indicated for selective Î²$_2$ -adrenergic agonist ingestion. MDAC enhances elimination of theophylline by gut dialysis. Such enhanced elimination by gut dialysis is not demonstrated, experimentally or otherwise, for caffeine or theobromine toxicity. Because caffeine is to some extent metabolized to theophylline, in cases of caffeine poisoning, MDAC would, at the very least, enhance elimination of theophylline metabolites. The pharmacologic similarity of the methylxanthines and the relative safety of MDAC therapy warrant the use of such treatment for any methylxanthine toxicity. MDAC is discussed in â€œEnhanced Eliminationâ€• later in this chapter.

Whole-Bowel Irrigation

Treatment of patients with significant ingestions of sustained-release pills may include whole-bowel irrigation (WBI) with a balanced electrolyte solution to enhance gastrointestinal elimination (Antidotes in Depth: Whole-Bowel Irrigation and Other Intestinal Evacuants). Polyethylene glycol electrolyte lavage solution used for WBI may displace theophylline already bound to charcoal.[84] This may be a particular problem in patients who have taken several doses of activated charcoal prior to WBI, in which desorption of methylxanthines from activated charcoal can result in a bolus of methylxanthines available for gastrointestinal absorption. Also, WBI is experimentally demonstrated to provide no additional benefit to activated charcoal in treatment of sustained-released theophylline ingestion.[36] Despite this data, WBI remains the recommended treatment of a patient with an ingestion of sustained-release theophylline.

Selecting a Method of Decontamination

The use of decontamination methods that involve more than minimal risk, specifically orogastric lavage, should only occur after careful consideration of the indications. Potentially life-threatening acute ingestions occurring not more than 1 hour earlier can be treated with orogastric lavage.

Treatment of Gastrointestinal System Toxicity

Phenothiazine antiemetics are contraindicated in methylxanthine poisoning because they are typically ineffective and may lower the seizure threshold. Metoclopramide may be used, but a more potent 5-HT_3 antagonist antiemetic such as ondansetron or granisetron may be required.[48 , 142 , 152] Histamine (H_2) blockers or proton pump inhibitors may be administered to any patient with

hematemesis. Cimetidine is contraindicated because it inhibits CYP450, delaying clearance of methylxanthines.

Treatment of Cardiovascular Toxicity

Hypotension should initially be treated by administration of isotonic intravenous fluid, such as 0.9% sodium chloride solution or lactated Ringer solution, in bolus volumes of 20 mL/kg. If acceptable blood pressure cannot be maintained despite several fluid boluses, or if there are contraindications to fluid bolus, vasopressor therapy should be considered.

Methylxanthine and selective Î²$_2$ -adrenergic agonist toxicity may cause hypotension via Î²$_2$ -adrenergic agonism, therefore administration of vasopressors with Î²$_2$ -adrenergic agonist effects such as epinephrine, dobutamine, or isoproterenol are not preferable. A pure Î±-adrenergic agonist such as phenylephrine is the first-line pressor of choice in such a situation, although norepinephrine is also acceptable (Table 63-1).

Hypotension may be refractory to treatment with intravenous fluid and vasopressor therapy, and in such cases the administration of a Î²-adrenergic antagonist may be warranted.[53] Administration of a Î²-adrenergic antagonist to a hypotensive patient may seem counterintuitive. Methylxanthine-induced hypotension is to a significant extent mediated by Î²$_2$ -adrenergic vasodilation. Nonselective Î²-adrenergic antagonists suppress Î²$_2$ -adrenergic stimulation. In addition, Î²$_1$ -adrenergic antagonism treats tachycardia and any decreased cardiac output that may result from inefficient cardiac

activity. In canines with aminophylline-induced tachycardia and hypotension, administration of esmolol results in a return to normal heart rate and blood pressure, and does not exacerbate hypotension.[65] Propranolol, esmolol, and metoprolol have been used successfully to treat methylxanthine-induced hypotension.[25] ,

[139] It is most appropriate to use a Î²-adrenergic antagonist with a brief duration of action, such as esmolol at least initially, in such circumstances. In the event of an adverse reaction or side effect such as hypotension or bronchospasm, the duration of such a Î²-adrenergic antagonist will be relatively brief. Ideally, any Î²-adrenergic antagonist therapy should be preceded and accompanied by measurement of cardiac output and central venous blood pressure with a device such as a pulmonary artery catheter or a transcutaneous bioinpedance device.[100]

Cardiovascular
Hypotension
Vasopressors
  Phenylephrine
  Norepinephrine

Î²-Adrenergic antagonists
Relatively contraindicated in asthmatic patients.
Only with hemodynamic monitoring.
Supraventricular dysrhythmias
Calcium channel blockers
Î²-Adrenergic antagonists
Relatively contraindicated in asthmatic patients.
Only with hemodynamic monitoring.
Ventricular dysrhythmias
Antidysrhythmics
  Lidocaine

Î²-Adrenergic antagonists
Relatively contraindicated in asthmatic patients.
Only with hemodynamic monitoring.
Gastrointestinal
Emesis
Antiemetics

Metoclopramide
Ondansetron
Granisetron

Hematemesis
Proton pump inhibitors

H_2 antagonists
Cimetidine may decrease clearance of methylxanthines and prolong toxicity.
CNS
Anxiety
Benzodiazepine

Agitation
Barbiturates

Seizure prophylaxis
Propofol

Seizures

Metabolic
Metabolic acidosis
Sodium bicarbonate

Hypokalemia
Potassium chloride

Î²-Adrenergic antagonists
Not routinely recommended for this purpose.

Relatively contraindicated in asthmatic patients.

System	Indication	Therapeutics	Comments

TABLE 63-1. Therapeutics for Methylxanthines and Selective Î²2 -Adrenergic Agonist Poisoning

In situations where drug toxicity is not in question, adenosine or electrical cardioversion are the preferred treatment for SVT, but this is not so for SVT resulting from methylxanthine toxicity. Because of the antagonist effects, administration of adenosine should not be expected to convert a methylxanthine-induced SVT. However, even if adenosine is successfully used to convert an SVT, the effect is likely to be transient. Because methylxanthine toxicity has a global effect on the myocardium, cardioversion, which is effective in electrically â€œreorganizingâ€• depolarization, is unlikely to work, as this SVT does not result from a single locus of aberrant electrical activity.

Primary treatment for methylxanthine-induced SVT includes administration of benzodiazepines, which work to abate CNS stimulation and concomitant release of catecholamines. More focused pharmacologic therapy to treat SVT would be through administration of a conduction-attenuating calcium channel blocker such as diltiazem.

In animal models, treatment of acute theophylline toxicity with the calcium channel blockers verapamil, diltiazem, and nifedipine results in decreased cardiac-related deaths and prevents dysrhythmias, hypotension, myocardial necrosis, and seizures.[185] In addition to their cardiovascular benefit, calcium channel blockers may also afford some neurologic protection and prevent seizures. In the nonasthmatic patient, methylxanthine-induced supraventricular tachycardia and other tachydysrhythmias may be treated by administration of a Î²-adrenergic antagonist.

Correction of hypokalemia may be crucial in methylxanthine poisoning associated with ventricular dysrhythmias. Hypokalemia is a well-described consequence of excess adrenergic agonism, including poisoning from methylxanthines and sympathomimetic

agents. In the absence of associated dysrhythmia, the clinical significance of such hypokalemia is unclear. Such hypokalemia has been experimentally demonstrated to respond to treatment with Î²-adrenergic antagonists.

Treatment of Central Nervous System Toxicity

Administration of a benzodiazepine, such as diazepam or lorazepam, is appropriate treatment for anxiety, agitation, or seizure. The seizures associated with methylxanthine toxicity are severe and often refractory to treatment. Seizures not controlled with one or two therapeutic doses of a benzodiazepine should be treated with a barbiturate such as pentobarbital or phenobarbital, or another suitable sedative-hypnotic such as propofol. No delay should occur before administering such medications. Unsuccessful treatment of methylxanthine-induced seizures with any particular drug should quickly be abandoned in favor of treatment with an additional or more efficacious anticonvulsant. The administration of barbiturates may result in or exacerbate hypotension. Treatment of any aforementioned problem with benzodiazepines, barbiturates, or other sedative-hypnotic may require repeated dosing until clinical effect is achieved.

Administration of phenobarbital to prevent seizures in theophylline-poisoned rabbits and mice increased survival by decreasing the incidence of seizures.[46, 69] Although historically phenobarbital was the recommended drug for such prophylaxis, use of a benzodiazepine, such as lorazepam, seems preferable. Patients at risk for seizure include patients older than 60 years or

younger than 3 years of age; those with chronic overdose and a serum concentration of 40â€“60 Âµg/mL; and acutely overdosed patients with serum levels >100 Âµg/mL.

Phenytoin and fosphenytoin are of no benefit in controlling methylxanthine-induced seizures and they have no role in such treatment.[83 , 118] Retrospective review of human cases demonstrated phenytoin to be ineffective in treating seizures in 21 of 22 cases.[89] Phenytoin is ineffective in the treatment of seizures, results in the occurrence of seizures at an earlier time after overdose, and results in higher mortality when administered to theophylline-poisoned mice.[26]

Treatment of Metabolic Derangements

Patients with symptomatic hypokalemia or hypocalcemia should be treated accordingly. Most cases of mild hypokalemia are well tolerated, but any patient with symptomatic hypokalemia, particularly those associated with ECG changes of T waves or QTc prolongation, should be treated. The frequency of ventricular dysrhythmias in methylxanthine poisoning, may be exacerbated by hypokalemia coupled with increased intrinsic catecholamine release. There is no specific level of hypokalemia that absolutely necessitates treatment.

Cautious administration of potassium to treat symptomatic hypokalemia may be indicated, but this is distinct from higher doses of potassium used in total body potassium repletion. In cases of hypokalemia secondary to Î²-adrenergic agonism, after the Î²-adrenergic agonism returns to baseline, an efflux of potassium from the intracellular compartment occurs along with a concomitant rise of the serum potassium concentration. Overly aggressive attempts to correct hypokalemia may result in hyperkalemia after the Î²-adrenergic agonist effects abate. Acute methylxanthine-induced hypokalemia may be treated with potassium supplementation, but because of the nature of the

problem, excess Î²-adrenergic agonism, potassium supplementation is typically ineffective.

Experimentally, administration of propranolol to theophylline-poisoned dogs prevented or partially reversed hypokalemia, hypophosphatemia, hyperglycemia, and metabolic acidosis, as well as hypotension.[98] Prevention or correction of the metabolic derangements associated with theophylline toxicity by administration of a Î²-adrenergic antagonist is congruent with the fact that these derangements, particularly hypokalemia, are the consequence of Î²-adrenergic agonism. The efficacy of Î²-adrenergic antagonists as therapy for hypokalemia resulting from acute methylxanthine poisoning in humans has not been studied.

The importance of treating hypomagnesemia, hypophosphatemia, and hypocalcemia must be addressed depending on the extent and clinical manifestation as they would for other patients experiencing them. As with hypokalemia, QTc prolongation is an absolute indication for treatment.

Hyperglycemia, likely resulting from increased circulating catecholamines, is common. This hyperglycemia does not necessitate treatment with any type of hypoglycemic agent, both because it is a transient effect and because, in other situations of hyperglycemia resulting from adrenergic agonism, a rebound hypoglycemia may occur.

Treatment of Musculoskeletal Toxicity

The use of benzodiazepines is appropriate treatment for fasciculations, hypertonicity, myoclonus, or rhabdomyolysis. Rhabdomyolysis necessitates aggressive intravenous fluid therapy, possibly with sodium bicarbonate (Antidotes in Depth: Sodium Bicarbonate).

Enhanced Elimination

Fortunately, methylxanthine toxicity lends itself well to several methods of enhanced elimination, including gut dialysis with MDAC, charcoal hemoperfusion, and hemodialysis, as well as lesser-used methods such as continuous arteriovenous hemoperfusion (CAVHP), and plasmapheresis.[16 , 106 , 112]

Infants with methylxanthine poisoning may be too ill, unstable, or small to be treated with hemodialysis or hemoperfusion. Both MDAC and exchange transfusion are effective methods of enhanced elimination in infants, and may be the preferred method of treatment in these patients.[136 , 138 , 166 , 164]

The therapeutic effects of activated charcoal in such cases are much greater than simply limiting absorption of ingested methylxanthines. Activated charcoal, particularly MDAC, allows elimination of theophylline, by way of gastrointestinal dialysis.[13] MDAC is extremely effective in enhancing elimination of theophylline.[22 , 66 , 111 , 134] Experimentally in dogs, rabbits, and human volunteers, activated charcoal administered after IV aminophylline administration resulted in increased systemic clearance and decreased half-life of theophylline.[86 , 103 , 122 , 140] The pharmacologic similarity of the methylxanthines suggest that MDAC may be effective in gut dialyzing caffeine or theobromine, and MDAC certainly will be effective in eliminating any theophylline generated from metabolism of caffeine or theobromine. The efficacy of MDAC, combined with the safety and ease with which this therapy can be administered, makes MDAC the mainstay of enhanced elimination in methylxanthine toxicity. Severe emesis associated with methylxanthine poisoning may result in intolerance of MDAC, and in case series has been shown to necessitate abandonment of MDAC for definitive enhancement of methylxanthine elimination by charcoal hemoperfusion (Antidotes in Depth: Activated Charcoal).[159]

Charcoal hemoperfusion is an effective method of enhanced

elimination of methylxanthines, decreasing theophylline's half-life to 2 hours and increasing its clearance possibly up to 6-fold.[35, 129, 150, 188] Variations of charcoal hemoperfusion, including albumin colloid hemoperfusion, resin hemoperfusion, and charcoal hemoperfusion, in series with hemodialysis, are reported.[38, 85, 107, 143, 172]

Charcoal hemoperfusion in series with hemodialysis may be superior to either method alone because it extends the life of the charcoal hemoperfusion cartridge, increases overall methylxanthine extraction and clearance, and allows fluid and electrolyte abnormalities to be corrected. Charcoal hemoperfusion is typically less readily available and somewhat more complicated than hemodialysis, which may influence selection between charcoal hemoperfusion and hemodialysis as therapy options. Combined hemodialysis and MDAC is an easily performed regimen that provides superior theophylline clearance to hemodialysis alone.

Although employed as an effective treatment modality, hemodialysis has always been less efficient than hemoperfusion in the extracorporeal removal of methylxanthines.[8, 108, 110, 169] Traditionally, hemodialysis was not preferred because methylxanthine elimination rates by hemodialysis were much lower than that those achieved by charcoal hemoperfusion and even lower than MDAC, a much safer, easier, noninvasive method.

Improvement of hemodialysis equipment allows blood flow rates as much as 2 times greater than in the recent past, and has tremendously increased the potential rates of methylxanthine clearance by hemodialysis. As a result, the difference in elimination achieved by hemoperfusion and hemodialysis is insignificant. This fact, in combination with the ability of hemodialysis to correct fluid and electrolyte imbalances, the greater availability of hemodialysis, greater technical ease, and lower complication rates, are resulting in a paradigm shift from considering charcoal hemoperfusion to be the definitive treatment

for significant methylxanthine toxicity to one in which charcoal hemoperfusion and hemodialysis are considered equivalent treatment options.[167]

In the treatment of methylxanthine poisoning, the specific indications for therapy to enhance elimination are not agreed upon. Several studies and clinical experience are the basis for the following suggested indications for extracorporeal elimination by charcoal hemoperfusion, hemodialysis, combined charcoal hemoperfusion/hemodialysis or combined hemodialysis and MDAC.

Most cases of methylxanthine toxicity and overdoses occur with theophylline, and theophylline concentrations tend to be both readily available and to correlate with toxicity. Therefore, many recommendations regarding hemoperfusion and/or hemodialysis for theophylline toxicity use serum theophylline concentration as a guideline. Serum concentrations may not be available in instances of caffeine poisoning and do not exist for theobromine poisoning. The clinical aspects of theophylline management guidelines can be generalized to all methylxanthines.

When indicated, charcoal hemoperfusion and/or hemodialysis should be initiated while patients are still hemodynamically stable, or considered alternately, while they are stable. Charcoal hemoperfusion and/or hemodialysis therapy should be considered for chronic theophylline poisoning associated with a serum theophylline concentration >40â€“60 Âµg/mL or with a deteriorating clinical status.

Charcoal hemoperfusion and/or hemodialysis should be performed any time a methylxanthine exposure results in a serum theophylline concentration >90 Âµg/mL and symptoms, regardless of clinical stability (Table 63-2). Any methylxanthine exposure resulting in a serum theophylline concentration >40 Âµg/mL that is associated with ventricular dysrhythmias, seizures, hypotension unresponsive to fluids, or emesis unresponsive to antiemetics should also be treated with charcoal hemoperfusion and/or

hemodialysis.

1. Acute theophylline serum level >90 Âµg/mL and symptomatic
2. Theophylline serum level >40 Âµg/mL and
   A. Seizures or
   B. Hypotension unresponsive to intravenous fluid or
   C. Ventricular dysrhythmias

TABLE 63-2. Methylxanthine Poisoning: Indications for Charcoal Hemoperfusion and/or Hemodialysis

Seizures, dysrhythmias, or hemodynamic instability are not contraindications for extracorporeal drug removal. To the contrary, these events make administration of such therapy more critical to ensure survival of the patient.

Treatment of Chronic Methylxanthine Toxicity

Treatment of chronic methylxanthine toxicity is determined by the patient's clinical status and by the efficacy of MDAC. The precise serum theophylline or caffeine concentration at which patients with chronic theophylline or caffeine toxicity should receive activated charcoal hemoperfusion or hemodialysis is controversial. For a hemodynamically stable patient without signs of life-threatening methylxanthine toxicity such as ventricular dysrhythmias or seizures, therapy with MDAC may be sufficient. If the serum theophylline or caffeine concentration does not decline following the administration of activated charcoal, or if the patient's clinical status deteriorates, charcoal hemoperfusion or hemodialysis is indicated.

Treatment of Acute-On-Chronic

Methylxanthine Toxicity

Patients chronically receiving theophylline or caffeine who acutely overdose should be initially managed in the same manner as patients with acute overdose, although action concentrations for dialysis are the same as for chronic toxicity. Because total body stores of the methylxanthines are higher in patients who are chronically exposed, the threshold for toxicity may be reached at lower serum concentrations.

Summary

Selective $Î^2_2$ -adrenergic agonists are widely used for the treatment of bronchospasm. Methylxanthines are ubiquitously used by cultures throughout the world. Selective $Î^2_2$ -adrenergic agonist toxicity results from medicinal use of these xenobiotics, and methylxanthine toxicity results from the use of xenobiotics as well as from consumption of methylxanthine-containing foods and beverages. There are significant differences in the clinical presentation and management of patients with acute and chronic methylxanthine poisoning. Supportive care and treatment of gastrointestinal, cardiovascular, CNS, metabolic, and musculoskeletal toxicities are the mainstay of therapy. The unique properties of methylxanthines necessitate specific therapies for the gastrointestinal, cardiovascular, and CNS toxicities of methylxanthines. With some unique exceptions, selective $Î^2_2$ -adrenergic agonist toxicity is usually well tolerated and only requires supportive care. Methods of enhanced elimination, particularly extracorporeal elimination by activated

charcoal hemoperfusion, hemodialysis, or activated charcoal hemoperfusion and hemodialysis in series, as well as gut dialysis with MDAC, are effective treatments for methylxanthine toxicity.

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Chapter 64
Local Anesthetics

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Brian Kaufman

A 30-year-old woman presented to the emergency department 4 hours after she had undergone a laser epilation treatment. In preparation for the procedure, 150 g EMLA (eutectic mixture of local anesthetics) cream (5 tubes) was applied to her lower extremities under occlusive dressings. One hour later, she began to experience light-headedness, dyspnea, tongue numbness, and muscular twitching. The only medications she was taking were sertraline and an oral contraceptive. On physical examination she was alert and in mild respiratory distress with both perioral and acral cyanosis, which was unresponsive to supplemental oxygen. Her vital signs were: blood pressure, 130/80 mm Hg; heart rate, 120 beats/min; respiratory rate, 20 breaths/min; temperature 98.6Â°F (37Â°C). Her height was 163 cm, and she weighed 74 kg. Her lungs were clear, and her heart sounds were normal. Her abdomen was soft and nontender with normal bowel sounds. Bilateral pretibial first-degree burns were still present from a prior laser treatment. The remainder of her physical examination was

normal. Pulse oximetry revealed 84% saturation while she was breathing 100% oxygen. An arterial blood gas (ABG) obtained on 100% oxygen was: pH, 7.45; PCO_2 , 36 mm Hg; PO_2 , 385 mm Hg. Her methemoglobin level was 20% by cooximetry. The patient received methylene blue 70 mg IV over 5 minutes, and all symptoms and signs improved within 1 hour. A repeat methemoglobin level was 2.7%. Her lidocaine concentration, drawn several hours after initial placement of the EMLA cream, was 0.68 Âµg/mL, confirming systemic absorption from the EMLA cream. The patient remained stable and was discharged home.[41]

Local anesthetics are drugs that block excitation of, and transmission along, a nerve axon in a predictable and reversible manner. The anesthesia produced is selective to the chosen body part in contrast to the nonselective effects of a general anesthetic. Local anesthetics do not require the circulation as an intermediate carrier, and they usually are not transported to distant organs. Therefore, the actions of local anesthetics are largely confined to the structures with which they come into direct contact. Local anesthetics may provide analgesia in various parts of the body by topical application, injection in the vicinity of peripheral nerve endings and major nerve trunks, or via instillation within the epidural or subarachnoid spaces. The various local anesthetic agents differ with regard to potency, duration of action, and degree of effects on sensory and motor fibers. Toxicity may be local or systemic. With systemic toxicity, the central nervous system (CNS) and cardiovascular systems typically are affected.

History

Until the 1880s, the only drugs available for pain relief were centrally acting depressants such as alcohol and opioids, which blunted the perception of pain rather than attacking the root cause. The coca shrub (*Erythroxylon coca*) was brought back to Europe from Peru by Karl Von Scherzer, an Austrian explorer, in

the mid-1800s. Some of the coca leaves were analyzed by the chemist Albert Niemann, who in 1860 successfully extracted and named the active principle, the *alkaloid cocaine* (Chap. 74). Although Niemann noted that cocaine crystals numbed his tongue, it was not until 1868 that the Peruvian army surgeon Moreno y Mayz initially suggested that cocaine might have medical applications as a local anesthetic. Sigmund Freud was interested in the analeptic actions of cocaine, which he hoped would help cure morphine addiction. Freud obtained a supply of cocaine from the manufacturing firm Merck and shared the supply with his good friend Carl Koller, who was a junior intern in the Ophthalmological Clinic at the University of Vienna. After dissolving coca powder in distilled water, Koller instilled the solution in the conjunctival sacs of a frog, a rabbit, and a dog. He then was able to touch their cornea without any evidence of a reflex blink. He then experimented on his own eye and that of his laboratory assistant, and he demonstrated that the eye became insensitive to touch and injury within 1 minute. In 1884, Koller performed an operation for glaucoma with topical cocaine anesthesia. Four days later, his findings were presented at the Congress of Ophthalmology in Heidelberg. Dr. Henry Noyes, an American who attended the Heidelberg meeting, reported the discovery in a letter to the *New York Medical Record* , and the news

spread rapidly. Within 1 year, cocaine was in worldwide use as a pain-relieving drug for surgery of the eye and was being tested on other mucous membranes, such as the upper airway.

After the 1884 publication of Noyes' letter, several surgeons investigated the direct injection of cocaine into tissues. One year after Koller's discovery, Halsted reported on more than 1000 cases in which cocaine infiltration anesthesia was used at the Johns Hopkins Hospital.[42] Bier reported human spinal anesthesia and the associated spinal headache in 1899.

Although the clinical benefits of cocaine anesthesia were great, so

were its toxic and addictive potential. At least 13 deaths were reported in the first 7 years following the introduction of cocaine. Within 10 years following the introduction of cocaine as a regional anesthetic, reviews of â€œcocaine poisoningâ€• appeared in the literature.[65, 83] The toxicity of cocaine, coupled with its tremendous advantages for surgery, led to a search for less toxic substitutes. After the elucidation of cocaine's chemical structure (the benzoic acid methyl ester of the alkaloid ecgonine) in 1895, other benzoic acid esters were examined. Synthetic compounds with local anesthetic activity were introduced, but they either were highly toxic or irritating or had an impractical brief clinical effectiveness. In 1904, Einhorn synthesized procaine, but its short duration of action limited its clinical utility. Research then focused on synthesis of drugs with more prolonged duration of action.

The potent, long-acting local anesthetics dibucaine and tetracaine were synthesized in 1925 and 1928, respectively, and were introduced into clinical practice. However, these anesthetics could not be used safely for regional anesthetic techniques because of systemic toxicity. From the large volumes of drug that were required. These drugs were very useful, however, for spinal anesthesia.

Lofgren synthesized the prototypical local anesthetic lidocaine from a series of aniline derivatives in 1943. This amino amide combined high tissue penetrance and moderate duration of action with acceptably low systemic toxicity. Additionally, the metabolites of lidocaine did not include *para* -aminobenzoic acid, which was the reported cause of allergic reactions to the amino ester anesthetics. Subsequent to lidocaine's release in 1944, several other amino amide compounds were synthesized and introduced into clinical practice. These include mepivacaine in 1956, prilocaine in 1959, bupivacaine in 1963, etidocaine in 1971, and ropivacaine in 1996.

Epidemiology

Considering the frequency with which local anesthetics are administered, both within and outside healthcare facilities, clinically significant toxic reactions are few and usually iatrogenic. In a report of 1106 fatalities resulting from toxic exposures reported to US Poison Control Centers in 2003, 3 were secondary to local anesthetics.(See Chap. 130) Most poisonings result from inadvertent injection of a therapeutic dose into a blood vessel, repeated use of a therapeutic dose, or unintentional administration of a toxic dose. The amide local anesthetics have largely replaced the esters because of increased stability and relative absence of hypersensitivity reactions. Differences in metabolism of these agents, however, result in a much higher likelihood of systemic toxicity. Bupivacaine, a potent and long-acting amide anesthetic, has the highest potential for cardiovascular toxicity, which can be refractory to conventional therapy. Its pure S-enantiomer levobupivacaine and the structurally similar amide ropivacaine are alternatives having similar anesthetic properties and less potential for cardiovascular toxicity.

Poisoning from topical benzocaine is relatively common because of the large number of nonprescription products available for treatment of teething and hemorrhoids and because of the widespread use of benzocaine, mostly as a spray, for topical mucosal anesthesia prior to intubation, upper endoscopy, and esophageal echocardiography. Methemoglobinemia accounts for the majority of adverse events. With nonprescription use, toxic effects following exposure typically are mild, and death rarely occurs. Toxicity usually occurs as a therapeutic misadventure, but child abuse or neglect should be considered if the patient is younger than 2 years, and suicide should be considered in older children and adults. On the other hand, benzocaine spray may be the most important cause of severe acquired methemoglobinemia in the hospital setting.[3] Between November 1997 and March 2002,

the US FDA received 198 reported adverse events secondary to benzocaine products. One hundred thirty-two cases (66.7%) involved definite or probable methemoglobinemia; most were serious adverse events, and 2 deaths occurred.[74] In these cases, a single spray of unspecified duration of 20% benzocaine was the dose most commonly reported. Because of the difficulty in limiting the dose to the manufacturer's recommendation given the current formulations available, these authors recommend a metered dosing preparation and prominent package warnings.

Pharmacology

Chemical Structure

Local anesthetics fall into 1 of 2 chemically distinct groups: amino esters and amino amides (Figure 64-1). The basic structure of all local anesthetics has three major components. A lipophilic, aromatic ring is connected by an ester or amide linkage to a short alkyl, intermediate chain that is bound to a hydrophilic tertiary (or, less commonly, secondary) amine. The amine is a base (proton acceptor) that is partially charged in the physiologic pH range.

Mode of Action

All local anesthetics function by reversibly binding to specific receptor proteins within the membrane-bound sodium channels of conducting tissues. These receptors can be reached only via the cytoplasmic side of the cell membrane, that is, by intracellular drug. Blockade of ion conductance through the sodium channel eventually leads to failure to form and propagate action potentials. The analgesic effect results from inhibiting axonal transmission of the nerve impulse in small-diameter myelinated and unmyelinated nerve fibers carrying pain and temperature sensation. Conduction block of these fibers occurs at lower concentrations than in the

larger fibers responsible for touch, motor function, and proprioception.[22] This likely occurs in myelinated nerves because smaller fibers have closer spacing of the nodes of Ranvier. Given that a fixed number of nodes must be blocked in order for conduction failure to occur, the shorter critical length of nerve is reached sooner by the locally placed anesthetic in small fibers.[36] For unmyelinated fibers, the smaller diameter limits the distance that such fibers can passively propagate the electrical impulse. In addition, differential nerve block may relate to voltage and time dependence of the affinity of local anesthetics to the sodium channels. The sodium channel can exist in three states. (See Chap. 23 .) At resting membrane potential or in the hyperpolarized membrane, the channel is closed to sodium conductance. With an appropriate

activating stimulus, the channel opens, allowing rapid sodium influx and membrane depolarization. Milliseconds later, the channel is inactivated, terminating the fast sodium current. Blockade is much stronger for channels that are activated (open) or inactivated than for channels that are resting. Pain fibers have a higher firing rate and longer action potential (ie, more time with the sodium channel open or inactivated) than other fiber types and therefore are more susceptible to local anesthetic action.[48]

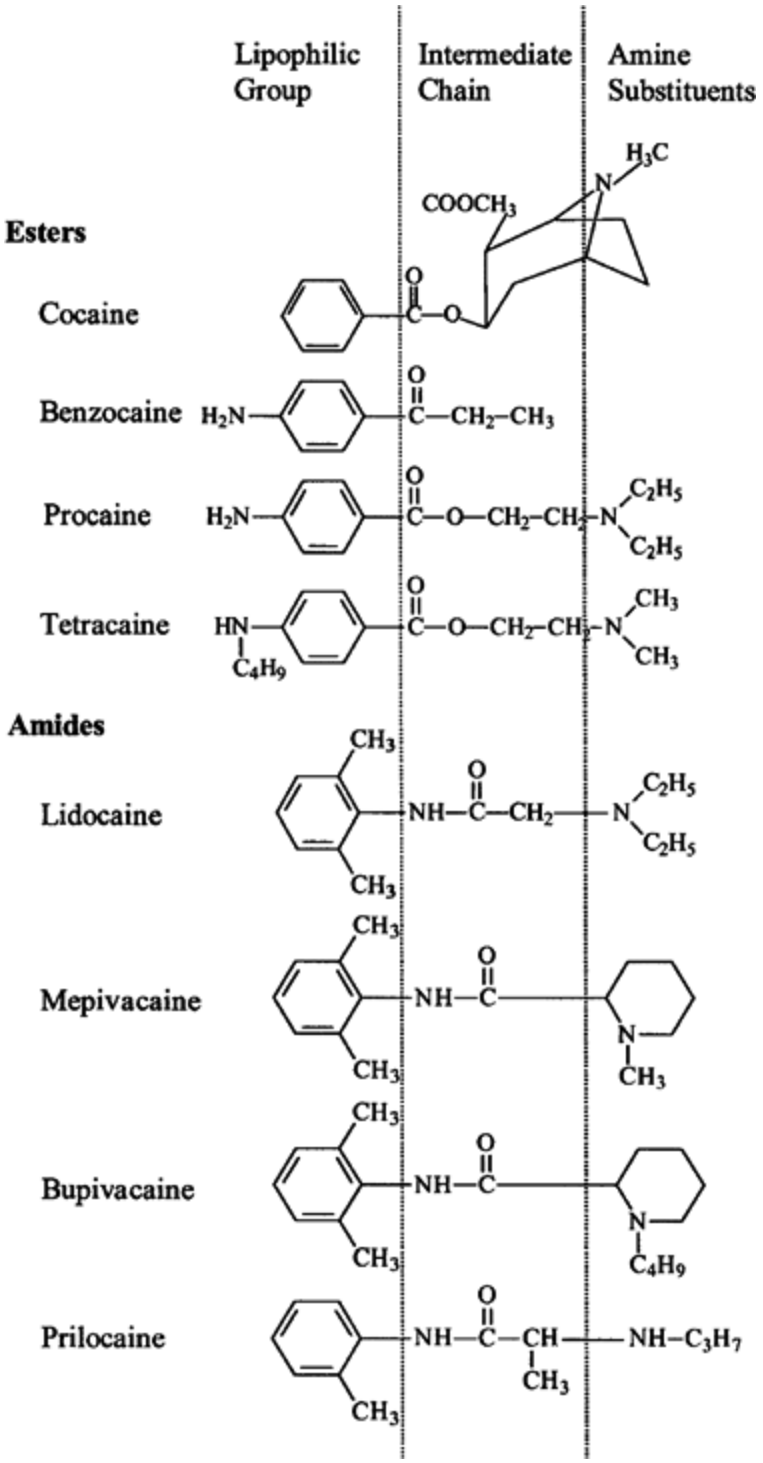

Figure 64-1. Representative local anesthetics in common clinical use.

These effects also occur in other conductive tissues in the heart and brain that rely on sodium current. As such, sodium channel blockade initially was believed to be the sole cause of systemic toxic reactions. However, the mechanisms of toxic effects are more complex, especially in the heart, and can occur at systemic concentrations lower than previously thought.[67] Local anesthetics may interact with other cellular systems at clinically relevant concentrations. For example, lidocaine inhibited muscarinic signaling in *Xenopus* oocytes at <50% of the concentration required for sodium channel blockade.[47] Growing evidence indicates that local anesthetics can directly affect many other organ systems and functions (eg, coagulation, immune, and respiratory systems) at concentrations much lower than those required to achieve sodium channel blockade.[16, 46, 47] Study of these less well-described effects may help elucidate both therapeutic and toxic phenomenon that are incompletely explained.

Physicochemical Properties

The primary determinant of a local anesthetic's onset of action is pK_a which affects the drug's lipophilicity (Table 64-1). All of the local anesthetics are weak bases, with a pK_a between 7.6 and 9.1. At physiologic pH (7.4), drugs with a lower pK_a have more uncharged molecules that are free to cross the nerve cell membrane, producing a faster onset of action than drugs with a higher pK_a . Onset of action also is influenced by the total dose of local anesthetic administered, which affects the concentration available for diffusion.

Local anesthetic potency is highly correlated with the drug's lipid solubility. Therefore, the aromatic side of the anesthetic is the primary determinant of potency. The hydrophilic amine is important in occupying the sodium channel, which involves an ionic interaction with the charged form of the tertiary amine. The

length of the intermediate chain is another determinant of local anesthetic activity, with 3â€“7 carbon-equivalents providing maximal activity.[22] Shorter or longer intermediate chain length is associated with rapid loss of local anesthetic action, suggesting that a critical length of separation of the aromatic group from the tertiary amine is required for sodium channel blockade to occur.

The degree of protein binding influences the duration of action of a local anesthetic. Drugs with greater protein binding remain associated with the neural membrane for a longer time interval and therefore have a longer duration of action.[22] When high plasma concentrations are achieved, a higher degree of protein binding increases the risk for cardiac toxicity.

Pharmacokinetics

A distinction must be made between local disposition (distribution and elimination) and systemic disposition. Local distribution is influenced by several factors, including spread of local anesthetic by bulk flow, diffusion, transport via local blood vessels, and binding to local tissues. Local elimination occurs through systemic absorption, transfer into the general circulation, and local hydrolysis of amino ester anesthetics. Systemic absorption decreases the amount of local anesthetic that is available for anesthetic effect, thereby limiting the duration of the block. Systemic absorption is dependent on the avidity of binding of local anesthetics to tissues near the site of injection and on local perfusion. Both of these factors vary with the site of injection.

Because of their lipophilicity, local anesthetics readily cross cell membranes, the bloodâ€“brain barrier, and the placenta. Once absorbed, systemic tissue distribution is highly dependent on tissue perfusion. After local anesthetics enter into the venous circulation, they pass through the lungs where significant uptake may occur, thereby lowering peak arterial concentrations. Thus, the lung may serve as a buffer to systemic toxicity.[58] This

mechanism, however, has saturable kinetics. Part of the reason why most local

anesthetic-induced seizures result from unintentional intravascular injection rather than absorptive uptake is that lung uptake of these drugs appears to exceed 90%. The very high peak venous concentrations produced by rapid injection usually are necessary to produce toxic arterial drug concentrations.

Esters
Chloroprocaine
9.3
Unknown
Intermediate
Short
10
Cocaine
8.7
92
Low
Medium
3
Procaine
9.1
5
Low
Short
10
Tetracaine
8.4
76
High
Long
3
Amides

Bupivacaine	8.1	95	High	Long	2	
Etidocaine	7.9	95	High	Long	4	
Lidocaine	7.8	70	Low	Medium	4.5	
Mepivacaine	7.9	75	Intermediate	Medium	4.5	
Prilocaine	8.0	40	Intermediate	Medium	8	
Ropivacaine	8.2	95	Intermediate			

Long
3
Modified after references 48 and 97.

pK_A	Protein Binding (%)	Relative Potency	Duration of Action	Approximate Maximum Allowable SQ Dose (mg/kg)

TABLE 64-1. Pharmacologic Properties of Local Anesthetics

All local anesthetics, except cocaine, cause peripheral vasodilation by direct relaxation of vascular smooth muscle. Vasodilation enhances vascular absorption of the local anesthetic. Addition of epinephrine (5 Âµg/mL or 1:200,000) to the local anesthetic solution decreases the rate of vascular absorption, thereby improving the depth and prolonging the duration of local action. An epinephrine/local anesthetic mixture also decreases bleeding into the surgical field and serves as a marker for inadvertent intravascular injection when a test dose of the mixture is injected through a needle or catheter.[71]

Significant drawbacks to epinephrine use include uncomfortable side effects such as palpitations and tremors, local tissue ischemia (eg, if used in the digits), and life-threatening systemic adverse reactions in susceptible patients (eg, myocardial ischemia, hypertensive crisis). Inadvertent intravascular injection of local anesthetics mixed with epinephrine can be fatal.[62]

The two classes of local anesthetics undergo metabolism by different routes (Chap. 74). The amino esters are rapidly metabolized by plasma cholinesterase to the major metabolite *para* -aminobenzoic acid (PABA). The amino amides are metabolized more slowly in the liver to a variety of metabolites unrelated to PABA.[21] Patients with atypical or low concentrations

of plasma cholinesterase are at increased risk for systemic toxicity from ester local anesthetics. Factors that decrease hepatic blood flow or impair hepatic function increase the risk for toxic reactions to the amino amides and make management of serious reactions more difficult. The patient's age, as it relates to liver enzyme activity and plasma protein binding, influences the rate of metabolism of local anesthetics. The lidocaine half-life following intravenous administration averaged 80 minutes in volunteers aged 22â€“26 years, whereas the half-life was 138 minutes in those aged 61â€“71 years[79] (Chap. 61). Newborn infants with immature hepatic enzyme systems have prolonged elimination of amino amides, which is associated with seizures when high continuous infusion rates are used.[1 , 68]

Lidocaine elimination is reduced by congestive heart failure or coadministration of xenobiotics that reduce hepatic blood flow, thus explaining the increased risk of toxicity with cimetidine and propranolol.[89] Propranolol also potentially decreases hepatic enzyme activity. Administration of one local anesthetic increases the free plasma fraction of another drug by displacement from protein-binding sites.[51]

Local anesthetics are often mixed to take advantage of desirable pharmacokinetics. Ideally, rapid-acting, relatively short-duration drugs such as chloroprocaine or lidocaine can be combined with longer latency, long-acting drugs such as tetracaine or bupivacaine. In practice, the advantages of the mixtures are small and toxicities are additive.[5]

Local anesthetics usually cannot penetrate intact skin in sufficient quantities to produce reliable anesthesia.[11] Efficient skin penetration requires the combination of a high water content and a high concentration of the water-insoluble base form of the local anesthetic. This combination of properties has been achieved by mixing lidocaine and prilocaine in their base forms in a 1:1 ratio (eutectic mixture of local anesthetics (EMLA).[14] Application for at

least 45 minutes is required to achieve adequate dermal analgesia. Local anesthetic uptake continues for several hours during application. A liposomal formulation of 4% lidocaine (ELA-Max) facilitates skin absorption. It is as effective as EMLA for topical anesthesia and is not associated with methemoglobinemia or significant systemic lidocaine absorption.[31]

Clinical Manifestations of Toxicity

Toxic Reactions

Regional Side Effects and Tissue Toxicity

All local anesthetics, at some concentration, are directly cytotoxic to nerve cells. However, in clinically relevant doses, these drugs rarely produce localized nerve damage.[55, 78] Significant direct neurotoxicity can result from intrathecal injection or infusion of local anesthetics for spinal anesthesia. In this setting, studies suggest lidocaine has increased risk for both persistent lumbosacral neuropathy and a syndrome of painful but self-limited postanesthesia buttock/leg pain or dysesthesia referred to as *transient neurologic symptoms*.[50] Nerve damage often is attributed to use of excessively concentrated solutions or inappropriate formulations. Several reports of cauda equina syndrome are associated with use of hyperbaric 5% lidocaine solutions

for spinal anesthesia. Hyperbaric solutions are more dense than cerebrospinal fluid. This neurotoxicity appears to be a phenomena that occurs when the anesthetic is injected through narrow-bore needles or through continuous spinal catheters. This process can result in very high local concentrations of the anesthetic that might pool around the sacral roots because of inadequate mixing.[90] The mechanism of this neurotoxic effect is unknown but

is believed to be independent of sodium channel blockade.[50] Because an equally effective block can be achieved with injection of larger and volumes of less concentrated drug, 5% lidocaine should be avoided and bupivacaine used instead.

Similar severe neurotoxic reactions have occurred following massive subarachnoid injection of chloroprocaine during attempted epidural anesthesia.[87] The neurotoxicity initially appeared to be associated with use of the antioxidant sodium bisulfite and the low pH of the commercial solution rather than use of the anesthetic per se.[105] Although chloroprocaine has been reformulated without bisulfite, new animal data suggest that the anesthetic itself may have been responsible for the neurotoxicity.[101] Skeletal muscle changes are observed following intramuscular injection of local anesthetics, especially the more potent, longer-acting agents. The effect is reversible and muscle regeneration is complete within 2 weeks following injection of local anesthetics.[8]

Systemic Side Effects and Toxicity

Allergic Reactions

Allergic reactions to local anesthetics are extremely rare. Less than 1% of all adverse drug reactions caused by local anesthetics result from true immunoglobulin (Ig)E-mediated allergic reactions.[39] In fact, in a study designed to determine the prevalence of true local anesthetic allergy in patients referred to an allergy clinic for suspected hypersensitivity, skin prick and intradermal testing were negative for all 236 subjects tested.[9] The amino esters are responsible for the majority of true allergic reactions. When hydrolyzed, the amino ester local anesthetics produce PABA, a known allergen. Cross-sensitivity to other amino ester anesthetics is common. Some multidose commercial preparations of amino amides may contain the preservative methylparabens, which is chemically related to PABA and is the

most likely cause of the much rarer allergic reaction to amino amides. Thus, preservative-free amino amides, including lidocaine, can be used safely in patients who have reactions to drug preparations containing methylparabens, unless the patient is specifically sensitive to lidocaine. If the patient with a history of prior allergic reaction to a particular drug requires a local anesthetic, a drug from the opposite class can be chosen because there is no cross-reactivity between the amides and esters.

Methemoglobinemia

Methemoglobinemia is reported frequently as an adverse effect of topical and oropharyngeal benzocaine use and occasionally with lidocaine, tetracaine, or prilocaine use. The diagnosis can be made by direct measurement of methemoglobin concentration with a cooximeter. Most reports of methemoglobinemia associated with local anesthetics are the result of an excessive dose, a break in the normal mucosal barrier for topical anesthetics, or deficiency of a congenital reducing enzyme such as methemoglobin reductase (Chap. 122).

Benzocaine is metabolized to aniline and then further metabolized to phenylhydroxylamine and nitrobenzene, all potent oxidizing agents (Chap. 122). Although reports describe methemoglobinemia resulting from standard doses of benzocaine topical oropharyngeal spray given for laryngoscopy or gastrointestinal upper endoscopy,[29 , 74] affected patients commonly have abnormal mucosal integrity, as occurs with thrush or mucositis. Prilocaine is an amino ester local anesthetic primarily used in obstetric anesthesia because of its rapid onset of action and low systemic toxicity in both mother and fetus. Use of large doses of prilocaine can lead to development of methemoglobinemia.[45 , 60] Prilocaine is an aniline derivative that, when metabolized in the liver, produces *ortho* -toluidine, another oxidizing agent.[45] A direct relationship exists between the amount

of epidural prilocaine administered and the incidence of methemoglobinemia. A dose greater than approximately 8 mg/kg is generally necessary to produce symptoms, which may not become apparent until several hours after epidural administration of the drug. Standard doses of EMLA cream used for circumcision in term neonates are associated with minimal production of methemoglobin, but risks may be increased in the neonate with metabolic disorders.[99] EMLA-associated methemoglobinemia is reported in children and, rarely, in adults. When clinically indicated, affected patients with symptomatic methemoglobinemia should be treated with intravenous methylene blue (Chap. 122 and Antidotes in Depth: Methylene Blue).

Other Reactions

The most common adverse reactions to local anesthetics are vasovagal reactions.[103]

Systemic Toxicity

Systemic toxicity for all local anesthetics correlates with plasma concentrations. Factors that determine the concentration include (1) dose of the drug, (2) rate of administration, (3) site of injection (absorption occurs more rapidly and completely from vascular areas, such with neck blocks and intercostal blocks), (4) presence or absence of a vasoconstrictor, and (5) drug-specific factors such as the degree of tissueâ€“protein binding, fat solubility, and pK_a of the drug.[72] The brain and heart are the primary target organs for systemic toxicity because of their rich perfusion, moderate tissueâ€“blood partition coefficients, lack of diffusion limitations, and presence of cells that rely on voltage-gated sodium channels to produce an action potential. Recommendations for maximal local anesthetic doses designed to minimize the risk for systemic toxic reactions have been published.[97] These maximal recommended doses aim to prevent

infiltration of excessive drug. However, because most episodes of systemic toxicity from local anesthetics, with the exception of methemoglobinemia from topical drug, occur secondary to unintentional intravascular injection rather than from overdosage, limiting the maximal dose is irrelevant for preventing most toxic systemic reactions.[96] Toxicity also is related to the metabolism for a given local anesthetic. The rapidity of elimination from the plasma influences the total dose delivered to the CNS or heart. The amino esters are rapidly hydrolyzed in the plasma and eliminated, explaining their relatively low potential for systemic toxicity. The amino amides have a much greater potential for producing systemic toxicity because termination of the therapeutic effect of these drugs is achieved through redistribution and slower metabolic inactivation.[35] Another factor that creates difficulty in specifying the minimal toxic plasma concentration of lidocaine results from the fact that its *N* -dealkylated metabolites are pharmacologically active. These factors make it difficult to establish safe doses of local anesthetics. Table 64-2 summarizes the estimates of minimal toxic doses of various local anesthetics.

Procaine
19.2
Chloroprocaine
22.8
Tetracaine
2.5
Lidocaine
6.4
Mepivacaine
9.8
Bupivacaine
1.6
Etidocaine
3.4
Adapted with permission from Durrani Z, Winnie AP: Brainstem

toxicity with reversible locked-in syndrome after intrascalene brachial plexus block. Anesth Analg 1991;72:249â€“252.

Local Anesthetic	Minimum IV Toxic Dose of Local Anesthetic in Humans (mg/kg)

TABLE 64-2. Toxic Doses of Local Anesthetics

CNS Toxicity

Systemic toxicity in humans usually presents with CNS symptoms. Intravenous infusion studies in volunteers demonstrated an inverse relationship between the anesthetic potency of various local anesthetics and the dosage required to induce signs of CNS toxicity.[95] A similar relationship exists between the convulsive serum concentration of various local anesthetics and their relative anesthetic potency. In humans, seizures are reported at serum concentrations of approximately 2â€“4 Âµg/mL for bupivacaine and etidocaine. Concentrations in excess of 10 Âµg/mL usually are required for production of seizures when less potent drugs such as lidocaine are administered. Despite the strong relationship between local anesthetic potency and CNS toxicity, several other factors influence the CNS effects, including the rate of injection, drug interactions, and acidâ€“base status.[24]

The rapidity with which a particular serum concentration is achieved influences the toxicity of the anesthetic. Volunteers could tolerate an average dose of 236 mg etidocaine and a serum concentration of 3 Âµg/mL before onset of CNS symptoms when the anesthetic was infused at a rate of 10 mg/min. However, when the infusion rate was increased to 20 mg/min, the same individuals could tolerate only an average of 161 mg of the drug, which produced a serum concentration of approximately 2 Âµg/mL.[94]

Centrally acting drugs can modify the clinical presentation of a systemic toxic reaction. In general, CNS-depressant drugs minimize the signs and symptoms of CNS excitation (raise the threshold for local anesthetic-induced seizures), whereas flumazenil increases the sensitivity of the CNS to the amino amide anesthetics.[13]

Both metabolic and respiratory acidosis increase local anesthetic-induced CNS toxicity. Acidemia decreases plasma protein binding, increasing the amount of free drug available for CNS diffusion despite promoting the charged form of the amine. The convulsive threshold of various local anesthetics is inversely related to arterial PCO_2 .[26 , 32 , 33] Hypercarbia can lower seizure threshold by several mechanisms: (1) increased cerebral blood flow, which increases drug delivery to the CNS; (2) increased conversion of the drug base to the active cation in the presence of decreased intracellular pH; and (3) decreased plasma protein binding, which increases the amount of free drug available for diffusion into the brain.[15 , 26 , 32 , 33]

A gradually increasing lidocaine serum concentration produces a common pattern of symptoms and signs (Figure 64-2). In the awake patient, the initial symptoms are subjective and include tinnitus, light-headedness, circumoral numbness, disorientation, confusion, auditory and visual disturbances, and lethargy. Subjective side effects occur at serum concentrations between 3 and 6 Âµg/mL. Significant psychological effects of local anesthetics also are reported. Near-death experiences and delusions of actual death have been described as specific symptoms of local anesthetic toxicity.[63] Thus, appearance of psychologic symptoms during administration of local anesthetics should not be disregarded as unrelated nervous reactions or effects of sedatives given as premedication but rather as a possible early sign of CNS toxicity.

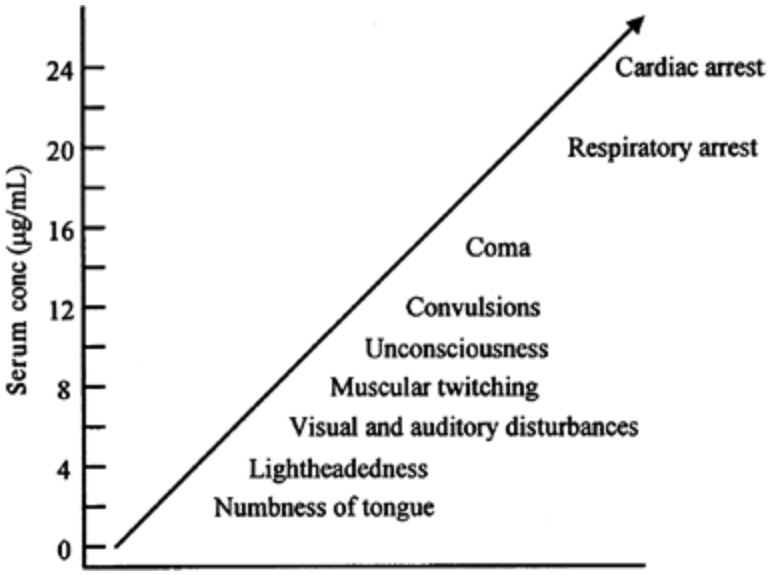

Figure 64-2. Relationship of signs and symptoms of lidocaine toxicity to lidocaine serum concentrations.

Objective signs, usually excitatory, then develop and include shivering, tremors, and ultimately generalized tonicâ€“clonic seizures. Objective CNS toxicity usually is evident at concentrations between 5 and 9 Âµg/mL. Seizures can occur at concentrations above 10 Âµg/mL, with higher concentrations producing coma, apnea, and cardiovascular collapse. The excitatory phase has a wide range of intensity and duration, depending on the chemical properties of the local anesthetic. With the highly lipophilic, highly protein-bound drugs, the excitement phase is brief and mild. Toxicity from a large intravenous bolus of bupivacaine can even present without any CNS excitement and with bradycardia, cyanosis, and coma as the first signs.[92] Rapid intravascular injection of lidocaine can produce a brief excitatory phase, followed by generalized CNS depression with respiratory arrest. Seizures may follow even a small dose injected into the vertebral or carotid artery (as may occur during stellate ganglion block).[54] A relative overdose produces a slower onset of symptoms (usually within 5â€“15 minutes of drug injection), with irritability progressing into seizures.

The mechanism of the initial CNS excitation involves a selective block of cerebral cortical inhibitory pathways in the amygdala.[100, 104] The resulting increase in unopposed excitatory activity leads to seizures. As the concentration rises further, both inhibitory and excitatory neurons are blocked, and generalized CNS depression ensues.

Treatment of Local Anesthetic CNS Toxicity

At the first sign of possible CNS toxicity, administration of the drug must be discontinued. One hundred percent oxygen should be supplied immediately, and ventilation should be supported if necessary. Minor symptoms usually do not require treatment,

provided adequate respiratory and cardiovascular function are maintained. The patient must be followed closely so that progression to more severe effects can be detected.

Although most seizures caused by local anesthetics are self-limited, they should be treated quickly because the hypoxia and acidosis produced by prolonged convulsions may increase both CNS and cardiovascular toxicity.[75, 77] Intubation is not mandatory, and the decision to intubate must be individualized. Maintaining adequate ventilation is of proven value, but modest hyperventilation in theory might decrease CNS toxicity. By decreasing CNS extraction of drug, lowering extracellular potassium, and hyperpolarizing the neuronal cell membrane, normalizing (lowering) PCO_2 may decrease the affinity or accelerate separation of the local anesthetic from the sodium channel. Barbiturates and benzodiazepines have been used for treatment of local anesthetic-induced seizures. An induction dose of thiopental can rapidly terminate a seizure and acts more quickly than benzodiazepines, but any of these agents can exacerbate

circulatory and respiratory depression.[24, 70] Propofol 1 mg/kg IV was as effective as thiopental 2 mg/kg IV in stopping bupivacaine-induced seizures in rats and has been used successfully in a patient with uncontrolled muscle twitching secondary to local anesthetic toxicity.[10, 44] However, propofol can cause significant bradydysrhythmias and even asystole, especially when propofol is used with other drugs that cause bradycardia. Whether propofol interacts with local anesthetics to enhance their bradydysrhythmic effects is not known, and it is not possible to generally recommend propofol over barbiturates and benzodiazepines for treatment of local anesthetic CNS toxicity. Neuromuscular blocking agents have been proposed as adjunctive treatment for local anesthetic-induced seizures. They block muscular activity, decreasing oxygen demand and lactic acid production. However, neuromuscular blocking agents should never be used to treat seizures per se because they have no anticonvulsant effect and can make clinical diagnosis of ongoing seizures problematic by abolishing muscle contractions. To avoid this potentially lethal complication, chemical paralysis should be used only to facilitate endotracheal intubation if needed. Use of short-acting drugs is desirable to allow for subsequent repeated neurologic assessments. Succinylcholine may not be the ideal drug because of its significant side effects, including hyperkalemia and dysrhythmias. Newer short-acting nondepolarizing agents with less potential for cardiac side effects, such as rocuronium, should be considered (Chap. 66).

When severe systemic toxicity occurs, the cardiovascular system must be monitored closely because cardiovascular depression may go unnoticed while the seizures are being treated. Because local anesthetic-induced myocardial depression can occur even with preserved blood pressure, it is important to be aware of early signs of cardiac toxicity, including ECG changes.

If toxicity results from an oral ingestion, activated charcoal and orogastric lavage are indicated but unproven therapeutic considerations. Induction of emesis is contraindicated even after

oral administration because of the risk of seizures and aspiration. Contaminated mucous membranes should be washed off. Hemodialysis probably is not useful. Hemoperfusion might be useful for severe lidocaine toxicity but is difficult to perform in the presence of significant cardiovascular depression.

Cardiovascular Toxicity

Cardiovascular side effects are the most feared manifestations of local anesthetic toxicity. Shock and cardiovascular collapse may be related to effects on vascular tone, inotropy, and dysrhythmias related to indirect CNS and direct cardiac and vascular effects of the local anesthetic. Animal studies and clinical observations clearly demonstrate that, for most local anesthetics, CNS toxicity develops at lower serum concentrations than those needed to produce cardiac toxicity, that is, they have a high CV/CNS toxicity ratio. When cardiac toxicity occurs, management can be exceedingly difficult. Some of the discrepancy between the incidence of CNS and cardiac toxicity may result from a detection bias. Not only can the treating physicians fail to recognize cardiac effects because of preoccupation with CNS manifestations of toxicity, but significant early cardiac toxicity may be quite subtle. An experimental study attempting to identify early warning signs of bupivacaine-induced cardiac toxicity in pigs evaluated bupivacaine-induced changes in cardiac output, heart rate, blood pressure, and ECG.[82] A 40% reduction in cardiac output was not associated with any significant change in heart rate or blood pressure, the latter secondary to a direct vasoconstrictive effect of bupivacaine at the concentrations produced. Typical changes on the ECG parallel the drop in cardiac output.[17]

Changes in systemic vascular tone induced by local anesthetics may be mediated by direct effect on vascular smooth muscle or indirectly via effects on spinal cord sympathetic outflow. Predictably, sympathetic blockade after spinal anesthesia or

epidural anesthesia above the T5 dermatome results in peripheral venodilation and arterial dilation. Shock can result when high doses of anesthetic are used in hypovolemic patients. Local anesthetics have a biphasic effect on peripheral vascular smooth muscle. Whereas lower doses produce direct vasoconstriction, higher doses are associated with severe cardiovascular toxicity and cause vasodilation, contributing to cardiovascular collapse.

All local anesthetics directly produce a dose-dependent decrease in cardiac contractility, with the effects roughly proportional to their peripheral anesthetic effect. Although the classic anesthetic action of sodium channel blockade in heart muscle accounts in large part for the negative inotropy by affecting excitationâ€“contraction coupling, it does not explain the entire difference in myocardial depression produced by different anesthetics.[28] Poorly understood effects on calcium handling or effects of the intracellular drug directly on contractile proteins or mitochondrial function may be operable.[28]

Blockade of the fast sodium channels of cardiac myocytes decreases maximum upstroke velocity (V_{max}) of the action potential (Chap. 23 and Fig. 61-1). This effect slows impulse conduction in the sinoatrial and atrioventricular nodes, the His-Purkinje system, and atrial and ventricular muscle.[20] These changes are reflected on ECG by increases in PR interval and QRS duration. At progressively higher drug concentrations, hypotension, sinus arrest with junctional rhythm, and eventually cardiac arrest occur.[4] Asystole is described in patients who received unintentional intravenous bolus injections of 800â€“1000 mg lidocaine.[4, 34] Cardiovascular toxicity of local anesthetics usually occurs following a sudden increase in serum concentration, as in unintentional intravascular injection. Cardiovascular toxicity is rare in other circumstances because a large dose of the drug is necessary to produce this effect, and because CNS toxicity precedes cardiovascular events, thus providing a warning. Cardiac toxicity usually is not observed with lidocaine use in humans until

the serum lidocaine concentration greatly exceeds 10 Âµg/mL, unless the patient is also receiving drugs that depress sinus and atrioventricular nodal conduction (eg, calcium channel blockers, Î²-adrenergic antagonists, or cardioactive steroids).

Bupivacaine is significantly more cardiotoxic than most other local anesthetics in common use. Inadvertent intravascular injection produces near-simultaneous signs of CNS and cardiovascular toxicity.

Animal studies have compared the dosage or serum concentrations of local anesthetics required to produce irreversible circulatory collapse to those necessary to produce seizures.[25 , 76 , 77] This cardiovascular collapse/central nervous system toxicity ratio (CC/CNS) for lidocaine is approximately 7; therefore, CNS toxicity should become evident well before potentially cardiotoxic concentrations are reached. In contrast, the CC/CNS ratio for bupivacaine is 3.7. Bupivacaine produces myocardial depression out of proportion to its anesthetic potency and, more importantly, can cause refractory ventricular dysrhythmias.[93] Enhanced cardiovascular toxicity may relate to enhanced CNS effects at cardiovascular centers,[102] direct effects on myocyte metabolism, and important differences related to sodium channel blockade. Although lidocaine and bupivacaine both block sodium channels in the open or inactivated state, lidocaine quickly dissociates from the channel at diastolic potentials, allowing rapid recovery from block during diastole (fast onâ€“fast off). Therefore, sodium channel blockade with lidocaine is much more pronounced at rapid heart rates (accounting for the antidysrhythmic effects for ventricular tachycardia). On the other hand, at high concentrations bupivacaine rapidly binds to, and slowly dissociates from, sodium channels (fast onâ€“slow off), with significant block accumulating at all physiologic heart rates.[20] Accordingly, at heart rates of 60â€“150 beats/min, approximately 70 times more lidocaine is needed than bupivacaine to produce an equal effect on V_{max} .

Enhanced conduction block in Purkinje fibers and ventricular muscle cells can set up a reentrant circuit responsible for the ventricular tachydysrhythmias induced by bupivacaine.[69]

Bupivacaine has an asymmetrically substituted carbon, and the kinetics of sodium channel binding are stereospecific.[56] The S (levo)-enantiomer is significantly less cardiotoxic than the R (dextro)-enantiomer.[6, 67] Consequently, bupivacaine, the racemic mixture of both enantiomers, is more cardiotoxic than levobupivacaine, which contains only the levo-enantiomer.[40] The stereospecific effect on sodium channels seems to differ between the heart and the peripheral nerves, however, because the local anesthetic potency of levobupivacaine is the same as, or perhaps even greater than, that of bupivacaine.[30, 80] Ropivacaine is a pure enantiomer and is less cardiotoxic than bupivacaine, but it also is slightly less potent as an analgesic.[84, 85]

Effects other than sodium channel blockade may contribute to cardiac toxicity. Lipophilic local anesthetics such as bupivacaine can directly impair mitochondrial energy transduction via two mechanisms: (1) uncoupling of oxygen consumption and adenosine triphosphate (ATP) synthesis and (2) inhibition of complex 1 in the respiratory chain.[98] This effect is related to the lipophilic properties of the drug rather than to stereospecific effects on ion channels. Lidocaine has no effect on mitochondrial respiration, and ropivacaine has less effect compared to bupivacaine.[107] There is no difference between the two bupivacaine enantiomers. These effects occur with higher concentrations of the drug, as occur after unintentional intravascular injection.

Low-dose bupivacaine-induced cardiotoxic effects are described in humans under certain circumstances and at concentrations that are not associated with seizure activity in pigs.[52, 106] Severe cardiac toxicity has been described after injection of a small subcutaneous dose of bupivacaine in a patient with secondary carnitine deficiency.[106] Myocytes are highly dependent on

oxidation of fatty acids for energy turnover. Interference with this mechanism via bupivacaine-induced inhibition of carnitine-acylcarnitine translocase has been proposed to contribute to the cardiotoxicity of lipophilic local anesthetics[106] (Chap. 47 and Fig. 47-2). Bupivacaine may produce dysrhythmias by blocking GABAergic neurons that tonically inhibit the autonomic nervous system.[43] In addition to its other effects on the heart, bupivacaine can induce a marked decrease in cardiac contractility by altering Ca^{2+} release from sarcoplasmic reticulum.[61]

In a large series of patients receiving bupivacaine published in 1978, systemic toxicity occurred in only 15 of 11,080 nerve blocks.[73] Of these patients, 80% convulsed; the other 20% had milder symptoms. However, during the late 1970s and early 1980s, a series of cases were described in which bupivacaine use, particularly at 0.75% concentration, was associated with severe cardiovascular depression, ventricular dysrhythmias, and even death. Pregnant women were disproportionately affected. Some of these cases required prolonged and difficult resuscitation.[88] In 1983, 49 incidents of cardiac arrest or ventricular tachycardia that occurred over a 10-year period were presented to the US FDA's Anesthetic and Life Support Advisory Committee. Among these cases, 0.75% bupivacaine was used in 27 obstetric patients with 10 deaths, and 0.5% bupivacaine was used in 8 obstetric patients with 6 deaths. Among the 14 nonobstetric patients, 5 died. The overall mortality was 21 of 49 (43%). Partly as a result of these reports, in 1984 the US FDA withdrew approval of bupivacaine 0.75% for use as obstetric anesthesia.[88]

Acidâ€“base and electrolyte status influence the cardiac toxicity of a given drug because all depressant properties are potentiated by acidosis, hypoxia, or hypercarbia.[12] Table 64-3 outlines the spectrum of acute local anesthetic reactions.

Laboratory

In cases of possible local anesthetic toxicity, an ECG should be obtained to detect dysrhythmias and conduction disturbances. Serum electrolytes, blood urea nitrogen (BUN), and creatinine should be obtained to help assess the cause of cardiac dysrhythmias. A methemoglobin level should be obtained in patients in whom significant methemoglobinemia is clinically suspected. Rapid sensitive assays are available for measuring concentrations of lidocaine and its monoethylglycylxylidide (MEGX) metabolite. When properly interpreted, the results of these assays can be used to prevent lidocaine toxicity and to identify lidocaine toxicity in the nontherapeutic setting. Assays for determining serum concentrations of other local anesthetics are not routinely available. Treatment should never be delayed while waiting for results of drug concentration determinations.

Etiology	Major Clinical Features
Local anesthetic toxicity (intravascular injection)	Immediate seizure and/or cardiac toxicity
Reaction to catecholamine	Tachycardia, hypertension, headache
Vasovagal reaction	Rapid onset and recovery, bradycardia, hypotension, pallor
Allergic reaction	Anaphylaxis
High spinal or epidural block	Bradycardia, hypotension, respiratory distress, respiratory arrest

TABLE 64-3. Types of Local Anesthetic Reactions

Treatment

Treatment of Local Anesthetic Cardiac Toxicity

Treatment of cardiovascular complications of local anesthetics is complicated by the complex effects of local anesthetics on the heart. Initial therapy should focus on correcting the physiologic derangements that may potentiate the cardiac toxicity of local anesthetics, including hypoxemia, acidosis, and hyperkalemia.[12, 91] Prompt support of ventilation and circulation will limit hypoxia and acidosis. Early recognition of potential cardiac toxicity is critical to achieving a good outcome because cardiac toxicity that goes unrecognized for any interval is more difficult to resuscitate.[7] If a potentially massive intravascular local anesthetic injection is suspected, maximizing oxygenation of the patient before cardiovascular collapse occurs is critical.

Despite multiple small studies suggesting the efficacy of various individual pharmacologic approaches, no convincing data suggest deviation from standard advanced cardiac life support (ACLS) protocols when dealing with most episodes of local anesthetic cardiac toxicity. Hypotension in sinus rhythm results from both peripheral vasodilation and myocardial depression and should be treated with Î±- and Î²-adrenergic agonists. Atropine supplemented with electrical pacing should be used to treat bradycardia. The effectiveness of epinephrine in reversing local anesthetic-induced cardiac depression is inconsistent in various animal models. The dysrhythmic effects of epinephrine are of particular concern. Amrinone, a phosphodiesterase III inhibitor, was evaluated for treatment of bupivacaine-induced cardiac toxicity.[38, 57] Anesthetized pigs with cardiovascular collapse induced by bupivacaine infusion survived when they were treated with amrinone; all of the control animals died of irreversible cardiac arrest.[57] A phosphodiesterase III inhibitor would be a good choice for reversing bupivacaine-induced cardiac depression.[94]

Bupivacaine-induced dysrhythmias often are refractory to cardioversion, defibrillation, and pharmacologic treatment. Lidocaine, phenytoin, magnesium, bretylium, amiodarone, calcium channel blockers, and combined therapy with clonidine and dobutamine have all been used in animal models, with variable results.[27 , 64 , 66] Therapy for bupivacaine toxicity should be directed toward dissociating bupivacaine from the myocardial sodium channel, thereby reversing the drug's effects on cardiac conduction. Lidocaine competes with bupivacaine for cardiac sodium channels and at high doses may displace it. Anecdotal reports suggest that lidocaine has occasionally helped in this application.[23] However, concern persists about additive CNS effects when lidocaine is used to treat bupivacaine cardiac toxicity, and we do not recommend its routine use.

With toxicity from the longer-acting, highly lipid-soluble, protein-bound amide local anesthetics (bupivacaine and etidocaine), if the patient does not respond promptly to therapy, cardiopulmonary resuscitation can be expected to be difficult and prolonged (1â€“2 hours) before depression of the cardiac conduction system spontaneously reverses as a result of redistribution and metabolism of the drugs.[2 , 86] Vital organ perfusion is seriously compromised during cardiopulmonary resuscitation despite optimal chest compression. The significance of this problem increases with the duration of resuscitation; therefore, rapid initiation of cardiopulmonary bypass should be considered, if practical. Its use has resulted in a successful outcome in some cases of lidocaine and bupivacaine overdose.[37 , 59] Cardiopulmonary bypass provides circulatory support that is far superior to that provided by closed-chest cardiac massage. The improved perfusion prevents tissue hypoxia and the development of metabolic acidosis, which in turn decreases the binding of local anesthetics to myocardial sodium channel receptors. Hepatic blood flow is better maintained, enhancing local anesthetic metabolism, and increased myocardial blood flow helps redistribute local anesthetics out of the

myocardium.[59]

Cardiac pacing was used successfully for treatment of cardiac arrest following unintentional administration of a 2-g bolus of lidocaine into a cardiopulmonary bypass circuit as the patient was being removed from bypass.[81] Pharmacologic therapy was unsuccessful, and resumption of bypass was necessary. Forty-five minutes after the injection, atrioventricular pacing restored perfusion and permitted discontinuation of bypass.

Use of sodium bicarbonate early in resuscitation to prevent acidosis-mediated potentiation of cardiac toxicity may have been beneficial in some cases,[23] but paradoxical effects on intracellular pH during cardiopulmonary resuscitation suggest against its use in the absence of strong experimental or clinical data.

Although human studies do not exist, small animal trials suggest a possible future role for infusions of lipid or insulin/glucose to treat serious cardiac toxicity induced by bupivacaine. A 20% lipid infusion and internal cardiac massage given 10 minutes after cardiac arrest induced by a bupivacaine bolus in dogs produced 100% survival in a model that was otherwise lethal.[108] The authors postulate that extracellular or intracellular lipid prevented or reversed interaction of the lipophilic local anesthetic with intracellular targets. In another canine model, an infusion of 2 mL/kg 50% dextrose plus 1 unit/kg insulin was superior to saline or dextrose alone in reversing bupivacaine-induced cardiac depression.[19] Effects on potassium current, calcium handling, and myocardial energy utilization all may have contributed to the salutatory effects of the insulin infusion.

Prevention of Systemic Toxicity of Local Anesthetics

Despite the development of new, relatively less toxic amide local anesthetics such as levobupivacaine and ropivacaine, severe CNS

and cardiovascular effects are not eliminated. Several cases of ropivacaine-induced cardiac arrest have been reported.[18, 49, 53] In these cases, both asystolic arrest and ventricular fibrillation-associated arrest were successfully resuscitated. Nonetheless, it is clear that prevention is more prudent and effective than treatment of toxicity. The keys to prevention are to use the lowest possible anesthetic concentration and volume consistent with effective anesthesia and to avoid a significant intravascular injection. The latter is accomplished by careful slow aspiration of a needle or catheter prior to injection, injection of a small test dose of anesthetic mixed with epinephrine to assess a cardiovascular response, if injection is intravascular, and use of slow fractional dosing of large-volume injections with vigilance for early signs of CNS or cardiac toxicity.

Summary

Local anesthetics are frequently used drugs that provide surgical analgesia and acute and chronic pain relief. The analgesic effect of local anesthetics is primarily caused by inhibition of neural conductance secondary to sodium channel blockade. Systemic toxicity, which primarily effects the heart and brain, is also largely related to

sodium channel blockade. Severe systemic toxicity usually occurs secondary to inadvertent intravascular injection. In most cases of systemic toxicity, CNS manifestations precede cardiovascular events. If cardiovascular collapse and cardiac arrest occur, resuscitation may be difficult and prolonged. Cardiopulmonary bypass may be useful because it provides cardiovascular support, limits exacerbating factors such as tissue hypoxia and acidosis, and improves hepatic blood flow, thereby increasing local anesthetic metabolism. Avoidance of intravascular injection and vigilance for early signs of CNS or cardiac toxicity are keys to preventing serious adverse events.

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Chapter 65
Inhalational Anesthetics

Brian Kaufman

Martin Griffel

A 40-year-old dentist was found unresponsive in his procedure room by his office staff. The paramedics noted that the mask on his face was attached to a supply of nitrous oxide and oxygen. The oxygen tank was empty. His vital signs were: blood pressure, 140/90 mm Hg; pulse, 120 beats/min; respiratory rate, 22 breaths/min and regular. In the emergency department, his oxygen saturation by pulse oximetry was 63%. His pupils were dilated and minimally reactive. He remained unresponsive to painful stimulation. His rapid bedside glucose concentration was 110 mg/dL. His serum electrolytes and complete blood count were normal, as was a noncontrast CT scan of the head. A presumptive diagnosis of anoxic encephalopathy secondary to inhalation of pure nitrous oxide was made. Neurologic improvement did not occur.

General anesthesia occurs as a result of reversible changes in neurologic function caused by drugs that modulate synaptic neurotransmission. The commonly accepted elements of general

anesthesia include hypnosis, amnesia, analgesia, inhibition of noxious reflexes, and skeletal muscle relaxation.[8] However, precise definitions for some of these terms are lacking. In addition, different effects occur at varying concentrations of inhaled agents. Side effects of the drugs may be redefined as toxicity, depending on the clinical situation.

History

Modern anesthetic practice often is stated to have begun in 1846 at the Massachusetts General Hospital, when the dentist William Morton gave the first public demonstration of the ability of inhaled ether vapor to alleviate the pain of surgery. Following this feat, John C. Warren, the chief of surgery, remarked to the assembled gallery, â€œGentleman, this is no humbug.â€• Oliver Wendell Holmes then chose the Greek-related noun *anesthesia* (without feeling) to characterize the process.

The earliest description of the use of an inhalational anesthetic was made by Paracelsus, a Swiss physician and alchemist who prepared a mixture of diethyl ether, alcohol, and water called sweet oil of vitriol. He described how he gave this preparation to hens who fell into a deep sleep from which they recovered unharmed. In 1735, Wilhelm Froben gave this substance its modern name of â€œether.â€• Ether was used topically, particularly via the intranasal route, as a treatment of headache, nervous diseases, and fits.

Observations on the circulatory and respiratory physiology eventually led to an understanding of the effects of inhalation gases and vapors. In the last decade of the 18th century, centers for the pneumatic treatment of disease were established in Birmingham and Bristol, England. Experiments with ether that was inhaled via a funnel and with nitrous oxide were conducted at these institutions. After Humphry Davy described his own pleasurable and exhilarating experience when he inhaled the â€œlaughingâ€• gas, many of his colleagues and friends inhaled nitrous oxide to experience its

inebriating effects. Davy also described how inhalation of nitrous oxide relieved headache and the pain of an erupting molar tooth. Although Davy recognized the analgesic properties of nitrous oxide and its possible application for surgery, he failed to pursue the idea.

The public soon took up the use of nitrous oxide in the form of nitrous oxide frolics. Audiences to itinerant medicine shows volunteered to experience the exhilarating effects of nitrous oxide inhalation. At one such show in 1844 in Hartford, Connecticut, a man under the influence of nitrous oxide injured his leg but did not feel any pain. Dr. Horace Wells, a dentist in the audience that day, inhaled nitrous oxide the following day and had his partner painlessly remove a troublesome tooth. A subsequent public demonstration of the use of nitrous oxide for dental extraction went poorly, impeding the general acceptance of this agent as a surgical anesthetic.

In Great Britain in 1847, James Simpson, an obstetrician, first used ether to relieve the pain of labor. He subsequently adopted chloroform for this purpose because of its more pleasant odor and more rapid induction and emergence. The clergy and other physicians opposed the concept of relieving pain during childbirth, but the method ultimately was accepted after Queen Victoria gave birth to Prince Leopold with chloroform given by John Snow.

Over the next century, several volatile anesthetics were introduced, including ethyl chloride in 1848, divinyl ether in 1933, trichloroethylene in 1934, and ethyl vinyl ether in 1947. All of these agents had significant safety problems associated with their use, including combustibility and direct organ toxicity.

Advances in fluorine chemistry led to the cost-effective incorporation of fluorine into molecules used in the development of modern anesthetics. Fluroxene was the first of the new fluorinated anesthetics to be widely used clinically. However, this anesthetic was flammable and hepatotoxic. It was largely replaced by the nonflammable halothane, which was synthesized in 1951 and introduced into clinical practice in 1956. Methoxyflurane was

evaluated in humans in 1960 but is no longer used because of nephrotoxicity and hepatotoxicity. Other halogenated hydrocarbons with improved

clinical properties have been introduced, including enflurane, isoflurane, desflurane, and sevoflurane (Figure 65-1). The inert gas xenon has been shown to be a useful anesthetic and is being studied. Although xenon is environmentally friendly compared to presently used anesthetics, its toxicity is relatively unknown.

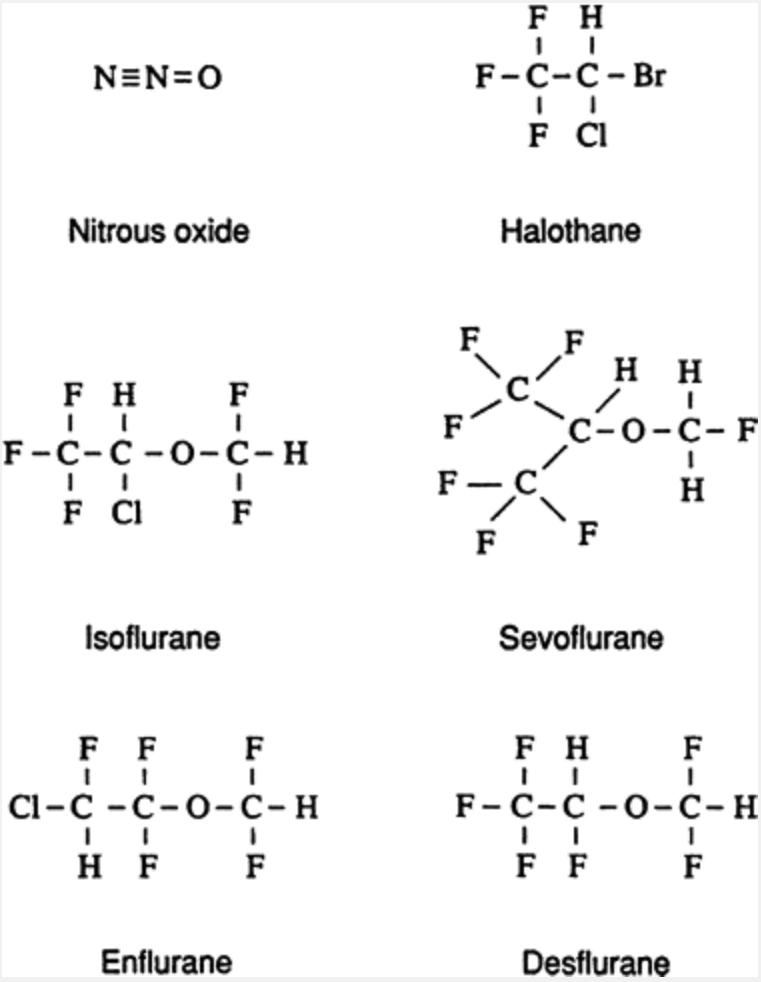

Figure 65-1. The inhalational anesthetics.

Pathophysiology

Because a wide range of chemically distinct compounds can produce anesthesia, a unique receptor for the inhaled anesthetics is improbable. More likely, the volatile anesthetics cause general anesthesia by modulating synaptic function from within cell membranes. Anesthetics are known to interact with many proteins. The most likely, but not yet proven, target for the inhalational agents are the ion channels that control ion flow across the cytoplasmic membrane. An in-depth discussion is beyond the scope of this chapter, but several concepts are important to consider. First, more than 20 different ion channels are identified, each controlling various anion and cation flows. The results of these ion channel effects include release of inhibitory neurotransmitters and inhibition of excitatory neurotransmitters. In fact, each anesthetic type has variable actions. The receptor for Î³-aminobutyric acid type A ($GABA_A$) is the best studied and plays an important role because $GABA_A$ is an inhibitory neurotransmitter. Finally, the interaction of all of these effects from a single anesthetic produces the condition we refer to as *general anesthesia.* Many of the side effects of the inhalational anesthetics result directly from ion channel effects in nonneural tissue, primarily cardiac cell membranes.

Reversible changes in neurologic function cause loss of perception and reaction to pain, unawareness of immediate events, and loss of memory of those events. The exact mechanism by which the inhaled (volatile) anesthetics produce general anesthesia is uncertain, but experimental data support several theories. The pharmacologic mechanisms for general anesthesia include the physicalâ€“chemical behavior of volatile hydrocarbons within the hydrophobic regions of biologic membrane lipids and proteins.

Pharmacokinetics

The potency of the various inhaled anesthetics correlates with their physicochemical properties. The dominant theories of the molecular mechanisms by which volatile agents affect membrane function are based on the lipid solubility of the drugs and experimental demonstration of pressure reversal of anesthesia. The anesthetic potency of volatile anesthetics correlates directly with the relative lipid solubility of each drug, which suggests that the primary molecular actions of anesthetics occur in the lipid portion of cell membranes. This mechanism is known as the *Meyer-Overton lipid solubility theory.* Potential membrane regions for anesthetic action include the hydrophobic areas of proteins and proteinâ€“lipid interface regions, as well as the phospholipid matrix. High pressures (100â€“200 atm) can reverse the anesthetic effects of several drugs, which suggests that the drugs cause anesthesia by increasing membrane volume at normal atmospheric pressure, an effect known as the *volume expansion theory*.

Because the inhaled anesthetics enter the body through the lungs, the factors that influence their absorption by blood and distribution to other tissues include the solubility of the drug in blood, blood flow through the lungs, blood flow distribution to the various organs, solubility of the anesthetic in tissue, and the mass of the tissue. The goal of inhalation anesthesia is to develop and maintain a satisfactory partial pressure of anesthetic in the brain, the primary site of action.

The pharmacokinetics of anesthetics can be linked to their pharmacodynamics by considering anesthetic potency. The linkage exists because anesthesia strives to achieve and maintain a desired alveolar concentration. For the inhaled drugs, potency is commonly referred to as the *minimum alveolar concentration* (MAC) of the anesthetic. MAC is the alveolar concentration at 1 atm that prevents movement in 50% of subjects in response to a painful stimulus. MAC

is used when comparing the effects of equipotent doses of anesthetics on various organ functions.

Nitrous Oxide

Nitrous oxide is the most commonly used inhalational anesthetic in the world. Its advantages include a mild odor, absence of airway irritation, rapid induction and emergence, potent analgesia, and minimal respiratory and circulatory effects. When administered in a modern operating room using current standards of monitoring to prevent unintentional hypoxia, nitrous oxide is a remarkably safe agent. Unfortunately, nitrous oxide also has a potential for abuse, particularly among hospital and dental personnel.[26] Death and permanent brain damage are reported but do not result from direct toxic effects; instead they are secondary to asphyxia.[13] If a patient who is exposed to nitrous oxide fails to regain consciousness within several minutes after breathing fresh air or oxygen, other etiologies for the altered mental status (eg, hypoxic encephalopathy or a concomitant central nervous system [CNS]â€“depressant xenobiotic) should be suspected.

Death may occur when patients receive commercially prepared nitrous oxide from tanks contaminated with impurities such as nitric oxide or nitrogen dioxide. Pulmonary toxicity resulting from similar contaminants produced by individual preparation of nitrous oxide by combustion of ammonium nitrate fertilizer is reported.[32]

Injury can result from the physical properties of this anesthetic. Nitrous oxide is 35 times more soluble in blood than is nitrogen. When nitrous oxide is inhaled, any compliant air-containing space, such as bowel, increases in size, whereas noncompliant spaces, such as the eustachian tubes, exhibit an increase in pressure. These effects occur because nitrous oxide diffuses along the concentration gradient from the blood into a closed space much more rapidly than nitrogen can be transferred in the opposite direction. Clinical

consequences include rapid progression of a pneumothorax to tension pneumothorax, tympanic membrane rupture with hearing loss, bowel distension, and tracheal or laryngeal trauma caused by increased endotracheal cuff pressure resulting from replacement of air by a larger volume of nitrous oxide. Nitrous oxide can be particularly dangerous in patients who have suffered air emboli, and its use should be immediately discontinued upon recognition of these events. When intracranial or neuraxial air is injected during placement of an epidural catheter, it also can theoretically expand upon subsequent exposure to nitrous oxide.

Hematologic Effects

Bone marrow depression was first recognized as a complication of long-term nitrous oxide exposure in the 1950s, when the gas was used to sedate intubated patients who had severe tetanus.[25] Leukopenia with hypoplastic bone marrow and megaloblastic erythropoiesis typically developed 3â€“5 days after initial exposure and was followed by thrombocytopenia. Recovery usually occurs within 4 days after the anesthetic is discontinued. Healthy patients undergoing routine surgical procedures demonstrate mild megaloblastic bone marrow changes after 12 hours of exposure to 50% nitrous oxide and marked changes after 24 hours.[36] Critically ill patients may be more sensitive to the effects of nitrous oxide on the bone marrow, with megaloblastic changes described after only 1 hour of exposure.[3]

The hematologic effects of exposure to nitrous oxide strongly resemble the biochemical characteristics of pernicious anemia.[2,34,35] Vitamin B_{12}, or cyanocobalamin, is a bound coenzyme of cytoplasmic methionine synthase. The cobalt moiety in the enzyme functions as a methyl carrier in its transfer from 5-methyltetrahydrofolate to homocysteine to form methionine (Figure 65-2). Nitrous oxide oxidizes the cobalt, converting vitamin B_{12} from the active monovalent form (cob(I)alamin) to the inactive bivalent form

(cob(II)alamin), which irreversibly inhibits methionine synthase.[34] The metabolic consequences of this block are significant because methionine and tetrahydrofolate are required for both DNA synthesis and myelin production. This interference is responsible for the development of bone marrow depression and polyneuropathy resembling those that occur in pernicious anemia.[34]

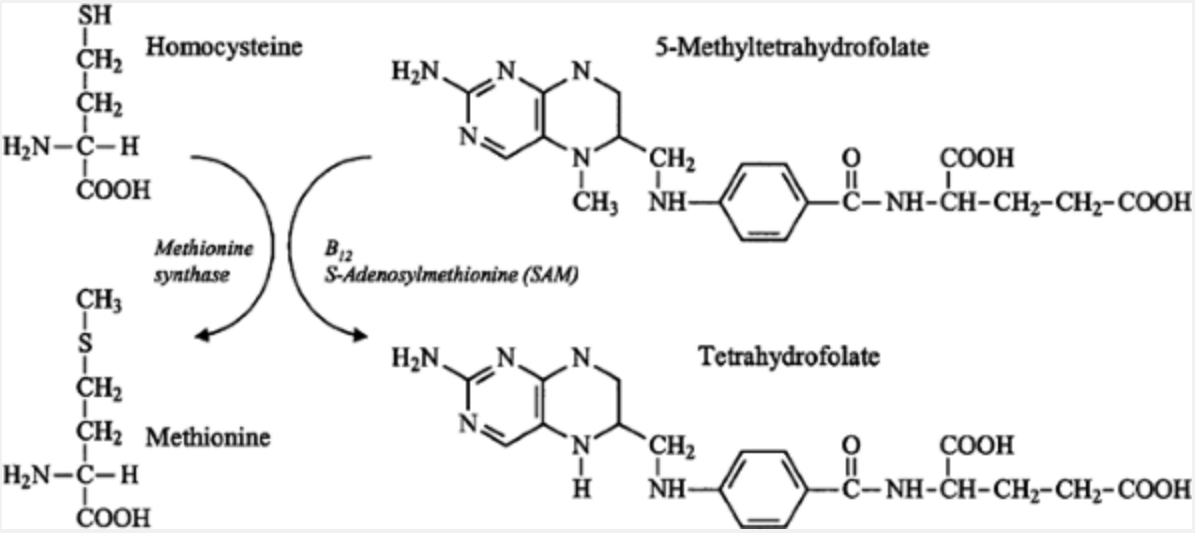

Figure 65-2. Hematologic effects of exposure to nitrous oxide resemble those characteristic of pernicious anemia and are related to oxidation and inactivation of vitamin B_{12}. The irreversible blockade of methionine synthase is consequential with regard to DNA synthesis and myelin production.

Neurologic Effects

Disabling polyneuropathy in healthcare workers who habitually abused nitrous oxide was first described in 1978.[26] The neurologic disorder improved slowly when the patients abstained from further nitrous oxide abuse. As discussed, this neuropathy is clinically indistinguishable from subacute combined degeneration of the spinal

cord associated with pernicious anemia. The syndrome of nitrous oxide neuropathy is characterized by sensorimotor polyneuropathy, often combined with signs of posterior and lateral spinal cord involvement. Signs and symptoms include numbness and paresthesias in the extremities, weakness, and truncal ataxia. Neurologic changes develop only after several months of frequent exposure to nitrous oxide. Those at risk include individuals who chronically abuse the gas and those who are occupationally exposed to grossly contaminated environments for prolonged periods.[4] This scenario is highly unlikely in the modern operating room, where inhalational anesthetics are scavenged, but it may occur in poorly ventilated dental offices, where personnel are exposed to >1000 parts per million (ppm) nitrous oxide. This problem probably is markedly underdiagnosed because the neurologic changes that occur in mild cases mimic other more common neurologic conditions.[7]

Chronic Exposure to Trace Levels of Nitrous Oxide

Dentists and dental assistants are often exposed to greater concentrations of waste anesthetic gases than are individuals working in well-vented operating rooms. Animal studies demonstrate that methionine synthase may be inactivated by exposure to >1000 ppm of nitrous oxide, a level often exceeded in dental procedure rooms. An epidemiologic survey compared 15,000 dentists who used and 15,000 dentists who did not use nitrous oxide in their practices.[7] A

1.2- to 1.8-fold increase in liver, kidney, and neurologic disease was found in the dentists and their chairside assistants who were chronically exposed to trace levels of nitrous oxide. For those with heavy office use of nitrous oxide, a 4-fold increase in the incidence of neurologic complaints compared to the nonexposed group was observed. Female dental assistants who were exposed to nitrous

oxide had a 2- to 3-fold increase in spontaneous abortion rates, reduced fertility, and a higher rate of congenital abnormalities in their offspring.

Treatment

General

Removal of the acutely affected person from the toxic environment should be the initial intervention. Individuals who have developed toxicity from abuse of the gas should be educated about the relationship between their recreational activities and their clinical findings.

Specific

Vitamin B_{12} may help patients with a masked vitamin B_{12} deficiency who develop megaloblastic anemia and neurologic dysfunction after brief exposure to nitrous oxide, but it is not beneficial in patients who have toxicity resulting from more chronic exposure.[38] The reason for the ineffectiveness of vitamin B_{12} in this situation is uncertain.

The bone marrow abnormalities associated with nitrous oxide toxicity may be reversed by administration of a single 30-mg, intravenous dose of folinic acid (the active form of folate)[31] (Antidotes in Depth: Folic Acid and Leucovorin). In primates, a methionine-supplemented diet greatly reduced demyelination and neurologic damage from chronic exposure to 15% nitrous oxide.[39]

Halogenated Hydrocarbons

The inhaled anesthetics initially were considered biochemically inert drugs. Initial reports of toxicity following their administration were poorly explained and attributed to direct effects on susceptible organs. It now is clear that the inhalational anesthetics are not inert

but are metabolized in vivo, and that their metabolites are responsible for acute and chronic toxicity.

Halothane Hepatitis

Two distinct types of hepatotoxicity are associated with halothane use. The first is a mild dysfunction that develops in approximately 20% of exposed patients. Patients often are asymptomatic but exhibit modestly elevated serum aminotransferase concentrations within a few days of anesthetic exposure. Recovery is complete.[32] In contrast, a life-threatening hepatitis occurs in approximately 1 in 10,000 exposed patients and produces fatal massive hepatic necrosis in 1 of 35,000 patients.[42] Because the histologic findings of massive hepatocellular necrosis are indistinguishable from those of viral hepatitis,[46] differentiating halothane hepatitis from other causes of hepatitis in the postoperative period is difficult without positive serologic studies. Jaundice, which is common after anesthesia and surgery, usually results from factors such as preexisting liver disease, blood transfusion, sepsis, or other causes of hepatitis. Thus halothane hepatitis is a diagnosis of exclusion.

Factors that may increase the risk of developing hepatotoxicity from halothane include multiple exposures, obesity, female gender, age, and ethnic origin.[33]

Several studies report an association between multiple exposures to halothane and subsequent development of hepatitis.[45,50] In 1 study, 95% of cases of halothane hepatitis followed multiple exposures, 55% of which involved reexposure within 4 weeks.[50] Under these circumstances, liver dysfunction usually is more severe and the latency before clinical presentation usually is shorter than when the syndrome develops after initial exposure to halothane.[45]

Obesity is a risk factor commonly implicated in halothane hepatotoxicity.[1,47] Increased fat stores may act as a â€œreservoirâ€• for halothane, with slow and prolonged release into

the circulation and subsequent increase in production of potentially hepatotoxic metabolites.

Most cases of halothane hepatitis occur in middle-aged patients, with women having twice the risk.[22] Genetic factors may play a role in some patients, as indicated by a report of this syndrome in three pairs of related women of Mexican-Indian or Mexican-Spanish ancestry.[21]

Mechanism of Toxicity

Halothane is the most extensively metabolized inhalational anesthetic. Approximately 20% of the absorbed drug undergoes oxidative metabolism, principally by cytochrome P450 in the liver, to trifluoroacetic acid. Reduction to trifluorochloroethane and difluorochloroethylene (Figure 65-3) is a minor route of halothane metabolism that requires the absence of oxygen and the presence of an electron donor. These volatile metabolites are free radicals, which may directly produce acute hepatic toxicity by irreversibly binding to and destroying intracellular structures in the hepatocyte. Alternatively, by acting as haptens they may trigger an immune-mediated hypersensitivity response.[37,48] The high percentage of patients with halothane hepatitis who had recent prior exposure to the drug is most consistent with the latter mechanism.[22]

Enflurane, used extensively in North America since 1966 but rarely used now, is weakly associated with hepatotoxicity. Some authorities believe the evidence does not support the existence of enflurane-induced hepatic necrosis.[14,16,41] Isoflurane, desflurane, and sevoflurane all appear to have low hepatotoxic potential. The immune form of hepatitis has been reported with all agents except sevoflurane. Cross-sensitivity may be operable, such that prior exposure to one anesthetic triggers hepatotoxicity upon subsequent exposure to a different anesthetic.

Nephrotoxicity

The kidneys are the only other organ at risk for toxicity from modern inhalational anesthetics. Methoxyflurane is an anesthetic introduced in 1962. By 1966, it was linked to the development of vasopressin-resistant polyuric renal insufficiency (nephrogenic diabetes insipidus) in 16 of 94 patients receiving prolonged methoxyflurane anesthesia for abdominal surgery[11] (Chap. 17). Polyuria was associated with a negative fluid balance; elevated serum sodium, osmolality, and urea nitrogen concentrations; and a fixed urinary osmolality close to that of serum. Renal abnormalities lasted from 10â€“20 days in most patients but persisted for more than 1 year in 3 patients. Subsequent studies demonstrated that renal toxicity was caused by inorganic fluoride (F) released during biotransformation of methoxyflurane.[44] The risk of toxicity was highly correlated with both the total dose of methoxyflurane (concentration times duration) and the peak serum (F^-) concentration.[10,31] The nephrotoxic serum fluoride concentration is 50â€“60 Âµmol/L.[10] Factors that enhance biotransformation (obesity, enzyme induction) increase the risk of toxicity. Although the precise mechanism

by which fluoride produces its toxic effect on the kidney is not clear, one hypothesis is that fluoride inhibits adenylate cyclase, thereby interfering with the normal action of antidiuretic hormone on the distal convoluted tubules.

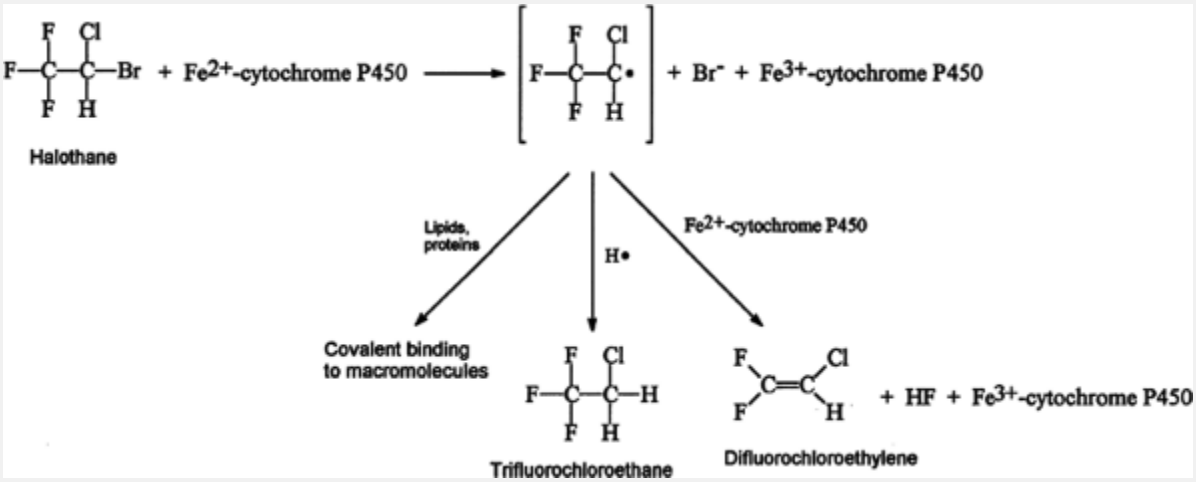

Figure 65-3. Reductive metabolism of halothane results in formation of trifluorochloroethane and difluorochloroethylene.

Although methoxyflurane is no longer used, lessons learned regarding its toxicity are applied when evaluating the nephrotoxic potential of other fluorinated anesthetics. Of the currently used anesthetics (halothane, isoflurane, enflurane, desflurane, sevoflurane), only enflurane and sevoflurane undergo biotransformation by defluorination.

Approximately 5% of sevoflurane is metabolized. This process occasionally results in sufficient serum fluoride concentrations to produce transient decreases in urine-concentrating ability.[24] However, clinically evident renal impairment almost never occurs with use of either enflurane or sevoflurane.[18] In addition, volunteer studies failed to show any urine-concentrating defect after exposure to sevoflurane that resulted in high fluoride plasma concentrations. In patients with preexisting renal insufficiency, the risk of postoperative renal dysfunction is believed to be worse with exposure to inhalational agents. However, studies demonstrate that deterioration of renal function does not occur after exposure to desflurane and isoflurane,[28] possibly because intrarenal fluoride

concentrations are more important than plasma fluoride concentrations in the development of nephrotoxicity.

Pharmacokinetics

Chronic use of isoniazid induces CYP2E1, the enzyme responsible for enflurane metabolism. This induction results in elevated serum fluoride concentrations in approximately 50% of isoniazid-treated patients who receive an enflurane anesthetic.[31] The fluoride concentrations, however, are neither high enough nor sustained enough to produce clinically significant renal dysfunction. Nonetheless, a prudent course is to avoid prolonged use of enflurane in patients taking isoniazid or other xenobiotics, such as ethanol, phenobarbital, and phenytoin, which elevate the hepatic activity of cytochrome CYP2E1 (Chap. 9).

Unusually high serum fluoride concentrations are reported in morbidly obese patients anesthetized with enflurane.[9] This finding may be related to a large storage capacity for fat-soluble anesthetics. Although prolonged postoperative release and metabolism of enflurane may occur, renal dysfunction is not reported with enflurane use even in obese patients.

Sevoflurane reacts with the alkali within carbon dioxide absorbers to produce several degradation products, including a vinyl ether called compound A ($CF_2C(CF_3)OCH_2F$), which is nephrotoxic and hepatotoxic in rats.[23,49] The site of compound A-induced nephrotoxicity in the rat is the renal tubule, especially at the corticomedullary junction.[23] The extent of nephrotoxicity is determined by both the concentration of compound A and the duration of exposure. Compound A is also conjugated, and its breakdown products are nephrotoxic.

Technical Issues

Extensive clinical experience with sevoflurane involving several million patients and 4000 closely studied volunteers failed to

demonstrate nephrotoxicity.[30] Higher levels of compound A are generated during low-flow anesthesia, use of high concentrations of sevoflurane, fresh Baralyme use, and increased temperature conditions. A high fresh-gas flow rate dilutes the concentration of compound A. Concern that higher compound A concentrations are generated when a low fresh-gas flow rate (eg, <2 L/min) is used in a closed circuit led to the current sevoflurane package labeling, which warns the anesthesia care provider against fresh-gas flow rates <2 L/min in a circle absorber system.[29]

Some controversy exists regarding the safety of low-flow sevoflurane anesthesia. Although there are no clinical reports of sevoflurane-induced nephrotoxicity as measured by changes in blood urea nitrogen (BUN), serum creatinine, or creatinine clearance, clinical data demonstrate transient nephrotoxicity when more subtle measurements of glomerular and tubular function are used.[15,20] For example, when young healthy patients without underlying renal disease were anesthetized with low-flow sevoflurane for a mean of 6.7 hours, transient but statistically significant increases in urinary glucose and protein excretion were documented without any changes in BUN, creatinine, or creatinine clearance.[20] The clinical significance of such transient abnormalities in renal function is uncertain. Regardless, it seems prudent to not use low-flow sevoflurane

in patients with preexisting renal disease until clinical data document the safety of this practice. Newer carbon dioxide absorbents that are free of strong alkali have been identified and studied in an attempt to find products that generate less compound A.

Inhalational Anesthetic-Related Carbon Monoxide Poisoning

Pharmacology

Desflurane, enflurane, and isoflurane contain a difluoromethoxy moiety that can be degraded to carbon monoxide (CO). This process occasionally results in patient exposure to toxic CO concentrations and, in rare instances, severe CO poisoning.[6] The true incidence of CO exposure during clinical anesthesia is unknown, and no adequate means for routine detection of intraoperative exposure are available at this time.

CO production is inversely proportional to the water content of CO_2 absorbents. Soda lime and Baralyme, the two most frequently used CO_2 absorbents, are sold wet (13â€“15% water by weight), but wet absorbents may dry with high gas-inflow rates. Higher levels of CO are most apt to be present during the first case following a weekend because of drying of CO_2 absorbent from a continuous inflow of dry oxygen over the weekend.[17]

Other factors influence the concentration of CO that may result from anesthetic degradation, including temperature (higher temperature increases CO formation), type of absorbent, choice of anesthetic, and concentration of anesthetic. Strong alkalis, such as potassium and sodium hydroxide, initiate the reaction that forms CO. Baralyme, which contains potassium hydroxide, forms more CO than does soda lime, which contains a combination of both.

In one experiment, Baralyme was exposed to 48 hours of dry gas flowing at 10 L/min. Nine swine were then anesthetized with desflurane. Three of the animals died of cardiac arrest within 20 minutes; the other 6 were successfully resuscitated with intravenous epinephrine and discontinuation of desflurane.[19] Extremely high concentrations of CO (mean peak concentration 37,000 ppm) were detected in the circuit within 15 minutes of initiating desflurane anesthesia. All the animals had carboxyhemoglobin concentrations >80%, with a concentration >90% in 7 of the swine. Lower CO concentrations were detected when the CO_2 absorbent was exposed to only 24 hours of dry gas and when soda lime was substituted for Baralyme.

Clinical monitors routinely used in the operating room cannot detect CO. Mass spectrometry (available in some operating rooms) cannot directly detect CO because its molecular weight is equivalent to that of nitrogen, a gas usually present in much greater amounts. In addition, detection of CO by fragmentation products is not possible by mass spectrometry because CO_2 is present in greater amounts and has similar fragmentation products. However, the presence of CO should be suspected if the mass spectrometer shows the presence of enflurane when this agent is not being administered.

Trifluoromethane is produced by degradation of isoflurane and desflurane and is responsible for the false readings for enflurane.[54] Simultaneous production of trifluoromethane and CO during chemical decomposition of isoflurane and desflurane allows the false reading of the former as enflurane by mass spectrometry to serve as a gross CO monitor and allows for interventions to prevent further CO production and enhance CO elimination. The overall incidence of CO exposure from anesthetic degradation was 6 of 1372 (0.44%) first cases of the day in which either isoflurane or desflurane was administered.[54] Mass spectrometry is a useful monitor for indirect detection of CO poisoning in the clinical setting.[53]

Although no case reports document patient morbidity or mortality from intraoperative CO exposures, carboxyhemoglobin levels reportedly as high as 36% can cause morbidity and mortality in patients with concurrent disease.[6] Unfortunately, the diagnosis of CO poisoning during anesthesia is difficult because the main clinical features of toxicity are masked by anesthesia, and no routinely available means can identify CO within the breathing circuit or detect when the CO_2 absorbent has been desiccated. Delayed neurologic sequelae from intraoperative CO poisoning will be likely missed on the anesthesiologist's postoperative patient evaluation.[52]

The product labels of desflurane and isoflurane have been altered to include a precaution that the CO_2 absorbent should be replaced if a practitioner suspects the absorbent is desiccated. However, the

problem associated with this warning is the lack of a reliable method for determining when the absorbent is fully or partially desiccated.

If an anesthetic machine is found with the fresh-gas flow â€œonâ€• at the beginning of the day, a reasonable practice is to replace the absorbent. Changing from Baralyme to soda lime use also should be considered as a protective measure. Newer CO_2 absorbents that are less likely to degrade anesthetics are being evaluated but are not yet available in the United States.

Extreme heat and fires within the anesthesia circuits have been reported in a warning distributed by the manufacturer of sevoflurane. The cases involved desiccated carbon dioxide absorbents, high sevoflurane concentrations, and primarily but not exclusively Baralyme adsorbent. The exact mechanisms have not been entirely elucidated but again point to the need to change absorbent when it is dry or routinely every Monday morning prior to the first case.

Abuse of Halogenated Volatile Anesthetics

Fatal or life-threatening complications occur when halogenated inhalational anesthetics are used for nonanesthetic purposes (suicide attempts, mood elevation, topical treatment of herpes simplex labialis). When ingested, halothane usually produces gastroenteritis with vomiting, followed by depressed consciousness, hypotension, shallow breathing, bradycardia with extrasystoles, and acute lung injury. Coma usually resolves within 72 hours.[12,51] The diagnosis should be suspected when these features occur in a patient with the sweet/fruity odor of halothane on the breath. Supportive care, including endotracheal intubation and nasogastric lavage, should be provided with protection for potentially exposed staff. Full recovery can occur without permanent organ injury.

Intravenous injections of halothane may occur as a suicide attempt or unintentionally during anesthesia induction. A young patient who

was found unconscious and hypotensive with acute lung injury following IV injection of halothane was not successfully resuscitated.[5] A 16-year-old girl received an unintentional IV injection 2.5 mL halothane during anesthesia induction.[43] She became unconscious and apneic within 30 seconds but began to awaken within 2â€“3 minutes. Four hours later she developed respiratory distress from acute lung injury but subsequently made a full recovery. Transient coma and apnea probably are secondary to a halothane bolus reaching the brain on its first pass through the

bloodstream. Redistribution then occurs, explaining the rapid awakening. The acute lung injury that develops following injection of halothane may result from a direct toxic effect of high concentrations of this hydrocarbon drug on the pulmonary vascular bed. Following injection, the anesthetic likely travels as a bolus during the first passage through the pulmonary circulation because of its poor solubility in blood.

Hospital personnel are involved in most reported cases of halothane abuse by inhalation.[40] Inhalation of halothane produces a pleasurable sensation similar to that described with glue sniffing. Death may result from upper airway obstruction following loss of consciousness or from dysrhythmias. Death occurred in a student nurse anesthetist who applied a full 250-mL bottle of enflurane over 3 hours to â€œcold soresâ€• on her lower lip.[27]

Summary

Inhalational anesthetics remain popular choices for maintenance of general anesthesia. Their advantage over intravenous drugs is that their drug level within the body can be increased or decreased at will. Toxicity with use of these drugs may result through a variety of mechanisms, including excessive physiologic drug effect, direct drug effects on metabolic pathways, and toxic effects of drug metabolites. Although life-threatening adverse reactions occur infrequently,

physicians who use these drugs should be knowledgeable about their pharmacology and potential toxicity.

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Chapter 66
Neuromuscular Blockers

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A 28-year-old otherwise healthy man presented to the emergency department (ED) complaining of palpitations and dry mouth that develope shortly after he intentionally consumed a marijuana-laced cookie. Althoug he was having troubling illusions, he had no true hallucinations. He had n chest pain, dyspnea, dizziness, abdominal pain, or extremity pain. His in vital signs were: blood pressure, 154/80 mm Hg; pulse, 126 beats/min; respiratory rate, 18 breaths/min; and he was afebrile. On physical examination the patient was in no distress, his lungs were clear to auscultation bilaterally, and his heart sounds were rapid but regular and otherwise normal. His extremities were normal. He was neurologically int except for occasional drifts in attention during mental status testing. An electrocardiogram demonstrated sinus tachycardia. Serum chemistry ana and blood count were normal.

Approximately 1 hour after arrival, the patient had persistent complaints anxiety and troubling illusions. The treating physician ordered lorazepam

mg IV, which was administered promptly by the patient's nurse. Approximately 5 minutes later, the same nurse noted the patient was unresponsive to painful external stimulation. His repeat vital signs were: blood pressure, 210/102 mm Hg; pulse, 145 beats/min; respiratory rate, The patient had normally reactive pupils, but his protective reflexes, including gag reflex, and his muscle tone were absent. Naloxone 1 mg an flumazenil 0.2 mg were administered intravenously with no response whi the patient was ventilated by bag-valve-mask. Because of apnea, the pat was intubated and placed on mechanical ventilation.

Approximately 2 hours later, the patient was awake and extubated by the physician in the ED. Following extubation, the patient reported that he ha been fully aware of his surroundings and all activity and conversations during the entire previous period of â€œunresponsivenessâ€• although h was unable to move. He stated that he felt himself being intubated and w extremely frightened.

A count of the contents of the narcotics cabinet at the nurses station revealed that an excess of lorazepam was available compared to the amo that had been signed out. Further investigation noted that a vial of pancuronium that was located nearby in the locked portion of the medica refrigerator was missing. The vials of pancuronium and lorazepam were o identical size and shape, both had similar labels (a green outline with bla lettering), and both contained 2 mg/mL of drug. The cap colors were different. The event was reported to the hospital leadership.

History

Curare is the generic term for the resinous arrowhead poisons used to paralyze hunted animals.[102] The curare alkaloids are derived from the ba of the ligneous *Strychnos* vine, and the most potent alkaloids, the toxiferines, are derived from *Strychnos toxifera* . Fortunately for the hun who used curare, ingestion of their prey did not cause paralysis. Sir Walt Raleigh discovered the use of curare in Guyana in 1595, and he was the person to bring curare to Europe. In 1898, King's American Dispensatory stated, â€œCurare is a frightfully poisonous extract, prepared by the

savages of South America.â€• Today, curare is available in a purified for as tubocurarine.

Curare played a pivotal role in the discovery of the mechanism of neuromuscular transmission. In 1844, Claude Bernard placed a small piec of dry curare under the skin of a live frog and observed that the frog bec limp and died.[7] He performed an immediate autopsy and discovered the heart was beating. Because direct muscle stimulation produced contractio whereas nerve stimulation did not, Bernard concluded that curare paralyz the motor nerves. He later observed that bathing the isolated nerve did r affect neuromuscular transmission, leading Bernard to conclude â€œcura must act on the terminal plates of motor nerves.â€•[13] Curare was also u by Nobel Laureate physiologists Charles Sherrington, John Eccles, and Bernard Katz to further elucidate neuromuscular physiology. Its first clin use was described in 1878 when Hunter used curare to treat tetanus and seizures.[102] In 1932, Raynard West used curare to reduce the muscular rigidity of hemiplegia.

More recent uses of succinylcholine have been less benign.[2] The anesthesiologist Dr. Carl Coppolino was accused of murdering his wife in 1965 by succinylcholine injection. Her autopsy revealed an abnormally hi concentration of succinylcholine metabolites (succinic acid and choline) ir the brain and liver.[69] Although this assay was not in general use in the medical community, the evidence was deemed admissible.

In 1983, Dr. Michael Swango began his internship at Ohio State Universit Hospital. Shortly after he started his neurosurgery rotation, patients beg dying inexplicably, and he was relieved of his duties.[94] The elusive trail o Dr. Swango followed almost 14 years, through multiple residencies and j and extended as far as Mnene Hospital in Zimbabwe. At one point, the Federal Bureau of Investigation (FBI) estimated Dr. Swango might have murdered 35â€“60 people. The authorities disinterred several victims wh they believed most likely were murdered. Toxicologic analysis of the 7-ye old remains of Thomas Sammarco revealed succinylcholine in the liver an gallbladder and its metabolite succinylmonocholine in multiple organs. Th findings helped the prosecution to secure Swango's guilty plea for the

murder of three victims.

With the advent of new modalities of drug delivery, the toxicologist must attuned to possible malicious intent. Emergency personnel responding to 911 call observed the widow removing an insulin pump reservoir from he dead husband's body with the stated intent to donate the costly equipme A natural cause of death was presumed, yet surprisingly, subsequent forensic analysis revealed etomidate and laudanosine (a metabolite of atracurium) in the victim's liver.

Mechanism of Neuromuscular Transmission and Block

The purpose of a neuromuscular blocker (NMB) is to reversibly inhibit transmission at the skeletal neuromuscular junction (NMJ). All NMBs poss at least 1 positively charged quaternary ammonium moiety that binds to postsynaptic nicotinic acetylcholine (nACh) receptor at the NMJ, inhibiting normal activation by acetylcholine (ACh). The nACh receptor is a ligand-gated ion channel that consists of 4 different protein subunits in a pentameric structure surrounding a central channel. The nACh receptor found in human skeletal muscle is present in 2 primary forms: a mature found at the NMJ (Î±Î±Î²eÎ´) or as a fetal (immature) type found on mus at extrajunctional regions of the muscle fiber (Î±Î±Î²Î³Î´). Before discus the mechanism of neuromuscular block, it is helpful first to describe norn neuromuscular transmission and excitationâ€“contraction coupling (Figure 66-1).

Therapeutic and toxicologic skeletal muscle paralysis can occur by severa mechanisms. For example, tetrodotoxin blocks voltage-sensitive sodium channels, preventing action potential conduction by the motor neuron. On the other hand, botulinum toxin blocks ACh release from the presynaptic neuron by inhibiting the binding of ACh-containing vesicles to the neuron membrane in the region of the synaptic cleft. Modulation of postsynaptic receptor activity at the NMJ can produce paralysis by 1 of 2 mechanisms:

depolarizing (phase I block) and nondepolarizing (phase II block). Succinylcholine is the only depolarizing neuromuscular blocker (DNMB) in current clinical use. Nicotine at high doses can also cause a depolarizing block. The other agents discussed are all nondepolarizing neuromuscular blockers (NDNMBs).

The process of DNMB requires several steps. First, 2 molecules of succinylcholine must bind to each Î± site of the nACh receptor. This actic causes a prolonged open state of the nACh receptor ion channel. The init depolarization causes a muscle action potential and usually causes brief contractions (fasciculations). In contrast to ACh, succinylcholine is not hydrolyzed efficiently by junctional (true) acetylcholinesterase (AChE); th the effect of succinylcholine lasts much longer than ACh. The persistent presence of succinylcholine at the ACh receptor causes a sustained local muscle endplate depolarization that, in turn, causes the voltage-gated sodium channel in the perijunctional region to remain in a prolonged inac state, inducing a desensitization block. The muscle is temporarily refracto to presynaptic release of ACh (phase I block).

The NDNMBs cause skeletal muscle paralysis by competitively inhibiting t effects of ACh and thus preventing muscle depolarization. One molecule o an NDNMB bound to a single nACh receptor (on the Î± site) competitively inhibits normal channel activation. The NDNMBs do not block voltage-gate sodium channels on the muscle membrane, and direct electrical stimulati of muscle contraction is still possible. The NDNMBs are classified by dura of action as ultrashort, short, intermediate, and long. They also are classified by chemical structure as either synthetic benzylisoquinolinium drugs or aminosteroids (Table 66-1), which are derived from plant alkal

NDNMBs also block nACh receptors on the prejunctional nerve terminal ar inhibit ACh-stimulated ACh production and release.[85] This effect reduces available pool of ACh and augments the extent of neuromuscular block.[9]

Pharmacokinetics

The NMBs are highly water soluble and relatively insoluble in lipids. Thus,

they are rapidly distributed in the extracellular space and very slowly permeate lipid membranes such as the placenta and the normal bloodâ€“brain barrier. For this reason, they are devoid of central nervous system (CNS) effects. Because these drugs distribute in the extracellular space, their dosage is based on ideal body mass. Dosing according to the total body mass in obese patients can result in an exaggerated or prolon drug effect.

The speed of onset of an NMB is inversely related to its molar potency (ie ED_{95} expressed as Âµmol NMB drug per kilogram body weight).[56 , 57] Sta differently, the greater the affinity of the NDNMB for the ACh receptor, th fewer molecules per kilogram of tissue are required to produce a given degree of ACh receptor occupancy. Atracurium is the only drug that does follow this generalization because it is a mixture of isomers each having a different receptor affinity.

In general, small, fast contracting muscles such as the extraocular muscl are more susceptible to neuromuscular block than are larger, slower mus such as the diaphragm. This is the so-called *respiratory sparing effect.* Following an IV bolus of NDNMB, paralysis of the diaphragm is coincident with paralysis of laryngeal muscles because their high perfusion results in rapid drug diffusion into the NMJ.[20] Recovery from NMB is fastest for the diaphragm and intercostal muscles, intermediate for the large muscles of trunk and extremities, and slowest for the adductor pollicis, larynx, phary and extraocular muscles.[20]

Complications of Neuromuscular Blockers

Complications associated with the use of NMBs include (1) problems associated with the care of a patient who is therapeutically or otherwise paralyzed (eg, undetected hypoventilation resulting from ventilator or air problems, impaired ability to monitor neurologic function, unintentional patient awareness, peripheral nerve injury, deep vein thrombosis, and sk breakdown); (2) immediate side effects; and (3) effects occurring followi prolonged drug exposure.[75 , 76]

Patient Awareness

The NMB drugs do not affect consciousness, yet misconceptions about the drugs persist.[66] The pupillary light reflex, an important

indicator of midbrain function, is preserved in healthy subjects who receive NDNMBs[41] because pupillary function is mediated by muscarinic cholinergic receptors, for which the NMBs have no affinity. Atropine paralyzes the papillary constrictors and produce fixed mydriasis. Many drugs used in combination with NMBs, such as sedatives, opioids, and inhalational anesthetics, increase the amplitude of pupillary constriction in response to light, but do not produce paralysis.

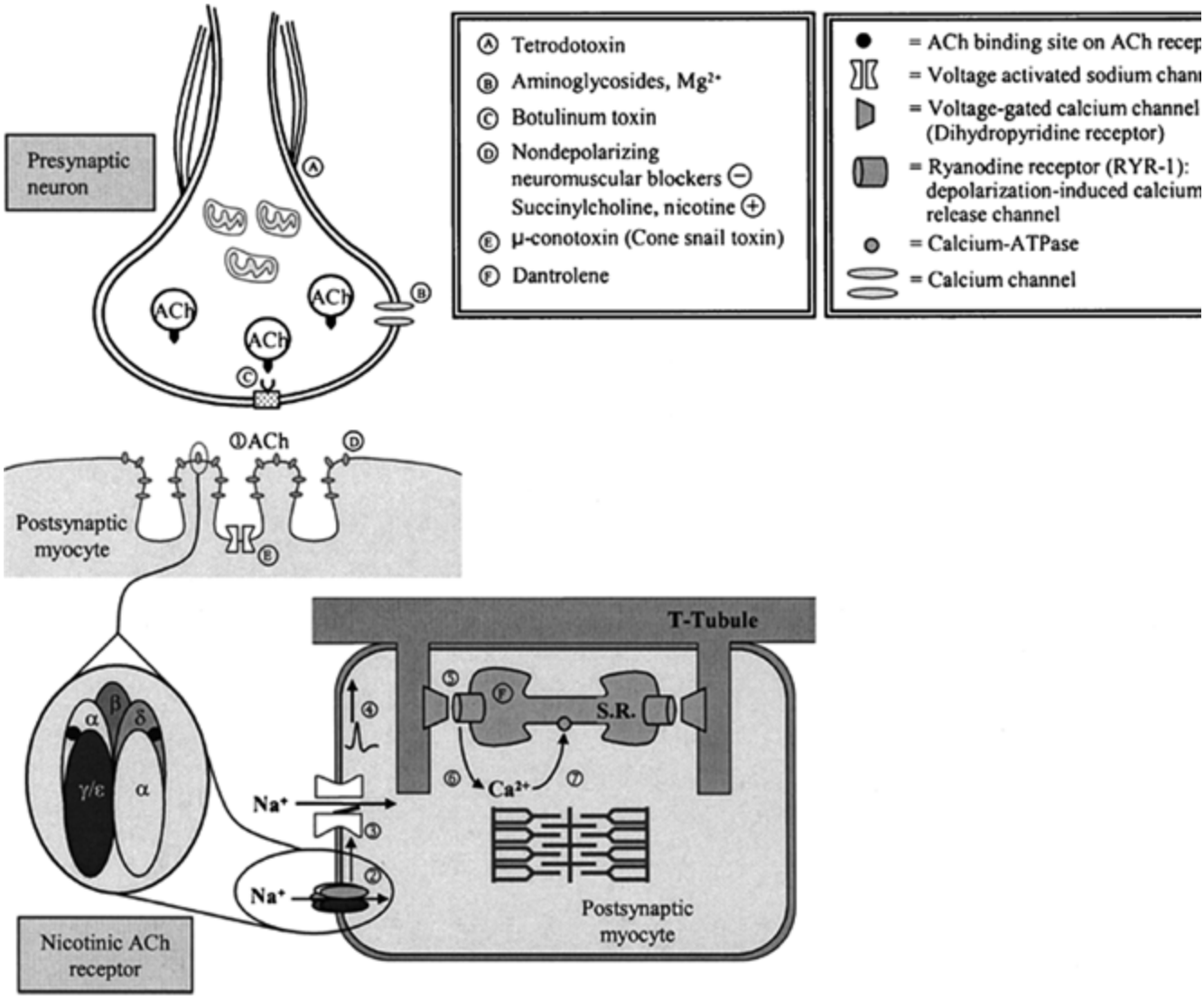

Figure 66-1. Excitationâ€“contraction coupling in skeletal muscle. At the neuromuscular junction (NMJ), acetylcholine (ACh) released from the presynaptic nerve terminal â‘ crosses the 50-nm synaptic cleft to reach t nicotinic ACh receptor â‘¡. The basal lamina, a thin layer of connective tissue, extends into the synaptic cleft and is associated with acetylcholinesterase (AChE). There are two types of receptors, a mature receptor (Î±Î±Î²ÎµÎ´) found in normal adult NMJ and a fetal or immature receptor (Î±Î±Î²Î³Î´) found on the muscle at extrajunctional sites. Proliferation of immature receptor occurs during normal embryonic development and during certain pathologic states, such as denervation injury. On the nicotinic ACh receptor, there are two negatively charged s

that can bind ACh; one at the Î±â€“Î³ interface and one at the Î±â€“Î´ interface. All neuromuscular blockers (NMBs) possess at least 1 positively charged quaternary ammonium group that can competitively bind with the ACh binding site. Only when agonist simultaneously occupies both receptor sites does the ion channel open, becoming nonselectively permeable to monovalent cations and resulting in an influx of Na^+ and an efflux of K^+ . This produces local membrane depolarization (endplate potential) that, in turn, opens voltage-activated Na^+ channels â‘¢. A depolarization of sufficient amplitude generates a propagated muscle action potential (MAP â‘£), which is conducted along the muscle membrane and down the transverse (T) tubules. In the T tubule, the MAP triggers a voltage-activated calcium channel (dihydropyridine receptor [DHPR], â‘¤), which then activates the skeletal muscle ryanodine receptor/channel (RYR-1, ⑥). To allow the fast activation of mammalian skeletal muscle, calcium diffusion is not necessary for activation of RYR-1; instead there is a direct electrical (protein) linkage between the DHPR and RYR-1.[29] This intimate association of DHPR, RYR-1, and junctional sarcoplasmic reticulum (SR) is called the *calcium release u* In contrast, in cardiac muscle, calcium entry through the DHPR is required for activation of the cardiac ryanodine receptor RYR-2. In the skeletal muscle calcium leaves the SR through the RYR-1 channel to enter the myoplasm where it binds to troponin C, activating the contractile actinâ€“myosin protein complex to produce muscular contraction. Active ATPase-driven reuptake of calcium into the longitudinal SR ⑦ terminates muscle contraction. Many factors influence the activity of the RYR-1 channel such as Ca^{2+} , Mg^{2+} , and anesthetic drugs such as inhalation agents that accelerate Ca^{2+} release in persons susceptible to malignant hyperthermia

Histamine Release

The benzylisoquinolinium muscle relaxants (Table 66-1) produce direct, nonimmunologic dose- and rate-related histamine release

from tissue mast cells. The approximate rank order for histamine release is tubocurarine > atracurium and mivacurium > succinylcholine.[27]

Name[a]	Class	Duration	Initial Dose (mg/kg)[b,c]	Onset (min)[d]	Clinical Duration (min)[e]	Recovery Index 25–75% (min)[f]
Succinylcholine	Depolarizer	Ultrashort	0.6–1	1–1.5	3–7	2
Atracurium	Nondepolarizer, benzylisoquinolinium	Intermediate	0.4	2–4	20–40	11
Cisatracurium		Intermediate	0.1	2–4	35–50	10–15
Doxacurium		Long	0.05	4–6	90–120	30–45
Mivacurium	Nondepolarizer, aminosteroid	Short	0.16	2–4	15–20	6–12
Tubocurarine		Long	1	4–6	60–90	48
Pancuronium		Long	0.14	3–6	60–100	55
Rocuronium		Intermediate	0.6	1.5–3	30–40	10–15
Vecuronium		Intermediate	0.1	2–4	20–40	10–15

	Renal Excretion (%)[g]	Biliary Excretion (%)[h]	Effect of Renal Failure	Effect of Hepatic Failure	Active Metabolite	Histamine Release	Effect on HR	Prolonged Block Reported
Succinylcholine	<10	Minimal	Minimal	Minimal	? Succinic acid	Minimal	(Rare) severe bradycardia	Atypical/deficient plasma AChE, phase II Block
Atracurium	5–10	Minimal	No effect	Minimal to none	No, but laudanosine	Minimal	No	Yes
Cisatracurium	10–20	Minimal	No effect or minimal	No effect	No, but laudanosine	No	No	Yes
Doxacurium	50–70	Minimal	Duration	Minimal	?	No	No	Yes
Mivacurium	<10	Minimal	Duration	Duration	No	Minimal	No	Atypical/deficient plasma AChE
Tubocurarine	40–50	10	Duration	Minimal	No	Marked	Tachycardia	No
Pancuronium	40–60	10–20	Duration drug and metabolites	Mild	3-Desacetyl-pancuronium	No	Tachycardia	Yes
Rocuronium	10–20	50–70	Minimal duration	Duration	No	No	Tachycardia at high dose	Yes
Vecuronium	20–40	40–70	Duration drug and metabolites	Duration drug and metabolites	3-Desacetyl-vecuronium	No	No	Yes

[a] Generic name (trade name, year introduced): succinylcholine (Anectine, 1951), atracurium (Tracrium, 1983), cisatracurium (Nimbex, 1995), doxacurium (Nuromax, 1991). Mivacurium (Mivacron, 1992), pancuronium (Pavulon, 1972), rocuronium (Zemuron, 1994), tubocurarine (Curare, 1942), vecuronium (Norcuron, 1984).
[b] Cisatracurium is labeled as mg of base per mL. Other drugs are labeled and packaged as mg of salt per mL.
[c] Typical initial dose is approximately $2 \times ED_{95}$ (mg/kg).
[d] Onset = time from bolus to 100% block.
[e] Clinical duration = time from drug injection until 25% recovery of single twitch height.
[f] Recovery Index = time from 25% to 75% recovery of single twitch height.
[g] % Renal excretion in first 24 hours of unchanged drug.
[h] % Biliary excretion in first 24 hours of unchanged drug.
Adapted from Donati F: Neuromuscular blocking drugs for the new millenium: Current practice, future trends—Comparative pharmacology of neuromuscular blocking drugs. Anesth Analg 2000;90:S2–S6; McManus MC: Neuromuscular blockers in surgery and intensive care, part 1. Am J Health Syst Pharm 2001;58:2287–2299; Murray MJ, Cowen J, DeBlock H, et al: Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. Crit Care Med 2002;30:142–156.

TABLE 66-1. Pharmacology of Selected NMB Drugs

Anaphylaxis

Of the anaphylactic reactions occurring during general anesthesia, approximately 60% are the result of NMBs, whereas only 17% are the re of latex.[72] Rocuronium is responsible for 43% and succinylcholine for 23% all NMB-associated anaphylaxis. Pancuronium is the agent least associate with serious allergic reactions.[101]

Control of Respiration

At subparalyzing doses, NDNMBs blunt the hypoxic ventilatory response (HVR) but not the ventilatory response to hypercapnia.[25, 26] HVR returns normal when the chemical paralysis is completely reversed. Hypoventilati resulting from blunting of the HVR, especially when combined with the residual effects of other drugs used during anesthesia (eg, opioids or inhalational anesthetics), can cause delayed respiratory failure.

Autonomic Side Effects

Neuronal nACh receptors found in autonomic ganglia, such those at the N are pentamers composed of Î± and Î² subunits. In general they are less susceptible to block by NMBs.[6,7] There is one notable exception. At the sa dose that produces neuromuscular block, tubocurarine also blocks nACh receptors at the parasympathetic ganglia, causing tachycardia, and at the sympathetic ganglia, blunting the sympathetic response.[8,8] In combinatio with tubocurarine-related histamine release, the sympathetic block can cause significant hypotension, especially in patients with heart failure or hypovolemia.[10]

Aminoglycosides (eg, amikacin, gentamicin)
Potentiates
Potentiates
Dose-related decrease in presynaptic ACh release. May decrease postjunctional response to ACh. Partially reversible with calcium supplementation. Effect of neostigmine unpredictable.
Anticholinesterase, peripheral acting: neostigmine, edrophonium
Prolongs succinylcholine (except edrophonium)
Inhibits, prolongs mivacurium (except edrophonium)
Neostigmine, pyridostigmine, and physostigmine inhibit plasma AChE and prolong mivacurium and succinylcholine block. Edrophonium does not inh plasma cholinestarase.
Anticholinesterase, centrally acting: donepezil
Potentiates

Potentiates mivacurium

Inhibits AChE (junctional >> plasma), long half-life (70 h)

Î²-Adrenergic antagonist: propranolol

Potentiates in cats, effects in humans uncertain

Potentiates

Given alone may unmask myasthenic syndrome. Blocks ACh binding at postsynaptic membrane. Reversal of block with neostigmine can cause severe bradycardia.

Î²-Adrenergic antagonist: esmolol

? Mild prolongation

Slows onset of rocuronium and mivacurium

Competes for plasma AChE, slows degradation of mivacurium.

Botulinum toxin

Early potentiation, delayed resistance

Single case report: Acutely, subclinical systemic denervation leads to vecuronium hypersensitivity. Subsequent NMJ remodeling and ACh recept upregulation leads to vecuronium resistance.

Calcium channel blockers: nifedipine, verapamil

Potentiates

Potentiates

Causes calcium channel block pre- and postjunctionally. Verapamil has lo C-I effect on nerve. May inhibit block reversal by cholinesterase inhibitor.

Carbamazepine

?

Inhibits, shortened duration

Chronic therapy causes resistance to NDNMB, except for mivacurium and atracurium.

Dantrolene

?

Potentiates

Blocks excitationâ€“contraction coupling by blocking ryanodine calcium channel in sarcoplasmic reticulum of skeletal muscle.

Digitalis

More prone to cardiac dysrhythmias
Pancuranium increases catecholamines and may cause dysrhythmias

Furosemide

Biphasic dose response in cats; protein kinase inhibition at low doses and phosphodiesterase inhibition at high doses. Diuretic-related hypokalemia potentiates pancuronium in cats.

<10 Âµg/kg
Potentiates
Potentiates
1â€“4 mg/kg
Inhibits
Inhibits
Glucocorticoids

Inhibits
Chronic steroid use induces resistance to pancuronium and decrease plas cholinesterase activity by 50%. Steroids Â± NDNMB associated with myopathies.
Inhalational anesthetics: isoflurane
Potentiates
Potentiates
Decrease CNS activity and potentiates NMB in dose-dependent fashion (postsynaptic and muscle effects). Halothane causes less muscle relaxati than isoflurane.
Lidocaine
Potentiates
Low-dose lidocaine potentiates block. High-dose lidocaine inhibits nerve terminals and blocks ACh binding site at postsynaptic membrane.
The fast Na^+ channel blockers decrease action potential propagation, ACh release, postsynaptic membrane sensitivity, and muscle excitability. Wea inhibitor of plasma cholinesterase.
Lithium carbonate

Prolongs onset and duration
Prolongs effect of pancuronium
Inhibits synthesis and release of ACh. Lithium alone may cause myasther reaction.
Magnesium
Potentiates, may block fasciculations
Potentiates, may also prolong block
Decreases prejunctional ACh release, postjunctional membrane sensitivity and muscle excitability.
Nondepolarizing neuromuscular blocker: pancuronium
â€œPrecurarizationâ€• with NDNMB shortens the onset and decreases si effects of succinylcholine. Tubocurarine decreases and pancuronium increases block duration.
Chronic NDNMB induces resistance to their effect. Mixing different NDNMB may cause greater than additive effects, especially combining pancuroniu with tubocuranine or metocurine
Prior NDNMB inhibits plasma AChE and prolongs mivacurium and succinylcholine block. Rank order: pancuronium > vecuronium > tubocura > atracurium. Heterozygote for atypical plasma AChE may develop phase block when given succinylcholine and pancuronium.
Organic phosphorus compounds echothiophate
Potentiates

Irreversible plasma AChE inhibitor. May totally block enzyme activity.
Phenelzine (MAO inhibitor)
Prolongs

Decreases plasma AChE activity.
Phenytoin
?
Resistant, shortened duration
Acutely, potentiates NDNMB paralysis. With chronic use (except for mivacurium and atracurium) phenytoin induces resistance to NDNMB and increases drug metabolism. This increases the initial dose and decreases

repeat dosing interval.
Polypeptide antibiotics: polymyxin
Potentiates
Potentiates
Can cause severe weakness. May induce postsynaptic neuromuscular bloc
Neostigmine increases block.
Succinylcholine
Self-taming dose of succinylcholine may be used to limit muscular fasciculations.
Tubocurarine, pancuronium, and vecuronium slightly prolonged by prior succinylcholine

Theophylline

Inhibits
Pancuronium and theophylline can increase cardiac dysrhythmias.
Tricyclic antidepressants (TCA)

Pancuronium and TCA may cause cardiac dysrhythmias due to sympatheti effects.

Drug	Response to Succinylcholine	Response to Nondepolarizer	Commer

TABLE 66-2. Effect of Prior Administration of Many Drugs on Subsequent Response to Succinylcholine or Nondepolarizing Neuromuscular Blockers (NDNMBs)

The muscarinic receptors (M_1 â€“M_5) are members of the seven-transmembrane G-proteinâ€“coupled receptor family. As such they are structurally unique and mostly unaffected by NMBs. At clinical doses,

pancuronium elicits dose- and injection rate-related increases in heart ra blood pressure, cardiac output, and sympathetic tone.[89 , 91 , 95] This is attributed to a selective block of parasympathetic transmission at the ca muscarinic receptors (atropinelike effect),[89] block of presynaptic muscari receptors at sympathetic nerve terminals, and perhaps an indirect norepinephrine-releasing effect at postganglionic fibers.[91] Sympathetic stimulation from pancuronium may increase cardiac dysrhythmias, espec when combined with halothane and a tricyclic antidepressant.[24]

Dysrhythmias including bradycardia, junctional rhythms, ventricular dysrhythmias, and cardiac arrest occur rarely after succinylcholine. This situation most likely results from stimulation of the cardiac muscarinic receptors and can be prevented by pretreatment with atropine 15â€“20 Âµg/kg IV. Bradycardia is uncommon, but it may be especially severe in children during anesthetic induction when large or repeated doses of succinylcholine are given. For this reason, atropine is generally given beforehand.

Interactions of Muscle Relaxants with Othe Drugs and Pathologic States

NMB has significant interactions with many medications (Table 66-2) and coexisting medical conditions. These interactions can affect the neuromuscular system at any level from the CNS to the muscle itself.[81 , For example, potent inhalation anesthetics depress CNS activity, local anesthetics inhibit propagation of nerve action potentials, chronic lithium therapy inhibits presynaptic synthesis of ACh, magnesium and aminoglycoside antibiotics inhibit presynaptic release of ACh, donepezil inhibits AChE, polypeptide antibiotics (eg, polymyxin) inhibit the postjunctional muscle membrane, and dantrolene inhibits calcium release from muscle sarcoplasmic reticulum. All of these drugs potentiate the eff of NMBs.

In most neuromuscular diseases, such as muscular dystrophy, Guillain-BarrÃ© syndrome, myasthenia gravis, and postpolio syndrome, sensitivity

NDNMB is increased, so a small dose of NMB produces a profound degree block.[1,11,45] Persons with myasthenia gravis typically demonstrate resistance to the effects of succinylcholine.[1,11] In individuals with myopathy of unknown etiology, a prudent course is to avoid succinylcholi because of the potential for malignant hyperthermia (MH), hyperkalemia, rhabdomyolysis and to use a short-acting NDNMB to help decrease the possibility of prolonged weakness.

Many systemic pathologic states potentiate the duration or intensity of NDNMB, such as respiratory acidosis, hypokalemia, hypocalcemia, hypermagnesemia, hypophosphatemia, hypothermia, shock, and liver or kidney failure.[84] Alternatively, acute sepsis and inflammatory states are associated with mild resistance to the effect of NDNMB.[77]

Pharmacology of Depolarizing Neuromuscular Blocking Drugs (Succinylcholine)

Succinylcholine is a bis-quaternary ammonium ion composed of 2 ACh molecules attached by their acetate groups.[22] Following a conventional IV induction dose (1 mg/kg), typical serum concentrations are approximately Âµg/mL.[79]

Succinylcholine is hydrolyzed mostly by plasma (pseudo) cholinesterase (ChE) and to a slight extent by alkaline hydrolysis. Hydrolysis is a 2-step reaction; first succinylmonocholine and choline and then succinic acid and choline are formed (both are normal products of intermediary metabolism The first reaction is approximately 6 times faster than the second reactio Less than 3% of the administered dose is excreted unchanged in the urin Following an IV bolus, the serum succinylcholine concentration rises abru and there is a rapid onset of NMJ block. Later the serum succinylcholine concentration undergoes a rapid decline as a result of drug redistribution extravascular tissues and hydrolysis in the serum. Finally succinylcholine leaves the NMJ to reenter the serum as a result of reversal of the

concentration gradient.[38 , 52]

Succinylcholine 1 mg/kg IV usually increases cerebral blood flow, cortical electrical activity, intracranial pressure,[58] and intraocular pressure, especially in lightly anesthetized patients. These effects, when they occur usually are modest.

Toxicity of Depolarizing Neuromuscular Blockers

The important adverse drug reactions associated with succinylcholine inc (1) anaphylaxis, (2) prolonged drug effect, (3) hyperkalemia, (4) acute rhabdomyolysis in patients with muscular dystrophy, (5) MH in susceptibl patients, (6) muscle spasms or trismus in myotonia congenita, and (7) cardiac dysrhythmias.

Prolonged Effect

The effects of succinylcholine may last for several hours if metabolism is slowed because of decreased plasma ChE, abnormal plasma ChE activity (genetic variant or drug inhibition), or a phase II block.[15] Plasma ChE deficiency may be caused by hepatic disease, malnutrition, plasmapheres and pregnancy.[15] Inactivation of plasma ChE can be caused by fluoride intoxication, organic phosphorus compounds, and carbamates. On the oth hand, even with only 20â€“30% of normal plasma ChE activity, the effec duration of succinylcholine is less than doubled.[31]

Many genetic variants of plasma ChE are known. The most common atypi plasma ChE (atypical type, homozygous incidence 1:3000) can be assayed its resistance to inhibition by the local anesthetic dibucaine.[82] A history o uneventful exposure to succinylcholine excludes the possibility of atypical plasma ChE, except in case of hepatic transplantation. Dibucaine inhibits ability of normal plasma ChE to hydrolyze benzoylcholine by >70% (ie, dibucaine number >70), heterozygous atypical enzyme by 40â€“60%, and homozygous atypical enzyme by â‰¤30%. Fresh-frozen plasma or plasm ChE concentrates can be infused to hasten recovery in the case of a gene

enzyme defect or an acquired ChE deficiency. However, to avoid the risks transfusion, it is best to simply keep the patient sedated, intubated, and ventilated until the drug is metabolized. In this setting, spontaneous rev usually requires 3â€“4 hours, although in rare cases full recovery require up to 12 hours.[15] When the duration of succinylcholine is very prolonged, blood samples should be drawn for measurement of plasma ChE concentration and activity.

Prolonged nondepolarizing block can occur when large doses of succinylcholine (2â€“8 mg/kg IV) are given over a short period. This is c *phase II block.* It can be partially reversed by neostigmine.

Hyperkalemia

Succinylcholine 1 mg/kg IV typically causes serum [K^+] to increase by approximately 0.5 mEq/L in normal individuals and in persons with renal failure. The acute hyperkalemic response to succinylcholine is exaggerate with coexisting myopathy or proliferation of extrajunctional muscle ACh receptors. However, the mortality is highest (30%) when rhabdomyolysis occurs.[42] Severe, precipitous, potentially life-threatening hyperkalemia occurs following succinylcholine administration in several conditions associated with proliferation of ACh receptors. These conditions include denervation (head or spinal cord injury, stroke, neuropathy, prolonged us of NDNMBs), muscle pathology (direct trauma, crush or compartment syndrome, muscular dystrophy), critical illness (hemorrhagic shock, neuropathy, myopathy, prolonged immobility), thermal burn or cold injur and sepsis lasting several days (eg, intraabdominal infections). Following neurologic injury, susceptibility to hyperkalemia begins within 4â€“7 days and may persist indefinitely. In patients who have been in the ICU for mo than 1 week, a prudent course is to avoid succinylcholine altogether beca of the risk of hyperkalemic cardiac arrest, which is associated with a mortality rate of at least 19%.[6 , 8 , 42 , 43] Severe hyperkalemia is modif but not prevented, by a dose of an NDNMB sufficient to prevent succinylcholine-induced muscle fasciculations.

Severe or even fatal hyperkalemia has been reported in a few patients wh

received succinylcholine immediately following exsanguinating hemorrhag or massive trauma. The mechanism for this condition is not the same as following neurologic injury because of inadequate time for proliferation of extrajunctional ACh receptors. Succinic acid, a tricarboxylic acid cycle intermediate (which is also a metabolite of succinylcholine), facilitates activation of voltage-gated sodium channels in a dose-dependent fashion, increasing skeletal muscle excitability.[46] In hemorrhagic shock, accumula of succinic acid as a result of cell breakdown and anaerobic metabolism possibly augments the potassium-releasing effect of succinylcholine.

Rhabdomyolysis

Severe hyperkalemia rarely occurs in the absence of a clinical history tha readily discloses an obvious risk factor, with one important exception. Ac or delayed onset of rhabdomyolysis, hyperkalemia, ventricular dysrhythn cardiac arrest, and death have been reported in apparently healthy childı who subsequently were found to have a myopathy.[59] Since March 1995, a black box warning on the package insert has stated that succinylcholine should be avoided in elective surgery in children, particularly those youn than 8 years, because of the small risk of a previously undiagnosed skele myopathy, especially Duchenne muscular dystrophy. Sudden cardiac arre occurring immediately following succinylcholine should always be assumed be caused by hyperkalemia. If fever, muscle rigidity, hyperlactatemia, or metabolic and respiratory acidosis also is present, the presumptive diagr of MH should prompt immediate therapy with dantrolene.

Malignant Hyperthermia

Malignant hyperthermia is a heterogeneous syndrome that typically affec individuals who are otherwise healthy, although it may be associated with certain myopathies, including Duchenne muscular dystrophy, central core disease, King-Denborough syndrome, osteogenesis imperfecta, and myotonia. The disorder is associated with a

defect of a skeletal muscle regulatory/receptor protein. Inheritance is

autosomal dominant with variable penetrance.[68] In humans, multiple pro defects are causally associated with MH, which may account for the heterogeneity of its inheritance and clinical presentation. In human MH, 1 at least 42 different mutations in the skeletal muscle ryanodine receptor type 1 (RYR-1, chromosome 19q13.1) is present in 50â€“80% of patients (Figure 66-1).[96] RYR-1 is present in both fast-twitch and slow-twitch skeletal muscle, whereas only RYR-2 is found in cardiac muscle. This situation may explain why the myocardium is hyperdynamic and relatively spared in the early phase of MH.[86] Of practical importance, the existence multiple mutations across multiple alleles means that genetic testing like will not prove useful in detecting all susceptible individuals.

The incidence of MH is approximately 1/20,000 in children and 1/50,000 adults. MH most often occurs in the operating room shortly after initial exposure to anesthetic agents, but it may commence several hours after general anesthetic is given[74] or as long as 12 hours after surgery. In addition, recurrence can occur 24â€“36 hours after an initial episode.

Malignant hyperthermia is caused inconsistently by exposure to certain anesthetic agents that trigger abnormal calcium release from the skeletal muscle sarcoplasmic reticulum. In patients who are MH susceptible, clinic manifestations develop less than half the time following exposure to triggering agents. For this reason, a previous uneventful anesthetic expo does not preclude development of MH on subsequent exposure.[3]

Drugs associated with precipitating an attack of MH include succinylcholin and volatile inhalational anesthetics (the prototypical agent is halothane) Drugs that can be administered safely to individuals considered susceptib to MH include NDNMBs, nitrous oxide, propofol, ketamine, etomidate, benzodiazepines, barbiturates, opioids, and local anesthetics.

The immediate systemic manifestations of MH result from skeletal muscle hypermetabolism. Uncontrolled release of calcium from the terminal cisternae of the sarcoplasmic reticulum causes skeletal muscle contractio Muscular rigidity is a specific sign of MH, but it is not consistently observ Futile cycling of calcium in the skeletal myocyte by sarcoplasmic Ca^{2+} - ATPase causes depletion of cellular ATP, hypermetabolism, excess heat

production, core hyperthermia, increased O_2 consumption and CO_2 production, venous O_2 desaturation and hypercarbia, anaerobic metabolis and lactic acid generation.[47] The extreme elevation of metabolic rate cau severe mixed venous oxygen desaturation (far below the normal of 75%) Cardiac dysrhythmias, hyperkalemia, rhabdomyolysis, and disseminated intravascular coagulopathy may occur.

The earliest signs of MH include an early and rapid increase in CO_2 production and arterial, venous, and end-tidal CO_2 ; tachycardia; tachypı hypertension or labile blood pressure; and skeletal and jaw muscle rigidit Despite the name of the syndrome, hyperthermia is not a universal findin MH. Moreover, when it occurs, it is often a late sign.[99] Acute potassium release from muscle cells may result in life-threatening hyperkalemia. Subsequent rhabdomyolysis can exacerbate the problem by causing renal failure. In late-stage MH, cardiac decompensation results from hyperkale heart failure, vascular collapse, and/or myocardial ischemia (especially w coexisting coronary artery disease).

The differential diagnosis of MH includes neuroleptic malignant syndrome propofol infusion syndrome, serotonin syndrome, thyroid storm, pheochromocytoma, baclofen withdrawal, malignant syndrome in Parkinso disease, tetanus, meningitis, poisoning by salicylates, amphetamines, cocaine or antimuscarinics, unintentional intraoperative hyperthermia, he stroke, and transfusion reactions. Of note, early septic shock is also associated with hypermetabolism, increased cardiac output, and fever, bu typically the mixed venous O_2 saturation is >75%.

Rarely, MH is triggered by severe exercise in a hot climate, IV potassium (which depolarizes the muscle membrane), antipsychotic drugs, and infection.[18 , 51] Patients with hypermetabolism or rhabdomyolysis have responded to dantrolene, but this finding does not necessarily confirm th patients have MH. Such confirmation requires a muscle biopsy.

One theory of the pathogenesis of MH states that MH-triggering agents interact with an abnormal RYR-1 channel, causing it to stay in a prolonge open state and leading to rapid efflux of calcium from the skeletal muscle sarcoplasmic reticulum into the myoplasm. Succinylcholine triggers a

prolonged muscle depolarization leading to elevated myoplasmic calcium. This action initiates accelerated calcium-activated calcium release from t myoplasmic reticulum.[44] However, not all cases of MH can be explained b an RYR-1 mutation.[35] For example, the association of defects in skeletal muscle sodium channels in certain myotonic disorders has generated inte in the role of the sodium channel in MH.[35] Also, certain MH-susceptible persons manifest increased skeletal muscle fatty acid production, and fat acids augment halothane-induced sarcoplasmic calcium release.[32 , 33 and Although definition of one pathogenic mechanism is not yet possible, any unitary hypothesis must account for these observations.

By partially blocking calcium release from skeletal muscle sarcoplasmic reticulum, dantrolene rapidly reverses the signs and symptoms of hypermetabolism: fever, mottled skin, dysrhythmias, muscle rigidity, tachycardia, metabolic acidosis, and hypercapnia. Before the discovery of dantrolene, the mortality rate from MH was 70%. When acute MH is treat immediately with dantrolene, volume resuscitation, active cooling, control hyperkalemia, and supportive care, the mortality is <5%. Therefore, the most important aspects of MH therapy are rapid initial diagnosis and immediate therapy (within minutes) with dantrolene. Even if administrati is delayed for hours or days, dantrolene may still improve survival follow an acute episode. Significant dysrhythmias can be treated with standard antidysrhythmic agents; however, calcium channel blockers must *not* be given with dantrolene because they may precipitate hyperkalemia and se hypotension[87] (Table 66-3).

Persons who have experienced a possible episode of MH or have a positiv family history can be considered for muscle biopsy and muscle testing. Th fresh tissue specimen is placed in a tissue bath perfused with Krebs solut and halothane or caffeine is added. According to the North America Malignant Hyperthermia Group, an MH-susceptible individual has a positiv muscle contraction in response to either halothane or caffeine.

Muscle Spasms

Masseter muscle rigidity (MMR) is observed in 0.3â€“1% of pediatric pati

induced with succinylcholine and halothane. MMR is clinically significant because it may complicate airway management and herald the onset of MH.[80]

When administered to persons genetically predisposed to myotonia, succinylcholine can precipitate tonic muscular contractions, ranging from trismus (which may prevent orotracheal intubation) to severe generalized myoclonus and chest wall rigidity (which may prevent ventilation).[28] Because the myotonic contractions are independent of neural activity, the cannot be aborted by an

NDNMB. Usually the contractions are self-limited, but occasionally they ca be life-threatening if an airway cannot be established and hypoxemia ensues.

Acute Phase Treatment of Malignant Hyperthermia (MH)

1. Call for help. Immediately summon experienced help when MH is suspected.
2. Stop triggering agents, including volatile inhalational anesthetics a succinylcholine.
3. Hyperventilate with 100% O_2 .
4. Administer dantrolene sodium. Give the initial bolus of 2.5 mg/kg rapidly, followed by additional boluses until signs of MH are controlled (tachycardia, rigidity, increased end-tidal CO_2 , hyperthermia). Typic total dose of 10 mg/kg controls symptoms, but occasionally up to 3 times this dose may be required.
5. Monitor core temperature closely. Excessive treatment may lead t hypothermia.
6. Actively cool the hyperthermic patient , simultaneously with the above.
    - Immersion in ice-water slurry is best. Peritoneal or gastric lavage can also be useful.
    - Surface cool with ice and hypothermia blanket.
7. Aggressively treat hyperkalemia. Hyperkalemia is common and sh be treated with hyperventilation, sodium bicarbonate, intravenous

glucose, and insulin. Severe hyperkalemia can also be treated with calcium administration. Hypokalemia should treated with great cautio because hyperkalemia may occur due to rhabdomyolysis.

8. Monitor end-tidal CO_2 , arterial and mixed venous blood gases, ser potassium and calcium, clotting studies, and urine output.
9. Administer sodium bicarbonate to correct metabolic acidosis as guided the arterial blood gas.
10. Dysrhythmias usually respond to dantrolene and correction of acidosi and hyperkalemia. If dysrhythmias persist or are life-threatening, standard antidysrhythmics can be used.
    - Calcium channel blockers should *not* be used (especially verapamil) to treat dysrhythmias because they can cause hyperkalemia and cardiovascular collapse.
11. Ensure adequate urine output by hydration and/or administration of mannitol of furosemide. Consider central venous or PA monitoring.
12. For emergency consultation to help with patient management (http://www.mhaus.org/hotline.html) call the MH Emergency Hotline:
    - Inside United States or Canada call: 800-MH-HYPER (800-644-9737)
    - Outside the United States and Canada call: 001 315-464-7079

Postacute Phase Treatment of Malignant Hyperthermia

1. Observe the patient in an ICU setting for at least 24â€“48 hour because recrudescence of MH occurs in 25% of cases, particularly following a fulminant case resistant to treatment.
2. Administer dantrolene 1 mg/kg IV q4â€“6h for 24â€“48 hours after the episode.
3. Follow arterial blood gases, creatine phosphokinase, potassium, calci phosphorus, urine and serum myoglobin, PT, PTT, platelet count, and core body temperature until they return to normal values (eg, q6h). Central temperature (eg, rectal, esophageal) should be monitored continuously.
4. Counsel the patient and family regarding MH and further precautions.

- For nonemergency patient referrals, contact MHAUS: 888-274-7899, 11 East State Street, PO Box 1069, Sherburne, NY 13460.
- Report patients who have had an acute MH episode to the North American MH Registry of MHAUS: 412-692-5464
- Alert family members to the possible dangers of MH and anesthesia.

5. Recommend an MH medical ID for the patient and have the individual wear it at all times.

Notes:

1. Each vial of dantrolene contains 20 mg of dantrolene and 3 g mannitol (to improve water solubility). Each vial should be reconstituted with 5 mL distilled sterile water for injection. Dissolution of the lyophilized solution in water is slow and requires thorough mixing.
2. The guideline above may not apply to every patient and of necessity must be altered according to specific patient needs.
3. Sudden unexpected cardiac arrest in children: Children younger than about 10 years who experience sudden cardiac arrest after succinylcholine in the absence of hypoxemia and anesthetic overdose should be treated for acute hyperkalemia first. In this situation, calcium chloride should be administered along with other means to reduce serum potassium. They should be presumed to have subclinical muscular dystrophy, and a neurologist should be consulted.

TABLE 66-3. Suggested Therapy for Malignant Hyperthermia

Pharmacology of Nondepolarizing Neuromuscular Blocking Drugs

Table 66-1 lists the details of the pharmacology and toxicity of these drugs.[50, 70, 71, 76]

Atracurium is composed of 10 different isomers, each having its unique

pharmacokinetic and pharmacodynamic profile, whereas cisatracurium contains only the 1R-*cis* 1â€²R-*cis* isomers. Both atracurium and cisatracurium exhibit organ-independent elimination and are rapidly metabolized by spontaneous (nonenzymatic) temperature- and pH-depen Hofmann degradation and, to a lesser extent, by ester hydrolysis. The la is catalyzed by nonspecific plasma esterases, distinct from the plasma Ch that hydrolyzes succinylcholine. In addition, significant drug metabolism elimination occurs in the liver and kidney.[30]

Toxicity of Nondepolarizing Neuromuscular Blocking Drugs

The most important toxic effects of the NDNMB are accumulation of laudanosine and persistent weakness. In general, limiting the drug dose a monitoring the drug effect with a portable nerve stimulator reduce the incidence of prolonged weakness.

Laudanosine

When metabolized, each atracurium molecule generates, on average, <2 molecules of laudanosine and an acrylate moiety, neither of which posses neuromuscular blocking activity.[78] Cisatracurium is an improvement over atracurium; it is 3 times more potent and generates approximately one th as much laudanosine.[37 , 55] Laudanosine is excreted primarily in the bile and, to a lesser extent, by the kidney; thus

its elimination is prolonged in patients with liver disease, biliary obstruct and renal insufficiency.[83] Laudanosine crosses the bloodâ€“brain and placental barriers.[23] In the CNS, laudanosine has an inhibitory effect at t Î³-aminobutyric acid, nACh, and opioid receptors. At high plasma concentrations in experimental animals, laudanosine causes dose-related neuroexcitation, myoclonic activity (>14 Âµg/mL), and generalized seizu (>17 Âµg/mL).[12 , 37] In humans, the toxic plasma laudanosine concentra is unknown, and seizures directly attributable to atracurium have not bee

observed even following prolonged drug infusion in the ICU.[37 , 103] In ICU patients who received a 72-hour infusion of atracurium 1 mg/kg/h), the highest plasma laudanosine concentrations (10â€“20 Âµg/mL) were obse in patients with renal insufficiency.[62]

Persistent Weakness Associated with Nondepolarizing Neuromuscular Blockers

Short-term use of an NDNMB usually results in prompt termination of the block. When an NDNMB is administered for more than 48 hours, there is a risk that weakness will persist longer than anticipated based on the kinet of drug elimination. In addition, critical illness is associated with dysfunc of the peripheral nerve, NMJ, and muscle (Table 66-4). For instance, in t ICU, persistent weakness is observed in 68â€“100% of patients with seps or multiple organ failure[17 , 36 , 98] and in 20â€“30% of patients who rece NDNMB for only 48â€“72 hours.[64] Persistent weakness is multifactorial a associated with illness severity (Acute Physiology and Chronic Health Evaluation [APACHE] III score), sepsis, acute respiratory distress syndro multiorgan failure, hyperglycemia, NDNMB, systemic glucocorticoids, mus injury, thermal injury, and electrolyte, endocrine, and nutritional disorders.[16 , 21 , 48 , 63] Many drugs given to patients in the ICU can caus weakness by themselves or potentiate the effects of NDNMB.[49 , 81] Progressive weakness and acute respiratory failure have been described *following* discharge from the ICU and can present a life-threatening situa if not immediately recognized.[60] Patients who develop persistent weakne have a 2.5- to 3.5-fold increase in ICU mortality[64] and ICU stay.

Sensory
Moderate to severe, distal > proximal
Normal
Normal
Normal
Motor
Symmetric weakness, lower > upper extremity, proximal > distal or diffu

respiratory failure
Diffuse symmetric weakness, respiratory failure
Diffuse weakness, proximal > distal
Symmetric weakness, proximal > distal or diffuse, respiratory failure
Creatine phosphokinase
Normal
Normal
Normal
Elevated in â‰¤50%
Electrodiagnostic studies
(electromyogram [EMG], nerve conduction studies [NCS] including nerve conduction velocity [NCV])
Axonal degeneration of motor > sensory, reduced sensory and motor compound action potentials, normal NCV
Fatigue at NMJ assessed by fade on repetitive nerve stimulation
Normal EMG and NCV
Myopathic changes, muscle membrane inexcitability, normal NCV
Muscle biopsy
Denervation atrophy
Normal
Atrophy of type 2 fibers, no myosin loss, no necrosis
Atrophy of type 2 (fast-twitch) fibers, myosin loss, mild myonecrosis, no inflammatory infiltration
Adapted from Bolton CF: Critical illness polyneuropathy and myopathy. C Care Med 2001;29:2388â€“2390; Lacomis D: Critical illness myopathy. C Rheumatol Rep 2002;4:403â€“408; Lacomis D, Campellone JV: Critical illness neuromyopathies. Adv Neurol 2002;88:325â€“335; Leijten FSS, de Weerd AW: Critical illness polyneuropathy: A review the literature, defini and pathophysiology. Clin Neurol Neurosurg 1994;96:10â€“19.

Critical Illness Polyneuropathy (CIP)	Residual Neuromuscular Block	Disuse (Cachectic) Myopathy	Critical Illness Myopath (CIM)

TABLE 66-4. Acute Neuromuscular Pathology Associated with Critical Illness and/or NDNMB

Pharmacology of Reversal Agents

Termination of NMB effect initially results from drug redistribution and la from drug elimination, metabolism, and/or chemical antagonism. Pharmacologic antagonism of a partial NDNMB is achieved by giving a reversal agent that inhibits junctional AChE and increases ACh at the NM This increase in ACh can overcome the competitive inhibition caused by residual NDNMB. The commonly used anti-ChEs are polar molecules that possess a quaternary ammonium (Table 66-5). Neostigmine and pyridostigmine are hydrolyzed by ChE and form carbamyl complexes ($t_{1/2}$ 15â€“20 minutes) with the esteratic site of the enzyme.[5] The half-life of carbamylâ€“ester complex is much less than the plasma half-life of neostigmine or pyridostigmine, which explains why the latter determines duration of clinical effect. In contrast, edrophonium is not hydrolyzed by ChE. Rather, it forms an electrostatic interaction and a hydrogen bond wi the cationic site of ChE that is both competitive and reversible. In additic neostigmine and pyridostigmine, but not edrophonium, inhibit plasma ChE and thus prolong the effects of drugs metabolized by this enzyme, such a succinylcholine and mivacurium.[19 , 31]

Toxicology of Reversal Agents

The most common and troublesome clinical side effect of ChE inhibition is bradycardia, which usually is prevented by coadministration of an antimuscarinic drug.[14] Bradydysrhythmias may be severe and lead to noc or idioventricular rhythm, complete heart block, or even asystole.[65] Thes side effects occur more frequently in patients with preexisting bradycardia those receiving chronic

Î²-adrenergic antagonist therapy. They are not necessarily prevented by

prior administration of atropine.[93] Other problems that may result from excess ChE inhibition are hypersalivation, bronchospasm, increased bron secretions, abdominal cramping from intestinal hyperperistalsis, cell divis tearing, and increased bladder tone. Side effects of excess antimuscarinic administration include tachycardia, bronchodilation, pupillary dilatation, a increased intraocular pressure. Following general anesthesia, use of anticholinesterases may increase the incidence of nausea, vomiting, and abdominal cramps.[54] Because atropine crosses the bloodâ€“brain barrier, can produce central anticholinergic syndrome.

Initial dose (mg/kg)
0.04â€“0.08
0.2â€“0.4
0.5â€“1.0
Onset (min)
7â€“11
10â€“16
1â€“2
Duration (min)
60â€“120
60â€“120
60â€“120
Recommended antimuscarinic
Glycopyrrolate
Glycopyrrolate
Atropine
Structure
Quaternary ammonium
Tertiary amine
Initial dose (mg/kg)
0.01â€“0.02
0.02â€“0.03
Onset (min)
2â€“3
1

Duration (min)			
30â€“60			
30â€“60			
Elimination			
Renal			
Renal			
Crosses blood-brain barrier			
No			
Yes			

Antimuscarinics			
	Glycopyrrolate	Atropine	

Adapted from Bevan DR, Donati F, Kopman AF: Reversal of neuromuscula blockade. Anesthesiology 1972;77:785â€“805; Cronnelly R: Muscle relax antagonists. In: Katz R, eds: Muscle Relaxants: Basic and Clinical Aspects New York, Grune and Stratton, 1985, pp. 197â€“212.

Anticholinesterases		
Neostigmine	Pyridostigmine	Edrophonium

TABLE 66-5. Pharmacology of Intravenous Neuromuscular Blocki Reversal Drugs

Diagnostic Testing

Quantitative methods for analysis of blood and tissue NDNMB and metab concentrations using high-performance liquid chromatography and mass spectrometry are described.[53, 90]

Succinylcholine and succinylmonocholine can be assayed by gas chromatography and mass spectrometry in blood, urine, or the site of intramuscular injection.[79, 92] Less than 3% of administered succinylchol and 10% of its metabolite succinylmonocholine are excreted in the urine.

However, both parent drug and metabolite undergo spontaneous hydrolys especially in alkaline conditions.[97] Historically, detection of succinylcholir has proved difficult because of its rapid hydrolysis. However, techniques detecting this parent compound in tissues even after embalming are described.[40] Because succinic acid is a product of intermediary metabolis assay of this metabolite is not useful for positive identification of prior succinylcholine exposure.[73] Surprisingly, the presence of succinylmonocholine in forensic samples also cannot prove prior exposure succinylcholine. Succinylmonocholine in concentrations of 0.01â€“0.20 Âµ has been detected in tissues of 6 autopsy cases with no history of succinylcholine exposure.[61]

Summary

The two types of NMBs are depolarizing (DNMB) and nondepolarizing (NDNMB). Succinylcholine is the only DNMB in current clinical use. The primary action of an NMB is to reversibly inhibit transmission at the skele NMJ. Immediate side effects include dose- and rate-related histamine rel and modulation of autonomic tone.

Acute and potentially fatal hyperkalemia can occur after succinylcholine administration. Succinylcholine is contraindicated in certain myopathies (Duchenne muscular dystrophy) because of the risk for MH, rhabdomyolys and hyperkalemia. In MH, acute onset of severe hypermetabolism causing acidosis, rhabdomyolysis, hyperkalemia, and death occurs if treatment w dantrolene and aggressive cooling is not given. The effect of succinylchol is prolonged when there is an atypical genetic variant of plasma cholinesterase, when it is inhibited (eg, by pancuronium, organic phosph compounds, or donepezil), or when it is deficient (eg, from liver disease plasmapheresis).

The most important complications associated with use of NDNMBs arise fr problems with patient care: undetected hypoventilation and prolonged dr effect. At subparalyzing doses, NDNMBs blunt the hypoxic ventilatory response without affecting the response to hypercapnia. NMBs have clini important interactions with many xenobiotics and coexisting medical

conditions. In most neuromuscular diseases, sensitivity to NDNMB is increased. In renal failure, active metabolites of pancuronium and vecuronium can accumulate and cause prolonged block.

Quantitative methods for analysis of blood and tissue NMB and metabolite concentrations have been described. Postmortem detection of succinylmonocholine or succinic acid cannot confirm the presence of premortem succinylcholine.

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Antidotes in Depth

Dantrolene Sodium

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Dantrolene is an intracellular muscle relaxant. As such, it is the only drug proven to be effective for treatment and prophylaxis of malignant hyperthermia (MH). Although dantrolene is a hydantoin derivative that is structurally similar to local anesthetics and anticonvulsants, it possesses none of their properties.[16,29]

History and Epidemiology

Dantrolene was first synthesized in 1967.[25] Four years later, the drug was first used clinically to treat muscular spasticity.[6] Dramatic reversal of the course of porcine MH was described in 1975,[11] and shortly thereafter dantrolene was studied in humans.[15]

Pharmacokinetics

Dantrolene is lipophilic and relatively insoluble in water. In plasma, dantrolene is reversibly bound to plasma proteins, especially albumin. The drug is metabolized in the liver by hydroxylation of the hydantoin ring or by reduction of the nitro group.[29] Up to 25% of administered dantrolene is excreted in the urine as the 5-hydroxydantrolene metabolite, which is about half as potent as the parent drug.[29] The elimination half-life is 4â€“8 hours for dantrolene and 15 hours for its primary metabolite. Dantrolene exhibits variable absorption by the small intestine, and peak blood concentrations are achieved 3â€“6 hours after ingestion. Oral bioavailability can be as high as 70%.[16] Quantitative analysis of dantrolene and its metabolites has been performed using high-performance liquid chromatography.[17] After a 2.4 mg/kg dose, the mean whole blood dantrolene concentration was 4.2 Âµg/mL.[9]

Mechanism

Dantrolene acts at the skeletal muscle ryanodine receptor type 1 (RYR-1), causing dose-dependent inhibition of both steady and peak components of sarcoplasmic calcium release,[26] reducing free myoplasmic calcium and thereby directly inhibiting excitationâ€“contraction coupling.[18] Dantrolene causes weakness but not total paralysis, and this plateau effect may be related to its poor solubility in water. In normal adults, a plateau in the twitch depression of the adductor pollicis muscle is reached at a dantrolene dose of 2.4 mg/kg IV, at which point the twitch suppression is 75% of baseline.[9] Dantrolene does not change the electrical properties or excitation of nerve, neuromuscular junction (NMJ), or muscle, and it does not alter sarcoplasmic calcium reuptake. Because dantrolene does not bind to the cardiac ryanodine receptor RYR-2, it has minimal effects on the myocardium.[10,28,32] It does not affect smooth muscle.

Data indicate that the dantrolene binding site is at the N-terminus

of the RYR-1 receptor, specifically at the epitope composed of amino acids 590â€“609.[20] [^{3}H]Dantrolene and [^{3}H]ryanodine appear to bind to the same sites on sarcoplasmic reticulum membrane fractions. At therapeutic concentrations, dantrolene inhibits binding of [^{3}H]ryanodine to the RYR-1 receptor.[10]

Indications

Dantrolene is indicated for treatment of fulminant skeletal muscle hypermetabolism characteristic of MH and following an acute episode of MH to prevent recrudescence. Long-term oral dantrolene therapy is used rarely to treat chronic spasticity.[14] Historically, dantrolene was used prophylactically in MH-susceptible individuals; however, current practice is simply to avoid exposure to MH-triggering drugs during anesthesia.

Dantrolene should be considered for patients with severe hyperthermia when the diagnosis of MH cannot be excluded with certainty, especially with coexisting metabolic acidosis, coagulopathy, or rhabdomyolysis.[8] Atypical presentations of MH in the presence or absence of triggering anesthetics are reported, especially in susceptible persons. In typical fulminant MH, the diagnosis is not subtle, and the course of treatment is obvious once the diagnosis is considered. This is not true when the clinical presentation is atypical. MH should be considered when hyperthermia is associated with severe hypermetabolism, increased CO_2 production, lactic acidemia, hyperkalemia, and/or rhabdomyolysis, especially when the course is fulminating and refractory to supportive therapy. One important caveat: dantrolene given for hyperthermic disorders is not a substitute for aggressive cooling. For example, in heat stroke, the lowering of body temperature by active cooling alone is not accelerated when dantrolene is added.[2,4]

There are reports of dantrolene use for treatment of acute hyperthermia of other etiologies, including neuroleptic malignant

syndrome,[1,24] heat stroke, monoamine oxidase inhibitor overdose,[12] methylenedioxymethamphetamine (â€œecstasyâ€•) overdose,[22] intrathecal baclofen withdrawal,[13] and thyroid storm.[5] There is only anecdotal support for these indications, and scientifically rigorous proof that patients with any of these syndromes benefit from dantrolene therapy is lacking. However, it is worth emphasizing that the diagnosis of heat stroke[7] or hyperthyroidism[19] does not necessarily exclude the diagnosis of MH.

Dosing

Dantrolene is supplied as a sterile lyophilized solution in a 70-mL vial that contains 20 mg dantrolene sodium and 3 g mannitol. Following reconstitution with 60 mL sterile water for injection, the pH is approximately 9.5. The initial dose of dantrolene for treatment of acute MH is an IV bolus of 2â€“3 mg/kg IV. It is repeated every 15 minutes until the signs of hypermetabolism are reversed or until a total dose of approximately 10 mg/kg has been administered. Occasionally higher doses are required. Following initial treatment, at least 1â€“2 mg/kg IV or PO should be given every 6 hours for 1â€“3 days to prevent recrudescence of the syndrome. Initial dosing probably should be determined by total body weight

given that dantrolene is lipophilic; however, its pharmacokinetics in obesity are not determined.[9] The key point is that the total dose of dantrolene is determined by titration to a metabolic endpointâ€”resolution of skeletal muscle hypermetabolism. When an effective dose of dantrolene is given, signs of muscle hypermetabolism start to normalize within 30 minutes.[15]

Side Effects and Toxicity

Following dilution, dantrolene has an alkaline pH and can cause

venous irritation and thrombophlebitis. No evidence indicates allergic cross-reactivity with dantrolene in patients with prior phenytoin allergy.

Dantrolene and verapamil used in combination can cause hyperkalemia and decreased cardiac output; therefore, these drugs should not be combined.[16,21] The mechanism of their interaction is unclear.[23]

Dantrolene given to healthy persons or for MH prophylaxis caused subjective skeletal muscle and diaphragm weakness (experienced as dyspnea) but not muscle paralysis.[30,31] In healthy volunteers, dantrolene 2.5 mg/kg does not depress peak expiratory flow rate or vital capacity or alter end-tidal CO_2 or respiratory rate.[9] However, dantrolene may precipitate respiratory failure in patients with impaired respiratory reserve.[16]

Oral dantrolene may cause gastrointestinal upset, nausea, and vomiting. Other reported side effects include dizziness, light-headedness, ptosis, difficulty focusing, and difficulty swallowing.[9,31] When dantrolene is given orally for more than 2 months for treatment of muscular spasticity, there is a 1.8% risk of dose- and duration-related chronic hepatic inflammation, including elevated aminotransferase concentrations, hyperbilirubinemia, or jaundice[27] that may not be reversible after dantrolene is discontinued.[3]

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Chapter 67
Antipsychotics

David Juurlink

A lethargic 41-year-old woman was brought to the emergency department paramedics. Her husband found her unresponsive in the bedroom with an bottle at her side. He stated that she had a history of delusions and was of a psychiatrist.

The patient was moderately obese, somnolent, and difficult to rouse. Her were: blood pressure 95/50 mm Hg; pulse 128 beats/min and regular; re 10 breaths/min; and rectal temperature 100.6Â°F (38.1Â°C). The patient' flushed, and her mucous membranes and axillae were dry. Gag reflex was there was no evidence of tongue biting or trauma. Both pupils were 3 mm and minimally responsive to light. The fundi could not be visualized. Exar cardiovascular and respiratory systems was unremarkable. Her abdomina revealed diminished bowel sounds but no tenderness or masses. The patie respond to verbal commands, but she moaned and moved all extremities vigorous sternal rub. Deep tendon reflexes were normal, the plantar resp flexion, and no clonus was present.

Two successive 2-mg boluses of naloxone were given intravenously (IV) w response. Thiamine 100 mg IV also was given. When 2 L of 0.9% sodium

solution was administered IV, the blood pressure rose to 110/70 mm Hg. blood gases determined on 40% oxygen were: pH, 7.38; PCO_2 , 43 mm H mm Hg; and HCO_3^- , 24 mEq/L. Blood samples were sent for determinati electrolytes, glucose, creatinine, creatine kinase (CK), complete blood co acetaminophen.

A nasogastric tube was inserted. An abdominal radiograph showed a non gas pattern. The tip of the nasogastric tube was seen in the distal stomac activated charcoal was instilled. An electrocardiogram revealed sinus tach normal QRS duration but a slightly prolonged QTc interval (QTc 450 msec treating physician was preparing to intubate the patient, she roused som became agitated. Her speech was unintelligible, and she began thrashing stretcher.

The patient was placed in loose restraints to prevent her from injuring he medical staff. Review of the patient's medication history revealed she wa with olanzapine 10 mg daily, in addition to omeprazole, a transdermal ni and multivitamins. The olanzapine bottle was empty, and approximately 3 mg) were unaccounted for. Suspecting olanzapine overdose with promine anticholinergic features, the physician administered 0.5 mg physostigmine reviewing the electrocardiogram for widening of the QRS complex.

The patient received 2 more doses of physostigmine 0.5 mg over the nex Her agitation lessened dramatically, and her heart rate fell to 92 beats/m she remained somnolent, she became much more communicative and beg admitted to deliberately ingesting all of her olanzapine tablets following a dispute regarding financial difficulties.

The restraints were removed, and the patient was transferred to an obse where she was observed closely overnight. She received 3 additional 0.5- physostigmine over the next 12 hours, during which time her vital signs and her mental status improved considerably. The following day she was the inpatient psychiatry ward for further evaluation and treatment.

History and Epidemiology

Prior to the introduction of chlorpromazine in 1950, patients with schizop

treated with nonspecific sedative agents such as barbiturates. Highly agi were housed in large mental institutions and often placed in physical rest approximately 500,000 patients with psychotic disorders were hospitalized States. The advent of the antipsychotics in the 1950s revolutionized the c patients. These drugs, originally termed *major tranquilizers* and subsequ *neuroleptics* , dramatically reduced the characteristic hallucinations, delu paranoia that were characteristic of schizophrenia.

Shortly following the introduction of these drugs, however, it became app were potentially dangerous in overdose (a common occurrence in mentall and that they caused

a host of adverse drugs effects, principally involving the endocrine and r The latter included the extrapyramidal syndromes (EPS), a constellation c were relatively common, sometimes irreversible, and occasionally life-th

The search for new drugs led to the development of several antipsychotic potencies and differing adverse effect profiles. The novel antipsychotic cl first synthesized in 1959, but it did not enter widespread clinical use until 1970s. Clozapine was not only relatively free of EPS, it was an extremely antipsychotic even in patients who had not responded well to other drugs unlike its predecessors, it often improved the negative symptoms of schi as avolition, alogia, and social withdrawal. Reports of agranulocytosis, sc led to the withdrawal of clozapine from the market in 1974, although it w in 1990.[9 , 43] However, clozapine's unique therapeutic and pharmacologic rendered it an *atypical* antipsychotic, the forerunner and prototype of mor compounds that have collectively become the most widely used antipsych past decade.

Most antipsychotic drug toxicity occurs by 1 of 2 mechanisms. Following (intentional or unintentional), toxicity is dose related and reflects an exte drug's effects on neurotransmitter systems and other biologic processes. idiosyncratic adverse reactions also can occur in the context of routine t This toxicity results from individual susceptibility, usually is pharmacogen and generally is unrelated to the antipsychotic dose. In both instances, th illness can range from minor to life threatening, depending on a host of

including concomitant drug exposures, comorbidity, and access to medica

The true incidence of antipsychotic drug reactions is not known with cert patients may not seek medical attention, whereas others may be misdiag among those who seek medical attention and are correctly diagnosed, nc poison centers or other adverse event reporting systems is discretionary (Chap. 130). With these limitations in mind, a few observations can be r

In 2003, poison information centers in the United States were contacted antipsychotic drug exposures. Of these reports, 32,422 were related to a antipsychotic agents and 4704 to phenothiazines.[99] Other antipsychotics a reported. By comparison, in 1993 phenothiazines were the sole category antipsychotics and were the subject of 10,975 calls, despite 27% fewer to poison centers.[60] The changing pattern of antipsychotic overdose reflects of antipsychotic drug prescribing trends over the past decade.[25 , 31 , 67]

The vast majority of poison center calls pertain to intentional overdoses i years or older. Most of these patients have a good outcome. However, 94 reported in 2003, and only a minority of them occurred in patients with antipsychotic overdose. A substantial body of clinical experience and son data suggest that the low-potency, typical antipsychotics, such as thiorid chlorpromazine and mesoridazine, are associated with greater toxicity tha antipsychotics.[16 , 18 , 37] Inferences based upon aggregated population d fatal toxicity should be extrapolated to individual patients with caution,[16] least one well-done retrospective cohort study supports the notion that t associated with greater adverse cardiovascular toxicity than other antips

Pharmacology

Classification

Antipsychotics can be classified in a variety of ways, according to their c structure, their receptor binding profiles, or as â€œtypicalâ€• or â€œat antipsychotics. Table 67-1 outlines the taxonomy of some commonly use Classification by chemical structure was most useful prior to the 1970s, v phenothiazines and butyrophenones constituted most of the antipsychotic

clinical use. Currently, the surfeit of different compounds and their struc heterogeneity renders this scheme cumbersome and of limited use to clin worth noting, however, that the phenothiazine antipsychotics bear a high structural similarity to the tricyclic antidepressants (TCAs) (Figure 67-1) share many of their manifestations in overdose. The phenothiazines can l subclassified according to the nature of the substituent on the nitrogen a 10 of the center ring as aliphatic, piperazine, or piperidine compounds.

Of greater clinical use is the classification of antipsychotics according to affinities for various receptors (Table 67-2). However, the most widely u classification system categorizes antipsychotics as either *typical* or *atypic* called *traditional* or *conventional*) antipsychotics dominated the first 40 antipsychotic therapy. They were categorized according to their affinity fo receptor as either low potency, as exemplified by thioridazine and chlorp high potency, exemplified by haloperidol. These agents ameliorated the symptomsâ€• of schizophrenia, hallucinations, delusions, paranoia, and of thought, but they were of little benefit for the sometimes disabling â€ symptomsâ€• of schizophrenia: avolition, alogia, flattening of affect, and withdrawal. Moreover, they were associated with acute, subacute, and lo disturbances collectively referred to as *extrapyramidal syndromes* (EPS).

The notion of antipsychotic atypicality has evolved over time with the int compounds[78 , 90] and connotes different properties to pharmacologists a From a clinical perspective, an atypical antipsychotic treats both the posi negative symptoms of schizophrenia, is less likely than traditional drugs t at clinically effective doses, and causes little or no elevation of the serun concentration.[49] From a pharmacologic perspective, most atypical antips inhibit the action of serotonin at the 5-HT_{2A} receptor. More than a dozen antipsychotics are now in clinical use or under development. Despite the higher cost, these drugs have largely supplanted traditional antipsychotics their effectiveness in treating the negative symptoms of schizophrenia an somewhat more favorable adverse effect profile.

Mechanisms of Antipsychotic Drug Action

Of the many contemporary theories of schizophrenia, the most enduring h

dopamine hypothesis .[87] First advanced in 1967 and supported by in vivo theory holds that the â€œpositive symptomsâ€• of schizophrenia (hallu delusions, paranoia, and disorganization of thought) occur because of ex dopaminergic signaling in the mesolimbic and mesocortical pathways.[63] T was borne in part from the observation that hallucinations and delusions produced in otherwise normal individuals by drugs that increase dopamin transmission, such

as cocaine and amphetamine, and that these effects could be blunted by antagonists.

Typical Antipsychotics
Butyrophenones
Droperidol
1.25â€“30
2â€“3
2â€“10
85â€“90
N
Haloperidol
1â€“20
18â€“30
14â€“41
90
Y
Diphenylbutylpiperidines
Pimozide
1â€“20
11â€“62
28â€“214
99
Y
Phenothiazines
Aliphatic
Chlorpromazine

100â€“800
10â€“35
18â€“30
98
Y
Methotrimeprazine
2â€“50
23â€“42
17â€“78
NR
Y
Promazine
50â€“1000
30â€“40
8â€“12
98
N
Promethazine
25â€“150
9â€“25
9â€“16
93
Y
Piperazine
Fluphenazine
0.5â€“20
220
13â€“58[b]
99
NR
Perphenazine
8â€“64
10â€“35
8â€“12

>90
NR
Prochlorperazine
10â€“150
13â€“32
17â€“27
>90
NR
Trifluoperazine
4â€“50
NR
7â€“18
>90
Y
Piperidine
Mesoridazine
100â€“400
3â€“6
2â€“9
98
Y
Thioridazine
200â€“800
18
26â€–36
96
Y
Pipotiazine
25â€“250 (monthly IM depot)
7.5
3â€–11
NR
N
Thioxanthenes

Chlorprothixene
30â€“300
11â€“23
8â€“12
NR
NR
Flupentixol
3â€“6
7â€“8
7â€“36
NR
NR
Thiothixene
5â€“30
NR
12â€“36
>90
NR
Zuclopenthixol
20â€“100
10
20
NR
NR
Atypical Antipsychotics
Benzamides
Amisulpride
50â€“1200
5.8
12
16
N
Raclopride
3â€“6

1.5
12â€“24
NR
N
Remoxipride
150â€“600
0.7
3â€“7
80
Y
Sulpride
200â€“1200
0.6â€“2.7
4â€“11
14â€“40
N
Benzepines
Dibenzodiazepine
Clozapine
50â€“900
5.4 Â± 3.5
6â€“17
95
Y
Dibenzooxazepine
Loxapine[a]
20â€“250
NR
2â€“8
90â€“99
Y
Thienobenzodiazepine
Olanzapine
5â€“20

10â€“20
21â€“54
93
N
Dibenzothiazepine
Quetiapine
150â€“750
10
3â€“9
83
N
Indoles
Benzisoxazole
Risperidone
2â€“16
0.7â€“2.1
3â€“20
90
Y
Imidazolidinone
Sertindole
12â€“24
20â€“40
24â€“200
99
Y
Benzisothiazole
Ziprasidone
40â€“160
2
4â€“10
99
N
Quinolinones

	Aripiprazole	10â€“30	5	47â€“68	99
					Y

NR = not reported.

[a] Loxapine's atypical profile is lost at doses >50 mg/d; hence it is some as a typical antipsychotic.

[b] For hydrochloride salt; enanthate and decanoate have ranges of 3â€“4 5â€“12 days, respectively.

Adapted from references [10,12,14,35,47,51].

Classification	Compound	Usual Daily Adult Dose (mg)	Volume of Distribution (L/kg)	Half-Life (Range, h)	Protei Bindin (%)

TABLE 67-1. Classification of Commonly Used Antipsychotics

There are five subtypes of dopamine receptors (D_1 â€“D_5), but schizoph involves excess signaling at the D_2 subtype.[87] Antagonism of D_2 neurotra sine qua non of antipsychotic activity. Antipsychotics have different poten receptor, reflected by the dissociation constant (K_d), which in turn reflec the drug from the D_2 receptor. For example, the receptor releases clozap quetiapine more rapidly than it does any other drugs.[86,87]

Dopamine receptors are present in many other areas of the central nervo (CNS), including the nigrostriatal pathway (substantia nigra, caudate, and which collectively govern the coordination of voluntary movement), tube pathway, hypothalamus and pituitary, and area postrema of the brainster contains the chemoreceptor trigger zone (CTZ). Antipsychotic-related bloc neurotransmission in these areas is associated with many of the other be adverse effects of these drugs. For example, D_2 antagonism in the CTZ a

and vomiting, whereas blockade of hypothalamic D_2 receptors increases by the pituitary, resulting in breast tenderness and galactorrhea. Blockad nigrostriatal D_2 receptors underlies many of the movement disorders ass antipsychotic therapy.[93, 103]

Antipsychotics interfere with signaling at other receptors, including acety M_2 muscarinic receptors, H_1 histamine receptors, and Î±-adrenergic rece extent to which these other receptors are blocked at doses that effectivel transmission is antipsychotic specific and can be used to predict a drug's profile.[20] For example, drugs that antagonize muscarinic receptors at cli doses (primarily the aliphatic and piperidine phenothiazines, clozapine,

loxapine, and olanzapine) often cause anticholinergic adverse effects duri and can cause anticholinergic delirium following overdose (Table 67-2). blockade of peripheral $Î±_1$ -adrenergic receptors by the aliphatic and pip phenothiazines, clozapine, risperidone, and several other drugs more like postural hypotension during therapy and supine hypotension following ov

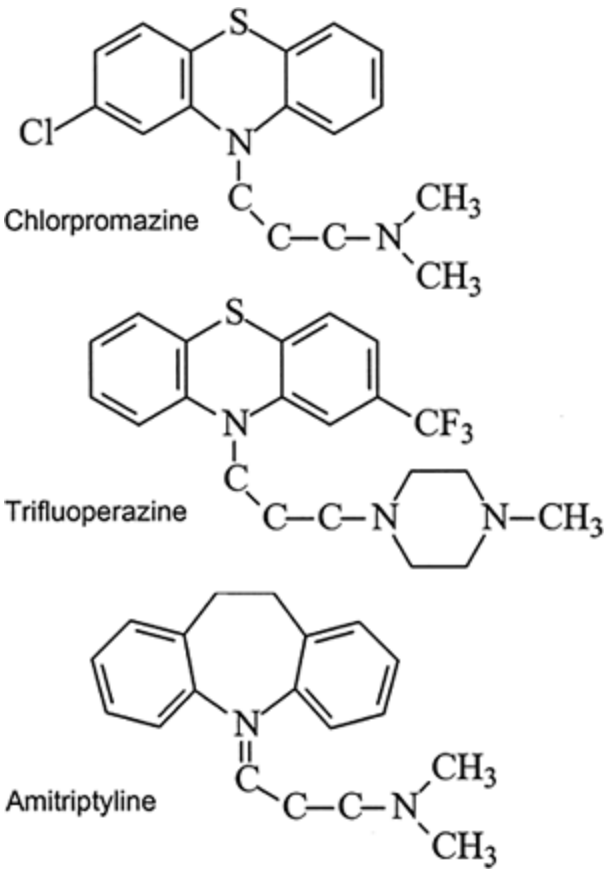

Figure 67-1. Structural similarity between phenothiazines and tricyclic

Several antipsychotics also block voltage-gated fast sodium channels (I_{Na} this effect is of little consequence during therapy, in the setting of overdo slow cardiac conduction (phase 0 depolarization) and impair myocardial This effect, most notable with the phenothiazines, is both rate and voltag and therefore is more pronounced at faster heart rates and less negative potentials.[17] Blockade of the delayed rectifier potassium current (I_{Kr}) ca prolongation of the QTc interval, creating a substrate for development of pointes.[68] QTc prolongation is sometimes evident during maintenance th particularly in patients with previously unrecognized congenital QTc prolo additional risk factors. This effect may partly explain the apparent increas cardiac death among patients treated with antipsychotic drugs.[77]

Clinical effect

Hypotension

Central and peripheral anticholinergic effects
QRS widening; rightward T40msec; myocardial depression
QTc prolongation; torsades de pointes
Typical agents
Chlorpromazine
+ + +
+ +
+ +
+ +
Fluphenazine
-
-
+
+
Haloperidol
-
-
+
+ +
Loxapine
+ + +
+ +
+ +
+
Mesoridazine
+ + +
+ + +
+ + +
+ +
Perphenazine
+
-
+
+ +

Pimozide
+
-
+
+ +
Thioridazine
+ + +
+ + +
+ + +
+ + +
Trifluoperazine
+
-
+
+ +
Atypical agents
Aripiprazole
+ +
-
-
-
Clozapine
+ + +
+ + +
-
+
Olanzapine
+ +
+ + +
-
-
Quetiapine
+ + +
+ + +

+
- to +
Remoxipride
-
-
-
-
Risperidone
+ +
-
-
-
Sertindole
+
-
-
+ +
Ziprasidone
+ +
-
-
+ + +

Adapted from references [17,20,41,79,81].

	Î ±1 -Adrenergic Antagonism	Muscarinic Antagonism	Fast Sodium Channel (I_{Na}) Blockade	Delay (I_K E

TABLE 67-2. Toxic Manifestations of Selected Antipsychotics

Several antipsychotics exhibit a relatively high degree of antagonism at t receptor, which conveys two important therapeutic properties: (1) greate treatment of the negative symptoms of schizophrenia and (2) a significar incidence of extrapyramidal side effects. Several antipsychotics are distin

unique effects at other receptors. For example, loxapine and clozapine in reuptake of catecholamines and antagonize Î³-aminobutyric acid $(GABA)_A$ which may explain the apparent increase in seizure activity with these ag detailed description of the pharmacology of the commonly used atypical warranted given their increasing role in therapy.

Clozapine, a dibenzodiazepine compound, binds to dopamine receptors (D serotonin receptors ($5\text{-}HT_{1A/1C}$, $5\text{-}HT_{2A/2C}$, $5\text{-}HT_3$, and $5\text{-}HT_6$) with mo affinity.[9 , 75 , 81] It also antagonizes $Î±_1$ -adrenergic, $Î±_2$ -adrenergic, an receptors. It has the highest binding affinity of any atypical antipsychotic muscarinic receptors.[80] Despite this feature, clozapine paradoxically activ genetic subtype of the muscarinic receptor and frequently produces sialo therapy.[79]

Olanzapine, a thienobenzodiazepine, binds avidly to serotonin ($5\text{-}HT_{2A/2C}$ $5\text{-}HT_6$) and dopamine receptors (D_1 , D_2 , and D_4), although its potency is lower than that of

most traditional antipsychotics.[51 , 81] It is an exceptionally potent H_1 ant more avidly than pyrilamine, which is a widely used antihistamine. It is al affinity for M_1 receptors and is a relatively weak $Î±_1$ antagonist.

Risperidone, a benzisoxazole derivative, has high affinity for several rece serotonin receptors ($5\text{-}HT_{2A/2C}$), D_2 dopamine receptors, and $Î±_1$ and H_1 [79 , 81] It has no appreciable activity at M_1 receptors. Its primary metabol hydroxyrisperidone) is nearly equipotent as the parent compound at D_2 a receptors.[51]

Quetiapine, a dibenzothiazepine, is a weak antagonist at D_2 , M_1 , and 5- but it is a relatively potent antagonist of $Î±_1$ and H_1 receptors.[51 , 81] Of metabolites, at least 2 are pharmacologically active. However, they circula levels and likely contribute little to the drug's clinical effect.

Ziprasidone, a benzothiazole derivative, is a potent antagonist at dopamin several serotonin ($5\text{-}HT_{2A/2C}$, $5\text{-}HT_{1D}$, and $5\text{-}HT_7$) receptors, but it also agonist activity at $5\text{-}HT_{1A}$ receptors.[51 , 52 , 81] Its $Î±_1$ antagonist activity strong, with a binding affinity approximately one tenth that of prazosin.

Aripiprazole, a quinolinone derivative, is a novel compound that binds avi D_2 and D_3 receptors and serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2B} receptor evidence suggests that its efficacy in the treatment of schizophrenia and propensity for EPS may relate to partial agonist activity at dopamine D_2 Aripiprazole acts as a partial agonist at serotonin 5-HT_{1A} receptors but is at serotonin 5-HT_{2A} receptors. Its principal active metabolite, dehydroari affinity for dopamine D_2 receptors and thus has some pharmacologic acti that of the parent compound.[66]

Pharmacokinetics and Toxicokinetics

With a few exceptions, the antipsychotics have similar pharmacokinetic regardless of their chemical classification. Most are lipophilic, have a larg distribution, and are generally well absorbed, although anticholinergic effe absorption of some agents. Plasma concentration generally peak within 2 a therapeutic dose, but this can be prolonged following overdose.

Most antipsychotics are substrates for the various isozymes of the hepati P450 (CYP) enzyme system. For example, haloperidol, perphenazine, thi sertindole, and risperidone are extensively metabolized by the CYP2D6 sy functionally absent in approximately 7% of white patients and overexpres of patients, depending on ethnicity.[53] These polymorphisms appear to inf tolerability and efficacy of treatment with these antipsychotics during the [28, 29, 48, 72, 98] but likely do not alter the severity of antipsychotic ov

Drugs that inhibit CYP2D6, such as paroxetine, quinidine, and metoclopra increase the levels of these antipsychotic drugs and increase the risk of In contrast, metabolism of clozapine is primarily mediated by CYP1A2, ar clozapine levels can result following exposure to fluvoxamine, macrolide, antibiotics and after smoking cessation, which normally induces CYP1A2.[3] plays a relatively small role in the elimination of antipsychotics, and dose generally is not necessary for patients with renal disease.

Pathophysiology and Clinical Manifestation

Table 67-3 lists the adverse effects of antipsychotics. Some of these effe

following overdose, but many can occur during the course of therapeutic

Adverse Effects During Therapeutic Use

Extrapyramidal Syndromes

The EPSs (Table 67-4) are a heterogeneous group of disorders that share abnormal muscular activity. Among the typical antipsychotics, the incidenc appears to be highest with the more potent agents such as haloperidol a and lower with the less potent agents chlorpromazine and thioridazine. A antipsychotics are associated with an even lower incidence of EPS. Althou physiologic mechanisms for this observation are not fully understood, se have been put forth. In addition to the aforementioned antagonism of 5-H some atypical agents dissociate more rapidly from the D_2 receptor and in degree of nigrostriatal dopaminergic hypersensitivity during chronic use.[4] However, EPS can occur during treatment with any antipsychotic drug, re typicality or potency.

Acute Dystonia

Acute dystonia is a movement disorder characterized by sustained involu contractions, often involving the muscles of the head and neck, including muscles and the tongue, but occasionally involving the extremities. Thes are sometimes referred to as *limited reactions* , reflecting their transient than their severity. All of the currently available antipsychotics are assoc dystonic reactions.[93] Spasmodic torticollis, facial grimacing,

protrusion of the tongue, and oculogyric crisis are among the more comm manifestations. Laryngeal dystonia is a rare but potentially life-threatenin is easily misdiagnosed because it can present with throat pain, dyspnea, dysphonia rather than the usual features of dystonia.[36]

CNS
Somnolence, coma
Respiratory depression or loss of airway reflexes

Hyperthermia
Seizures
Extrapyramidal syndromes
Central anticholinergic syndrome
Cardiovascular
Clinical
Tachycardia
Hypotension (orthostatic or resting)
Myocardial depression
Electrocardiographic
QRS complex widening
Right deviation of terminal 40 msec of frontal plane axis
QTc interval prolongation
Torsades de pointes
Nonspecific repolarization changes
Endocrine
Amenorrhea, oligomenorrhea, or metrorrhagia
Breast tenderness and galactorrhea
Gastrointestinal
Impaired peristalsis
Dry mouth
Genitourinary
Urinary retention
Ejaculatory dysfunction
Priapism
Ophthalmic
Mydriasis or miosis
Visual blurring
Dermatologic
Impaired sweat production
Cutaneous vasodilation

TABLE 67-3. Adverse Effects of Antipsychotics

Acute dystonia
Hours to a few days
Sustained, involuntary muscle contraction, torticollis, including blepharos oculogyric crisis
Imbalance of dopaminergic/cholinergic transmission
Anticholinergics, benzodiazepines
Akathisia
Hours to days
Restlessness and unease, inability to sit still
Mesocortical D_2 antagonism (?)
Dose reduction, trial of alternate drug, propranolol, benzodiazepines, ar
Parkinsonism
Weeks
Bradykinesia, rigidity, shuffling gait, masklike facies, resting tremor
Postsynaptic striatal D_2 antagonism
Dose reduction, anticholinergics, dopamine agonists
Neuroleptic malignant syndrome
2â€“10 days
Many (see Table 67-5): altered mental status, motor symptoms, hypertl autonomic instability
D_2 antagonism in striatum, hypothalamus, and mesocortex
Cooling, benzodiazepines, supportive care, consider dantrolene, bromocr amantadine
Tardive dyskinesia
3 months to years
Late-onset involuntary choreiform movements, buccolinguomasticatory r
Excess dopaminergic activity
Recognize early and stop offending drug; addition of other antipsychotic;
Adapted from references [73, 93].

Disorder	Time of Maximal Risk	Features	Postulated Mechanism	T

TABLE 67-4. The Extrapyramidal Syndromes

Acute dystonia often occurs within a few hours of starting of treatment bu delayed for up to a few days. Left untreated, dystonia resolves slowly ov Risk factors include male gender, young age (children are particularly su previous episode of acute dystonia, and recent cocaine use.[94 , 103] Althou may appear dramatic and sometimes is mistaken for seizure activity, it ra threatening. Of note, drugs other than antipsychotics can sometimes caus dystonia, particularly metoclopramide, the antidepressants, some antima histamine H_2 receptor antagonists, anticonvulsants, and cocaine.[94]

Treatment of Acute Dystonia

Acute dystonia is generally more distressing than serious, but rare cases respiration, necessitating supplemental oxygen and, occasionally, assiste [, 94] The response to parenteral anticholinergic agents often is rapid and every effort should be made to administer benztropine as the first-line age intramuscularly in adults, or 0.05 mg/kg in children). Diphenhydramine of readily available and can be used instead (50 mg IV or intramuscularly in mg/kg in children). Parenteral benzodiazepines such as lorazepam (0.05â IV or intramuscularly) or diazepam (0.1 mg/kg IV) should be used if patie respond to anticholinergics, but they also can be effective as initial therap important to recognize that because the elimination half-life of most ant shorter than that of most antipsychotics, dystonia can recur, and admini additional doses of anticholinergic agents may be necessary over the nex hours.[27] Patients in whom acute dystonia jeopardizes respiration should b at least 12â€“24 hours after initial resolution.

Akathisia

Akathisia (from the Greek, â€œnot to sitâ€•) is characterized by a feelin restlessness, anxiety, or sense of unease, often in conjunction with the of an inability to sit still. Patients with akathisia frequently appear uncom fidgety. They may rock back and forth while they are standing, or they n cross and uncross their legs while they are seated. Akathisia can be diffic and may be misinterpreted as a manifestation of the underlying psychiat especially anxiety.

Akathisia is common and may be an important determinant of adherence acute dystonia, akathisia tends to occur relatively early in the course of coincides with peak antipsychotic concentrations in plasma.[103] The incide highest with typical, high-potency antipsychotics and lowest with atypical Although most cases develop within days to weeks after initiation of treat increase in dose, a delayed-onset or tardive variant is recognized.

The pathophysiology of akathisia is incompletely understood but appears antagonism of postsynaptic D_2 receptors in the mesocortical pathways.[62] Interestingly, a similar phenomenon may occur in patients after commen with antidepressants, particularly the selective serotonin reuptake inhibit

Treatment of Akathisia

Akathisia can be difficult to treat. A reduction in the antipsychotic dose is helpful, as is substitution of another (generally atypical) antipsychotic dr with lipophilic Î²-adrenergic antagonists such as propranolol may reduce of akathisia, but little evidence supports their use.[56 , 73] Benzodiazepines term relief.[57] Anticholinergics such as benztropine or procyclidine may

reduce symptoms of akathisia, although they more likely will be effective induced by antipsychotics with little or no intrinsic anticholinergic activity

Parkinsonism

Antipsychotic drugs can produce a parkinsonian syndrome characterized l akinesia or bradykinesia, and postural instability. It is similar to the idio disease, although the classic â€œpill-rollingâ€• tremor is often less pro syndrome typically develops during the first few months of therapy, part high-potency agents. It is more common among older women. Parkinsonis result from antagonism of postsynaptic D_2 receptors in the striatum.[93]

Treatment of Drug-Induced Parkinsonism

The incidence of drug-induced parkinsonism can be minimized by using th effective dose of antipsychotic. The addition of an anticholinergic attenua

This strategy often is effective in younger patients, although the routine u prophylactic anticholinergics is not recommended. Addition of a dopamine as amantadine is sometimes used, particularly in older patients who may of anticholinergic drugs, but it occasionally aggravates the underlying ps disturbance.[61]

Tardive Dyskinesias

The term *tardive dyskinesia* was coined in 1952 to describe the delayed o persistent orobuccal masticatory movements occurring in 3 women after of antipsychotic therapy.[93] The adjective *tardive* , or late, was used to d movement disorders from those the parkinsonian movements described a incidence of tardive dyskinesia in younger patients is approximately 3â€“5 rises considerably with age. A prospective study of older patients treated potency typical antipsychotics identified a 60% cumulative incidence of t dyskinesia after 3 years of treatment.[46] Potential risk factors for tardive include alcohol use, affective disorder, prior electroconvulsive therapy, d and various genetic factors.[93]

Several distinct tardive syndromes are recognized, including the classic o masticatory stereotypy, chorea, dystonia, myoclonus, blepharospasm, and generally accepted that the atypical antipsychotics are associated with a of tardive dyskinesia and other drug-related movement disorders. Howeve is true of all atypical antipsychotics is unclear. Among the atypical antip clozapine is associated with the lowest incidence of tardive dyskinesia an with the highest incidence (when higher doses are used), although the re observation are uncertain.[73 , 91 , 93]

Treatment of Tardive Dyskinesia

Tardive dyskinesia is highly resistant to the usual pharmacologic treatmen movement disorders. Anticholinergics do not alleviate tardive dyskinesia a it. Calcium channel blockers, Î²-adrenergic antagonists, benzodiazepines, have been of limited success.[34] Clozapine appears to suppress tardive dy temporarily. Although discontinuation of the causative agent may not pro of symptoms, when possible the antipsychotic should be discontinued as s

symptoms begin.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a potentially life-threatening r emergency. First described in 1960 in patients treated with haloperidol, t has been associated with virtually every antipsychotic.[30] The reported inc ranges from 0.2â€“1.4% of patients receiving antipsychotics,[2,22] but les episodes may go undiagnosed or unreported. As a result, much of what is the epidemiology and treatment of NMS is speculative and based upon ca case series.

The pathophysiology of NMS is incompletely understood but appears to in reductions in central dopaminergic neurotransmission in the hypothalamus core temperature â€œset pointâ€•[39] and leading to altered thermoregula manifestations of autonomic dysfunction. Blockade of striatal D_2 receptors muscle rigidity and tremor.[13,24,95] In some cases, a direct effect on s may play a role in the pathogenesis of hyperthermia.[39] Altered mental sta multifactorial and may reflect hypothalamic and spinal dopamine receptor genetic predisposition, or the direct effects of hyperthermia and other dr also appears to play a role in the pathogenesis of NMS, because antipsyc antagonize $5\text{-}HT_{2A}$ receptors seem to be associated with a lower incidence

Although NMS most often occurs during treatment with a D_2 receptor an withdrawal of dopamine agonists can produce an indistinguishable syndro typically occurs in patients with long-standing Parkinson disease who abru discontinue treatment with dopamine agonists such as levodopa/carbidop or bromocriptine.[13] Hospitalization for aspiration pneumonia, a common older patients with Parkinson disease, is a particularly high-risk setting for particularly dangerous because the cardinal manifestations of NMS are ea misattributed to the combined effects of infection and the underlying mo

The vast majority of NMS cases occur in the context of therapeutic use o rather than following overdose. Postulated risk factors for the developmer include young age, male gender, extracellular fluid volume contraction, us potency antipsychotics, depot preparations, cotreatment with lithium, mul combination, and rapid dose escalation.[2,23,54]

The manifestations of NMS include the tetrad of altered mental status, m (classically â€œlead pipeâ€•), hyperthermia, and autonomic dysfunction. symptoms can appear in any sequence, although a review of 340 NMS cas mental status changes and rigidity usually preceded the development hyp autonomic instability.[96] Signs typically evolve over a period of several da majority occurring within 2 weeks of starting treatment. However, it is im recognize that NMS can occur even after prolonged use of an antipsycho following a dose increase or the addition of another drug.

There is no gold standard for the diagnosis of NMS, and at least 4 differer criteria are proposed.[32 , 3 , 22 , 54] The operating characteristics of these not been formally evaluated. The criteria set forth by the *Diagnostic and Manual of Mental Disorders* , 4th edition (DSM-IV) are perhaps the most their principal limitation is that they make no provision for a causal relat drugs other than antipsychotics.[32] Because NMS is an uncommon and po threatening disorder with highly variable clinical manifestations and no d standard, an algorithmic approach to diagnosis in inadvisable. Rather, cli be aware of its many

possible clinical and laboratory features (Table 67-5) and entertain the NMS in any unwell patient receiving an antipsychotic, particularly when a mentation, unexplained fever, or muscle rigidity is present.

Altered mental status
Delirium, lethargy, confusion, stupor, catatonia, coma
Motor symptoms
â€œLead pipeâ€• rigidity, cogwheeling, dysarthria or mutism, parkinson akinesia, tremor, mutism, dystonic posture, dysphagia, dysphonia, chor
Hyperthermia
Temperature >100.4Â°F (38Â°C)
Autonomic instability
Tachycardia, diaphoresis, sialorrhea, incontinence, respiratory irregulariti dysrhythmias, hypertension or hypotension
Laboratory findings
Increased muscle enzymes (creatine kinase, lactate dehydrogenase, aldo

leukocytosis, renal insufficiency (reflecting volume contraction and pigmentnephropathy), acidemia, myoglobinuria, modest aminotransferase hypoxia, hyponatremia, increased prothrombin time/partial thromboplastir These manifestations can occur in any combination, although hyperthermi degree of increased muscular activity usually are present. Some manifest fleeting. A supportive medication history (see text) is essential to the dia every effort should be made to exclude other potential causes, such as o illnesses and other drugs and toxins.
Adapted from references [2,23,54,95].

Feature	Potential Manifestations

TABLE 67-5. Clinical and Laboratory Features of the Neurolepti Syndrome

Treatment of Neuroleptic Malignant Syndrome: Measures

Treatment recommendations are largely based on general physiologic pri reports, and case series. Therapy should be individualized according to th duration of illness and the modifying influences of comorbidity.[13,97]

The provision of good supportive care is the cornerstone for treatment of essential to recognize the condition as an emergency and to withdraw the agent immediately. When NMS ensues after abrupt discontinuation of a d such as levodopa, the drug should be reinstituted promptly. Most patients should be admitted to an intensive care unit. Supplemental oxygen should administered, and assisted ventilation may be necessary in cases of resp which can result from central hypoventilation, loss of protective airway re rigidity of the chest wall muscles.

The hyperthermia associated with NMS is multifactorial in origin and, whe should be treated aggressively. For those with life-threatening hyperther in an ice-water bath is the most rapidly efficient technique (Chap. 16). I less severe illness, evaporative cooling can be accomplished by removing

clothing, spraying the patient with lukewarm water, and maintaining cons circulation with the use of fans.[100]

Hypotension should be treated initially with large volumes of 0.9% sodiu solution, followed by vasopressors if necessary. Alkalinization of the urine bicarbonate may reduce the incidence of myoglobinuric renal failure in pa creatine kinase concentrations, but maintenance of euvolemia and adequa perfusion are of greater importance. Tachycardia does not require specifi bradycardia may necessitate the use of transcutaneous or transvenous e Venous thromboembolism is a major cause of morbidity and mortality in NMS, and prophylactic doses of low-molecular-weight heparin should be patients who likely will be immobilized for more than 12â€“24 hours.

Pharmacologic Treatment of Neuroleptic Malig Syndrome

Benzodiazepines are the most widely used pharmacologic adjuncts for trea and are considered first line-therapy. Dantrolene and bromocriptine are n and their incremental benefit over good supportive care is debated.[83] Hov drugs are associated with relatively little toxicity, and the absence of de should not preclude their use, particularly in patients with moderate or s

Benzodiazepines are frequently used in the management of NMS because onset of action, which is particularly important when patients are agitated Benzodiazepine actions are nonspecific in nature, but they presumably at sympathetic hyperactivity that characterizes NMS[40] by facilitating GABA- chloride transport and producing neuronal hyperpolarization, in a fashion their beneficial effects in cocaine toxicity. The primary disadvantage of is that they may cloud the assessment of mental status.

Dantrolene reduces skeletal muscle activity by inhibiting ryanodine recep release channels, thereby interfering with calcium release from the sarco reticulum. In theory, this process should reduce body temperature and to consumption. It also should lessen the risk of myoglobinuric renal failure. been suggested to be more useful when muscular rigidity is a prominent NMS.[13] Dantrolene can be given by mouth (50â€“100 mg/d) or by IV infu

mg/kg/d, or up to 10 mg/kg/d in severe cases), although the latter requ reconstitution.[13]

Bromocriptine is a centrally acting dopamine agonist that is given orally o nasogastric tube at doses of 2.5â€“10 mg, 3â€“4 daily. The rationale for i the belief that reversal of antipsychotic-related striatal D_2 antagonism wi manifestations of NMS. Other dopamine agonists anecdotally associated v include levodopa[70, 88] and amantadine.[38, 45] When these drugs are use be tapered slowly after the patient improves to minimize the likelihood o NMS. In severe cases, combined therapy with dantrolene and a dopamine considered given their relative safety.

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) has been reported to dramatically improv manifestations of NMS, presumably by enhancing central dopaminergic tra report, 5 patients received an average of 10 ECT treatments, and resoluti generally seen after the third or fourth session.[69] Whether this result rep effect of ECT or

simply the natural course of NMS with good supportive care alone is not drug therapies for NMS, the efficacy of ECT remains unclear and its indic speculative, but its use seems reasonable in patients with severe, persist treatment-resistant NMS and for those with residual catatonia or psychos resolution of other manifestations.[13, 69]

Adverse Effects on Other Organ Systems

Sedation, dry mouth, and urinary retention occur commonly with antipsy particularly during the initial period of therapy. These symptoms occur m with drugs having potent antihistaminic and antimuscarinic activity. All dr the seizure threshold, but seizure activity rarely complicates therapeutic without additional risk factors. Because hypothalamic dopamine normally prolactin release by the pituitary gland, all antipsychotics with dopamine properties can cause hyperprolactinemia and galactorrhea.

The atypical antipsychotic agents are associated with weight gain, dyslip steatohepatitis, and rare but dramatic instances of glucose intolerance, i cases of diabetic ketoacidosis.[6, 42, 76, 92] Other idiosyncratic reactions use of antipsychotics include photosensitivity, skin pigmentation and cho (which occur with the phenothiazines), myocarditis, and agranulocytosis with several drugs but most notably clozapine, ie, between 0.38% and 2% Most of these conditions result from an immunologically based hypersens and develop during the first month of therapy.

Acute Overdose

Antipsychotic overdose can produce a spectrum of toxic manifestations a organ systems, but most serious toxicity involves the CNS and cardiovas Some of these manifestations are present to a minor degree during thera They tend to be most pronounced during the early period of therapy but continued use.

Impaired consciousness is a common and dose-dependent feature of ant overdose, ranging from somnolence to frank coma. It may be associated airway reflexes, but significant respiratory depression is uncommon. Man antipsychotics, including several of the atypical drugs, are potent musca and can produce dramatic anticholinergic manifestations in overdose.[11, Peripheral manifestations include tachycardia, decreased production of sw flushed skin, urinary retention, diminished bowel sounds, and mydriasis, also occurs. These findings may be present in isolation or coexist with ce manifestations, which can be highly variable and may be mistakenly attrib underlying psychiatric illness. These manifestations include agitation, de psychosis, hallucinations, and coma.

Mild elevations in body temperature are common and reflect impaired he because of impaired sweating and increased heat production in agitated Elevations in body temperature should always prompt a search for other of NMS. Tachycardia is a common finding in patients with antipsychotic o reflects peripheral anticholinergic effects as well as a compensatory respo hypotension. Bradycardia is distinctly uncommon. Although it may be a p event, its presence should prompt a search for alternate causes, including

(particularly Î²-adrenergic antagonists, calcium channel blockers, cardioa and opioids) and myocardial ischemia. Hypotension is a common feature overdose. Peripheral Î±$_1$ -adrenergic blockade reduces vasomotor tone. maintenance of vasomotor tone may be impaired, albeit by an unknown

The electrocardiographic (ECG) manifestations of antipsychotic overdose a those of TCA toxicity (Chaps. 5 and 71) and include widening of the QRS rightward deflection of the terminal 40 msec of the QRS complex (T40mse terminal component of the QRS complex in lead aVR). These changes refl the inward sodium current (I_{Na}). Prolongation of the QTc interval results of the delayed rectifier potassium current (I_{Kr}), creating a substrate for torsade de pointes.[68] This situation is sometimes evident during mainten and may underlie the apparent increase in sudden cardiac death among u antipsychotic drugs.[77] A published meta-analysis of the operating charact ECG in patients with TCA toxicity found the ECG was a relatively poor pre seizures, dysrhythmia, and death.[7] However, the ECG is a dynamic instru particularly in the initial hours following overdose, and few studies have longitudinal changes in the ECG.[55]

Diagnostic Tests

The diagnosis of antipsychotic poisoning is supported by the clinical histo examination, and a limited number of adjunctive tests. Both the clinical a electrocardiographic findings are nonspecific and can occur following over different drug classes, including TCAs, skeletal muscle relaxants, carbam first-generation antihistamines. Moreover, the absence of typical ECG cha exclude a significant antipsychotic ingestion, particularly early following o least 1 additional ECG should be performed in the following 2â€“3 hours.

Historically, positive urine colorimetric testing using ferric chloride or Ph test strips indicated the presence of phenothiazines. Abdominal radiograp densities in the gastrointestinal tract, as some solid dosage forms of phe radiopaque. However, these tests are neither sensitive nor specific, and t routinely recommended.

Plasma concentrations of antipsychotics are not widely available, do not

with clinical signs and symptoms, and do not help guide therapy. Compre drug screens using high-performance liquid chromatography or gas chro mass spectrometry may indicate the presence of antipsychotics, but these available at only a few hospitals and provide only a qualitative result. Blo immunoassays for TCAs may yield a false-positive result in the presence phenothiazines.[5 , 82]

Management

The care of a patient with an antipsychotic overdose should proceed with that other drugs, particularly other psychotropics, may have been coinges confound both the clinical presentation and management. Regularly enco coingestants include antidepressants, sedative-hypnotics, anticholinergic acid, and lithium, as well as ethanol and nonprescription analgesics such acetaminophen and aspirin.

Supportive care is the cornerstone for treatment of patients with antipsy Supplemental oxygen should be administered if hypoxia is present. Patier mental status should receive thiamine, naloxone, and parenteral dextrose Intubation and ventilation are rarely required but may be necessary for p very large overdoses of antipsychotic agents or ingestion of other CNS d symptomatic patients should undergo continuous cardiac monitoring. In a electrocardiogram should be recorded and reliable venous access obtaine Asymptomatic patients with a normal electrocardiogram 6 hours after exp exceedingly low risk of complications and no longer require cardiac moni Symptomatic patients and those with an abnormal ECG should have cont monitoring for a minimum of 24 hours.

Gastrointestinal Decontamination

Gastrointestinal decontamination with activated charcoal (1 g/kg by mouth nasogastric tube) should be considered for patients who present within a large or polydrug overdose. Although this intervention is unproven and ti many antipsychotics exhibit significant antimuscarinic activity and slow g

which increase the likelihood that activated charcoal will be beneficial. O
and whole-bowel irrigation likely will not improve clinical outcomes, and
is absolutely contraindicated because of the high potential for pulmonary

Treatment of Cardiovascular Complications

Vital signs should be monitored closely. Hypotension may result from per
blockade and most likely occurs with older, low-potency antipsychotics su
thioridazine. The hypotension should be treated initially with appropriate
0.9% sodium chloride solution (30â€“40 mL/kg). If vasopressors are req
acting Î± agonists such as norepinephrine or phenylephrine are preferred
dopamine, which is an indirect agonist and likely will be ineffective. Vaso
analogs also can be used. Continuous, intraarterial blood pressure monito
warranted in these cases. Central venous pressure monitoring and pulmo
catheterization rarely influence treatment decisions and should be used or
patient's clinical status is obfuscated by significant coingestion or comorl

Progressive widening of the QRS complex (usually with thioridazine and
reflects sodium channel blockade and slowing of phase 0 depolarization in
Purkinje system. This condition may be associated with reduced cardiac c
malignant ventricular dysrhythmias. Sodium bicarbonate (1â€“2 mEq/kg)
therapy for ventricular dysrhythmias and should be considered for patient
dysrhythmias or QRS widening >0.12 seconds. The rationale for this strat
upon the treatment of cyclic antidepressant overdose (Antidotes in Depth
Bicarbonate and Chap. 71) At least 2 mechanisms underlie the beneficial
sodium bicarbonate. First, the degree of sodium channel blockade is lesse
increase in extracellular sodium. In fact, hypertonic saline alone may be
Second, the binding of these drugs to the sodium channel is pH depender
extensive binding at higher pH.

Repeated doses of bicarbonate can be given to achieve a target blood pH
patient is intubated, hyperventilation also can be used but is not compar
If ventricular dysrhythmias persist despite sodium bicarbonate, lidocaine
followed by continuous infusion) is a reasonable second-line antidysrhyth
Class IA antidysrhythmics (procainamide, disopyramide, and quinidine), c
antidysrhythmics (propafenone, encainide, and flecainide), and class III

(amiodarone, sotalol, and bretylium) can aggravate cardiotoxicity and sho used. When administering sodium bicarbonate to patients with antipsych caution must be taken to avoid hypokalemia, as many of these antipsych cardiac potassium channels thereby prolonging the QT_c . Hypokalemia ca this blockade and potentially produce torsades de pointes.

Sinus tachycardia should not be treated unless it is associated with activ which, although uncommon, may complicate antipsychotic overdose in pa existing coronary disease. Should sinus tachycardia occur, a short-acting antagonist such as esmolol may be preferable. Prolongation of the QTc i no specific treatment other than correction of potential contributing cause hypokalemia and hypomagnesemia. Torsades de pointes should be treated magnesium sulfate, taking care to prevent hypotension, which is dose an dependent. Overdrive pacing with isoproterenol or transcutaneous or tra should be considered if the patient does not respond to magnesium sulfat theory this therapy may worsen the rate-dependent sodium channel bloc

Treatment of Seizures

Seizures associated with antipsychotic overdose are generally short-lived require no pharmacologic treatment. Multiple or refractory seizures shoul search for other causes, including hypoglycemia and ingestion of other p medications. When treatment is necessary, benzodiazepines such as loraz diazepam generally suffice, although phenobarbital may be necessary. A phenytoin is part of the standard algorithm for status epilepticus, it is in xenobiotic-induced seizures; barbiturates are preferred. Refractory seizur respond to propofol infusion or general anesthesia. Seizures complicated hyperthermia are considerably more ominous and warrant aggressive lowe temperature with aggressive rapid cooling measures. Finally, seizures can serum pH and abruptly increase the cardiotoxicity of these drugs; therefo should be recorded following resolution of seizure activity.

Treatment of the Central Antimuscarinic S

Many of the older-generation and newer-generation antipsychotics have

anticholinergic properties. Case reports and observational studies suggest cholinesterase inhibitor physostigmine (Antidotes in Depth: Physostigmin can safely and effectively ameliorate the agitated delirium associated with anticholinergic syndrome by indirectly increasing synaptic acetylcholine l , [101] Although benzodiazepines will control agitation, they will further imp status, obfuscating the assessment of mental status and increasing the ris complications.[21]

Physostigmine should be used with caution. It should not be used in patie dysrhythmias, any degree of heart block, or widening of the QRS complex physostigmine is used, it should be given in 0.5-mg increments every 3â with close observation of the patient. If bradycardia, bronchospasm, or develop, they can be treated with glycopyrrolate 0.2 to 0.4 mg IV. Atropi

be used, although it crosses the bloodâ€“brain barrier and may further w underlying delirium. Physostigmine's effects are transient, typically rangir 30â€“90 minutes, and additional doses are often necessary. Of note, phy not prevent other complications of antipsychotic overdose, particularly th the cardiovascular system.

Other commonly used cholinesterase inhibitors, such as edrophonium, ne pyridostigmine, should not be used to treat anticholinergic delirium becaus cross the bloodâ€“brain barrier. Case reports involving other anticholiner that cholinesterase inhibitors used for treatment of dementia (eg, tacrine galantamine) may be alternatives to physostigmine for patients who can medications orally.[44 , 64 , 71]

Enhanced Elimination

No pharmacologic rationale supports the use of multiple-dose charcoal or urinary pH to increase the clearance of antipsychotics. One volunteer stuc urinary acidification may increase remoxipride elimination,[102] but this pra impractical and possibly dangerous. Because most antipsychotics have lar distribution and extensive protein binding (Table 67-1), neither hemodia hemoperfusion is expected to significantly increase clearance. These mod be considered only if the patient has concomitantly ingested other xenob

to extracorporeal removal, such as lithium.

Summary

Over the past decade, the atypical antipsychotics have largely supplante drugs, which were associated with greater toxicity in overdose and a high extrapyramidal reactions. Consequently, atypical antipsychotics are now i majority of overdoses.

With both typical and atypical antipsychotics, toxicity can occur either du of therapy or following overdose. Of the various toxicities that arise duri use, NMS is the most dangerous. Its manifestations are protean, and it m to recognize. Altered mental status, muscle rigidity, fever, and autonomic its hallmarks, but the diagnosis should be considered in any unwell patien antipsychotics, particularly in the 2 weeks following a change in the anti regimen. Treatment of NMS is largely supportive and often dependent on benzodiazepines. Dantrolene, dopamine agonists such as bromocriptine, electroconvulsive therapy are anecdotally associated with dramatic clinic

The principal manifestations of antipsychotic overdose involve the CNS ar cardiovascular system. Depressed mental status, hypotension, and antich are nonspecific features that support the diagnosis of antipsychotic overd particularly in conjunction with typical ECG findings of sodium channel blo prolongation. Most fatalities following antipsychotic overdose occur in cas coingestion of other CNS depressants or cardiotoxic medications. Supporti mainstay of therapy for patients with antipsychotic overdose, although se nonspecific antidotes, such as activated charcoal, sodium bicarbonate, an physostigmine, may improve outcomes in some patients.

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Chapter 68
Lithium

Howard A. Greller

Lithium

MW	=	6.94 daltons

Lithium levels (serum):

Therapeutic level for bipolar depression	=	0.6â€“1.2 mEq/L (mmol/L)

A 55-year-old man was brought to the emergency department (ED) with a 3-day history of progressively worsening confusion and tremor. The patient was an accountant and normally was a highly functioning, intelligent person. Eight days prior to presentation, he saw his primary care physician for complaints of fever, chills, cough, myalgias, arthralgias, and malaise. Symptomatic therapy with an oral decongestant, acetaminophen, and oral hydration was prescribed. His symptoms improved, but he became progressively more confused and tremulous.

Upon questioning the family, the patient was found to have a medical history significant for bipolar disorder, for which he was receiving a stable dose of lithium carbonate for more than 10 years. He had no psychiatric hospitalizations, no history of suicide attempts, and took no other psychiatric medications. No other medications were available in the household.

On physical examination, the patient was a well-appearing, slightly disheveled man in no apparent respiratory distress. His vital signs were: blood pressure, 135/86 mm Hg; pulse, 105 beats/min and regular; respiratory rate, 14 breaths/min; temperature, 99.5Â°F (37.5Â°C); oxygen saturation, 97% on room air; and a rapid bedside glucose concentration, 106 mg/dL.

Examination revealed prominent horizontal nystagmus. Pupils were equal, round, and reactive to light and accommodation. The oral mucosa were dry, but the remainder of the head and neck examination was unremarkable. The chest was clear to auscultation and percussion. Cardiac examination revealed a regular rate and rhythm, without the presence of murmurs, rubs, or gallops. Abdominal examination was unremarkable, and rectal examination revealed good rectal tone, a normal prostate, and no occult blood. The skin was warm, dry, and free of rashes or other findings.

The patient had difficulty complying fully with the neurologic examination because of his altered level of consciousness. He was alert and oriented to person but disoriented to time and place. Throughout the examination, he continuously attempted to get off the bed so that he could â€œattend an important meeting.â€• He was mildly agitated and had a noticeable tremor in his upper extremities. His cranial nerves were normal with the exception of his horizontal nystagmus. His motor strength was normal and symmetric. All deep tendon reflexes were hyperactive and symmetric with clonus in both ankles. The patient was unable to comply with formal cerebellar function testing.

The patient was attached to a cardiac monitor, and 2 L oxygen was administered by nasal cannula. A large-bore intravenous catheter was inserted, and blood samples were obtained for determination of serum electrolytes, complete blood count (CBC), acetaminophen, salicylate, ethanol and lithium concentrations. An infusion of 0.9% sodium chloride solution was started. An electrocardiogram showing sinus tachycardia at a rate of 105, with normal axis, intervals, and T waves and no evidence of acute ST-segment changes. A chest radiograph showed no evidence of active or acute pulmonary disease. The patient was sedated with 1 mg intravenous lorazepam for persistent agitation.

The serum lithium concentration was reported as 2.74 mEq/L, and a repeat specimen was drawn and sent for analysis. The acetaminophen, salicylate and ethanol concentrations were negative. The blood urea nitrogen (BUN)/Cr ratio of 21/1.3 mg/dL was elevated compared to a ratio of 9/0.8 mg/dL determined 3 weeks earlier. All other laboratory values were unremarkable. Infusion of 0.9% sodium chloride solution was increased to 2 times the maintenance rate, and a nephrology consultation was requested.

The repeat lithium concentration was 2.38 mEq/L. Based on the combination of clinical and laboratory findings, hemodialysis was initiated. After 4 hours of hemodialysis the patient's mental status improved by all measures. The immediate postdialysis lithium concentration was 0.74 mEq/L, and the concentration 6 hours postdialysis was 1.41 mEq/L, after which the patient underwent a second

4-hour dialysis. The lithium concentration after the second dialysis was 0.97 mEq/L and did not rebound higher during the remainder of the hospitalization. When the patient was discharged on hospital day 3, he has a normal neurologic examination and had returned to his baseline mental status.

History

Lithium has a long history of use beginning in the mid-19th century, when lithium salts were used to treat gout. The therapy also improved symptoms of mania and depression.[91,161] Lithium was the original â€œactiveâ€• ingredient in the soft drink 7-Up.[3] During the 1930s and 1940s, it was used as a salt substitute (â€œWestsalâ€•) for patients with heart failure but was discontinued after several cases of acute lithium poisoning were described.[40,47,64,42] The beneficial effects of lithium on bipolar disorder were â€œrediscoveredâ€• by Cade in 1949, when he noticed the calming effect of lithium carbonate on guinea pigs.[31,32] The same year, however, the FDA banned the use of lithium in response to reported poisonings.[31,127,142] The FDA lifted the ban in 1970 and approved the use of lithium for treatment of mania.

Lithium is the most efficient long-term therapy for treatment and prevention of bipolar affective disorders,[161] with a demonstrated antisuicidal effect and an ability to improve both the manic and depressive symptoms of the illness.[12,13,60,144,161] Investigations on the use of lithium for compulsive gambling have also demonstrated beneficial results.[71] In most industrialized nations, approximately 1 in 1000 persons is using 1 or more of the various lithium formulations.[6,141]

Pharmacology

The simplicity of the lithium molecule belies the complexity of its mechanism of action. Although lithium has been used therapeutically for almost 50 years, the precise pharmacology of its therapeutic effects has not yet been elucidated.[56] Part of the difficulty in defining the precise mechanism of action of lithium is the difficulty in defining the precise pathophysiology of bipolar disorder. Early efforts focused on dysfunctional neurotransmitter systems, particularly the role of biogenic amines. Lithium

increases basal and stimulation-induced serotonin release and receptor sensitivity to serotonin.[29,162] Lithium modulates the effect of norepinephrine through its interactions with the G-proteinâ€“mediated effects on the Î²-adrenergic receptor, thereby stabilizing fluctuations in the intracellular pool of cyclic adenosine monophosphate (cAMP). It performs this function by inhibiting not only the inhibitory subunit G_i, which raises basal concentrations of cAMP, but also the stimulatory subunit G_s, preventing fluctuations from adrenergic stimulation.[29]

Clinically, the therapeutic effects of lithium (and other mood-stabilizing pharmaceuticals) become evident only after chronic administration, so their mechanism of action likely is not solely the result of acute biochemical interactions. Postulated mechanisms go beyond simple neurotransmitter function or dysfunction and focus on altered cellular signaling, neuronal plasticity, and neurogenesis. Rather than trying to identify any single neurotransmitter system as responsible for the complexity of depressive illness, efforts now are directed at elucidating the functional balance between interacting systems. Along with these advances, a clearer understanding of the action of lithium is developing.[18,29,56,67,90,91,144]

The prevailing theory for the mechanism of action of lithium is the inositol-depletion hypothesis. Inositol is a 6-carbon sugar that forms the backbone of a number of cellular signaling mechanisms. Therapeutic lithium treatment results in decreased myoinositol (the most biologically active stereoisomer of inositol) concentration in the cerebral cortex.[4,67,84] Abnormalities in regional brain myoinositol concentrations are thought to occur in bipolar patients. This theory is partially supported by experimental magnetic resonance spectroscopy data.[146,175] Myoinositol is phosphorylated to form phosphatidyl inositol (PIP), which is further phosphorylated and combined with diacylglycerol (DAG) to form phosphatidyl 4,5-bisphosphate (PIP_2). Upon stimulation of a cell, G-proteinâ€“coupled receptors activate phospholipase C

(PLC), which hydrolyzes PIP_2 to release the secondary messengers DAG and inositol 1,4,5-triphosphate (IP_3).[67,143,146,175] Each of these secondary messengers in turn initiates a cascade of events, including activation of protein kinase C (PKC), which is important for calcium homeostasis and neurotransmitter release,[106,107,118,146] as well as independent mobilization and regulation of intracellular calcium.[14,36,114,129,146] Many extracellular signals, including some serotonin receptor subtypes, activate PLC to exert their actions.[61,105,121]

Serial dephosphorylation of IP_3 leads to regeneration of myoinositol and recycling of the inositol pool. Two enzymes involved in this pathway are inhibited by lithium. The first enzyme, inositol 1,4-bisphosphate 1-phosphatase (IPPase), dephosphorylates the bisphosphate to inositol monophosphate (IMP). The second enzyme, inositol 1-monophosphatase (IMPase), dephosphorylates IMP to myoinositol.

The inhibition of IMPase is interesting and important. First, the mechanism of inhibition is uncommon. Lithium uncompetitively inhibits IMPase by binding to the enzymeâ€“substrate complex and preventing the release of a phosphate. It performs this function by displacing a magnesium ion from the active site after hydrolysis. Essentially, uncompetition means the higher the concentration of the substrate, the more the enzyme is inhibited.[7] This supports a theory about the pathophysiology of bipolar disorder involving an excess of myoinositol and is 1 reason why the mood-stabilizing effects of lithium are thought to be found only in bipolar patients.[67] That is, the uncompetitive nature of the action of lithium serves as a regulator to preferentially block pathologic signaling caused by excessive myoinositol while leaving the normal signaling intact. As described, IMPase is an important step in the cellular recycling of the inositol pool. Lithium inhibits the last step in this cycle.

Myoinositol is also generated de novo from glucose-6-phosphate

by inositol synthase, which forms IMP. The inhibition of IMPase by lithium subsequently leads to myoinositol depletion by preventing the conversion of the newly synthesized IMP to inositol. Interestingly, valproic acid (VPA) also inhibits inositol synthase, illustrating a potential mechanism for the synergy of these complementary mood stabilizers.[119] A third mechanism of intracellular diminution of inositol by lithium (as well as VPA and carbamazepine) is the effect of lithium on reducing activity and transcription of the sodium myoinositol transporter (SMIT), thereby preventing the uptake of exogenous myoinositol by the cell. This mechanism of inhibition can be overcome by increased extracellular concentration of myoinositol.[67,173]

The result of these effects is depletion of the inositol pool available to the cell, causing a series of events at different points in the signal transduction cascade that leads to differential gene transcription and expression. This sequence ultimately is responsible for the

observed clinical effects of lithium on the CNS.[29,143] Experimental data, using dextroamphetamine as a model for clinical mania, have shown that dextroamphetamine increases regional inositol signaling in the human brain, and that pretreatment with lithium attenuates this increase, lending support to the hypothesis.[21]

Another proposed theory for the mechanism of action of lithium is inhibition of the family of glycogen synthase kinase-3 (GSK-3) kinases. GSK-3Î² overactivity is associated with neuronal degeneration and sensitivity to apoptotic stimulation. GSK-3Î² is a key regulator of neuronal cell fate, with a proapoptotic effect in many settings.[42,50,70,78,79 and 80,133] GSK-3Î² is involved in regulating the activity of Î²-catenin, Jun, and cAMP response element-binding protein (CREB), transcription factors important in embryonic patterning, cell proliferation, neuronal modeling and plasticity, neuronal signal transduction, and cytoskeletal remodeling. Lithium inhibits GSK-3Î² indirectly through

phosphorylation (by activation of PKC) and directly through inhibition of enzymatic activity through magnesium mimicry. Inhibition of GSK-3Î² by lithium is thought to be neuroprotective.[29,63,68,126,134,176]

A link between GSK-3Î² activity and bipolar disorder and depression is supported by the finding that serotonergic activity inhibits GSK-3Î² in vivo.[92] Additionally, hypoxia contributes to increased GSK-3Î² activity, which can be counteracted or inhibited through mood-stabilizing drugs. Vascular depression, or depression following stroke, is an organic model of major depression.[111] The finding that this depressive state responds similarly to intervention with mood stabilizers lends additional support to the GSK-3Î² hypothesis.[81] Thus, the depressed serotonergic activity associated with depression, or the hypoxic-induced activation of GSK-3Î², may lead to impaired inhibition of GSK-3Î². Mood stabilizers counteract this dysregulation and may explain their effectiveness in depression. This theory is under active investigation.[29,61,67,68,126,171]

Lithium is implicated in the neuroprotective modulation of the *bcl*-2 gene, which is known for its role in preventing apoptosis and in downregulation of the proapoptotic protein p53. In rats treated with either Li^+ or VPA, concentrations of Bcl-2 protein doubled.[34] These findings, although not necessarily replicated in human beings, are supported by the findings that patients undergoing long-term therapy with either drug had prefrontal cortex volumes significantly greater than in patients not treated with either agent, suggesting a protective effect in human patients.[29,37,45]

In summary, although the precise mechanism of action of lithium is unknown, some common features of investigation have emerged. The potential targets, widely found and disparate in function, all seem to be inhibited by lithium in an uncompetitive fashion, most commonly through displacement of a divalent cation, usually Mg^{2+}. The systems affected by this inhibition vary widely.

Downstream targets seem to modulate secondary cell messengers and intracellular signal transduction, transcription factors and gene expression, and neuronal plasticity and cellular differentiation. Further study is needed to elucidate the complex interaction of these pathways with the action of lithium in order to form an integrated hypothesis.

Pharmacokinetics and Toxicokinetics

The volume of distribution of lithium is between 0.6 and 0.9 L/kg. It displays no discernible protein binding and distributes freely in total body water, except for the cerebrospinal fluid (CSF), from which it is actively extruded.[48,122,148] The extrusion is believed to occur through an active transport process involving sodium/lithium exchange at the arachnoid processes.[49] The immediate-release preparations of lithium are rapidly absorbed from the gastrointestinal (GI) tract. Peak plasma concentrations are achieved within 1â€“2 hours.[76] Sustained-release products demonstrate variable absorption, with a delay to peak of 6-12 hours. In overdose, a longer delay to reach peak concentrations or multiple peaks may occur.[46] Chronic therapy prolongs the elimination of lithium, as does advancing age.[122] Although lithium is rapidly absorbed, tissue distribution is a complex phenomenon, with a significant delay in reaching a steady state. Lithium exhibits preferential uptake into certain tissues (eg, kidney, thyroid, and bone) over others (eg, liver, muscle). Lithium distribution into the brain can take up to 24 hours to reach equilibrium. Lithium is concentrated in red blood cells (RBCs) by both passive diffusion and active transport. RBC concentration may correlate closely with brain concentrations, although further study to confirm this possibility is warranted.[33,128] The pharmacokinetic profile of lithium is described as an open, two-compartment model.[53,77]

Each 300-mg lithium carbonate tablet contains 8.12 mEq lithium.[161] Ingestion of a single 300-mg tablet is expected to

acutely raise the serum lithium concentration by approximately 0.1â€“0.3 mEq/L (assuming a volume of distribution of approximately 0.6â€“0.9 L/kg and a patient weight 50â€–100 kg).

Lithium is eliminated almost entirely (95%) by the kidneys, with a small amount eliminated in the feces.[76] Lithium is also found in sweat, saliva, and breast milk.[43,73,115] In an adult with normal renal function, lithium clearance ranges from 25â€“35 mL/min.[20,158,159] At steady-state equilibrium, as in patients undergoing chronic therapy, total body clearance equals renal clearance.

Lithium is handled by the kidneys much in the same way as sodium. Lithium is freely filtered, and more than 60% is reabsorbed by the proximal tubule. Evidence also indicates a small amount of reabsorption by the loop of Henle and distal tubule.[8,24,25,44,54,89,122,161] Lithium excretion is dependent on factors that affect the glomerular filtration rate (GFR) or decrease sodium concentration. Any condition that makes the kidney sodium-avid (eg, volume depletion or salt restriction) increases lithium reabsorption in the proximal tubule.[8] Risk factors for development of lithium toxicity therefore include advanced age with its associated decrease in GFR, thiazide diuretics, nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme (ACE) inhibitors, decreased sodium intake, and low-output heart failure.[76,89]

The therapeutic index for lithium is narrow. The generally accepted steady-state therapeutic range of serum lithium concentrations is 0.6â€“1.2 mmol/L, although much disagreement exists about whether this serum concentration truly reflects therapeutic efficacy.[58,59,135] Both in therapeutic and overdose situations, clinical signs and symptoms seem to be a more valuable indicator of brain lithium concentrations.[135]

Clinical Manifestations

Similar to other substances having prolonged redistributive phases and tissue burdens, lithium exposure can be divided into 3 main categories of toxicity: acute, acute-on-chronic, and chronic. In acute lithium toxicity, the patient has no body burden of lithium present at the time of ingestion. The toxicity that develops depends on the rate of absorption and distribution. In chronic toxicity, the

patient has a stable body burden of lithium as serum concentration is maintained in the therapeutic range, and then some factor disturbs this balance, either by enhancing absorption, or more commonly, decreasing elimination. For the chronic user of lithium small perturbations in the equilibrium between intake and elimination can lead to toxicity. In acute-on-chronic toxicity, the patient ingests an increased amount of lithium (intentionally or unintentionally) in the setting of a stable body burden. With tissue saturation, any additional lithium leads to signs and symptoms of toxicity.

Acute Toxicity

Lithium is a metal salt. Acute ingestions of lithium-containing preparations produce a clinical picture similar to that of ingestions of other metal salts, with predominant early GI symptoms. Nausea, vomiting, and diarrhea are prevalent. A large volume loss can result from these symptoms. Patients may complain of lightheadedness and dizziness, and they can be orthostatic on evaluation. Neurologic manifestations are a late finding in acute toxicity, as the lithium redistributes slowly into the CNS.

Lithium is associated with a number of electrocardiographic abnormalities, although the evidence for significant effects is tenuous. The most commonly reported manifestation is T-wave flattening or inversion, primarily in the precordial leads.[28,124,160] Lithium is associated with prolongation of the QTc interval.[174] A

study has associated elevated serum lithium concentrations with QTc prolongation >440 msec, although the number of patients studied was small.[72] Associations exist between lithium and sinoatrial nodal dysfunction, with bradycardia. Theoretically, this condition may result from lithium's effect on G-proteinâ€“mediated cAMP generation, and subsequent modification of calcium channel opening and calcium influx in the pacemaker cells.[28,72,124,160] For the most part, lithium has few consequential effects on cardiac function, even in overdose, and malignant dysrhythmias or significant dysfunction is rare.[99,117,122]

Chronic Toxicity

Lithium is primarily a neurotoxin.[2] The earliest case reports of lithium toxicity described predominantly neurologic symptoms.[41,169] Of note, neurotoxicity does not correlate with serum concentrations. The initial clinical condition of the patient and the duration of exposure to an elevated concentration seem to be more closely predictive of outcome than the initial serum lithium concentration.[2,6,16,65,87,116,140,166]

Tremor, a common finding in patients undergoing chronic therapy, can increase with toxicity. Other findings of chronic toxicity include fasciculations, hyperreflexia, choreoathetoid movements, clonus, dysarthria, nystagmus and ataxia.[122,161] Mental status often is altered and can progress from confusion to stupor, coma, and seizures.[30] Electroencephalographic changes are most frequently reported as â€œslowing.â€• The progression of these symptoms follows no order, and any patient undergoing chronic therapy can have 1 or any combination of these features.

The syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) is a descriptive syndrome of the irreversible neurologic and neuropsychiatric sequelae of lithium toxicity.[2] SILENT is defined as neurologic dysfunction caused by lithium in the absence of prior neurologic illness that persists for at least 2 months after

cessation of the drug. Case reports in the literature support these findings and this definition. However, as is true in most case reports, confounders make wide applicability of the findings difficult. Because of the polypharmacy prevalent in psychiatric treatment, long-term neurologic sequelae attributed to lithium are described in patients using lithium in combination with other medications, such as haloperidol, chlorpromazine, carbamazepine, phenytoin, aspirin, valproic acid, amitriptyline, Î²-adrenergic antagonists, calcium channel blockers, ACE inhibitors, diuretics and nonsteroidal antiinflammatory drugs.[2,10,38,52,53,66,104,113,166] However, patients who used lithium without coingestants and had no comorbid illness but sustained lasting dysfunction as a result of lithium toxicity are reported.[6,85,116,123,140,166] Cerebellar findings seem to predominate in SILENT.[2,62,82,85,108] One predictor of persistent neurologic dysfunction seems to be the concomitant finding of hyperpyrexia, an ominous finding in lithium toxicity.[62,108] The mechanism of persistent dysfunction is unclear, but demyelination and cellular loss are proposed.[2,108,116,138]

Acute-on-Chronic Toxicity

Patients undergoing chronic therapy who acutely ingest an additional amount of lithium (either intentionally or unintentionally) are at risk for signs and symptoms of both acute and chronic toxicity. Such patients display prominent GI and neurologic symptoms and can be difficult to diagnose and manage. Serum lithium concentrations in cases of acute or chronic toxicity can be difficult to interpret, and therapy should be guided by the patient's clinical status.

Other Systemic Manifestations of Chronic Lithium Therapy

The most common adverse effect of chronic lithium therapy is the

development of nephrogenic diabetes insipidus. The process thought to be involved is the interference of lithium on magnesium-dependent G proteins that activate vasopressin-sensitive adenylate cyclase, leading to decreased generation of cAMP in the cell membranes of distal tubular cells.[35,109,149,167] Decreased cAMP leads to reduced expression and translocation of the vasopressin-regulated water channel aquaporin-2 (AQP-2), making the distal tubules resistant to the action of vasopressin.[5,39,83,109,110,137,170] Lithium also inhibits the transport of sodium through the amiloride-sensitive Na^+ channel.[157]

Another theory proposed for the mechanism of lithium-induced nephrogenic diabetes insipidus suggests that lithium inhibits GSK-3Î², directly and through a phosphorylation pathway. GSK-3Î² exhibits tonic inhibition of cyclooxygenase-2 (COX-2). When this inhibition is removed by lithium, COX-2 activity leads to increased prostaglandin expression in the renal medulla. Increased prostaglandin expression is thought to play an important role in nephrogenic diabetes insipidus through regulation of glomerular blood flow.[102,130]

Chronic lithium therapy is associated with chronic tubulointerstitial nephropathy, as manifested by the development of renal insufficiency with little or no proteinuria and biopsy findings of tubular cysts. This association was demonstrated in 1 biopsy-based study of 24 chronically treated patients, although the overall prevalence of this condition is low.[109]

Lithium is associated with a number of endocrine disorders. The most prevalent endocrine manifestation of chronic lithium therapy is hypothyroidism. The causative etiology is multifactorial. Lithium is selectively concentrated in the thyroid gland and impairs iodine uptake, synthesis of triiodothyronine (T_3), responsiveness of the gland to thyroid-stimulating hormone (TSH), release of T_3 and

tetraiodothyronine (T_4), and peripheral conversion of T_4 to T_3. Additionally, lithium decreases responsiveness of peripheral tissues to T_3 and leads to the development of antithyroglobulin antibodies.[120,172] Although hypothyroidism is most common, hyperthyroidism and frank thyrotoxicosis also are reported.[15] However, hyperthyroidism, by altering proximal tubule function, leads to decreased lithium excretion.[19] Thus, hyperthyroidism may lead to chronic lithium toxicity through impaired elimination, and the elevated lithium concentrations may mask the manifestations of hyperthyroidism.[120] Further investigation of this condition is warranted.

The combination of hyperparathyroidism and hypercalcemia is frequently reported with chronic lithium therapy, most commonly in women. The mechanism is thought to be modification of calcium feedback on parathyroid hormone release, although stimulation of parathyroid hyperplasia and adenomas is suggested.[1,9,23,88,147,161]

Developmentally, in utero exposure to lithium increases the incidence of congenital heart defects, specifically Ebstein anomaly.[73,126,147] Additionally, many effects similar to those that occur in patients undergoing chronic therapy are found in infants exposed in utero, including thyroid disease and neurotoxicity.[73]

Lithium causes a leukocytosis and an increase in neutrophils. It has been proposed as an adjunct to chemotherapy-induced neutropenia, other marrow suppressive therapies, and acquired immunodeficiency syndrome (AIDS). Although lithium increases the total neutrophil count, no improved clinical outcomes are documented, and its use has been superseded by recombinant colony-stimulating factors.[26,126,132,147,151]

Diagnostic Testing

Because of the prevalence of lithium use, therapeutic drug

monitoring is readily available in most settings, and concentrations should be readily obtainable. A lithium concentration should be requested upon patient presentation and serial measurements requested or considered in most instances, especially in cases of sustained-release ingestions. Emphasis should be placed upon the lithium concentration as a marker of exposure and response to therapy, not necessarily as a determinant of toxicity. The choice of therapy should be guided by the patient's clinical signs and symptoms (and history) rather than an absolute lithium concentration. The sample must be sent in an appropriate lithium-free tube, because certain lithiated-heparin tubes can lead to false-positive results. Serum electrolyte concentrations including renal function should be monitored, because renal function is important in determining the need for more aggressive therapy, including enhanced elimination technique (ie, hemodialysis). If the patient is hypernatremic, nephrogenic diabetes insipidus should be suspected, and determinations of serum and urine osmolarity help confirm the diagnosis. If clinical thyroid disease is suspected, thyroid function tests can be obtained. As with all deliberate ingestions, a serum acetaminophen concentration should be obtained. An electrocardiogram is also indicated for this type of ingestion. The complete blood count may indicate a leukocytosis, which may merely be a stress response or caused by the effects of lithium.

Management

Initial management and stabilization begins with assessment of the basics of resuscitation: airway, breathing, and circulation. Lithium rarely, if ever, affects the airway or breathing of the patient, although coingestants may. Emesis, which occurs at a significant incidence and is associated with acute lithium exposure, may lead to aspiration and respiratory compromise. Once the patient is stable, the nature of the exposure should be determined while physical examination and laboratory assessment commence. The

formulation and nature of the product should be ascertained as immediate-release or sustained-release. Information should be obtained regarding whether or not lithium is part of the patient's medication regimen, which will help determine whether the ingestion is acute, acute-on-chronic, or chronic.

Gastrointestinal Decontamination

For patients who present after an acute (or acute-on-chronic) overdose, a risk-to-benefit analysis of GI decontamination must be undertaken. Two factors should be considered. With an acute overdose and predominance of early GI symptoms, including emesis, self-decontamination may have already started. Second, immediate-release preparations are often rapidly absorbed and may not lend themselves to GI evacuation.

Few GI decontamination options are available to the treating physician. Although syrup of ipecac is no longer generally recommended as a standard decontamination choice, emesis still may be useful in certain instances of sustained-release preparation ingestions when care may be delayed or is distant, as in remote or rural areas. Immediate-release preparations of lithium are rapidly absorbed and produce emesis, whereas sustained-release formulations of lithium (ie, controlled-release tablets) and a slowly dissolving film-coated formulation often are too large to fit through even the largest lavage tube. Thus, orogastric lavage has essentially no role in the acute management of a lithium overdose, unless indicated for a coingestant.

Lithium is a monovalent cation that does not bind readily to activated charcoal.[97] Because no beneficial effect from activated charcoal is expected, the danger of a depressed level of consciousness, potential loss of protective airway reflexes, and prominent emesis contraindicate activated charcoal use, except for treatment of a potential coingestant.

Sodium polystyrene sulfonate (SPS) is a cationic exchange resin often used for treatment of severe hyperkalemia. It binds potassium in exchange for sodium, allowing elimination of excess potassium in the feces. Because of the similarity between potassium and lithium, use of SPS has been proposed for decontamination of patients being treated for lithium toxicity. A number of animal models have been used to examine the effectiveness of this technique.[93,94,95,96,97 and 98,100,101] Use of SPS has many theoretical benefits, including demonstrated effectiveness of lithium binding compared to activated charcoal and the ability of orally administered SPS to reduce serum concentrations of intravenously administered lithium in mice.[95,97,98] Unfortunately, the finding that doses used to increase lithium elimination also lead to significant hypokalemia in human subjects limits the application of this technique.[94,136] In a murine model, potassium supplementation with SPS was found to mitigate process, but only at the expense of elevated lithium concentrations.[100] Two reports in the literature demonstrate increased lithium elimination with SPS, one in a healthy volunteer and another in a patient with an acute overdose. However, the serum potassium concentration was not reported in either case.[57,131] At present, use of SPS in the management of the lithium-poisoned patient cannot be recommended.

Whole-bowel irrigation (WBI) is the only GI decontamination modality that has shown any efficacy in eliminating lithium from human subjects. In one of the few clinical trials of WBI, the lithium serum concentrations of 10 normal volunteers who had ingested sustained-release lithium carbonate were plotted against time over a 72-hour period. In the second phase of the trial, the volunteers received 2 L/hour polyethylene glycol solution 1 hour after the ingestion. This study showed a significant reduction (67%) in the serum concentration, even as early as 1 hour after the ingestion.[150] Thus, use of WBI is recommended for sustained-

release preparations.

Fluid and Electrolytes

The critical initial management of the lithium-poisoned patient should focus on restoration of intravascular volume, both in acute poisonings, with GI losses, and in chronic poisonings, with toxic effects that are often the result of disturbances of renal function and lithium elimination. Many patients with lithium toxicity have volume-responsive decreases in renal function,[122] which can be managed by infusion of 0.9% sodium chloride solution at 1.5â€“2 times the maintenance rate. This therapy increases renal perfusion, increases the GFR, and increases lithium elimination. Urine output must be closely monitored. Electrolyte abnormalities should be corrected. Caution should be used in patients with renal insufficiency or failure or congestive heart failure. Monitoring for the development of hypernatremia in patients suspected of having nephrogenic diabetes insipidus is critical.[161]

Lithium-induced nephrogenic diabetes insipidus can be reversed by discontinuation of the drug and through repletion of electrolytes and free water. However, cases of permanence are reported.[103,109,156] Clinical application of amiloride to mitigate lithium-induced polyuria is reported, although the potential for volume contraction and stimulation of lithium reabsorption limits recommendation of this drug as a routine adjunct to acute care.[17,51,55,86]

Attempts to enhance lithium elimination through forced diuresis with loop diuretics (furosemide), osmotic agents (mannitol), carbonic anhydrase inhibitors (acetazolamide), or phosphodiesterase inhibitors (aminophylline) should be avoided. An initial small increase in elimination may be achieved but typically salt and water depletion develop and are followed by increased lithium retention. Use of sodium bicarbonate for urinary alkalinization does not significantly increase elimination over

volume expansion with sodium chloride and can lead to hypokalemia, alkalemia, and fluid overload; therefore, sodium bicarbonate also should be avoided.

Extracorporeal Drug Removal

Debate surrounds the efficacy and practicality of using enhanced elimination techniques in cases of lithium poisoning. Lithium has physicochemical properties that make it amenable to extracorporeal removal.[69,75,76,89] With these characteristics, lithium seems to be an ideal candidate for hemodialysis. In fact, hemodialysis is often recommended for treatment of acute, acute-on-chronic, and chronic lithium toxicity.[11,74,75 and 76,108,125,155,161,168] However, some characteristics of lithium make extracorporeal elimination difficult. Lithium is predominantly localized intracellularly and diffuses slowly across cell membranes.[122] When traditional intermittent hemodialysis is used for chronic exposures, clearance of the plasma compartment is often followed by a rebound phenomenon of redistribution from tissue stores leading to increased plasma concentrations, in some cases approaching predialysis concentrations.[27] An additional complicating factor is that the brain, the â€œtarget organâ€• of toxicity, is not amenable to rapid artificial elimination processes. Attempts have been made to correlate the serum concentration with the lithium concentration in the CSF and brain. In the few studies where CSF concentrations were obtained, serum and CSF lithium concentrations seemed to correlate, but brain concentrations and toxicity did not.[76,139] Magnetic resonance spectroscopic studies of bipolar patients with steady-state lithium concentrations demonstrated a significant variability between brain and serum concentrations, especially within the therapeutic range.[76,135,139] No consensus recommendation on the appropriate time to initiate therapy is available.[11,76,136] In addition, because of the toxicokinetic profile of lithium, serum concentrations do not correlate well with toxicity.[47,76,152,161]

Hemodialysis or an alternative extracorporeal technique is clearly indicated for 3 groups of patients. The first group consists of patients who are manifesting severe signs and symptoms of neurotoxicity, such as alterations in mental status. The second group consists of patients who have renal failure and show signs or symptoms of lithium toxicity. These patients are unable to eliminate their lithium burden and should be dialyzed. The third group consists of patients who show little or no sign of toxicity but who cannot tolerate sodium repletion therapy; these patients should be considered for early hemodialysis. This group includes patients with congestive heart failure or redistributive diseases such as liver failure, pancreatitis, or sepsis.

If the patient belongs to one of these groups, the next step is to determine the probability that the patient will develop toxicity if elimination is not enhanced. Serum concentrations do not necessarily correlate with toxicity. However, they can be a useful aid in making the decision for hemodialysis. As an adjunct to the clinical presentation, an absolute lithium concentration >4.0 mEq/L (mmol/L) with any type of overdose or a concentration >2.5 mEq/L with chronic toxicity should prompt dialysis. These criteria originate from a case series of 23 patients and review of 100 other patients published in 1978, prior to the introduction of sustained-release products.[65] Although this recommendation has never been prospectively evaluated, it still can serve as a useful guide in the management of the lithium-poisoned patient.[11,20]

The dialysate bath should contain bicarbonate rather than acetate. This composition should help lessen the intracellular sequestration of lithium that occurs because of activation of the sodium/potassium antiporter, with preferential intracellular transport of lithium.[125,155]

Whether hemodialysis diminishes or enhances the risk of permanent neurologic sequelae is a subject of debate.[153,154] Although no controlled studies have analyzed this important

management question, the preponderance of evidence suggests a reduced risk.[2,6,11,76,108,112,122,125,140,161]

Continuous venovenous hemodialysis and continuous venovenous hemodiafiltration are two continuous renal replacement therapies (CRRTs) commonly used for treatment of acute renal failure and volume overload and for elimination of exogenous substances.[20,89,163,164 and 165] Both techniques are effective in patients who are hemodynamically unstable, because blood flow through the filter is pump driven and is not dependent on the patient's arterial blood pressure.[69] Other continuous techniques that use patient blood pressure as the basis for flow through the system also may have application here.[164] Traditional intermittent hemodialysis offers clearance

rates that vary between 50 and 170 mL/min.[20,22,89,122,125,164] Although CRRT techniques offer lower clearance per hour than does intermittent hemodialysis, their overall daily clearances are similar.[20,89] With continued improvements in techniques, use of high volumes, and high dialysate flow rates, clearances are improving, approaching more than half the clearance per hour achieved by intermittent hemodialysis in some studies.[20,69,89,164] Although one case of a rebound phenomenon in a patient treated with continuous arteriovenous hemodiafiltration is reported,[22] no cases with use of venovenous techniques are reported, offering a clear advantage over intermittent hemodialysis. Unfortunately, CRRT requires prolonged anticoagulation with its inherent risks. Nevertheless, these techniques may be beneficial in patients who are hemodynamically unstable, or they can be used in series with traditional dialysis in other patients to prevent redistribution of lithium and rebound of serum concentrations.

Peritoneal dialysis (PD) has been recommended in the past but offers no increased efficacy in clearance of lithium ion over the natural clearance of normal kidneys.[11,69,76,136] Given the infrequent use of this technique and its potential for serious

complications (eg, bowel perforation), PD should not be used in the management of the lithium-poisoned patient.

Summary

Lithium is a simple ion with extremely varied and complex clinical and pathophysiologic effects. It is available in multiple formulations, both immediate-release and sustained-release. Lithium remains an essential part of the pharmacologic arsenal of clinical psychiatry. Because of the complexity of lithium's pharmacokinetic profile, toxicity can develop in a wide range of conditions and can be precipitated by both intentional overdose and therapeutic misadventure. The care of the lithium-poisoned patient should be predicated on rapid identification of the poisoning, followed by management that includes use of volume resuscitation and, when indicated, WBI and hemodialysis or other extracorporal techniques to prevent or treat severe neurologic morbidity and to prevent mortality.

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Chapter 69
Monoamine Oxidase Inhibitors

Lada Kokan

A 50-year-old man with a history of hypertension and depression was found face down on the floor in his home. He was last known to be well 24 hours before arrival of Emergency Medical Services (EMS). A medication list was found and listed clomipramine, tranylcypromine, olanzapine, rosuvastatin, and hydrochlorothiazide. EMS described the patient as nonverbal and diaphoretic but breathing spontaneously. He had mottled skin and involuntary movements of the right arm.

In the emergency department, the patient's vital signs were: blood pressure, 160/130 mm Hg; pulse, 120 beats/min; respiratory rate, 30 breaths/min; rectal temperature, 106.8Â°F (41.6Â°C). On physical examination, the patient was noncommunicative, incontinent of urine, and had shaking movements of his entire body. His pupils were 5 mm and sluggishly reactive bilaterally. Pulmonary, cardiac, and abdominal examinations were unremarkable. His neurologic examination revealed that all four extremities were stiff with neither cogwheel nor lead pipe rigidity

and reflexes that were 2+ in the upper extremities and 1+ in the lower extremities.

Rapid-sequence intubation was immediately performed, for which the patient was given benzodiazepines and neuromuscular blockers. A 500-mL intravenous bolus of 0.9% sodium chloride solution was empirically administered, and the patient was cooled in an ice bath until his temperature was 101Â°F (38.3Â°C).

The initial laboratory results were notable for the following: white blood cell (WBC) count, 14,000/mm^3 ; hemoglobin, 15 g/100 mL; sodium, 163 mEq/L; potassium, 4.6 mEq/L; chloride, 116 mEq/L; HCO^-_3 , 24 mEq/L; blood urea nitrogen (BUN), 69 mg/dL; creatinine, 4.6 mg/dL; glucose, 56 mg/dL. Creatinine kinase concentration was 13,000 U/L, hepatic aminotransferases were normal, and blood ethanol concentration was negative. An arterial blood gas prior to intubation while the patient was being ventilated with a bag-valve-mask on 100% oxygen showed: pH, 7.25; PCO_2 , 45 mm Hg; PO_2 , 127 mm Hg; lactate, 2.9 mmol/L. Initial urinalysis revealed light-red color with 100 red blood cells per high-power field (RBC/HPF) but no WBCs, leukocyte esterase, or nitrates. The cerebrospinal fluid obtained by lumbar puncture was normal. A propofol infusion was started, and cyproheptadine 6 mg was administered via a nasogastric tube.

After resuscitation, additional information regarding the patient's history was obtained from the psychiatrist. The patient had been taking olanzapine 20 mg daily and clomipramine 300 mg daily for an unspecified period. Tranylcypromine had successfully treated his depression in the past but it had been discontinued. However, because he continued to suffer from depression while on the olanzapine and clomipramine regimen, tranylcypromine was restarted 3 weeks prior to presentation. Approximately 1 week prior to presentation, his tranylcypromine dose was increased from 20 to 30 mg daily, and the clomipramine dose was lowered from 300 to 250 mg daily. Shortly after the dose change, he began to

experience palpitations and diaphoresis for which his psychiatrist prescribed terazosin. However, the terazosin was discontinued when the patient developed orthostatic hypotension.

During his hospital stay, the patient remained intubated for 6 days. His creatinine kinase concentrations continued to rise and peaked at 200,000 U/L, whereas his creatinine concentration dropped steadily. Both values normalized by the time of his discharge 8 days later. The patient was taking no antidepressants upon discharge, but his psychiatrist planned to restart tranylcypromine as monotherapy.

History and Epidemiology

The monoamine oxidase inhibitors (MAOIs) were first used in the early 1950s to treat tuberculosis and hypertension. Once their mood-elevating properties were recognized, they were prescribed for the treatment of depression.[3,4] Despite their effectiveness, the use of MAOIs was limited by their potential food and drug interactions and by their toxicity in overdose. As a result, the MAOIs were largely replaced by tricyclic antidepressants during the 1970s. In the 1980s, there was a resurgence of MAOI use for treatment of refractory depression, phobias, and anxiety disorders.[10] Use of MAOIs again declined following the appearance of less toxic antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs). Currently, patients are carefully selected for MAOI therapy based on strict clinical needs and their ability to comply with the rigorous dietary restrictions.[18]

In an attempt to decrease the problems associated with the first generation of MAOIs, drugs selective for the MAOI subtypes were explored. The monoamine oxidase type B (MAO-B) selective drugs, such as selegiline, are used for treatment of Parkinson disease but do not have antidepressant effects. The monoamine oxidase type A (MAO-A) selective drug clorgyline is an effective antidepressant but is associated with the same food and drug interactions as the

first-generation MAOIs. The third-generation MAOIs are both selective and reversible inhibitors of MAO-A (RIMA). The best studied drug of the third-generation MAOIs is moclobemide, which now is being used for an expanded range of indications, including depression, the phobias, anxiety disorders, obsessive-compulsive disorder, and posttraumatic stress disorder.[64]

In 2003, only 2 fatalities from MAOIs were reported to the American Association of Poison Control Centers (Chap. 130). MAOIs were involved in 0.3% of reported exposures to antidepressants and 0.7% of all reported antidepressant-related deaths. For comparison, SSRIs were involved in 55.3% of reported exposures to antidepressants and 38.7% of reported antidepressant-related deaths, whereas cyclic antidepressants were involved in 12.3% of reported exposures to antidepressants and 29.6% of reported antidepressant-related deaths. Thus, the ratio of deaths to exposures (by percent) attributed to each category of antidepressants is almost identical for MAOIs and cyclic antidepressants but approximately 3 times less for SSRIs.

Pharmacology

Monoamines, also known as *biogenic amines* , are a group of neurotransmitters, including norepinephrine, dopamine, and serotonin, that have in common the presence of a single amine group and metabolism by MAO. MAO is a flavin-containing enzyme present on the outer mitochondrial membrane of central nervous system (CNS) neurons, hepatocytes, and platelets. In a 2-step reaction, MAO catalyzes the oxidative deamination of its various substrates. Importantly, the reaction liberates $H_2 O_2$, a reactive oxygen species that is associated with neurodegenerative diseases, including Parkinson disease.

Two isoforms of MAO are differentiated by their anatomical location and substrate specificity (Table 69-1). MAO-A is located

primarily in cells of the gastrointestinal tract, including the liver, and in serotonergic neurons of the locus caeruleus.[52] Gastrointestinal MAO-A reduces the bioavailability of ingested serotonin, tyramine, and other biogenic amines. Circulating monoamines are inactivated in the liver. MAO-B is found primarily in the dopaminergic raphe neurons of the CNS and in platelets.[52] This substrate specificity explains the use of MAO-A inhibitors as antidepressants and MAO-B inhibitors for treatment of Parkinson disease. Certain xenobiotics are substrates for both MAO subtypes, including tyramine, dopamine, octopamine, and tryptamine.[63]

MAO degradation of monoamines helps regulate presynaptic neurotransmitter stores in the nerve terminal. Therefore, inhibition of MAO prevents presynaptic degradation of monoamines, ultimately resulting in increased neuronal release of monoamines (Figure 69-1). Elevated synaptic concentration of serotonin most closely is correlated with the antidepressant effects of MAOIs. As with other antidepressants, the enzymatic inhibitions produced by MAOIs precede their clinical effects by as long as 2 weeks. The reason for this finding is not well characterized but may relate to a time requirement for downregulation of postsynaptic CNS serotonin receptors.[48] The antidepressant activity of MAOIs is correlated with a greater than 85% inhibition of platelet MAO enzymatic activity, and the effect continues to rise linearly above this level of inhibition.[20 , 23]

MAOIs are a chemically heterogeneous group of drugs (Figure 69-2). Iproniazid, the original MAOI, is a derivative of hydrazine, as are the currently available agents phenelzine and isocarboxazid. As with other hydrazine derivatives, seizures are expected after overdose. Tranylcypromine is structurally an amphetamine derivative. As with other amphetamines, release of stored presynaptic neurotransmitter occurs following therapeutic dosing and with overdose, resulting in varying degrees of autonomic hyperactivity.[36]

The first-generation MAOIs, including phenelzine, isocarboxazid, and tranylcypromine, are nonselective inhibitors of both MAO-A and MAO-B. Therefore, patients taking these drugs must be placed on a restrictive diet to prevent adverse events resulting from the ingestion of tyramine. These first-generation MAOIs bind covalently to MAO and irreversibly inhibit the enzyme's function. Thus, patients taking these MAOIs are depleted of the enzyme until new MAO is synthesized, a process that takes up to 2 weeks. Patients taking first-generation MAOIs remain at risk for food and drug interactions during much of this period.

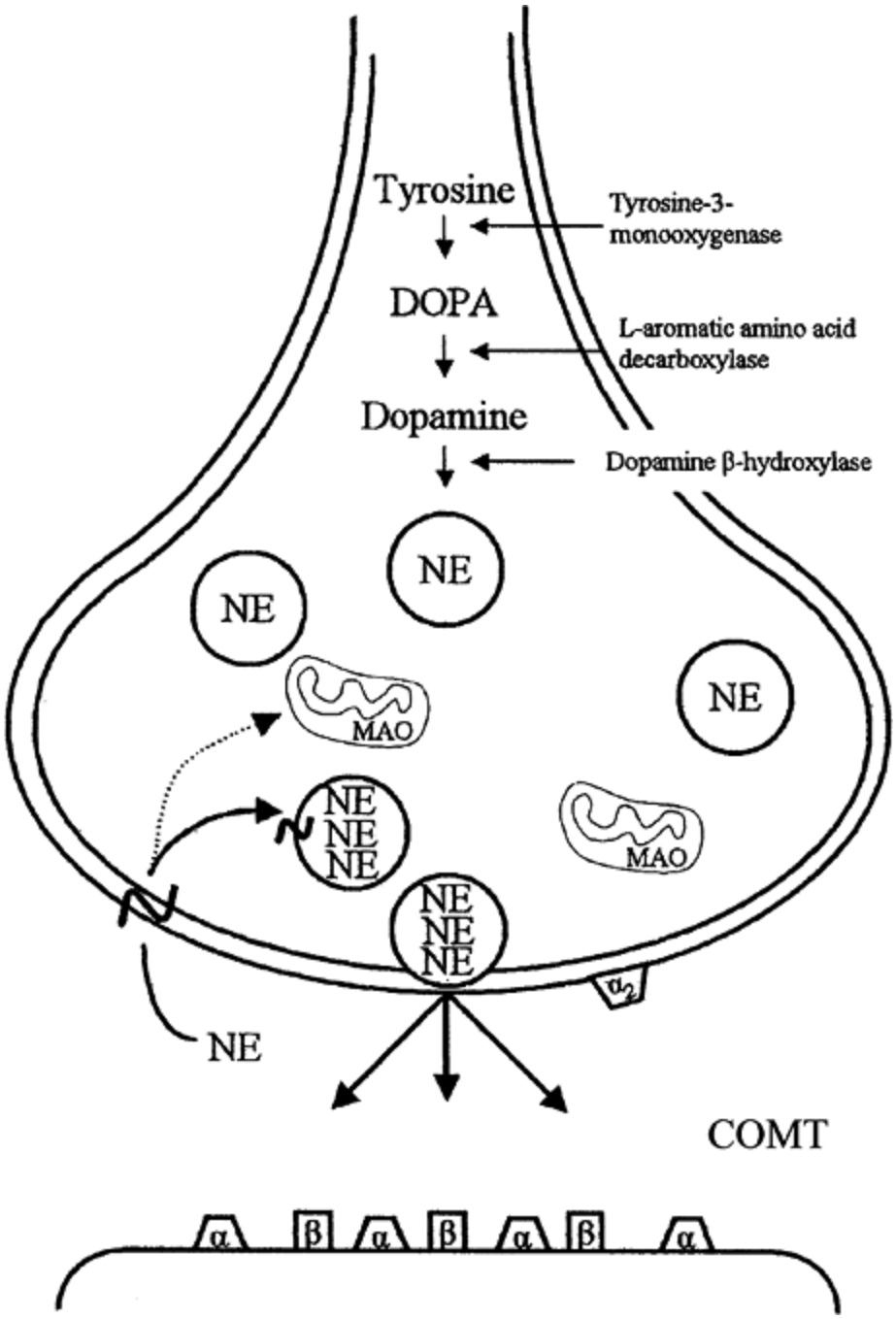

Figure 69-1. Sympathetic nerve terminal. Norepinephrine (NE) is synthesized in the sympathetic nerve cell and stored in vesicles. An action potential causes the vesicles to migrate to and fuse with the presynaptic membrane. NE diffuses across the synaptic cleft and binds with and activates postsynaptic Î±- and Î²-adrenergic receptors. NE then is taken back up into the neuron by the

monoamine reuptake pump and repackaged into vesicles. NE that is taken up by the neuron but escapes repackaging is inactivated by mitochondrial monoamine oxidase (MAO). NE that diffuses away from the synaptic cleft is inactivated by catechol-*O* -methyl transferase (COMT).

Selegiline (deprenyl) is an irreversible inhibitor of MAO-B when used at doses <20 mg/d; above this dose MAOI selectivity is lost. The specificity of MAO-B for dopamine explains the use of selegiline for treatment of Parkinson disease. Approximately 75% of MAO activity in the basal ganglia results from MAO-B.[52 , 66] Selegiline has no antidepressant activity.

Moclobemide, an RIMA, is readily metabolized by MAO, so full MAO function can resume just hours after exposure.[13] Because the enzyme is bound competitively, patients taking moclobemide can still metabolize some ingested monoamines and other drugs.[21]

Another medication with weak MAOI activity is procarbazine, an antitumor agent used for Hodgkin disease. The antibiotic linezolid also has MAOI activity, and patients taking it are placed on a

tyramine-restricted diet.[19 , 7] The plant extract St. John's wort (*Hypericum perforatum*) is licensed in Germany for use as an antidepressant. Although St. John's wort has some weak MAO-inhibiting activity, whether this activity is responsible for its antidepressant effect is debatable. However, it may be the cause of the hypertensive crises, cardiovascular collapse during anesthesia, and serotonin syndrome reported with use of this herbal medication.[32]

Substrate (preferred)
Serotonin
Epinephrine
Norepinephrine

Metanephrine
Benzylamine
Phenylethylamine
Tyramine
Î²-Phenylethylamine
Tryptamine
Dopamine
Octopamine
Location
Gastrointestinal
Liver
Exocrine pancreas
Monoaminergic neurons
Brain
Platelets
Pancreatic islets
Serotonergic neurons
Inhibitor
  Irreversible
Clorgyline
Selegiline[a]
Pargyline
Tranylcypromine[a]
Phenelzine[a]
Isocarboxazid[a]
Procarbazine[a]
  Reversible
Moclobemide
Brofaromine
Cimoxatone
Toloxatone
Harmaline
Befloxatone
Lazabemide

[a] Currently available in the United States.

MAO-A MAO-B MAO-A and MAO-B

TABLE 69-1. Comparison of Substrate Specificity, Distribution, and Inhibitors of Monamine Oxidase

The hallucinogenic beverage Ayahuasca used by South American natives is an intriguing ethnobotanical solution to the â€œproblemâ€• of gastrointestinal MAO. Dimethyltryptamine, which is derived from several local plant species, is a potent hallucinogen that is not orally bioavailable because of its first-pass metabolism by MAO. *Banisteriopsis caapi* , a plant containing the MAO inhibiting harmine alkaloids, is mixed with dimethyltryptamine-containing plants to improve the bioavailability of this hallucinogenic amine.[41 , 42]

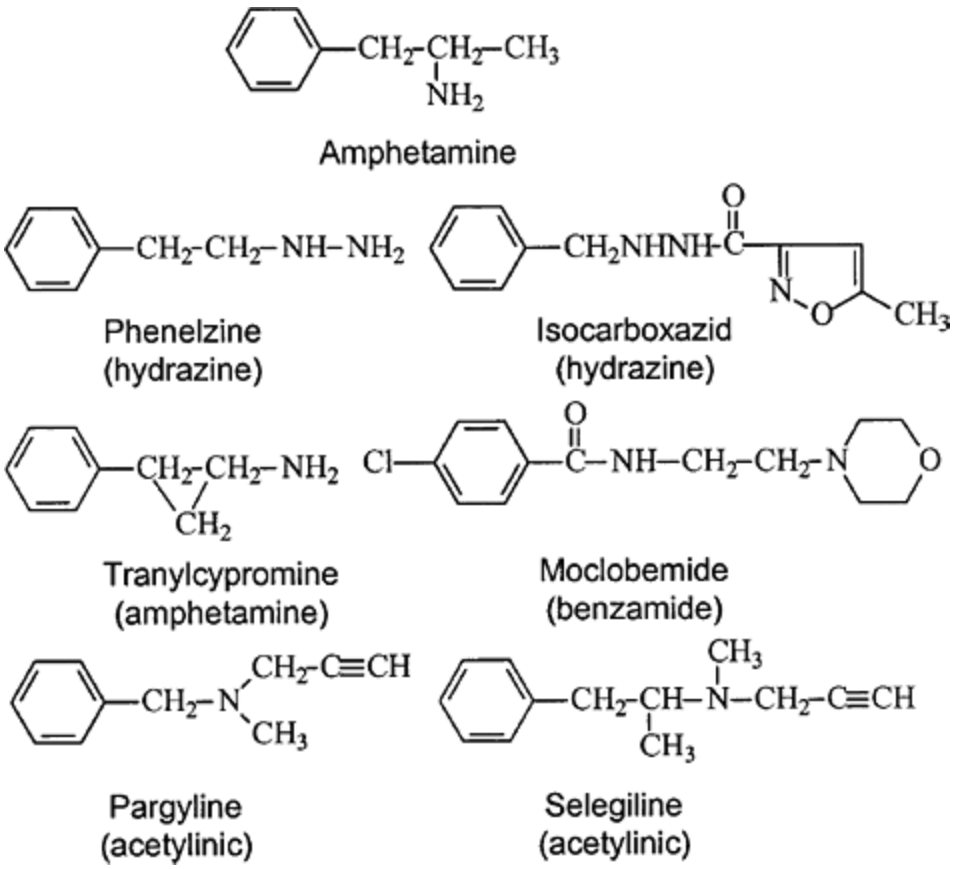

Figure 69-2. Structural similarities between amphetamine and the monoamine oxidase inhibitors.

MAO-B activity in tobacco plants has prompted studies to find a link between the lower platelet MAO-B activity of smokers and the lower rate of Parkinson disease in this group.[9] Selegiline prevents experimentally induced (by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine/methylphenyltetrahydropyridine [MPTP]) Parkinson syndrome in animal models.[53] This has lead to interest in studying selegiline and other MAO-B inhibitors as neuroprotective agents.

Other enzyme systems inhibited by MAOIs include amine oxidases such as diamine oxidase and semicarbazide-sensitive oxidases, arylamine *N* -acetyltransferase (by tranylcypromine), ceruloplasmin, alcohol dehydrogenase (by tranylcypromine), dopa

decarboxylase, L-glutamic acid decarboxylase, Î³-aminobutyric acid (GABA) decarboxylase and GABA transaminase (by hydrazine MAOIs), alanine aminotransferase (by phenelzine) and other pyridoxine (B_6)-containing enzyme systems.[30] The clinical implications of inhibiting these diverse enzyme systems, other than cytochrome P450, are poorly understood.

Pharmacokinetics and Toxicokinetics

MAOIs are well absorbed orally, and peak plasma concentrations are reached within 2â€“3 hours. MAOIs are hepatically metabolized by both oxidation and acetylation, and the metabolites are excreted in the urine.[3] The rate of phenelzine metabolism is dependent upon the *N* -acetyltransferase phenotype (ie, â€œacetylator statusâ€•) of the patient (ie, fast or slow). However, there is no correlation between

acetylator status and adverse effects of the drug. Moclobemide is metabolized by CYP2C19 to an array of oxidized metabolites that are generally inactive.

The therapeutic and toxic effects of MAOIs lag behind their absorption and excretion characteristics. The irreversible agents have durations of effect that far surpass their pharmacologic half-lives. Thus, when switching from 1 serotonergic agent (ie, MAOI, SSRI, tricyclic antidepressant), a sufficient â€œwashoutâ€• period must be allowed to prevent an adverse drug interaction. This period typically is several weeks, although some psychiatrists advocate cautious rapid conversion.[56]

Monoamine Oxidase Inhibitor Overdose

Significant morbidity and a high mortality are characteristic of patients who overdose with the irreversible, nonselective MAOIs. Mortality is reported from acute ingestions of as little as

170â€“680 mg tranylcypromine (typical daily dose 20â€“30 mg) and 375â€“1500 mg phenelzine (typical daily dose 60â€–90 mg).[58]

A delay in the onset of clinical effects of up to 32 hours following overdose is reported, but effects generally occur by 24 hours.[39] Overdose from irreversible MAOIs is characterized by a spectrum of sympathetic hyperactivity that is followed by cardiovascular collapse in severe cases. In a limited or early phase following overdose, patients typically have irritability, anxiety, flushing, diaphoresis, and tachycardia, and they may complain of a headache. Characteristic clinical findings of severe overdose include hyperthermia, hypertonia, seizures, and marked hypertension. Blood pressure may be normal initially but fluctuates markedly in severe overdose, with severe hypertension followed by hypotension and cardiovascular collapse. Dysrhythmias, marked hyperthermia, obtundation, and disseminated intravascular coagulopathy ensue as multiorgan failure occurs. Other symptoms may include tachypnea, nystagmus, mydriasis, opsoclonus (alternating â€œping-pongâ€• gaze), hallucinations, trismus, neuromuscular irritability, agitation, and delirium.[16, 39]

These effects are attributed to the same elevation of monoaminergic neurotransmitter levels and amphetaminelike activity that confers antidepressant activity to the MAOIs.[36] Thus, presynaptic monoamines are released, stimulating postsynaptic adrenergic and serotonergic receptors and initiating a multiorgan sympathetic response.

Secondary problems resulting from CNS and autonomic hyperactivity may include rhabdomyolysis, renal failure, myocardial infarction, dehydration, intracranial hemorrhage, and ischemia (Chap. 16).

In contrast, moclobemide has a much greater therapeutic index than the irreversible MAOIs. Thus, overdose with moclobemide often results in a relatively benign course if no other xenobiotics are ingested.[31, 43] Ingestion of <8000 mg (or 25 times the

therapeutic dose of moclobemide) typically results in mild or no symptoms (typical daily dose 150â€“600 mg). At lower doses, only fatigue, agitation, tachycardia, and hypertension are noted. No delayed reactions are reported after moclobemide overdose. Despite 1 case in which only 15 tablets reportedly were taken,[22] most deaths from moclobemide overdose also involve coingestion of xenobiotics capable of inducing the serotonin syndrome.[24, 49, 59]

Treatment of patients with MAOI overdose should focus on emergency treatment of the airway, followed by stabilization of blood pressure and assessment for and treatment of hyperthermia, seizures, and muscular rigidity. Patients who overdose with first-generation MAOIs are more likely to benefit from aggressive gastrointestinal decontamination (including orogastric lavage and activated charcoal 1 g/kg) than most other overdose patients because of their high potential for mortality. The lack of early clinical findings of poisoning should not dissuade the use of aggressive gastrointestinal decontamination given the potential for delayed clinical deterioration.

Because fluctuating vital signs are characteristic of MAOI overdose, hemodynamic monitoring should be instituted even for patients who initially are stable. When supporting the patient's vital signs, preference should be given to titratable drugs with a rapid onset and termination of action because of the potential for rapid hemodynamic changes. Sodium nitroprusside and nitroglycerin are best used to treat hypertension because they can be rapidly stopped if hypotension develops. The short-acting Î±-adrenergic antagonist phentolamine given at 2â€“5 mg IV can effectively control hypertension. Use of Î²-adrenergic antagonists is contraindicated for control of hypertension in this setting because of the potential for unopposed Î±-adrenergic mediated vasoconstriction, which could exacerbate hypertension.

Dopamine is not an acceptable agent of choice for hypotension

because its pressor effects are indirect and rely on catecholamine release from sympathetic neurons. Norepinephrine is preferred because it is a direct-acting agent and often is successful when dopamine fails, presumably secondary to catecholamine depletion.

Hyperthermia must be treated aggressively (Chap. 16). Use of ice baths, cold water, and fans are the mainstay of treatment. Benzodiazepines help control muscular rigidity, seizures, and agitation that may be contributing to hyperthermia and tachycardia. Neuromuscular blockade using nondepolarizing xenobiotics is essential for controlling rigidity and hyperthermia if first-line treatment is unsuccessful. Case reports of cyproheptadine added to this standard therapy describe resolution of neuromuscular rigidity and hyperthermia associated with MAOI overdose[4 , 16] (see Serotonin Syndrome).

Seizures should be treated with benzodiazepines (eg, diazepam) in incremental doses. Hypoglycemia should be excluded. Pyridoxine (vitamin B_6) should be empirically administered to patients with refractory seizures, particularly those who ingest a hydrazine-derived MAOI, in an effort to replete GABA stores (Chap. 55 and Antidotes in Depth: Pyridoxine).

All patients with presumed MAOI overdose must be monitored and observed in an intensive care unit for at least 24 hours regardless of the clinical findings because of the potential for delayed toxicity.

Serotonin Syndrome

The serotonin syndrome, more recently suggested to be better termed *serotonin toxicity* ,[15] is a potentially life-threatening complication of antidepressant drug therapy. It often is unrecognized because of its subtle and nonspecific symptomatology. The clinical findings of the serotonin syndrome include autonomic excitation, altered mental status, and increased

neuromuscular tone (Chap. 70). The differential diagnosis typically includes neuroleptic malignant syndrome, malignant hyperthermia, encephalitis, and thyroid storm. However, because no diagnostic test is available, the correct diagnosis of serotonin syndrome must be made on clinical grounds. Several diagnostic schemes exist,[15 , 27 , 47 , 55] but the key diagnostic criteria is the biologic plausibility, that is, the necessity that the patient was exposed to xenobiotic likely to produce serotonin excess in the CNS.

The syndrome is produced most often by concurrent use of 2 or more xenobiotics that increase CNS serotonin activity.[54] All types of MAOIs have been implicated, including the herbal medication St. John's wort.[32] Reports of serotonin syndrome following the combination of a MAOI with any of a number of commonly available prescription (tricyclic antidepressants, SSRIs, meperidine) or nonprescription (dextromethorphan) medications are widespread. The long duration of effect of the irreversible MAOIs explains the prolonged duration of risk for development of the syndrome following discontinuation of the medication. Thus, a washout period of at least 2 weeks is recommended before SSRI therapy is initiated in a patient who has stopped taking a first-generation MAOI.[5]

A washout period is less important with use of moclobemide because the MAOI inhibition with this xenobiotic is reversible within hours.[14] Although moclobemide and the other reversible MAOIs appear to be safer to combine with SSRIs than the older MAOIs,[29] serotonin syndrome following the combination of moclobemide and an SSRI is reported.[31 , 44] However, few fatalities are reported, and the syndromes often are mild.

Treatment of the serotonin syndrome is supportive and focuses on correcting the consequential clinical abnormalities. Hyperthermia is managed with benzodiazepines for sedation and aggressive

cooling measures; nondepolarizing neuromuscular blockade may be required if cooling is insufficient with these methods. Cyproheptadine, a clinically available serotonin receptor antagonist, prevents lethality in animal models of serotonin syndrome[45] and reportedly is beneficial in humans with serotonin syndrome.[26 , 37] It should be strongly considered when the diagnosis of serotonin syndrome is likely. The dose of 4â€“8 mg must be administered orally or by nasogastric tube. Use of dantrolene in patients with serotonin syndrome reportedly is beneficial.[35] Dantrolene is indicated for treatment of malignant hyperthermia, a disease generally considered to be unrelated to serotonin syndrome even though they share certain clinical features. However, because the pathogenesis of the 2 syndromes appear to be related,[61] use of dantrolene for treatment of the serotonin syndrome should be investigated although it cannot be supported at this time.

Hypertensive Crisis Resulting from Food and Drugs

Indirect-acting sympathomimetic agents (eg, tyramine and amphetamine) have a chemical structure and mechanism of action similar to the catecholamines. Like the catecholamines, they are taken up into presynaptic sympathetic nerve terminals and subsequently are moved into storage vesicles. Once in the vesicles, they buffer the pH, causing the stored norepinephrine to be released and transported in a reverse fashion into the synapse (Figure 69-1). In patients taking MAOIs, the decreased norepinephrine degradation increases presynaptic norepinephrine stores. Thus, an indirect-acting sympathetic agent that triggers norepinephrine release may cause a hyperadrenergic syndrome, with supranormal amounts of stored norepinephrine being released into the synapse to stimulate postsynaptic Î±- and Î²-adrenergic receptors. Direct-acting sympathetic agents (eg, epinephrine,

norepinephrine, and isoproterenol) can be used safely in patients taking MAOIs.[7] Rather than causing release of a stored pool of norepinephrine, these agents bind directly with postsynaptic Î±- and Î²-adrenergic receptors. Direct-acting and parenterally administered adrenergic agents are primarily cleared by cell reuptake and catechol-*O* -methyltransferase (COMT), a synaptic enzyme that is not inhibited by MAOIs.

Protein-rich foods are particularly likely to contain decarboxylating bacteria that convert amino acids into pharmacologically active monoamines, such as tyramine.[60] These monoamines normally are degraded by gastrointestinal and hepatic MAO-A before they enter the systemic circulation. However, with inhibition of the hepatic and gastrointestinal MAO, large quantities of monoamines may be absorbed into the systemic circulation. Food interactions occur when pharmacologically active dietary monoamines (eg, tyramine) are ingested by patients taking most MAOIs[40] (Table 69-2). Because this is historically closely associated with ingestion of certain cheeses, it is sometimes called a *cheese reaction.* Similarly, because the etiology of the syndrome is not limited to tyramine but may be caused by other indirectly acting sympathomimetic agents (eg, ephedrine from cold preparations), sometimes it is simply described as a *hypertensive reaction.* Unprovoked hypertensive reactions may occur in patients receiving MAOIs and are not well understood.[38]

Findings typically include hypertension and tachycardia. Headache, altered mental status, intracranial hemorrhage, myocardial ischemia, and seizures may be secondary sequelae of uncontrolled hypertension. Ingestion of as little as 6 mg tyramine may result in a significant vasopressor effect in MAO-inhibited patients.[60] This dose is 1â€“10% of the amount normally needed to achieve a vasopressor effect. Because the development of tyramine reaction requires inhibition of gastrointestinal MAO-A, it can be avoided by MAO-B selective inhibitors such as selegiline and limited by reversible MAOIs such as moclobemide.[5 , 62 , 66] However,

because the presynaptic quantity of norepinephrine is also increased in patients who take MAO-B selective inhibitors, parenteral administration of an indirect-acting catecholamine may produce a dramatic pressor response, even with selegiline.[50] A tyramine reaction associated with St. John's wort is reported.[46]

Because both the absorbed and the liberated monoamines have a short half-life, the clinical effects have a rapid onset and typically abate within several hours. However, as with the serotonin syndrome, the potential for a hypertensive reaction to tyramine or another indirect-acting catecholamine may last up to several weeks following the last dose of MAOI.[5] Interestingly, some psychiatrists advocate the combination of amphetamine-derived stimulant drugs

with MAOIs for treatment of patients with refractory depression or intolerable MAOI related side effects, such as orthostasis.[17]

High tyramine content
- Aged, mature cheeses (65â€“1500 mg/kg)
- Smoked, pickled, aged, putrefying meats or fish (0â€“470 mg/kg)
- Yeast and meat extracts (65â€“2250 mg/kg)
- Red wines (1.5â€“12 mg/kg)
- Broad beans

Moderate tyramine content
- Meat extracts (100â€“300 mg/kg)
- Pasteurized light and pale beers
- Avocados

Low tyramine content
- Distilled alcohol
- Cottage cheese, cream cheese
- Sour cream
- Chocolate, caffeine-containing beverages
- Fruit

Soy sauce
Yogurt

Patients should avoid high tyramine content meals, eat small quantities of meals containing moderate amounts of tyramine, and may eat foods low in tyramine content.

TABLE 69-2. Dietary Restrictions for Patients Taking MAOIs

Onset of toxicity
Clinical findings
Minutesâ€“hours
Hypertension
Hypotension
Hyperthermia
Muscular rigidity
Disorientation
Shivering
Seizures
Restlessness
Tremor
Death
Minutesâ€“hours
Hypertension Â± sequelae
Tachycardia
Bradycardia
Headache
Flushing
Seizures
Up to 32 hours
Hypertension or hypotension
Diaphoresis
Neuromuscular hyperactivity
Obtundation

Seizures
Death
Duration of toxicity
Hours
Hours
Days

	Interaction	
	Serotonin Syndrome	Hypertensive Crisis	MAOI Overdose

TABLE 69-3. Comparison of MAOI-Related Reactions

Normotensive patients who experience severe hypertension after drug or dietary interactions can be treated with an Î±-adrenergic antagonist such as phentolamine 2â€“5 mg IV. Again, titratable drugs such as nitroprusside and phentolamine are best because they allow controlled lowering of the blood pressure.[12] The dihydropyridine calcium channel blockers (eg, nifedipine) and possibly the oral Î±-adrenergic antagonists (eg, terazosin) can successfully control the hypertensive crisis but should be used carefully.[11 , 28] Particular caution must be exercised in patients with baseline hypertension because overly aggressive blood pressure lowering may reduce cerebral perfusion pressure sufficiently to cause ischemia.

Treatment of individual symptoms in patients with MAOIâ€“food or MAOIâ€“drug interactions is similar to the symptomatic and supportive care described for MAOI overdose. However, patients with MAOIâ€“food or MAOIâ€“drug interactions may not require hospital admission if the interaction is mild, resolution of symptoms is complete, and the patient can be observed for 4â€“8 hours. Patients who develop an altered mental status, seizures, or other end-organ damage must undergo appropriate diagnostic

studies and be managed accordingly.

Table 69-3 compares the characteristics of MAOI overdose with symptoms following interactions of MAOIs with foods and indirect-acting sympathomimetic agents. Interactions with sympathomimetic xenobiotics are predictable and may occur when a patient taking an MAOI also takes one of the several types of xenobiotics mentioned in Table 69-4 .

Other Adverse Drug Events

Several other types of adverse reactions can occur in patients taking MAOIs. Hepatotoxicity from the first generation of hydrazine MAOIs is an infrequent but serious event that led to the discontinuation of iproniazid as an antidepressant.[6] Peripheral neuropathy from vitamin B_6 depletion by the hydrazine-derived MAOIs can occur.[25]

Animal studies and human reports describe a potentiation of the hypoglycemic effects of insulin and sulfonylureas in the presence of MAO inhibition.[8] MAOIs, including selegiline, are insulin secretogogues.[51]

Selegiline

Selegiline overdose is not reported, and the clinical consequences of such an event are unpredictable. Selegiline is metabolized to L-methamphetamine, which may result in hypertension and tachycardia, even at therapeutic doses.[1] Patients taking selegiline may test positive for amphetamines on routine drug-abuse screens. Increased rates of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations are noted with therapeutic use of selegiline. Although rare, an increase in the incidence of cardiac dysrhythmias is reported with selegiline use. Interactions with foods and cold medications are limited, but caution should be exercised.[33] Transdermal administration of

selegiline may actually allow antidepressant effectiveness without the need for dietary restrictions,[2] that is, administration by this route allows delivery to the CNS of a dose sufficient to inhibit MAO-A while avoiding significant inhibition of gastrointestinal MAO. This promising route

of selegiline administration is pending FDA approval before it becomes available. Rasagiline is another irreversible MAO-B selective inhibitor that slows the progression of symptoms in patients with Parkinson disease.[65] However, unlike selegiline it is not metabolized to methamphetamine and may be better tolerated.

Indirect acting
- Amphetamine
- Cocaine
- Hydroxyamphetamine
- Benzphetamine
- Ritodrine
- Methamphetamine
- Methylphenidate
- Phenylpropanolamine
- Fenfluramine
- Pemoline
- Phencyclidine
- Propylhexedrine
- Phentermine
- Tyramine

Direct acting
- Albuterol
- Dobutamine
- Epinephrine
- Ergots
- Norepinephrine
- Isoetharine

- Isoproterenol
- Ethylnorepinephrine
- Isoproterenol
- Metaproterenol
- Methoxamine
- Phenylephrine
- Ritodrine
- Terbutaline

Direct and indirect acting

- Dopamine
- Metaraminol
- Ephedrine
- Mephentermine
- Phenylpropanolamine
- Pseudoephedrine

TABLE 69-4. Sympathomimetic Xenobiotics

Summary

The complex pharmacology of MAOIs makes the first-generation irreversible MAOIs dangerous in overdose and results in a number of interactions that limit their use. As a result, the older MAOIs are largely being replaced by SSRIs and other antidepressants that have less potential for food and drug interactions. In contrast, the newer, reversible MAOIs offer a significant advance in therapy because they are much safer and far less limiting. The serotonin syndrome includes altered mental status and autonomic instability that develop in patients who, among other things, combine MAOIs with other serotonergic xenobiotics. A hypertensive reaction develops from the combination of MAOIs with indirect-acting pressors, classically tyramine from various foods and ephedrine from cold preparations. Newer indications for MAOI administration, such as anxiety and phobias, are broadening the popularity of this

class of xenobiotics.

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Chapter 70

Serotonin Reuptake Inhibitors and A Antidepressants

Christine M. Stork

A 36-year-old woman presented to the emergency department 36 hours a intentional ingestion of 1000 mg citalopram. She complained of palpitatio numbness in her arms. Her medical history was significant for bulimia, a abuse, and suicide attempts. In the emergency department, her vital sign pressure, 84/44 mm Hg; pulse, 102â€“160 beats/min; respiratory rate, temperature 99.3Â°F (37Â°C). ECG revealed ventricular bigeminy with a C msec (Figure 70-1A). High-flow oxygen and 2 g intravenous magnesium administered. When she developed ventricular tachycardia, a lidocaine bol were instituted. Torsades de pointes developed (Figure 70-1B). Treatme potassium chloride and potassium phosphate for hypokalemia and a tran pacemaker. Twenty-four hours later, her ECG showed normal sinus rhythm 529 msec (Figure 70-1C). At 48 hours, the QTc narrowed to 442 msec. concentration was 477 ng/mL (therapeutic 40â€“110 ng/mL,) and the didesmethylcitalopram concentration was 123.2 ng/mL (therapeutic 14â€

History and Epidemiology

Most antidepressants inhibit serotonin and/or norepinephrine reuptake as achieve their therapeutic effect. The class of selective serotonin reuptake (SSRIs) includes citalopram, escitalopram (active enantiomer of citalopra fluvoxamine, paroxetine, and sertraline (Figure 70-2). Atypical antidepr past the pharmacologic principles of SSRIs and have other pharmacologic thought to be beneficial for patients with depression.

SSRIs initially were marketed in the United States in the early 1980s and considered a first-line therapy for treatment of depressive disorders.[119] S effective as the tricyclic antidepressants for treatment of major depressio less significant side effects[53] (Chap. 71). As such, they have become the prescribed class of medication for treatment of depression.[138 , 179] SSRIs to treat obsessive-compulsive disorders, panic disorder, alcoholism, obesi medical and psychologic disorders such as migraine headache and chronic syndromes.[52 , 124] The relative safety of the SSRIs when taken in overdo with cyclic antidepressants and monoamine oxidase inhibitors (MAOIs), al desirable.[55]

An increased risk of suicidal behavior is reported with the use of many a compared with nondrug therapy or no therapy.[5 , 109] The reason for this related to delayed onset of drug efficacy coupled with increased energy r initiation. The low fatality rate of SSRI overdose compared with cyclic a and MAOIs was demonstrated in a Swedish study of fatalities from 1994â Citalopram was the cause of only 1.4% of 358 overdose fatalities, even th the most frequently prescribed drug in 2000.[94]

Pharmacology

Table 70-1 lists the pharmacology, therapeutic doses, and metabolism of available SSRIs and other atypical antidepressants. Modulation of seroton norepinephrine neurotransmission has a definitive role in the treatment o depression.[145] The selectivity of SSRIs for serotonin reuptake is structura -trifluoromethyl or *p* -fluoro substitution, which is seen in many of these Serotonin neurons are located almost exclusively in the median raphe nuc

brainstem, where they extend into and are in close proximity to norepine that are located primarily in the locus caeruleus[7] (Figure 70-3). The inte norepinephrine and serotonin likely explains the effectiveness of other at antidepressants that do not directly modulate serotonin neurotransmissio

The exact etiology of depression and the mechanism by which increased and norepinephrine neurotransmission modulates mood remain unclear. S postulated causes of depression include decreased neuronal serotonin st decreased synaptic serotonin, increased serotonin receptor sensitivity, ar overactivity resulting in depressed dopamine neurotransmission.[145 , 164] According to the first theory, desensitization and downregulation of seroto somatodendritic and presynaptic inhibitory autoreceptors occur after exter SSRIs.[27] Ultimately this results in increased activity of raphe neurons, ir synthesis of serotonin, and increased release of serotonin. Unfortunately, in the concentration of serotonin binding sites is reported between depre who respond to SSRIs and those who do not respond.[153] In the second th potentiate the activity of neuronally released serotonin

at 5-HT_{2A} receptors and subsequently decrease the sensitivity of the ser receptor.[27] In depressed patients, these receptors are downregulated aft but no overall difference in receptor activity is observed between depress nondepressed populations. Finally, increased serotonergic activity, particu receptors, is theorized to result in antidepressant activity through reducti dopaminergic release.[187]

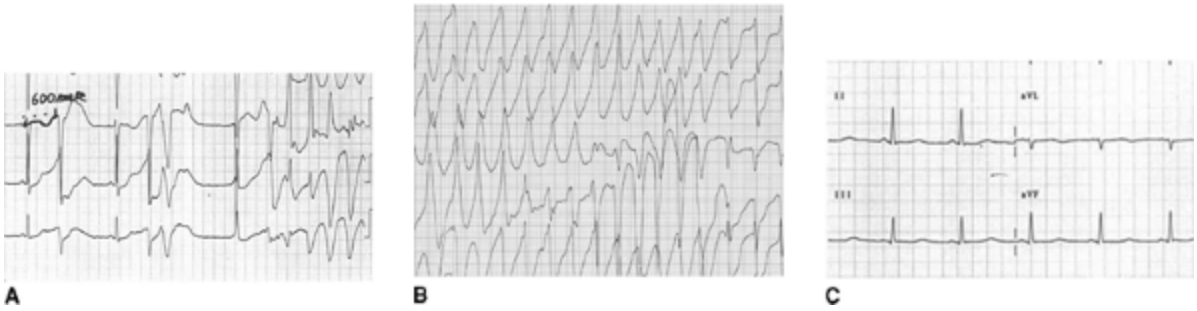


Figure 70-1. A. ECG showing bigeminy at point of transition to ventricu B. ECG demonstrating torsades de pointes. C. ECG following resolution of dysrhythmia showing persistent prolongation of the QTc interval.

Unlike tricyclic antidepressants and other atypical antidepressants, SSRIs direct interaction with cholinergic receptors, Î³-aminobutyric acid (GABA) sodium channels, or adrenergic reuptake (Table 70-2).

Pharmacokinetics and Toxicokinetics

The SSRIs display diverse elimination patterns and have numerous active which substantially increase both the duration of therapeutic effectiveness duration during which drug interactions and adverse drug effects can occu drug is discontinued (Table 70-1). Important pharmacokinetic and phar drug interactions are reported with therapeutic dosing (see Serotonin Sy SSRIs and their active metabolites are substrates for, and potent inhibito and other CYP isoenzymes.[73 , 144] For example, fluoxetine, fluvoxamine, venlafaxine, mirtazapine, paroxetine, and sertraline are substrates for C paroxetine, norfluoxetine, and fluoxetine inhibit the same isoenzyme[38] (T Alternatively, mirtazapine induces CPY3A4 isoenzymes, while trazodone r be decreased after this same enzyme is inhibited.[160 , 165] The consequenc interactions are manifest when the metabolism of xenobiotics that rely on isozymes for metabolic transformation is altered (Chap. 9).

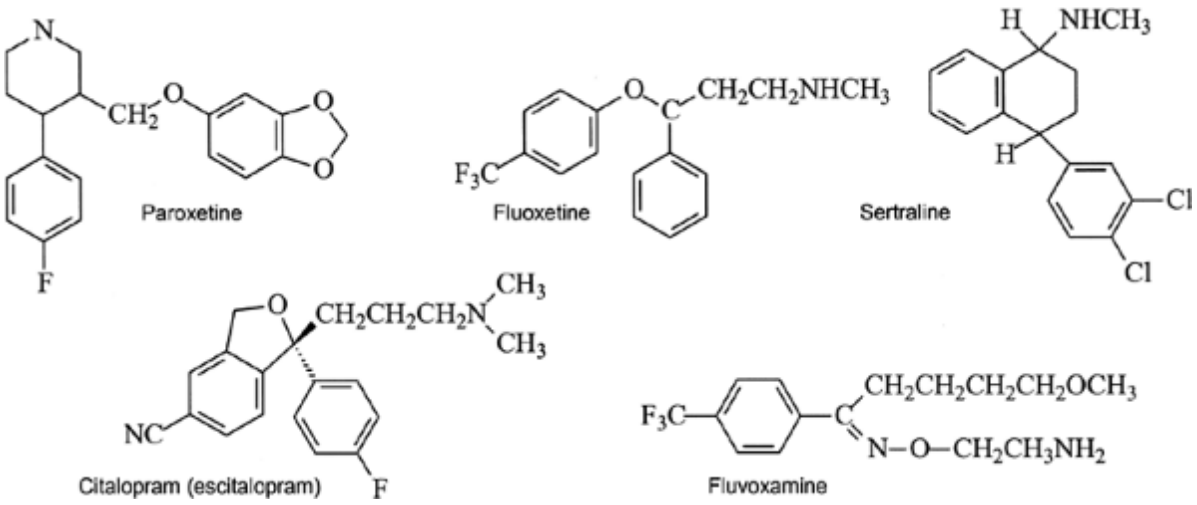


Figure 70-2. Structures of common selective serotonin reuptake inhibito is shown as the s-enantiomer (escitalopram).

Clinical manifestations

Acute Overdose

The majority of effects that occur following overdose are direct extensions pharmacologic activity of SSRIs in therapeutic doses. Excess serotonergic prominent and nonselective. Acute signs and symptoms include nausea, dizziness, blurred vision, and, less commonly, central nervous system (C and sinus tachycardia.[22 , 23] Seizures and QRS complex prolongation are rarely occur with most SSRIs, even after large overdoses[23 , 72 , 91] (Figur

Selective serotonin reuptake inhibitors (SSRI)
Citalopram (Celexa)
20â€“60
12â€“15
33â€“37
2C19, 3A4, 2D6
Monodesmethylcitalopram, didesmethylcitalopram
59 h
None/unknown
Escitalopram (Lexapro)
10â€“20
19
22â€“32
2C19,3A4,2D6,
S(+)-Desmethylcitalopram
59 h
None
Fluoxetine (Prozac)
10â€“80
14â€“100
24â€“144
2C9, 2D6
Norfluoxetine

4â€“16 d
2D6 (d,m), 2C19 (d,m), 2D6 (d,m), 3A4 (m)
Fluvoxamine (Luvox)
100â€“300
25
15â€“23
1A2, 2D6
None
N/A
1A2, 2C9, 2C19, 3A4
Paroxetine (Paxil)
10â€“50
8â€“28
2.9â€“44
2D6
None
N/A
2D6
Sertraline (Zoloft)
50â€“200
20
24
2C9, 2B6, 2C19, 2D6, 3A4
Desmethylsertraline
62â€“104 h
2C19 (d,m)
SSRI with Î±$_1$ -adrenergic antagonism
Trazodone (Desyrel)
50â€“600
0.47â€“1
3â€“9
2D6, 3A inhibitors may increase concentration
Metachlorophenylpiperazine
?

None/unknown
SSRI with inhibition of reuptake of norepinephrine
Venlafaxine (Effexor)
75â€“375
6â€“7
3â€“4
2D6
O -desmethylvenlafaxine, depends on 3A4 and 2C19 for metabolism
10 h
None/unknown
Duloxetine (Cymbalta)
40â€“60
23
8â€“17
2D6,1A2
4-hydroxyduloxetine, 5-hydroxy, 6-methoxy-duloxetine sulfate (unknown
?
2D6
SSRI with Î±$_2$ -adrenergic antagonism: 5HT$_2$ /5HT$_3$ antagonism
Mirtazapine (Remeron)
15â€“45
?
20â€“40
3A4
Desmethylmirtazapine
?
3A4 *induction*
Inhibition of reuptake of biogenic amines or dopamine
Bupropion (Wellbutrin, Zyban)
150â€“450
20
9.6â€“20.9
2D6
Hydroxybupropion, erythrohydrobupropion, threohydrobupropion

24â€“37 h
None/unknown

Drug	Typical Daily Dose Range (mg)	Vd (L/kg)	$t_{1/2}$ (h)	Major Metabolic Isozyme	Major Active Metabolites	Major Active Metabolite $t_{1/2}$

TABLE 70-1. Drug Mechanism and Drug Information for Current SSRIs and Atypical Antidepressants

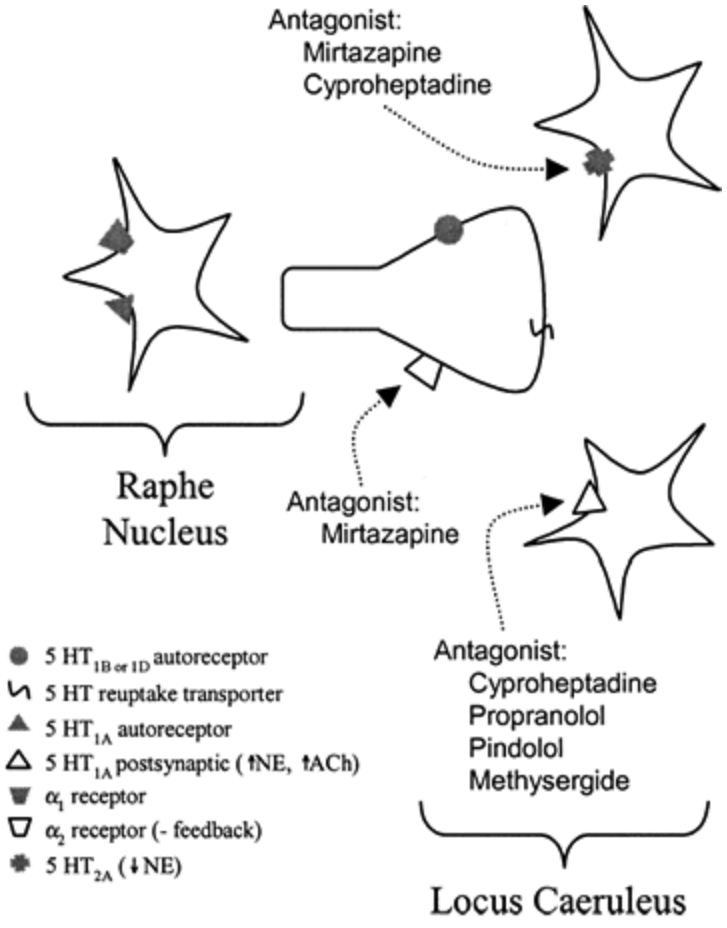


Figure 70-3. Neuroanatomy and effects of several common therapeutic d serotonin neurotransmission in the brain.

Infrequently, SSRI overdose results in life-threatening effects. In one fat patient reportedly ingested 75 times the maximum daily dose of fluoxetin fluoxetine concentration was 6000 ng/mL and the norfluoxetine concentra ng/mL; more than 10 times higher than therapeutic serum concentrations

SSRIs
Citalopram (Celexa)
SSRI, antimuscarinic
0
++++
0
0
Escitalopram (Lexapro)
SSRI
0
++++
0
0
Fluoxetine (Prozac)
SSRI
0
++++
0
0
Fluvoxamine (Luvox)
SSRI
0
++++
0
0
Paroxetine (Paxil)

SSRI, antimuscarinic
+
++++
+
0
Sertraline (Zoloft)
SSRI
0
++++
+
+
Other
Bupropion (Wellbutrin, Zyban)
Inhibits reuptake of biogenic amines
++
+
+
+++
Duloxetine (Cymbalta)
SRI, norepinephrine reuptake inhibitor
++
++++
0
++
Mirtazapine (Remeron)
Î±$_2$ -adrenergic antagonism, 5HT$_2$ /5HT$_3$ antagonism
0
++++
0
+
Reboxetine (Edronax, Vestra)
Selective norepinephrine reuptake inhibitor
++++
0

0
++++
Tianeptine
Unclear
?
?
?
?
Trazodone (Desyrel)
SRI,Î±-adrenergic antagonist
0
++++
0
0â€“+
Venlafaxine (Effexor)
SRI, norepinephrine reuptake inhibitor
++
++++
0
++
SSRI = selective serotonin reuptake inhibitor; SRI = serotonin reuptake
+ weak if any agonism; ++, weak agonism; +++, strong agonism; +++
agonism; 0, no effect.

Drug	Mechanism	Degree of Norepinephrine Reuptake Inhibition	Degree of Serotonin Reuptake Inhibition	Degree of Dopamine Reuptake Inhibition

TABLE 70-2. Receptor Activity of SSRIs and Related Antidepressa

Citalopram

Citalopram and its enantiomer escitalopram cause QTc interval widening a a dose-related manner. These effects are reported at doses as low as 400 citalopram.[33] Larger case series found that these effects typically occur a to doses exceeding 600 mg citalopram or in patients with serum concent than 40 times the expected therapeutic concentrations.[74, 133, 134] In or seizures were an early finding, whereas the development of ECG abnorm delayed for as long as 24 hours following ingestion.[134]

Although the mechanisms are unclear, experimental models suggest that didesmethylcitalopram metabolite of citalopram prolongs the QTc interval , whereas high concentrations of both the parent drug and this metabolite seizures[21, 30] (Chap. 23). The elimination half-life of the R-enantiomer appears to exceed that of the S-enantomer.[184] The implications of this di formation and effects of racemic forms of didesmethylcitalopram are unc

Management

Treatment of patients with acute SSRI overdose is largely supportive. De thiamine should be considered in patients who present with altered menta clinically warranted. Although cardiac manifestations after SSRI overdose a lead ECG should be obtained to identify other cardiotoxic drugs such as t antidepressants to which the patient may have access (Chaps. 5 and 23) citalopram or escitalopram is suspected, 24 hours of cardiac monitoring i to exclude the possibility of QTc prolongation and subsequent risk for ve dysrhythmias. Serum electrolytes and an acetaminophen concentration ma for monitoring and treatment of patients with intentional overdose. After stabilized, oral activated charcoal (1 g/kg) may be useful to adsorb drug the

gastrointestinal tract. Because SSRI overdose is rarely life threatening, g lavage is not generally indicated. Patients with small unintentional overdo other than citalopram and escitalopram are not expected to develop sign and symptoms of poisoning. Fatalities resulting from SSRIs are rare and occur after multiple drug ingestions and manifestations of drug interactio from excess serotonergic effects[66] (see Serotonin Syndrome). Forensic

suggests the minimum lethal concentrations of fluoxetine, paroxetine, an after isolated overdose are 0.63, 0.4, and 1.5 mg/L, respectively. Patien children, with well-defined small unintentional oral ingestions can be man home with close observation.[1][2][3]

Classic SSRIs

Citalopram (Celexa)

+ + +

+ + +

0â€“ +

Escitalopram (Lexapro)

+ + +

+ + +

0â€“ +

Fluoxetine (Prozac)

+

0

0â€“ +

Fluvoxamine (Luvox)

+

0

0â€“ +

Paroxetine (Paxil)

+

0

0â€“ +

Sertraline (Zoloft)

+

0

0â€“ +

Atypical Antidepressants

Bupropion (Wellbutrin, Zyban)

++++
0â€“+
0â€“+
Duloxetine (Cymbalta)
++++
Unknown
Unknown
Mirtazapine (Remeron)
Unknown
Unknown
++
Reboxetine (Edronax, Vestra)
++++
Unknown
Unknown
Tianeptine
Unknown
Unknown
Unknown
Trazodone (Desyrel)
0â€“+
0
0
Venlafaxine (Effexor)
+++
0â€“+
+++

0 does not cause; + very rarely causes; ++ rarely causes; +++ causes; commonly causes.

Drug	Seizures	QTc Prolongation	QRS Prolongation

TABLE 70-3. Predictive Analysis of the Relative Potential for Seizu
Abnormalities of SSRIs and Related Antidepressants

Adverse Effects After Therapeutic Doses

Adverse effects commonly attributed to therapeutic doses of SSRIs that a in overdose include gastrointestinal symptoms (anorexia, nausea, vomiti sexual dysfunction in both males and females, headache, insomnia, jitte dizziness, and fatigue.[189] Genetic polymorphism typing holds promise in patients at highest risk for adverse drug events with therapeutic dosing.[1] common adverse effects include sedation, particularly following citalopra paroxetine as a result of their weak anticholinergic activity, and anxiety fluoxetine treatment.[111] The mechanism of serotonin-mediated inhibition function is unclear; however, early human data show that the risk of blee very low.[102 , 105 , 106 , 115 , 135] Other rarely reported adverse effects in onset panic disorder, priapism, photopigmentation, bradycardia, hepatoto urinary incontinence.[25 , 46 , 89 , 90 , 120 , 168] Movement disorders, most akathisia, parkinsonism, myoclonus, and dystonia, also occur after SSRI These extrapyramidal side effects may be related to the complex interpla serotonergic and dopaminergic activity. Predisposing factors for the deve movement disorders include concomitant use of dopamine antagonists suc antipsychotics.[103]

The syndrome of inappropriate antidiuretic hormone (SIADH), in which s hyponatremia may occur rapidly, is associated with SSRI use. In an anim effect appears to be serotonin mediated, with increased concentrations of cortisol, adrenocorticotropin (ACTH), and vasopressin.[57] Rat studies dem stimulation of $5HT_{1C}$ receptors increases antidiuretic hormone secretion.[1] human case control studies have not confirmed defects in osmoregulated vasopressin through normal water loading tests and measurement of vas concentrations after 3â€“11 months of paroxetine use.[113] A review of th identified women older than 70 years who are concomitantly receiving di to be at greatest risk for developing SIADH.[93 , 98] Although reported to o days to 4 months after initiation of therapy, a case-matched control study patients identified that SIADH occurs most frequently within the first 2 w therapy.[121] As a class, hyponatremia is demonstrated to occur when swit SSRI to another.[6] Efforts to predict risk through poor CYP2D6 genotype status or high serum concentrations have not been successful.[170]

Serotonin Syndrome

The most common severe adverse effect associated with SSRIs is the dev serotonin syndrome. This syndrome, also referred to as the *serotonin be hyperactivity syndrome* , was first described in patients treated with MAO given other drugs that enhance serotonergic activity.[35 , 70 , 129 , 166] Hov ingestion of an MAOI is not required for this syndrome to develop, and it is unpredictable (Table 70-4).

Pathophysiology

The pathophysiologic mechanism of the serotonin syndrome is not compl understood but involves excessive selective stimulation of serotonin 5-HT 5-HT_{1A} receptors. Animal models demonstrate that specific stimulation of receptors results in signs and symptoms of serotonin syndrome even whe receptors were inactivated using a specific antagonist.[41] However, a subs study and a human retrospective case series showed that the potency of antagonist therapy was directly related to resolution of symptoms attribut serotonin syndrome.[65] 5-HT_{1D} receptors are not implicated in cases of se syndrome.

Clinical Manifestations

Symptoms of serotonin syndrome include altered mental status, agitation hyperreflexia, diaphoresis, tremor, diarrhea, incoordination, muscle rigidit hyperthermia (Table 70-5). The clinical manifestations of serotonin

syndrome are diverse, and minor manifestations are common after initiatio atypical antidepressant therapy. In fact, a prospective study of depressed given clomipramine demonstrated that 16 of 38 patients experienced syr consistent with the serotonin syndrome.[108] Fourteen of 16 cases demons spontaneous resolution within 1 week without discontinuation of therapy.

Drugs That Inhibit Serotonin Breakdown

- Monoamine oxidase inhibitors (nonselective)

Phenelzine, moclobemide, clorgyline, isocarboxazid[24 ,31 ,35 ,54 ,64 ,69 ,159 ,163 ,166 ,173 ,175]

Harmine and harmaline from Ayahuasca preparations, psychoactive b for religious purposes in the Amazon and Orinoco River basins[31]

Drug That Block Serotonin Reuptake

Clomipramine[99 ,137 ,148 ,166]

Cocaine[175]

Dextromethorphan[146]

Meperidine[64]

Pentazocine[79]

SSRIs

Fluoxetine, citalopram, paroxetine, fluvoxamine, sertraline[10 ,13 ,15 ,2 ,60 ,63 ,69 ,71 ,79 ,110 ,122 ,130 ,137 ,142 ,150 ,159 ,162]

Trazodone[60 ,67 ,126 ,141 ,142]

Venlafaxine[39 ,82 ,100]

Serotonin Precursors or Agonists

Lâ€“Tryptophan[167]

Lysergic acid diethylamide (LSD)[158]

Drugs That Enhance Serotonin Release

Amphetamines, especially MDMA (ecstasy)[96 ,163]

Buspirone[10 ,67]

Cocaine[175]

Lithium[99 ,122 ,127]

Mirtazapine[14 ,44]

TABLE 70-4. Potential Causes of Serotonin Syndrome

Life-threatening effects invariably result from hyperthermia caused by ex activity. Sustained severe hyperthermia can lead to death through denatu essential protein and enzymatic function that ultimately results in lactic rhabdomyolysis, myoglobinuria, renal and hepatic dysfunction, dissemina intravascular coagulation, or adult respiratory distress syndrome[116 , 171]

Diagnosis

The serotonin syndrome occurs most frequently following use of combinat serotonergic agents (Table 70-4). Drug interactions resulting in serotoni occur while switching serotonergic pharmacologic agents when an insuffici occurs before initiating the alternative therapy.[150 , 151] Residual pharmac receptor downregulation or upregulation, and the presence of active meta causative in these circumstances. For example, fluoxetine metabolism res active metabolite norfluoxetine, which has comparable pharmacologic effec life substantially longer than that of the parent drug. The metabolite pers result in serotonin syndrome when another serotonergic agent, usually a antidepressant, is given prior to complete clearance of norfluoxetine, whi approximately 2 weeks.[36]

This syndrome is reported in patients following a single dose, high therap or overdoses of certain serotonergic agents in adults and children.[39 , 63 130 , 141 , 148] Although sporadic reports occur, selective MAO subtype B inhibitor drug combinations are rarely reported to result in serotonin synd therapeutic doses.[48 , 118]

Mental Status
Consciousness altered
Restlessness
Elevated mood
Insomnia
Coma

Other Neurologic Signs and Symptoms
Coma
Incoordination
Myoclonus
Mydriasis
Tremor
Akathisia
Shivering

Rigidity

Hyperreflexia

Vital Signs and Autonomic Manifestations
Fever (Hyperthermia)
Tachycardia
Sweating
Tachypnea or Dyspnea
Diarrhea
Hypertension or hypotension

- Serotonin syndrome is diagnosed by the presence of at least 4 major major plus 2 minor symptoms following the addition or an increase in serotonergic agent.
- Underlying psychiatric disorder should be excluded.
- Other etiologies must be excluded, including initiation of a neuroleptic dopamine antagonist or withdrawal from a dopamine agonist.

Adapted from Radomski et al.[140]

Major Minor

TABLE 70-5. Diagnostic Criteria for Serotonin Syndrome

Currently no diagnostic test capable of determining whether a patient is serotonin syndrome is available. Although fulminant life-threatening cases recognize, mild cases are more difficult to distinguish from other causes. determine diagnostic criteria, a study that included 38 cases of presumed syndrome was performed. This trial led to suggested diagnostic criteria f syndrome to include three of the following signs and symptomsâ€”altered agitation, myoclonus, hyperreflexia, diaphoresis, tremor, diarrhea, and incoordinationâ€”when other etiologies are excluded.[171] A modification, t Serotonin Toxicity Criteria,[49] which included the variables myoclonus, ag diaphoresis, hyperreflexia, hypertonicity, and fever, was validated in 473

found to correlate best with a clinical toxicologic diagnosis of the seroton syndrome.[171] The most comprehensive review of signs and symptoms in review found altered mental status, other neurologic signs and symptoms and autonomic manifestations most commonly associated with the develo serotonin syndrome. Diagnostic criteria based on these clinical findings ar Table 70-5 .[140]

Management

Treatment of patients with serotonin syndrome begins with supportive ca on decreasing muscle rigidity. Because muscular rigidity is thought to be responsible for hyperthermia and death, rapid external cooling in conjunc aggressive use of benzodiazepines should limit complications and mortalit cases, neuromuscular blockade should be considered to achieve rapid mu The time course of the serotonin syndrome is variable and related to the to decrease drug concentrations of the offending agents. In most patients syndrome resolves within 24 hours after the offending drug is removed. serotonin syndrome can be prolonged when it is caused by drugs with lo protracted duration of effects, or active metabolites.

Animal models indicate that pretreatment with serotonin antagonists can development of the serotonin syndrome.[62 , 84 , 169] Several case reports successful use of 4 mg oral or intravenous cyproheptadine, an antihistam nonspecific antagonist effects at 5-HT_{1A} and 5-HT_{2A} receptors.[71 , 104] Pat responded typically had mild to moderate symptoms of serotonin syndrom not hyperthermic. Cyproheptadine use in this patient group is supported. research is warranted to determine the success of higher doses given to 5-HT_{2A} antagonistic effects in more severely affected patients.[65] Other dr anecdotally reported to be successful for treatment of symptoms caused b serotonin syndrome include methysergide, chlorpromazine, atypical antip propranolol.[64 , 65 , 67 , 75 , 152] Because all of these drugs are of unprove can be dangerous, aggressive cooling and sedation with a benzodiazepine basis of therapy.

Differential Diagnosis of the Serotonin Syndro the Neuroleptic Malignant Syndrome

Many features overlap between the serotonin syndrome and the neurolep syndrome (NMS) (Chap. 67). Some authors call these â€œspectrum disc can be caused by drugs with both antidopaminergic and/or proserotonerg [190] This position is supported by the finding that 5-HT_{2A} agonism results decrease in neuronal dopamine release. Some authors report NMS with u enhancing drugs. However, low concentrations of measured dopamine and concentrations of serotonin metabolites in the NMS patients reported sup hypothesis of central dopaminergic hypoactivity.[8 , 126] It now is clear tha implicated drugs, time course, pathophysiologic mechanism, and manifes distinct[65] (Table 70-6). Altered mental status, autonomic instability, and neuromuscular tone that may result in hyperthermia are common to both The development of NMS involves rapid blockade of dopaminergic neurons whereas the serotonin syndrome appears to result from acute overstimula serotonin receptors (5-HT_{2A}).

In addition to the associated medications, the time courses of the two sy substantially different. Signs and symptoms of the serotonin syndrome d minutes to hours after exposure to the offending agents, whereas NMS t develops days to weeks after daily exposure to the drug in question.[69] In symptoms develop and offending drugs are discontinued, NMS can last for weeks, whereas the serotonin syndrome usually resolves quickly, coincidir offending drug's pharmacokinetic metabolism. A review of the literature i patients presenting with serotonin syndrome were more likely to exhibit hyperactivity, clonus and myoclonus, ocular oscillations, shivering, tremor hyperreflexia, whereas patients presenting with NMS were more likely to bradykinesia and lead pipe rigidity.[65]

Historical Diagnostic Clue
  Inciting drug pharmacology
Dopamine antagonist
Serotonin agonist
  Time course of initiation of symptoms after exposure

Days to weeks
Hours
Duration of symptoms
Days to 2 weeks
Usually 24 hours
Symptoms
Autonomic instability
+++
+++
Fever
+++
+++
Altered mental status (depressed/confusion)
+++
+++
Altered mental status (agitation/hyperactivity)
+++
+
Lead pipe rigidity
+++
+
Tremor, hyperreflexia, myoclonus
+
+++
Shivering
-
+++
Bradykinesia
+++
-
- not found; + rare finding; +++ common finding.

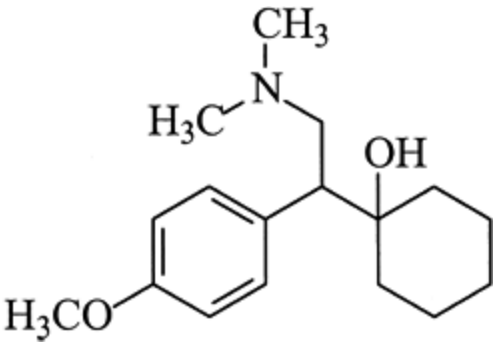
NMS SS

TABLE 70-6. Comparison of Neuroleptic Malignant Syndrome (
Serotonin Syndrome (SS)

Atypical Antidepressants

Atypical antidepressants are defined as not belonging strictly to a set cla antidepressants. They are not SSRIs, cyclic antidepressants, or MAOIs. In atypical antidepressants are the newer antidepressants, most of which ar SSRIs and have additional pharmacologic effects that were selected in an decrease the undesirable side effects of traditional antidepressants.

Serotonin/Norepinephrine Reuptake Inhib

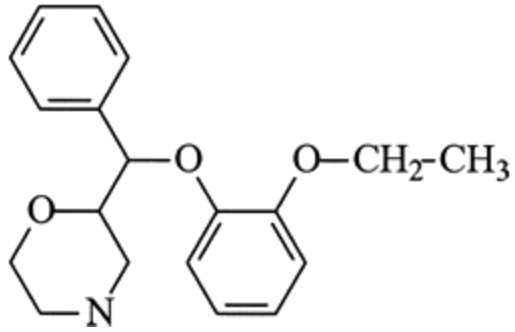


Venlafaxine

In addition to inhibiting serotonin reuptake, venlafaxine inhibits norepine reuptake. Venlafaxine produces rapid downregulation of central Î²-adren which may result in a faster onset of antidepressant effect.[157] Patients wi venlafaxine overdose may present with nausea, vomiting, dizziness, tach depression, hypotension, hyperthermia, elevated hepatic enzyme concent seizures.[86 , 186 , 194] Sodium channel blocking effects are rarely clinically however, QRS prolongation and ventricular tachycardia have resulted in [149 , 194] Although no clinical data regarding efficacy are available, sodiur may be helpful in attenuating these cardiotoxic effects (Antidotes in Dept Bicarbonate).

Overdose information on duloxetine, a similar drug, is limited, but duloxe expected to have similar effects.[177] Milnacipran is an investigational drug expected to have similar effects.[28 , 34]

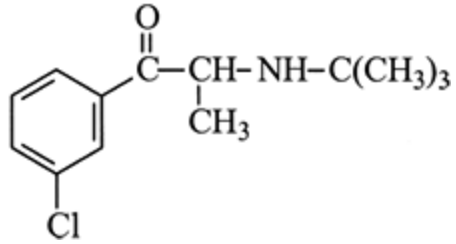
Norepinephrine Reuptake Inhibitors



Reboxetine

Reboxetine is a selective norepinephrine reuptake inhibitor.[182] Lack of e precludes an analysis of overdose data. However, toxicity can be extrapo adverse effects reported in clinical trials and from experience with other possessing similar pharmacologic characteristics. In particular, overdosed should be carefully monitored for tachycardia, hypertension or hypotensic development of seizures. Cases of acute mania and hepatotoxicity are re therapeutic use.[17]

Other Atypical Agents with Reuptake Inhib Part of Their Mechanism



Bupropion

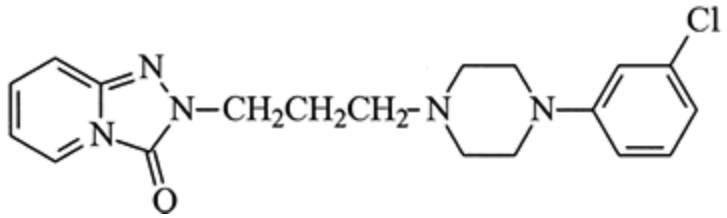
The pharmacologic mechanism of action of bupropion, a unicyclic antidep unclear, but both the parent drug and an active metabolite inhibit the reu dopamine and, to a lesser extent, serotonin and norepinephrine.[145] Exter formulations of bupropion are frequently used as adjuncts in smoking ces therapy.[88] Chronic doses greater than 450â€“500 mg/d place the patient seizures.[42 , 93]

Frequent effects after overdose include tachycardia, hypertension, gastr symptoms, and agitation.[11 , 16] Large acute overdoses may result in seizu without QRS complex prolongation.[29 , 81 , 131 , 161 , 172] In some cases, were delayed for up 10 hours, particularly after ingestion of sustained-re preparations.[80] Symptoms are reported to continue for up to 48 hours.

Several studies suggest that seizures following either bupropion overdose therapeutic doses are caused by its metabolite hydroxybupropion.[56 , 136] hydroxybupropion concentrations are documented after seizures when bu concentrations were no longer detectable. The exact mechanism for seizu hydroxybupropion is unclear at this time.[42 , 56 , 147]

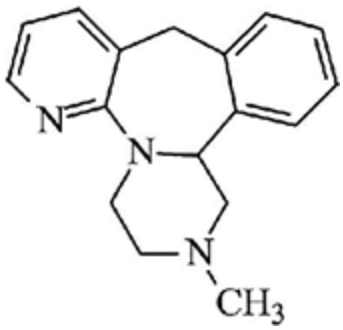
Treatment, when required for seizures, should be supportive and includes of benzodiazepines, followed by barbiturates. If QRS prolongation occurs, should be treated with sodium bicarbonate (Antidotes in Depth: Sodium Early after sustained-release bupropion overdose, activated charcoal shou considered, with use of multiple doses of activated charcoal or whole-bo after large, potentially life-threatening ingestions.

Other serious adverse effects reported after bupropion use include choles hepatocellular hepatic dysfunction, and rhabdomyolysis, with isolated repo pain, dystonia, trigeminal nerve dysfunction, mania, generalized erythro psoriasis, erythema multiforme, dyskinesia, altered vestibular and sensory serum sickness.[2 , 3 , 37 , 40 , 45 , 47 , 59 , 68 , 112 , 176 , 191]



Trazodone

Trazodone is a serotonin agonist that acts through inhibition of serotonin addition, trazodone may have some peripheral Î±-adrenergic antagonist depression and orthostatic hypotension are the most common complicatio overdose of trazodone.[58] Trazodone is rarely reported to cause SIADH. Tl be responsible for seizures, which rarely occur after acute overdose.[9 , 18] reported with therapeutic use of trazodone, may occur occasionally after [58] Management of hypotension includes supportive care and administratior vasopressors, if necessary.



Mirtazapine

The mechanism of mirtazapine action is unique. In addition to serotonin inhibition, mirtazapine increases neuronal norepinephrine and serotonin t adrenergic antagonism.[43] Mirtazapine also blocks some subtypes of 5-HT including 5-HT_2 and 5-HT_3 , which appear to have antidepressive effects.[effects that occur after acute mirtazapine overdoses include altered ment tachycardia.[26 , 181] Large overdoses may cause respiratory depression a of the QTc interval.[26 , 61 , 85 , 143] Because more overdose data are requi precise constellation of symptoms can be attributed to this drug, careful

monitoring is advised. Therapeutic use of mirtazapine causing serotonin hepatitis, hypertension, and reversible agranulocytosis is reported.[1, 83,

Tianeptine

Tianeptine is an investigational drug for treatment of anxiety and depres mechanism of tianeptine is unclear but may include serotonin reuptake e that ultimately reduces expression of serotonin transporter mRNA and se transporter binding sites.[101] No information about this drug in the overdo available. Careful observation is warranted until more information becom

Drug Discontinuation Syndrome

A drug discontinuation syndrome is defined as withdrawal manifestations pharmacologically based and occur after therapeutic use of a drug. Drug syndromes are commonly reported after withdrawal of conventional anti including tricyclic antidepressants and MAOIs[107] (Chaps. 69 and 71). SS reported to cause a discontinuation syndrome that typically begins within drug discontinuation and may last up to 3 weeks.[76] The most frequently symptoms include dizziness, lethargy, paresthesias, nausea, vivid dream and depressed mood.[77, 78, 155, 193] The risk factors associated with de discontinuation syndrome are not fully clarified, although the syndrome is with SSRIs having a shorter elimination half-life (paroxetine > fluvoxamir > fluoxetine). In addition, SSRIs with high-potency serotonin

reuptake inhibition are more frequently implicated (paroxetine > sertralin clomipramine > fluoxetine > venlafaxine > trazodone). Of the SSRIs, par often results in discontinuation syndrome, which is estimated to occur at a cases per million prescriptions. A meta-analysis of published cases from found that 65% of cases were attributed to paroxetine, 17% to sertraline, fluoxetine, and 7% to fluvoxamine.[18] Fluoxetine discontinuation syndrome frequently, at only two cases per million prescriptions.[139] The long elimi of fluoxetine and its active metabolite norfluoxetine probably decrease th discontinuation syndrome by providing a tapered effect after cessation. A compared to the other SSRIs, citalopram appears to have a low incidence

discontinuation symptoms.[114]

Because of difficulty in distinguishing symptoms of discontinuation syndrc underlying disease, many authors have proposed diagnostic criteria for th discontinuation syndrome.[19] All proposed criteria include discontinuation c concordance with CNS effects, gastrointestinal distress, or anxiety.[174]

The biochemical basis of the discontinuation syndrome is hypothesized to serotonin receptor downregulation leading to alterations in serotonergic including interactions with other neurotransmitters (GABA, norepinephrine dopamine).[154] Although postulated, antimuscarinic withdrawal seems an because the antimuscarinic effects of desipramine failed to protect agains withdrawal in a human model.[51]

Treatment of patients exhibiting discontinuation symptoms should include care and reinitiation of the discontinued drug or administration of another reinitiation of the drug is contraindicated. The drug then should be tapere that allows for improved patient tolerance.

Many of the other antidepressants discussed in this chapter also result in discontinuation reactions. Symptoms appear similar to those reported aft discontinuation of SSRIs and are treated in a similar manner.[14 , 92]

Summary

In acute overdose SSRIs or atypical antidepressants usually are not life although a few drugs produce seizures or cardiac toxicity. Treatment is g supportive for all of these drugs. However, significant drug interactions a drug effects are associated with serotonin reuptake inhibitors and may lea life-threatening events. In addition, the management of these patients fr complicated because they likely have concomitant access to more life-th antidepressants such as tricycle antidepressants and MAOIs.

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Chapter 71
Cyclic Antidepressants

Erica L. Liebelt

A 2.5-year-old girl was brought to the emergency department (ED) for evaluation of a seizure. The child previously was well and had no other medical problems. The young girl and her sibling ate dinner at a neighbor's house 2 hours prior to this incident. After the girl returned home, the mother noticed that the child looked tired. The girl subsequently had a generalized tonic-clonic seizure that lasted approximately 1 minute. The paramedics described the young girl as postictal, with vital signs of blood pressure, 90/50 mm Hg; pulse 160 beats/ min; respiratory rate 26 breaths/min.

At the request of the paramedics and the ED physician on medical control, the mother called the neighbor to determine whether the girl could have accessed any prescription medications or other pills while she was in the house. The neighbor revealed that her son's amitriptyline bottle had been spilled. According to the neighbor's count, one or two 75-mg amitriptyline tablets were missing.

In the ED 15 minutes later, the girl was still sleepy, but she responded to the physician's questions and cried when the IV line

was placed. Vital signs were: blood pressure, 90/50 mm Hg; pulse, 200 beats/min; respiratory rate, 26 breaths/min; temperature 99.7Â°F (37.6Â°C); and pulse oximeter revealed 97% oxygen saturation on room air. Physical examination demonstrated large (6-mm) pupils that were sluggishly reactive to light, slightly dry mucous membranes, no meningismus, and altered mental status. Initial bedside rapid glucose concentration was 110 mg/dL. Arterial blood gas showed: pH 7.28; PCO_2, 38 mm Hg; PO_2, 94 mm Hg; [HCO_3^-], 13 mEq/L. Blood was obtained for determination of electrolytes, liver enzymes, complete blood count, and amitriptyline concentration. The 12-lead electrocardiogram (ECG) revealed a wide-complex tachycardia with a rate of approximately 200 beats/min and a variable QRS interval with a minimum duration of 220 msec (Figure 71-1A). The girl then had another generalized tonic-clonic seizure, which lasted approximately 60 seconds. Her blood pressure dropped to 60/30 mm Hg. Lorazepam 0.1 mg/kg IV was given, followed by an IV bolus of sodium bicarbonate 1 mEq/kg over 3 minutes and a 1 mg/kg bolus of lidocaine. A 20-mL/kg bolus of 0.9% sodium chloride solution was administered through a second intravenous line, and the blood pressure increased to 88/47 mm Hg. The patient was intubated, orogastric lavage was performed with a 24-French tube, and activated charcoal 1 g/kg was administered via the orogastric tube.

A second ECG obtained 30 minutes after initial interventions showed a heart rate of 150 beats/min and narrowing of the QRS complex to 140 msec with a terminal R wave in lead aVR (R_{aVR}) of 6 mm (Figure 71-1B). A continuous infusion of sodium bicarbonate and 0.9% sodium chloride solution was administered at 60 mL/h by adding 100 mEq hypertonic sodium bicarbonate (1 mEq/mL) to 5% dextrose/0.25% saline to give a cumulative sodium concentration of 138 mEq/L. A venous blood gas showed a pH of 7.43. Prior laboratory studies did not reveal any abnormalities except for a measured [HCO_3^-] of 14 mEq/L. The patient was transferred to the pediatric intensive care unit (PICU) of a tertiary care children's

hospital for further management.

On arrival to the PICU, the patient was sedated. Her blood pressure was 99/53 mm Hg and heart rate was 136 beats/min. A third ECG obtained 10 hours after the initial ECG showed heart rate of 120 beats/min, QRS interval of 80 msec, and R_{aVR} of 4.5 mm (Figure 71-1C). The patient was extubated within 6 hours and remained in the intensive care unit overnight for continuous ECG monitoring. The ECG abnormalities resolved, and the last ECG showed QRS duration of 80 msec and R_{avR} of 1 mm. The patient was awake, alert, and normotensive. The quantitative serum amitriptyline concentration from the sample obtained at the initial hospital was 1003 ng/mL. The patient was discharged home the next day after social service consultation and a total of 24 hours of observation following extubation, termination of sodium bicarbonate infusion, and resolution of ECG abnormalities.

Cyclic antidepressants (CAs) consist of a group of pharmacologically related drugs used for treatment of depression, as well as neuralgic pain, migraines, enuresis, and attention deficit hyperactivity disorder. Most CAs have at least 3 rings inherent in their chemical structure. They include the traditional tricyclic antidepressants (TCAs) imipramine, desipramine, amitriptyline, nortriptyline, doxepin, trimipramine, protriptyline, and clomipramine, as well as cyclic compounds such as maprotiline and amoxapine (Table 71-1). These drugs share unique toxicologic characteristics that have led to an array of basic science and clinical research primarily aimed at innovative and optimal treatment modalities.

History and Epidemiology

Imipramine was the first TCA used for treatment of depression in the late 1950s. However, the synthesis of iminodibenzyl, the â€œtricyclicâ€• core of imipramine, and the description of its chemical characteristics date back to 1889. Structurally related to the phenothiazines, imipramine originally was developed as a

hypnotic agent for the sedation of agitated or psychotic patients and was serendipitously found to alleviate depression. From the 1960s until the late 1980s, the TCAs were the major pharmacologic treatment

for depression in the United States. However, by the early 1960s, cardiovascular and central nervous system (CNS) toxicity were recognized as major complications of TCA overdoses. The newer CAs were developed in the 1980s and 1990s to decrease some of the adverse effects that occurred with older TCAs, improve the therapeutic index, and reduce the incidence of serious toxicity. The newer CAs included the tetracyclic drug maprotiline and the dibenzoxapine drug amoxapine (Table 71-1).

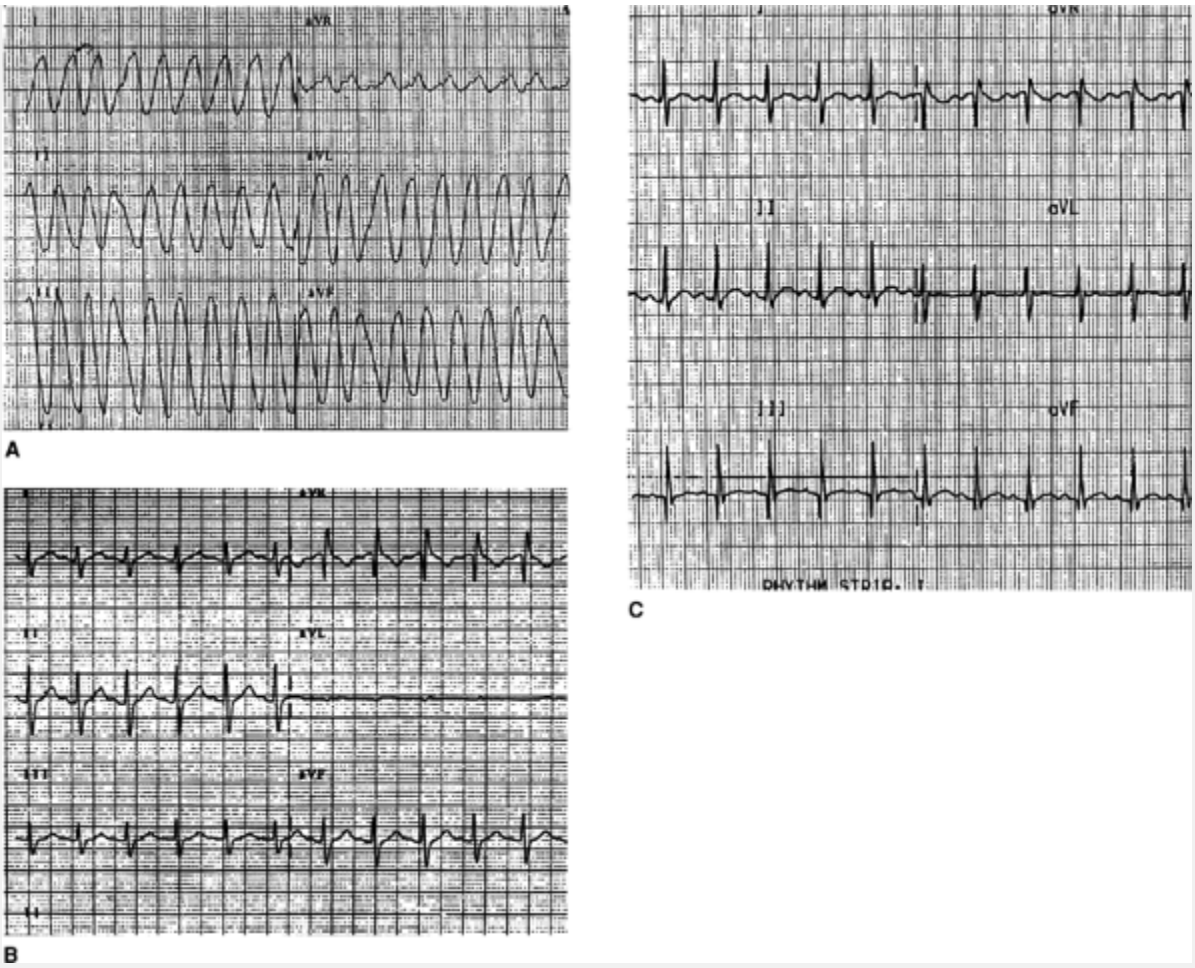


Figure 71-1. Case electrocardiograms. A. Initial ECG shows a wide-complex tachycardia with a variable QRS duration (minimum 220 msec). B. ECG 30 minutes after presentation following sodium bicarbonate shows narrowing of the QRS interval to a duration of 140 msec and an amplitude of R_{aVR} of 6.0 mm. C. ECG 9 hours after presentation shows further narrowing of the QRS interval to 80 msec and decrease in the amplitude of R_{aVR} to 4.5 mm. (Reproduced with permission from Liebelt EL: Targeted management strategies for cardiovascular toxicity from tricyclic antidepressant overdose: The pivotal role for alkalinization and sodium loading. Pediatr Emerg Care 1998;14:293â€“298.[74])

The epidemiology of CA poisoning has evolved significantly in the last 10 years, resulting in great part from the introduction of the newer selective serotonin reuptake inhibitors (SSRIs). The antidepressants are a leading cause of drug-related self-poisonings in the world, primarily because of their ready availability to people with depression who by virtue of the disease are at high risk for overdose. Between 1993 and 1997, 95% of poisoning deaths in England and Wales were associated with TCAs, particularly dothiepin and amitriptyline. TCAs were associated with 5.3 deaths per 100,000 prescriptions.[128] Numerous epidemiologic studies in both the United States and Europe demonstrate that the comparative risk of death is significantly greater with the TCAs as a group compared with the newer antidepressants, including the SSRIs.[60] However, over the last 10 years, more medical indications for TCA use, including chronic pain, obsessive-compulsive disorder, and, particularly in children, enuresis and attention deficit hyperactivity disorder, have emerged, thus increasing their availability even more.

Based on data from the American Association of Poison Control Centers' (AAPCC) Toxic Exposure Surveillance System (TESS), CAs (primarily TCAs) were the leading cause of poisoning fatalities in the United States until 1993, when they were overtaken by the analgesics (Chap. 130). In the last 10 years, the number of deaths caused by CAs reported to poison centers has remained relatively constant, although the total number of CA exposures has decreased slightly. There is a significant underreporting of deaths attributable to antidepressants through the AAPCC TESS data.[54] What cannot be determined from these particular poison center data is whether prehospital deaths have changed and whether the total number of prescriptions for CAs has declined or remained constant, factors that would contribute more meaning to the actual number of deaths.

Children younger than 6 years have consistently accounted for approximately 12â€“13% of all CA exposures during the last 10 years. Antidepressants (specifically TCAs) are the second most

commonly prescribed psychotropic medication in preschool children, with a

>200% increase from 1991â€“1995.[159] Despite the emergence of the SSRIs in the early 1990s, TCAs were still among the top 5 psychotropic drugs most frequently prescribed by pediatric office-based practices in 1995.[59] CA poisoning likely will continue to be among the most lethal unintentional drug ingestions in younger children because only 1 or 2 adult-strength pills can cause serious poisoning in children of this age.

Pharmacology

In general, the TCAs can be classified into tertiary and secondary amines based on the presence of a methyl group on the propylamine side chain (Table 71-1). The tertiary amines amitriptyline and imipramine are metabolized to the secondary amines nortriptyline and desipramine, respectively, which themselves are marketed as antidepressants. In therapeutic doses, the CAs exhibit numerous pharmacologic effects on the autonomic system, CNS, and cardiovascular system. However, the drugs can be distinguished from each other by their relative potencies with which they produce the diverse clinical effects. These pharmacologic differences appear to be pronounced even with therapeutic dosing.

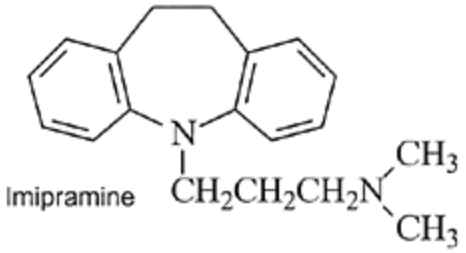
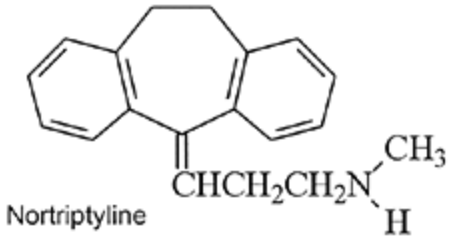
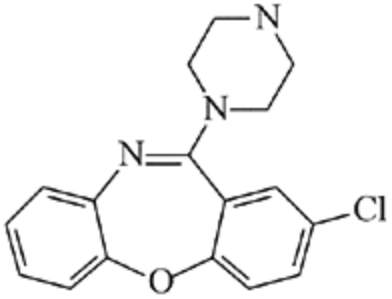
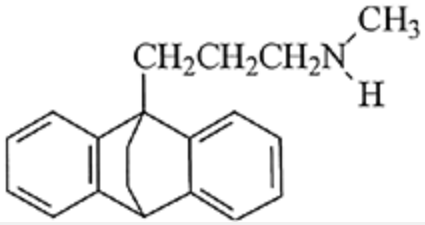
Tertiary Amines	
Amitriptyline Clomipramine Doxepin Imipramine Trimipramine	 Imipramine
Secondary Amines	
Desipramine Nortriptyline Protriptyline	 Nortriptyline
Amoxapine	
Maprotiline	

TABLE 71-1. Cyclic Antidepressantsâ€”Classification by Chemical Structure

Therapeutically, CAs inhibit presynaptic reuptake of norepinephrine and/or serotonin, thus functionally increasing the amount of these neurotransmitters at CNS receptors. The tertiary amines, especially clomipramine, are more potent inhibitors of serotonin reuptake, whereas the secondary amines are more potent inhibitors of norepinephrine reuptake. Although these pharmacologic actions formed the basis of the monoamine hypothesis of depression in the 1960s, antidepressant actions of these drugs appear to be much more complex.

Extensive research has led to the â€œreceptor sensitivity hypothesis of antidepressant drug action,â€• which postulates that following chronic CA administration, alterations in the sensitivity of various receptors are responsible for antidepressant effects. Chronic TCA administration alters the number and/or function of central Î²-adrenergic and serotonin receptors.[1,14] In addition, TCAs modulate glucocorticoid receptor gene expression and cause alterations at the genomic level of other receptors.[8,72] All of these actions play a role in the antidepressant effects of TCAs.

Additional pharmacologic mechanisms of CAs are responsible for their side effects and overdose presentations.[27] All of the CAs are competitive antagonists of the muscarinic acetylcholine receptors, although they have different affinities. Acetylcholine blockade is responsible for central and peripheral anticholinergic adverse effects, such as dry mouth, urinary retention, blurred vision, and sedation. The CAs also antagonize peripheral α_1-adrenergic receptors, producing vasodilation and orthostatic hypotension. The membrane-stabilizing effect of CAs is responsible for cardiac conduction abnormalities that occur even at therapeutic doses and, following overdose, is the mechanism of life-threatening cardiac toxicity.[42] Finally, animal research demonstrates interactions of CAs on the Î³-aminobutyric acid (GABA) receptorâ€“chlorideâ€“ionophore complex in the brain. The effects of chronic CA administration on chloride influx, chloride uptake, GABA transport, and specific GABA receptors may offer a novel mechanism of antidepressant drug action and a

mechanism for seizure occurrence after CA overdoses.[80,81,94,138]

Amoxapine is a dibenzoxapine CA derived from the active antipsychotic loxapine. Although it has a 3-ringed structure, this drug has little similarity to the other tricyclics. It is a potent norepinephrine reuptake inhibitor, has no effect on serotonin reuptake, and blocks dopamine receptors. Maprotiline is a tetracyclic antidepressant that predominantly blocks norepinephrine reuptake. Both of these CAs have a slightly different toxic profile than the traditional TCAs.

Pharmacokinetics and Toxicokinetics

CAs are rapidly and almost completely absorbed from the gastrointestinal (GI) tract, with peak concentrations 2â€“8 hours after administration of a therapeutic dose. CAs are weak bases (high pK_a); thus, changes in acidâ€“base status alter the proportion of ionized to nonionized drug. In CA overdose, the decreased GI motility caused by CA anticholinergic effects and the ionization in the acidic gastric media delay CA absorption. Because of extensive first-pass metabolism by the liver, the oral bioavailability of CAs is low and variable, although metabolism may become saturated in overdose, increasing bioavailability. These properties contribute to the recommendations and rationale for delayed GI decontamination and the need for aggressive decontamination.

CAs are highly lipophilic and possess large and variable volumes of distribution (15â€“40 L/kg). They are rapidly distributed to the heart, brain, liver, and kidney, where the tissue-to-plasma ratio generally exceeds 10:1. In the canine myocardium, CA concentrations exceed plasma concentrations by >200-fold.[57] Less than 2% of the ingested dose is present in blood several hours after overdose, and serum TCA concentrations decline biexponentially.[106,123] The CAs are extensively bound to $Î±_1$-acid glycoprotein (AAG) in the plasma, although differential binding among the specific drugs is observed.[2]

Changes in AAG concentration or pH can alter binding and the percentage of free or unbound drug.[107,124] Specifically, a low blood pH (which often occurs in a severely poisoned patient) may increase the amount of free drug, making it more available to exert its effects. Animal studies demonstrate that although administration of AAG increases the concentration of total desipramine and protein-bound desipramine in the serum, the concentration of active free desipramine does not significantly decline.[107] Redistribution of CAs from tissues may account for this small change in the free fraction of the drug. All of these pharmacokinetic properties limit the value of serum antidepressant concentrations in assessing toxicity.

The TCAs undergo demethylation, aromatic hydroxylation, and glucuronide conjugation of the hydroxy metabolites. The tertiary amines imipramine and amitriptyline are demethylated to desipramine and nortriptyline, respectively. The hydroxy metabolites of both tertiary and secondary amines are pharmacologically active and may contribute to toxicity after the first 12â€“24 hours. The glucuronide metabolites are inactive.

Genetically based differences in the activity of the CYP2D6 enzymes account for wide interindividual variability in metabolism and steady-state plasma concentrations. Genetic polymorphisms of the CYP2D6 gene, which is responsible for hydroxylation of imipramine and desipramine, are responsible for the slow metabolism in certain patients.[17,28] These â€œpoor metabolizersâ€• may recover more slowly from an overdose or demonstrate toxicity with therapeutic dosing.[13,136,142] The metabolism of CAs also may be influenced by concomitant ingestion of ethanol and other medications such as barbiturates, which may enhance their metabolism, or by drugs that inhibit the CYP2D6 isoenzyme (eg, SSRIs including fluoxetine, paroxetine, sertraline), which may increase the concentration of the parent CAs.[16,97,132] Patient variables such as age and ethnicity also affect CA metabolism.

Elimination half-lives for therapeutic doses of CAs vary from 7â€“58

hours (54â€“92 hours for protriptyline), with even longer half-lives in the elderly.[114,123] The half-lives may be more prolonged in overdose as a result of saturable metabolism. A small fraction (15â€“30%) of CA elimination occurs through biliary and gastric secretion.[39,82] The metabolites are then reabsorbed in the systemic circulation, resulting in enterohepatic and enterogastric recirculation and reducing their fecal excretion. Finally, <5% of CAs are excreted unchanged by the kidney.[39]

Pathophysiology

The effects on various neurotransmitters and the myocardial cells explain the pathophysiology of CNS and cardiac toxicity. Conduction delays, dysrhythmias, and hypotension characterize the cardiotoxicity caused by CAs. This toxicity results from drug effects on the myocardial action potential, direct effects on vascular tone, and effects mediated by the autonomic nervous system.

The CAs block the rapid inward movement of sodium ions into the fast sodium channel, slowing phase 0 depolarization of the action potential in the distal His-Purkinje system and the ventricular myocardium[42,151,154] (Figure 71-2 and Figure 23-2). Impaired depolarization within the conduction system slows the propagation of ventricular depolarization, which is manifested as prolongation of the QRS interval on the electrocardiogram. The right bundle branch has a relatively longer refractory period, and it is affected disproportionately by intraventricular conduction delay.[100] This slowing of depolarization results in a rightward shift of the terminal QRS axis and the right bundle-branch block pattern that is noted on the ECG of patients who are exposed to CA.[156]

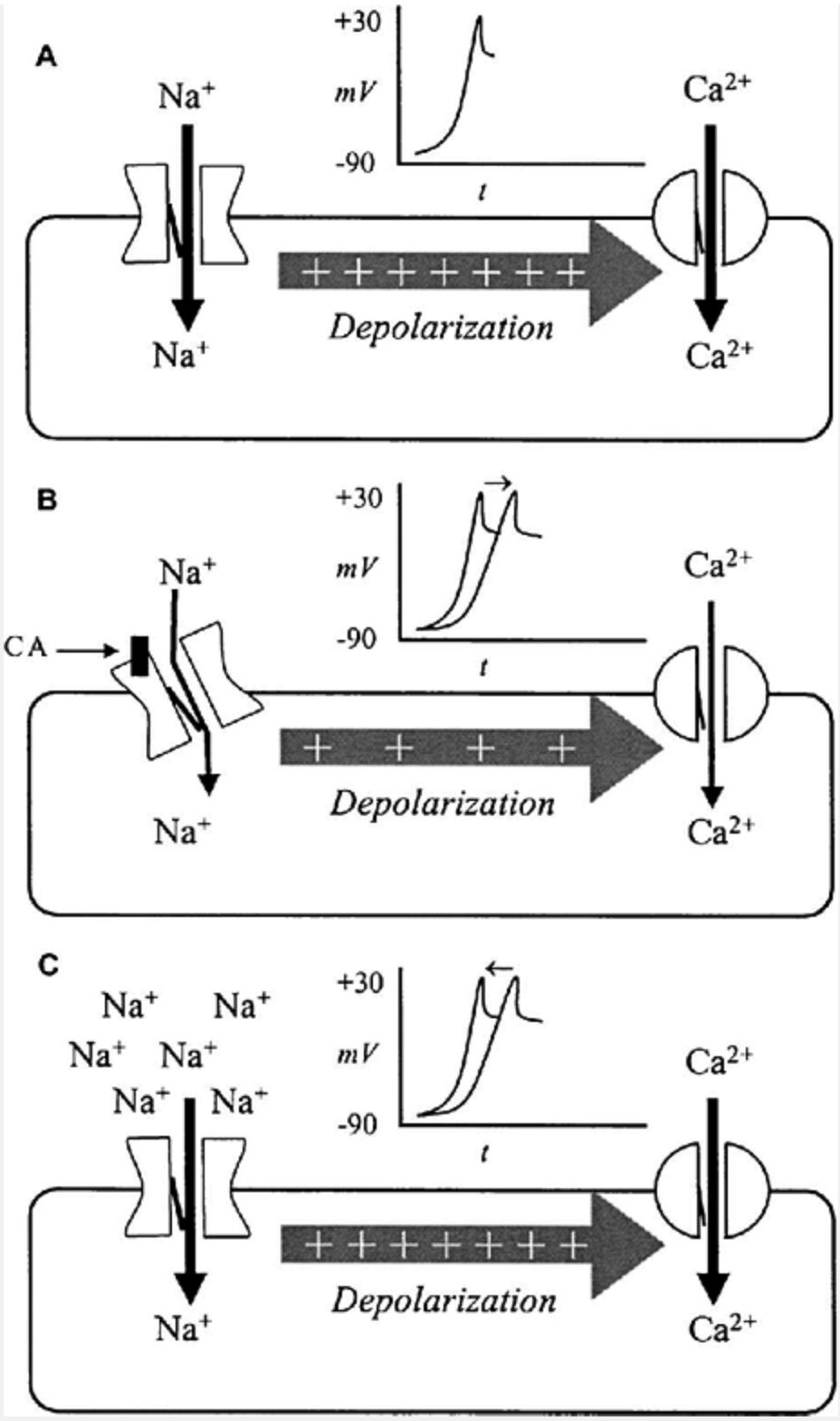

A
+30
mV
-90
t
Na+
Ca2+
Depolarization
Na+
Ca2+
B
+30
mV
-90
t
Na+
Ca2+
CA
Depolarization
Na+
Ca2+
C
+30
mV
-90
t
Na+ Na+
Na+ Na+
Na+ Na+
Ca2+
Depolarization
Na+
Ca2+

Figure 71-2. Effects of cyclic antidepressants on the fast sodium channel. A. Sodium depolarizes the cell, which both propagates conduction allowing complete cardiac depolarization and opens voltage-dependent Ca^{2+} channels producing contraction. B. Tricyclic antidepressants and other sodium channel blockers alter the conformation of the sodium channel, slowing the rate of rise of the action potential, which produces both negative dromotropic and inotropic effects. C. Raising the Na^{+} gradient across the affected sodium channel speeds the rate of rise of the action potential, counteracting the drug-induced effects. Raising the pH removes the CA from the binding site on the Na^{+} channel. See Figure 71-3 for the effects noted on the ECG.

QTc interval prolongation can occur in the setting of both therapeutic and toxic doses of CAs. This apparent prolongation of repolarization results primarily from slowed depolarization.[118] QTc prolongation can predispose to development of torsades de pointes. Because torsades de pointes is more likely to occur in the setting of bradycardia, it is an unlikely finding in patients with acute CA toxicity.

The associated hypotension is multifactorial. It is caused by direct myocardial depression secondary to sodium channel blockade, which disrupts the subsequent coupling of calcium entry into the cells, thereby impairing myocardial contractility. Downregulation of adrenergic receptors with subsequent blunted physiologic responses to catecholamines is suggested as another mechanism based on evidence of CA-poisoned patients with normal to high serum catecholamine concentrations.[93] Peripheral vasodilation from Î±-adrenergic blockade by CAs also contributes to hypotension, particularly when patients are standing.

The most common dysrhythmia observed following overdose is sinus tachycardia, which primarily results from peripheral muscarinic antagonism. Norepinephrine reuptake inhibition also contributes to

the tachycardia. Wide-complex tachycardia is the characteristic potentially life-threatening dysrhythmia observed in patients with severe CA toxicity. It also probably is multifactorial in etiology. By prolonging antegrade conduction, nonuniform conduction slowing may result, leading to reentrant ventricular dysrhythmias.[151] Ventricular tachycardia may occur in the setting of hypoxia and tissue ischemia, metabolic acidosis, and use of Î²$_1$-adrenergic therapy. However, most examples of wide-complex tachycardia actually are aberrantly conducted sinus tachycardia. In such cases, the preceding P wave may not be apparent because of prolonged AV conduction, widened QRS interval, or both. Electrophysiologic studies in a canine model demonstrate that QRS prolongation is rate dependent, that is, the faster the heart rate, the greater the conduction delay. In these studies, dogs in which heart rate could not accelerate because of a crushed sinus node never developed QRS prolongation. Furthermore, induction of bradycardia through experimental pharmacologic agents prevents or narrows wide-complex tachycardia by allowing time for recovery of sodium channel interaction.[4] Earlier studies demonstrated narrowing of the QRS interval with propanolol administration.[122] This physiologic characteristicâ€”use-dependent kineticsâ€”is characteristic of the sodium channel blockade of type IA antidysrhythmics (Chap. 61).

Attempts to find a causal relationship between TCA administration and myocardial disease through controlled trials have failed.[43,149] However, data suggest that chronic TCA drug treatment causes myocardial injury. Clinical studies using monoclonal antimyosin antibodies, a known marker for myocardial damage, demonstrate increased myocardial uptake of these antibodies in adults undergoing long-term amitriptyline treatment.[84]

Agitation, delirium, and depressed sensorium are primarily caused by the central anticholinergic effects of CAs. The pathophysiology of CA-induced seizures is not fully delineated but may result from a combination of increased concentrations of monoamines (particularly norepinephrine), antidopaminergic properties, anticholinergic

properties, inhibition of neuronal sodium channels, and interactions with GABA receptors. Animal studies demonstrate that the interaction of CAs with the GABA receptorâ€“chlorideâ€“ionophore complex in the brain may be primarily responsible for the convulsant effects of these drugs. Specifically, in drug-naive rats, some CAs inhibited GABA-mediated chloride conductance, which correlated with the frequency of induced seizures.[80] Another study in rats reported that amitriptyline actually augments chloride conductance in CNS tissue.[81] This property suggests yet another complex mechanism for seizures or actually may confer a protective anticonvulsant effect on patients who were chronically taking the drug prior to their overdose. The exact binding site of these drugs is not elucidated, although some evidence suggests at least indirect activity at the picrotoxin binding site on the GABAâ€“chloride complex.[137]

The pulmonary complications of CA overdose include acute lung injury. In one study, amitriptyline exposure caused dose-related vasoconstriction and bronchoconstriction in isolated rat lungs.[141] Many substances implicated in acute lung injury, such as platelet activating factor and protein kinase activation, were important in mediating amitriptyline-induced lung function impairment in this experimental model. Another animal model demonstrated that acute amitriptyline poisoning causes dose-dependent prolonged rises in pulmonary artery pressure, pulmonary edema, and sustained vasoconstriction that could be attenuated by either calcium channel inhibition or a nitric oxide donor.[79]

Clinical Manifestations of Toxicity

The toxic profile is qualitatively the same for all of the first-generation TCAs but is slightly different for some of the other CAs. The progression of clinical toxicity is unpredictable and may be rapid, depending on the patient's age and weight and the quantity of TCA ingested. Patients commonly present to the ED with minimal clinical abnormalities and then develop life-threatening cardiovascular and

CNS toxicity within a couple of hours (Table 71-2).

TABLE 71-2. Clinical Manifestations of Toxicity Resulting from Cyclic Antidepressants

Cardiovascular Toxicity
Conduction Delays
PR interval, QTc interval, and QRS complex prolongation
T40-ms axis rightward rotation (120Â°â€“270Â°)
Atrioventricular block
Dysrhythmias
Sinus tachycardia
Supraventricular tachycardia
Wide-complex tachycardia
Sinus tachycardia with rate-dependent aberrancy
Ventricular tachycardia
Torsades de pointes
Bradycardia
Ventricular fibrillation
Asystole
Hypotension
Central Nervous System Toxicity
Altered mental status
Delirium
Psychosis
Lethargy
Coma
Myoclonus
Seizures
Anticholinergic Toxicity
Altered mental status
Hyperthermia
Urinary retention

Paralytic ileus
Pulmonary Toxicity
Acute lung-injury aspiration

The CAs have a low toxicity threshold, so a small increase over the therapeutic range may result in toxicity. Acute ingestions of 10â€“20 mg/kg of most CAs cause significant cardiovascular and CNS manifestations (therapeutic dose 2â€“4 mg/kg/d). Thus, life-threatening overdose in adults usually is associated with ingestions. 1 g. However, in a 10-kg toddler, as few as two 50-mg imipramine tablets may cause significant toxicity (10 mg/kg), defined as CNS depression, seizures, and/or cardiovascular toxicity. In a series of TCA ingestions in children all patients with single unintentional ingestions >5 mg/kg had toxicity.[89]

Acute Toxicity

Most of the reported toxicity derives from acute ingestions, especially in patients who are chronically taking the medication. Clinical toxicity between these 2 cohorts do not appear to be different, and most studies do not distinguish between them.

Acute Cardiovascular Toxicity

Cardiovascular toxicity is primarily responsible for the morbidity and mortality attributed to CAs. Conduction delays include prolongation of the QRS complex duration and rightward shift of the terminal 40-msec QRS axis (T40-ms). PR, QRS, and QTc interval prolongation can occur in the setting of both therapeutic and toxic doses of TCAs.[83] Second- and third-degree atrioventricular blocks are rare. Sinus tachycardia (rate 120â€“160 beats/min in an adult) is the most common dysrhythmia associated with CA toxicity and usually does not cause hemodynamic compromise. It is present in most patients

with clinically significant TCA poisoning. Ventricular tachycardia is the most common lethal ventricular dysrhythmia but may be difficult to distinguish from sinus tachycardia with aberrant conduction. Ventricular tachycardia occurs most often in patients with prolonged QRS complex duration and/or hypotension.[77,144] Acutely poisoned patients with QRS widening usually have altered mental status. Hypoxia, acidosis, hyperthermia, seizures, and Î²-adrenergic agonists may predispose the patient to ventricular tachycardia.[77,144] However, true fatal dysrhythmias probably are rare, as ventricular tachycardia and fibrillation occur in only approximately 4% of all cases.[45] Both children and adults receiving cardiopulmonary resuscitation have recovered successfully despite periods of asystole exceeding 90 minutes.[102,134,146] Torsade de pointes is not common with acute TCA overdoses but is found more often in patients receiving therapeutic doses of CAs.

Refractory hypotension probably is the most common cause of death from CA overdose.[22,57,140] The etiology of CA-induced hypotension is multifactorial. Hypoxia, acidosis, volume depletion, seizures, or concomitant ingestion of other cardiodepressant or vasodilating drugs can exacerbate hypotension.

Acute Central Nervous System Toxicity

Seizures and altered mental status are the primary manifestations of CNS toxicity. Delirium, disorientation, agitation, and/or psychotic behavior with hallucinations may be present. These alterations in consciousness usually are followed by lethargy that rapidly progresses to obtundation and coma. The duration of coma is variable and does not necessarily correlate or occur concomitantly with electrocardiographic abnormalities.

CA-induced seizures usually are generalized and brief, most often occurring within 1â€“2 hours of ingestion.[30,119] The incidence of seizures is similar to ventricular tachycardia and estimated at 4% in patients presenting with overdose and 13% in fatal cases.[158]

Uncontrolled seizures are uncommon and may result in metabolic acidosis, hyperthermia, rhabdomyolysis, and myoglobinuria with acute renal failure. Abrupt deterioration in hemodynamic status, namely, hypotension and ventricular dysrhythmias, may develop during or within minutes after a seizure.[30,77,144] This rapid cardiovascular deterioration may be the result of seizure-induced acidosis that exacerbates cardiovascular toxicity. The risk of seizures with CA overdoses may be increased in patients undergoing long-term therapy or who have other risk factors such as history of seizures, head trauma, or concomitant drug withdrawal.[133] Myoclonus and extrapyramidal symptoms may occur in CA-poisoned patients.

Other Clinical Effects

Anticholinergic effects can occur early or late in the course of TCA toxicity. Pupils may be dilated and poorly reactive to light. Other anticholinergic effects include dry mouth, dry flushed skin, urinary retention, and ileus.

Reported pulmonary complications include acute lung injury, aspiration pneumonitis, and adult respiratory distress syndrome. Acute lung injury may be the result of coma, hypotension, pulmonary infection, and excessive fluid administration, along with the primary toxic effects of cas.[129,131] Bowel Ischemia, Pseudo-Obstruction, And Pancreatitis Are Associated With Ca Overdose.[91,117,152]

Death directly caused by ca toxicity usually occurs in the first several hours after presentation secondary to refractory hypotension in patients who reach a healthcare facility. Late deaths (>1â€“2 days after presentation) usually are secondary to other factors such as aspiration pneumonitis, adult respiratory distress syndrome from refractory hypotension, and/or infection.[22]

Chronic Toxicity

Chronic ca toxicity usually is manifested by exaggeration of adverse effects, such as sedation and sinus tachycardia, or defined by supratherapeutic drug concentrations in the blood in the absence of an acute overdose.[41] unlike chronic theophylline and aspirin poisoning, this category of toxicity does not appear to cause the same acute life-threatening toxicity. A sparse literature describes the clinical course of this cohort, which may even go unrecognized.

Several reports describe sudden death in children taking therapeutic doses of cas.[113,115,116,148] qtc prolongation with resultant torsade de pointes, advanced atrioventricular conduction delays, blood pressure fluctuations, and ventricular tachycardia are postulated mechanisms, although whether any of these effects contributed to the deaths is unknown. prospective studies using 12-lead ecg, 24-hour ecg recording, and doppler echocardiography in children receiving therapeutic doses of tcas have failed to find any significant cardiac abnormalities compared to children not taking tcas.[10,32] However, authors recommend that tcas not be initiated or continued in any child with a resting qtc interval >450 msec or with bundle-branch block.[32]

Unique Toxicity from â€œAtypicalâ€• Cyclic Antidepressants

Although the incidence of serious cardiovascular toxicity is lower in patients with amoxapine overdoses, the incidence of seizures is significantly greater than for the traditional tcas.[58,69,78] Moreover, Seizures May Be More Frequent Or Status Epilepticus May Develop.[92] similarly, the incidences of seizures, cardiac dysrhythmias, and duration of coma are greater with maprotiline toxicity compared to the tcas.[68]

Diagnostic Testing

Diagnostic testing for CA poisoning primarily relies on indirect bedside tests (ECG) and other nonspecific laboratory analyses. Quantification of CA concentration provides little help in the acute management of patients with CA overdose but provides adjunctive information to support the diagnosis.

Electrocardiography

The ECG can provide important diagnostic information and may predict clinical toxicity after a CA overdose. CA toxicity results in distinctive and diagnostic electrocardiographic changes that may allow early diagnosis and targeted therapy when the clinical history and physical examination are unreliable.

The maximal limb lead QRS complex duration is an easily measured ECG parameter that is a sensitive indicator of toxicity. One investigation reported that 33% of patients with a limb lead QRS interval â‰¥100 msec developed seizures and 14% developed ventricular dysrhythmias.[14] There was a 50% incidence of ventricular dysrhythmias among patients with a QRS duration â‰¥160 msec. No ventricular dysrhythmias occurred in patients with a QRS duration â‰¥ 160 msec. Subsequent studies confirmed that a QRS duration >100 msec is associated with an increased incidence of serious toxicity, including coma, need for intubation, hypotension, seizures, and dysrhythmias, making this ECG parameter a useful indicator of toxicity.[24,75]

A terminal 40-ms axis between 120Â° and 270Â° is associated with TCA toxicity and in 1 study was a more sensitive indicator of drug presence than the QRS complex duration alone.[24,100,156] A terminal QRS vector of 130Â°â€“270Â° discriminated between 11 patients with positive toxicology screens for TCAs and 14 patients with negative toxicology screens.[100] With further analyses, this report concluded that the positive and negative predictive values of this ECG parameter for TCA ingestions were 66% and 100%, respectively, in a population of 299 general overdose patients. A retrospective

study reported that a TCA-poisoned patient was 8.6 times more likely to have a T40-ms axis >120Â° than was a nonâ€“TCA-poisoned patient.[156] Again, this parameter was a more sensitive indicator of TCA altered mental status but not necessarily of seizures and/or dysrhythmias specifically. However, the T40-ms axis is not easily measured in the absence of specialized computer-assisted analysis, which limits its practical utility. An abnormal rightward axis can be estimated by observing a negative deflection (terminal S wave) in leads I and aVL and a positive deflection (terminal R wave) in lead aVR (Figure 71-1B and 71-3).

Easily quantifiable measurements in lead aVR on a routine ECG can predict toxicity (Figure 71-3). When prospectively studied, 79 patients with acute TCA overdoses demonstrated that the amplitude of the terminal R wave and R/S wave ratio in lead aVR (R_{aVR}, R/S_{aVR}) were significantly greater in patients who developed seizures and ventricular dysrhythmias.[75] The sensitivity of R_{aVR} = 3 mm and R/S_{aVR} = 0.7 in predicting seizures and dysrhythmias was comparable to the sensitivity of QRS = 100 msec. In this study, R_{aVR} â‰¥3 mm was the only ECG variable that significantly predicted these complications.

Thus, specific ECG measurements such as QRS interval duration and height of the R wave in lead aVR can be useful parameters in assessing and predicting CA toxicity, although neither is 100% sensitive in predicting cardiac and neurologic complications. However, documenting the absence of these abnormalities on sequential ECGs provides further evidence that cardiac toxicity is not developing. Serial ECGs should be obtained to monitor for worsening of these parameters, which might signal the need for further interventions. Based on published data demonstrating ongoing changes of the QRS and T40-ms axis despite therapeutic interventions, ECG parameters alone are not ideal and should be used in conjunction with the patient's clinical presentation, history, and course during the first several hours for decision making with regard to disposition and interventions.[76]

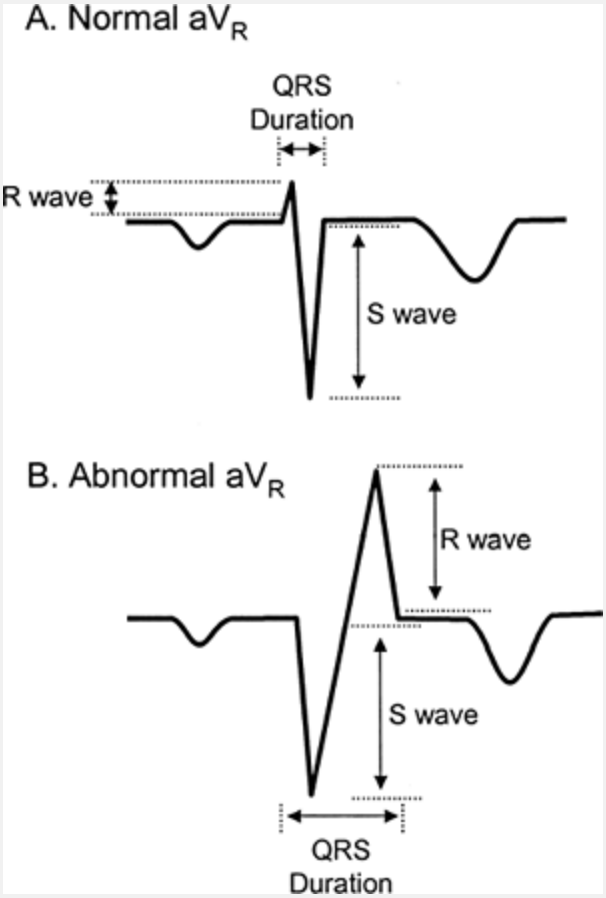


Figure 71-3. Normal QRS complex in lead aVR. B. Abnormal QRS complex in a patient with severe tricyclic antidepressant poisoning. R_{aVR} is measured as the maximal height in millimeters of the terminal upward deflection in the QRS complex. The S wave is measured in millimeters as the depth of the initial downward deflection.

Laboratory Tests

Quantitative determination of CA serum concentration has limited utility in the immediate evaluation and management of patients with

acute overdoses. The pharmacologic properties of CAsâ€”namely, large volumes of distributions, prolonged absorption phase, long distribution half-lives, pH-dependent protein binding, wide intrapatient variability of terminal elimination half-lives, and development of tolerance among people chronically taking these medicationsâ€”limit the value of serum concentrations in predicting acute toxicity. Serum concentrations usually do not correlate with acute clinical toxicity for these reasons. In 1 study, serum drug concentrations failed to accurately predict the risk of seizures or ventricular dysrhythmias.[14]

However, CA concentrations >1000 ng/mL usually are observed in patients with significant clinical toxicity (coma, seizures, and dysrhythmias), although life-threatening toxicity has also been observed in patients with serum concentrations <1000 ng/mL.[11,14,45,71,112,135] This serious toxicity at lower concentrations probably results from a number of factors, including the presence of coingestants, the

circumstances of ingestion (acute or acute on chronic), timing of the concentration in relation to the ingestion, and limitations of measuring the concentration in blood and not the affected tissue. Several studies demonstrate that both single and serial serum concentrations are not predictive of clinical outcome. Quantitative concentrations usually cannot be readily obtained in most hospital laboratories. However, qualitative screens for TCAs using an enzyme-multiplied immunoassay test are available at some hospitals, although false-positive results can occur with many drugs.

Analyzing CA concentrations may be helpful in diagnosing chronic CA toxicity. Therapeutic CA concentrations (including active metabolites) are generally in the range from 50â€“300 ng/mL. Any concentration outside this range, when measured at the appropriate time in association with onset or increase in adverse effects (tachycardia, dizziness, prolonged QTc), is an indication to decrease or stop the medication. Finally, quantitative concentrations may be helpful in

determining the cause of death in suspected overdose patients. Forensic studies have found lethal CA concentrations ranging from 1100â€“21,800 ng/mL. Measurement of liver drug concentrations or parent-to-metabolite drug ratios is preferable in the postmortem setting because CA concentrations may increase up to 5-fold because of postmortem redistribution from tissue to blood[5,6] (Chap. 33).

CAs can be detected qualitatively in the urine by thin-layer chromatography or by high-performance liquid chromatography. Bedside immunoassays are commercially available. False-positive results may occur in the presence of carbamazepine, cyclobenzaprine, diphenhydramine, and cyproheptadine.

Management

Any person with a suspected or known ingestion of a CA requires immediate evaluation and treatment (Table 71-3). The patient should be attached to a cardiac monitor and intravenous access should be secured. Early intubation is advised for patients with CNS depression and/or hemodynamic instability because of the potential for rapid clinical deterioration. A 12-lead ECG should be obtained for all patients. Laboratory tests including concentrations of glucose and electrolytes should be performed for all patients with altered mental status, as well as blood gas analysis to assess the degree of acidemia and to guide alkalinization therapy. Aggressive interventions for maintenance of blood pressure and peripheral perfusion must be performed early to avoid irreversible damage. The options for GI decontamination discussed below then should be considered.

Gastrointestinal Decontamination

Induction of emesis is contraindicated, given the potential for precipitous neurologic and hemodynamic deterioration. Because of the potential lethality of large quantities of CAs, orogastric lavage should be considered in the symptomatic patient with an intentional

overdose. Although the benefits of orogastric lavage for CA toxicity are not substantiated by controlled trials, the potential benefits of removing significant quantities of a highly toxic drug must be weighed against the risks of the procedure[15] (Chap. 8). Because the anticholinergic actions of some CAs may decrease spontaneous gastric emptying, attempts at orogastric lavage up to 12 hours after ingestion may yield unabsorbed drug. Patients with altered mental status or seizures should undergo orogastric lavage after endotracheal intubation only to protect the airway. The benefit of performing orogastric lavage in young children with unintentional ingestions of CAs may not be similar to that in adults with intentional ingestions. These scenarios usually do not result in ingestion of large quantities of pills, and the procedure may be associated with more risks and impracticalities, such as the size of holes in pediatric tubes. Activated charcoal should be administered in nearly all cases. Irrespective of age, an additional dose of activated charcoal several hours later is reasonable after a large ingestion, in a seriously poisoned patient in whom unabsorbed drug may still be present in the GI tract, in case of desorption of CAs from activated charcoal, or if the patient is a slow metabolizer. It is important to monitor for the development of a paralytic ileus to prevent abdominal complications from additional doses of activated charcoal.

TABLE 71-3. Treatment of Cyclic Antidepressant Toxicity

Toxic Effect	Treatment
Conduction Delays	
QRS >100 msec $R_a$vr â‰¥3 mm T40-ms axis >130	• Sodium bicarbonate: 1â€“2 mEq/kg IV boluses at 3- to 5-min intervals to reverse

	the abnormality or to a target serum pH no greater than 7.55 • Controlled ventilation (if clinically indicated for hypoventilation)
Dysrhythmias	
Sinus tachycardia	• No treatment
Wide-complex tachycardia/ventricular tachycardia	• Sodium bicarbonate: 1â€“2 mEq/kg IV boluses to reverse the dysrhythmia or to a target serum pH no greater than 7.55 • Correct hypoxia, acidosis, hypotension • Consider lidocaine: 1 mg/kg slow IV bolus, followed by infusion of 20â€“50 Âµg/kg/min • Consider hypertonic saline (3% NaCl) • Consider magnesium sulfate 25â€“50 mg/kg (maximum 2.0 g) IV over 2 min • Controlled ventilation (if clinically indicated)
Torsades de pointes	• Magnesium sulfate • Overdrive pacing

Hypotension	• Isotonic saline (0.9% NaCl) boluses (up to 30 mL/kg) • Correct hypoxia, acidosis • Sodium bicarbonate: 1â€“2 mEq/kg IV boluses to a target serum pH of no greater than 7.50â€“7.55 • Norepinephrine • Consider extracorporeal mechanical circulation (extracorporeal membrane oxygenation, cardiopulmonary bypass)
Seizures	• Benzodiazepines, propofol • Secure airway with intubation if necessary • Correct hypoxia, acidosis • Barbiturates • Continuous infusion of midazolam or propofol if barbiturates fail • Consider neuromuscular paralysis/general anesthesia if all other measures fail

Wide-Complex Dysrhythmias, Conduction Delays, and/or Hypotension

The mainstay therapy for treating wide-complex dysrhythmias and for reversing conduction delays and hypotension is the combination

of serum alkalinization and sodium loading. Controlled in vitro and in vivo studies in various animal models demonstrate that hypertonic sodium bicarbonate effectively reduces QRS complex prolongation, increases blood pressure, and reverses or suppresses ventricular dysrhythmias caused by CAs.[95,96,104,120,121,122] These studies also showed either equivalent or fewer beneficial effects of hyperventilation, hypertonic sodium chloride, and other nonsodium buffer solutions compared to sodium bicarbonate, suggesting multiple reasons for its effectiveness. A systematic review of all animal and human studies published until 2001 revealed that alkalinization therapy was the most beneficial therapy for consequential dysrhythmias and shock.[12]

Increasing the extracellular concentration of sodium, or sodium loading, may overcome the effective blockade of sodium channels through gradient effects (Figure 71-2). This mechanism explains why in some animal studies sodium bicarbonate was more effective in decreasing cardiotoxicity than were other sodium-free buffer solutions. Hypertonic sodium chloride loading reverses cardiotoxicity in several animal studies,[51,87,104] including doses as high as 15 mEq Na/kg.[86] However, the does of hypertonic saline for TCA poisoning has never been evaluated in humans, and the suggested dose in animals exceeds the amount that most clinicians would consider safe (1â€“2 mEq/kg). Unfortunately, no controlled human studies investigate which of the proposed mechanisms is most important, although the mechanism most likely is a combination. Furthermore, no controlled human studies demonstrate that sodium bicarbonate is effective; however, numerous reports and extensive clinical experience support its efficacy in treating serious CA cardiotoxicity.[12,18,19,52,53]

The optimal dosing and mode of administration of hypertonic sodium bicarbonate and the indications for initiating and terminating this treatment are unsupported by controlled clinical studies. Instead, the information is extrapolated from animal studies, clinical experience, and an understanding of the pathophysiologic mechanisms of CA

toxicity. A bolus, or rapid infusion over several minutes, of hypertonic sodium bicarbonate (1â€“2 mEq/kg) should be administered initially.[19,86,104] Higher doses have successfully treated patients, but experience is limited. Continuous ECG monitoring should be in place to follow the progression of ECG abnormalities. Additional boluses every 3â€“5 minutes can be administered until the QRS interval narrows and the hypotension improves. Blood pH should be monitored after several bicarbonate boluses, aiming for a target pH of no greater than 7.50â€“7.55. Because CA may redistribute from the tissues into the blood over several hours, it may be reasonable to begin a continuous sodium bicarbonate infusion to maintain the pH in this range. Differences in outcomes between repetitive boluses alone and boluses with further bicarbonate infusions are not well studied. Although diluting sodium bicarbonate in 5% dextrose in water and infusing it slowly renders it less able to raise the sodium gradient at the cell, the beneficial effects of pH elevation still may be warranted. No evidence supports prophylactic alkalinization in the absence of severe cardiovascular toxicity.

Use of hypertonic saline solutions (3% NaCl) or combined sodium bicarbonate and 0.9% sodium chloride solutions for rapid infusion theoretically should be efficacious, although these modalities are not adequately studied in humans. A case report describes the successful use of 7.5% NaCl to treat hypotension and QRS widening with ventricular ectopy in a patient with a nortriptyline overdose who was unresponsive to boluses of sodium bicarbonate and 0.9% sodium chloride solution.[90] The role of hypertonic saline remains undefined. However, it could be considered in situations of refractory hypotension, wide-complex tachycardia, and/or dysrhythmias. Potential risks of this treatment include fluid overload, sodium overload, and hyperchloremic metabolic acidosis.

Hyperventilation is a more rapid and easily titratable method of serum alkalinization but is not as effective as a single modality in reversing cardiotoxicity.[63,86] Simultaneous hyperventilation and sodium bicarbonate administration may result in profound alkalemia

and should be performed only with extreme caution and careful monitoring of pH.[157] Hyperventilation without bicarbonate administration may be indicated in patients with acute lung injury or congestive heart failure in whom administration of large quantities of sodium are contraindicated.

Alkalinization and sodium loading with hypertonic sodium bicarbonate and/or hypertonic saline along with controlled ventilation (if clinically indicated) should be administered to all overdose patients presenting with major cardiovascular toxicity. Indications include any conduction delays (QRS > 100 msec, R_{aVR} â‰¥3 mm, and/or an unexplained or new right bundle-branch block), wide-complex tachycardia, and hypotension. It is imperative to initiate treatment until CA toxicity can be excluded because of the risk for rapid and precipitous deterioration. Although commonly assumed, it is unclear whether the failure of the QRS complex to narrow with sodium bicarbonate treatment excludes CA toxicity.

Alkalinization may be continued for at least 12â€“24 hours after the ECG has normalized because of the drug's redistribution from the tissue. However, the time observed for resolution or normalization of conduction abnormalities is extremely variable, ranging from several hours to several days despite continuous bicarbonate infusion.[76] In some patients, clinical improvement occurred both before and during ECG changes. We recommend stopping alkalinization when the patient improves clinically and shows improvement, not necessarily normalization, of abnormal ECG findings.

Antidysrhythmic Therapy

Lidocaine is the antidysrhythmic most commonly advocated for treatment of CA-induced dysrhythmias, although no controlled human studies demonstrate its efficacy.[18,19,105] Because lidocaine has sodium channel-blocking properties, some investigators argue against its use in CA poisoning.[1] These theoretical concerns are not well supported in the literature or in theory. The use of class IA

(quinidine, procainamide, disopyramide, and moricizine) and class IC (flecainide, propafenone) antidysrhythmics is absolutely contraindicated because they have similar pharmacologic actions to CAs and thus may worsen the sodium channel inhibition caused by CAs and exacerbate cardiotoxicity. Class III antidysrhythmics (amiodarone, bretylium, and sotalol) prolong the QTc interval and, although unstudied, may be contraindicated as well.

Because magnesium sulfate has antidysrhythmic properties, it may be beneficial in the treatment of ventricular dysrhythmias. Animal studies of the effects of magnesium on CA-induced dysrhythmias yield conflicting results.[64,65] However, successful use of magnesium sulfate in the treatment of refractory ventricular fibrillation after TCA overdose is reported.[67] The routine use of magnesium requires further evaluation and currently is not recommended.

Based on electrophysiologic studies in animal models, the wide-complex tachycardia/ventricular tachycardia caused by CAs is rate dependent.[3,121] Slowing the heart rate in the presence of CAs may allow more time during diastole for drug unbinding from sodium channels and might result in an improvement in ventricular conduction, which then could abolish the reentry mechanism for

dysrhythmias. This mechanism was the rationale for the past use of physostigmine and propranolol. Thus, it is hypothesized that decreasing the sinus rate may itself be effective in abolishing ventricular dysrhythmias by eliminating rate-dependent conduction slowing. Propranolol terminated ventricular tachycardia in an animal model but unfortunately also caused significant hypotension.[122] In 1 case series, patients developed severe hypotension or had a cardiac arrest shortly after receiving a Î²-adrenergic antagonist.[37] Other animal studies suggest that preventing or abolishing tachycardia by sinus node destruction or by using bradycardic agents that impede sinus node automaticity without affecting myocardial repolarization or contractility may successfully prevent CA-induced ventricular dysrhythmias.[3,4] The combined negative inotropic effects of Î²-

adrenergic antagonists and CAs along with the significant cardiac and CNS effects reported with physostigmine use do not support their routine use in the management of CA-induced tachydysrhythmias.

Use of phenytoin as an antidysrhythmic agent in CA toxicity has been extensively studied. Several animal and human studies indicate phenytoin is successful in preventing or reversing some conduction abnormalities.[27,47,85] However, these studies were not well controlled for other confounding factors, such as blood pH and sodium bicarbonate administration, they had very small numbers, and, in some, the cardiotoxicity was not severe. Phenytoin may have a prodysrhythmogenic effect in the presence of CAs, thus inducing or worsening ventricular dysrhythmias.[23] Based on available evidence, phenytoin is not recommended for wide-complex tachydysrhythmias associated with CAs.

Hypotension

Hypotension is the most common cause of death secondary to CA toxicity.[130] Standard initial treatment for hypotension should include volume expansion with isotonic saline and alkalinization/sodium loading with hypertonic sodium bicarbonate (if conduction abnormalities also are present). Hypotension unresponsive to these therapeutic interventions necessitates the use of inotropic and/or vasopressor drug support and possibly extracorporeal cardiovascular support.

The choice of specific direct-acting or indirect-acting drug(s) for treatment of CA-associated hypotension is controversial. Available data are limited and contradictory. Norepinephrine, epinephrine, dopamine, and dobutamine are proposed to be effective drugs for hypotension, but no controlled human studies are available. Furthermore, the pharmacologic properties of CAs complicate the choice of a specific agent. Specifically, CA blockade of neurotransmitter reuptake theoretically could result in depletion of intracellular catecholamines. This blockade of norepinephrine and

dopamine reuptake then could blunt the effect of dopamine, which is dependent on the release of endogenous norepinephrine for its inotropic activity.[20] This Î±-adrenergic blockade and downregulation of receptors induced by CAs suggest that a direct-acting vasopressor such as norepinephrine is more efficacious than an indirect-acting catecholamine such as dopamine. Norepinephrine at high doses may be dysrhythmogenic and might exacerbate cardiovascular toxicity. Pure Î²-adrenergic agonists, such as isoproterenol and dobutamine, and even combination Î±- and Î²-adrenergic agonists, such as dopamine, theoretically could worsen the hypotension.

Animal data comparing various drugs are conflicting, and their direct applicability to clinical human poisoning is limited.[33,56,150] Both norepinephrine and epinephrine increased the survival rate in TCA-poisoned rats.[66] In addition, epinephrine was superior to norepinephrine when used both with and without sodium bicarbonate, and the most effective treatment regimen in their study was epinephrine plus sodium bicarbonate; neither drug precipitated dysrhythmias. The authors propose that epinephrine is more efficacious because it augments myocardial perfusion more than norepinephrine and improves the recovery of CA sodium channel blockade by hyperpolarization of the membrane potential through its stimulation of increased potassium intracellular transport.

Limited clinical data suggest that norepinephrine is more efficacious than dopamine.[145] In a retrospective study of 26 adult hypotensive patients, response rates to norepinephrine (5â€“53 Âµg/min) were significantly better than response rates to dopamine (5â€“10 Âµg/kg/min).[147] Patients who did not respond to dopamine at vasopressor doses (10â€“50 Âµg/kg/min) responded to norepinephrine (5â€“74 Âµg/min). However, the retrospective nature of this study, the subsequent lack of standard management therapies (which are indications for instituting vasoactive agents), and the heterogeneity of the population limit its generalizability. In another case report of CA toxicity, glucagon is reported to cause sustained increases in blood pressure.[126]

Based on the available data, pharmacologic effects, theoretical concerns, and experience, norepinephrine (0.1â€“0.2 Âµg/kg/min) is recommended for hypotension that is unresponsive to volume expansion and hypertonic sodium bicarbonate therapy. Central venous pressure and/or pulmonary artery catheterization may be necessary to guide the choice of additional vasopressor or inotropic agents, especially in the presence of other cardiodepressant drugs.

If pharmacologic measures fail to correct hypotension, extracorporeal life support measures should be considered. Extracorporeal membrane oxygenation, extracorporeal circulation, and cardiopulmonary bypass are successful adjuncts for refractory hypotension and life support when maximum therapeutic interventions fail.[46,70,155] These modalities can provide critical perfusion to the heart and brain and maintain metabolic function while giving the body time to metabolize and eliminate toxic concentrations of the drug by maintaining hepatorenal blood flow. Extracorporeal measures then may allow the impaired myocardium to recover.

Central Nervous System Toxicity

Endotracheal intubation should be performed in any comatose patient or in a patient with a significantly depressed mental status with acute CA toxicity. Use of flumazenil in the patient with known or suspected CA ingestion is contraindicated. Several case reports of patients with CA overdoses describe seizures following administration of flumazenil.[48,73,88] Physostigmine was used in the past to reverse the CNS toxicity of CAs[21,98] (Antidotes in Depth: Physostigmine). However, physostigmine is not recommended because it may increase the risk of cardiac toxicity, cause bradycardia and asystole, and precipitate seizures in CA-poisoned patients.[109]

Seizures caused by CAs usually are brief and may stop before treatment can be initiated. Recurrent seizures, prolonged seizures

(>2 minutes), and status epilepticus require prompt treatment to prevent worsening acidosis, hypoxia, and development of hyperthermia and rhabdomyolysis. Benzodiazepines are effective as first-line therapy for seizures.[9] If this therapy fails, barbiturates or propofol should be administered. Propofol also acts at the GABAâ€“chlorideâ€“ionophore complex. Propofol controlled refractory

seizures resulting from amoxapine toxicity.[92] Failure to respond to barbiturates should lead to consideration of neuromuscular paralysis and general anesthesia with continuous EEG monitoring. Phenytoin is not recommended for seizures because data do not demonstrate clear beneficial effects and administration could cause cardiovascular toxicity.[9,23]

Enhanced Elimination

No specific treatment modalities have demonstrated clinical significant efficacy in enhancing the elimination of CAs. Some investigators propose multiple doses of activated charcoal to enhance CA elimination because of their small enterohepatic and enterogastric circulation.[82] Human volunteer studies and case series of patients with CA overdoses suggest that the half-life of CAs may be decreased by multiple-dose activated charcoal (MDAC).[26,61,101,143] MDAC reduced the apparent half-life of amitriptyline to 4â€“40 hours in overdose patients, compared to previously published values of 30 to >60 hours.[143] Changes in the severity or duration of clinical toxicity, however, were not reported. Other investigators showed in human volunteers that MDAC reduced the half-life of therapeutic doses of amitriptyline approximately 20% compared with no activated charcoal administration.[61] However, the methodologic flaws and equivocal findings of these studies and the lack of any positive outcome data for this intervention from additional studies do not provide overwhelming evidence supporting its use in this setting.[25,44] The pharmacokinetic properties of CAs (large volumes of distribution, high plasma-protein binding) weighed against the small increases in

clearance and the potential complications of MDAC, such as impaction, intestinal infarction, and perforation, do not warrant its routine use.[25] However, MDAC conceivably might shorten the duration of clinical toxicity in patients who are â€œslow metabolizers.â€• One additional dose of activated charcoal may be given to patients with evidence of significant CNS and cardiovascular toxicity if bowel sounds are present.

Measures to enhance urinary CA excretion have a minimal effect on total clearance.[61] Hemodialysis is ineffective in enhancing the elimination of CAs because of their large volumes of distribution, high lipid solubility, and extensive protein binding.[50] Hemoperfusion overcomes some of the limitations of hemodialysis but should not be that effective because of the large volumes of distributions of CAs.[106] Several uncontrolled case reports anecdotally described improvement in cardiotoxicity during hemoperfusion, although the finding may have been coincidental.[36] Currently, little substantial evidence supports the use of hemoperfusion in the management of CA overdose.

Investigational Therapies

The development and investigation of an affinity-purified ovine polyclonal Fab fragment to TCAs spanned more than 10 years.[29,55,62,110] Initial clinical trials showed favorable results with TCA-specific Fab fragment treatment in improving both cardiovascular and CNS toxicity.[49] The emergence of the SSRIs with the resultant significant decrease in TCA prescriptions and the significant cost of producing the TCA-specific Fab have limited the interest in clinical trials and production of this new therapy.

Experimental studies demonstrate that induction of ventricular tachydysrhythmias during TCA toxicity is dependent upon heart rate.[3] The bradycardic agent UL-FS 49 effectively impedes the marked sinus tachycardia and frequency-dependent ventricular conduction delay associated with amitriptyline toxicity in a canine

model.[4] Pretreatment with this drug effectively prevented the onset of sustained ventricular tachydysrhythmias. In addition, unlike other Î²-adrenergic antagonists that have negative inotropic affects, UL-FS 40 did not appear to adversely influence hemodynamics, thereby potentially decreasing the risk of significant hypotension associated with its use. This investigational drug warrants further clinical studies in patients presenting with marked sinus tachycardia and conduction delays to determine its effectiveness in preventing wide-complex dysrhythmias and/or ventricular tachydysrhythmias.

Hospital Admission Criteria

All patients who present with known or suspected CA ingestion should undergo continuous cardiac monitoring and serial electrocardiography for a minimum of 6 hours. Fears of delayed complications and inability to predict toxicity led clinicians in the past to adopt all-inclusive admission guidelines for suspected CA ingestion. The once-standard practice of admitting all patients with CA ingestion for medical monitoring because of the risk of late complications or sudden death is not supported by the current literature. Most patients develop major clinical toxicity within several hours of presentation.[26] Several retrospective studies support a disposition algorithm that takes into account presenting clinical signs and symptoms.[7,26,39,144] If the patient is asymptomatic at presentation, undergoes GI decontamination, has normal ECGs, or has sinus tachycardia (with normal QRS complex) that resolves, and the patient remains asymptomatic in the healthcare facility for a minimum of 6 hours without any treatment interventions, the patient may be medically cleared for psychiatric evaluation (if appropriate) or discharged home as appropriate.

A prospective study of 67 patients used the Antidepressant Overdose Risk Assessment (ADORA) criteria to identify patients who were at high risk for developing serious toxicity and thus proposed the following criteria for hospitalization.[34] In this study, the presence of

QRS interval >100 msec, cardiac dysrhythmias, altered mental status, seizures, respiratory depression, or hypotension on presentation to the ED (or within 6 hours of ingestion if the time was known) was 100% sensitive in identifying patients with significant toxicity and subsequent complications. Furthermore, none of the low-risk patients (defined as absence of all these criteria) developed any further toxicity or complications, supporting the decision for medical clearance and/or discharge.

Criteria specifically for ICU admission (other than patients requiring ventilatory and/or blood pressure support) versus an inpatient bed with continuous cardiac monitoring are less clear and probably more institution dependent.[139]

The disposition of patients with persistent isolated sinus tachycardia or prolonged QTc with no concomitant altered mental status or blood pressure changes is not clearly defined. Previous studies demonstrate that these 2 parameters alone are not predictive of subsequent clinical toxicity or complications.[34,35,45] In addition, the sinus tachycardia may persist for up to 1 week following ingestion.[99,127] However, another study of pure TCA overdose patients reported that a heart rate >120 beats/min and QTc interval >480 msec were associated with an increased likelihood of major toxicity.[24] These patients might be good candidates for observation units with continuous ECG monitoring and serial ECGs for 24 hours.

Inpatient Cardiac Monitoring

The duration of cardiac monitoring in any patient initially exhibiting signs of major clinical toxicity depends on many factors.

Certainly the duration of CA cardiotoxicity and neurotoxicity may be prolonged, as might be expected from the long serum half-life of CAs, in patients who are slow hydroxylators, or in the presence of a coingestant that alters the metabolism of CAs or causes cardiac or neurologic toxicity. Recommendations in the older literature for

48â€“72 hours of ICU monitoring even in mild CA ingestions stem from isolated case reports of late-onset dysrhythmias, CNS effects, and sudden deaths.[38,40,108,125] However, review of these cases shows inadequate gastric decontamination, inadequate therapeutic interventions, and significant ongoing complications of overdose. Several retrospective studies demonstrate that late, unexpected complications in CA overdoses (eg, seizures, dysrhythmias, and death) do not occur in patients who had few or no major signs of toxicity at presentation or a normal level of consciousness and normal ECG for 24 hours.[22,31,45,111,139] All fatalities resulting directly from CA toxicity occur in the first 12â€“24 hours.

Using normalization of ECG abnormalities as an end point for therapy and discharge is problematic. Some studies document the variable resolution and normalization of QRS prolongation and T40-ms axis rotation.[103,131] Based on the available literature, it is reasonable to recommend that after the mental status and blood pressure normalize, patients should be monitored for another 24 hours off all therapy, including alkalinization, antidysrhythmics, and inotropics/vasopressors. If the patient shows improvement of ECG abnormalities with these criteria, the patient can be discharged to a monitored bed on the ward with a low risk of further complications.

Summary

CA poisoning continues to be a cause of serious morbidity and mortality worldwide. The distinctive characteristics of these drugs can cause significant CNS and cardiovascular toxicity, the latter being responsible for mortality as a result of overdose of these drugs. Cardiovascular toxicity ranges from mild conduction abnormalities and sinus tachycardia to wide-complex tachycardia, hypotension, and asystole. CNS toxicity includes delirium, lethargy, seizures, and coma. The ECG is a simple, readily available diagnostic test that can predict the development of significant toxicity, particularly seizures and/or dysrhythmias. Management strategies

are based primarily on the pathophysiology of these drugs, namely, sodium channel blockade in the myocardium. Alkalinization and sodium loading with hypertonic sodium bicarbonate and isotonic saline are the principal modes of specific therapy for cardiovascular toxicity. Guidelines for observing or admitting patients to the hospital may be based on initial clinical presentation and/or development of clinical symptomatology and ECG changes.

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Chapter 72
Sedative-Hypnotics

David C. Lee

A 73-year-old man was brought to the emergency department by ambulance after his family found him unconscious in his bedroom. On presentation, he was lethargic and intermittently followed commands. He had a medical history significant for hypertension and coronary artery disease. According to the family, he recently was prescribed a new medication as a sleeping aid. Initial vital signs were: blood pressure, 138/90 mm Hg; heart rate, 65 beats/min; respiratory rate, 12 breaths/min; oral temperature, 98.3Â°F (36.8Â°C); room air pulse oximetry, 94%. His pupils were 3 mm, and there were no signs of trauma. He had an appropriate gag reflex, and his physical examination was otherwise unremarkable. His bedside glucose concentration and electrocardiogram were normal. He was treated with 2 mg intravenous naloxone and 100 mg intravenous thiamine without response. He was placed on supplemental oxygen (FiO_2 28%), which raised his oxygen saturation to 96%. However, he had periods of bradypnea during which his saturation fell to 90%. His family produced a recently prescribed bottle of zolpidem. After firmly establishing with the family that he

did not have a history of seizures, use of cyclic antidepressants, or dependence on benzodiazepines, the decision was made to reverse his sedation with flumazenil (1 mg intravenously), upon which he awoke. He admitted to â€œhaving a few drinksâ€• and had taken his new medication to help him sleep. His blood alcohol concentration was 180 mg/dL, and results of routine laboratory screening was unremarkable. He was admitted to the hospital for medical observation and psychiatric evaluation. He required no further medical intervention other than supplemental oxygen, and he was discharged 24 hours later.

Sedative-hypnotics are drugs that are prescribed to induce a calming effect, limit excitability (sedative), or induce drowsiness and sleep (hypnotic). *Anxiolytics* or *tranquilizers* are other medical terms that are often used to describe drugs that are sedative-hypnotics. The term *tranquilizer* has fallen out of favor because of the lack of precision. The term *anxiolytic* is the preferred term because this medication diminishes feelings of anxiety. Other drugs that are not classically considered sedative-hypnotics, such as serotonin reuptake inhibitors, are used successfully to treat anxiety conditions. Because many different types of drugs and dietary supplements are used for their sedative or hypnotic effect, this group of xenobiotics actually encompasses a wide range of various compounds. This chapter focuses primarily on pharmaceutical drugs used solely for their sedative-hypnotics effects, specifically drugs that primarily interact with the Î³-aminobutyric acid (GABA) receptor (Table 72-1).

History and Epidemiology

Throughout history, sedative-hypnotic use and abuse have been commonplace. Mythology of ancient cultures is replete with stories of poisons or compounds that cause sleep or a state of unconsciousness (Chap. 1). Overdoses were reported soon after the commercial introduction of bromide preparations, the first commonly available class of sedative-hypnotic agent, in 1853. Other commercial

xenobiotics that subsequently were developed include chloral hydrate, paraldehyde, sulfonyl, and urethane.

The barbiturates were introduced in 1903 and quickly supplanted the older xenobiotics. This class of drugs dominated the sedative-hypnotic market for the first half of the 20th century. Unfortunately, because barbiturates have a relatively low therapeutic-to-toxic ratio and substantial potential for abuse, they quickly became a major health problem. By the 1950s and 1960s, barbiturates were frequently implicated in overdoses and were responsible for the majority of drug-related suicides. As fatalities from barbiturates increased, attention shifted to preventing their abuse and finding less toxic alternatives.[22, 141] These â€œsaferâ€• drugs included methyprylon, glutethimide, ethchlorvynol, and methaqualone. Unfortunately, many of these drugs also had significant undesirable effects. With the introduction of benzodiazepines in the early 1960s, barbiturates and the alternative drugs were quickly supplanted.

Intentional and unintentional overdoses with sedative-hypnotic agents are common. According to the American Association of Poison Control Centers, the sedative-hypnotic class of agents is consistently one of the top 5 classes of drugs associated with, although not usually causative of, overdose fatalities (Chap. 130). With the ubiquitous worldwide use of sedative-hypnotics, they probably also are associated with substantially more deaths than are officially reported.

Chlordiazepoxide, the first commercially available benzodiazepine, initially was synthesized by Hoffman-LaRoche in 1955 and marketed in 1960. Now more than 50 benzodiazepines are marketed, and more are being developed. In the 1980s, benzodiazepines captured >80% of the sedative market and >50% of the hypnotic market.[70, 159] Compared with an overdose of barbiturates, an overdose of a benzodiazepine alone accounts for relatively few deaths.[49] Most deaths associated with benzodiazepines result from mixed overdoses of benzodiazepines and other respiratory depressants, especially

alcohol.[61]

Because of the popularity of benzodiazepines and the perception of widespread abuse, changes in local regulations and restrictions in

prescribing practices for benzodiazepines led to a resurgence in the use of older sedative-hypnotic agents in specific areas. In New York State, where restrictions were implemented in 1989 for prescribing benzodiazepines by the use of designated prescriptions issued by the state to physicians, a 60% decrease in benzodiazepine prescriptions was noted, as well as a 125% increase in meprobamate, 136% increase in chloral hydrate, and 30% increase in butabarbital prescriptions in the following year[67 , 189] and a proportional increase in overdoses of some of these drugs. Although benzodiazepines represent most of the market for prescribed sedatives, the recently introduced hypnotic agents zolpidem, zaleplon and eszopiclone have replaced benzodiazepines as the most prescribed pharmaceutical sleeping aids.

Benzodiazepines
Agents with full agonist activity at the benzodiazepine site
Alprazolam
Xanax
1.0
10â€“14
80
0.8
No
Chlordiazepoxide
Librium
50
5â€“15
96
0.3
Yes

Clorazepate
Tranxene
15
97
0.9
Yes
Unclear
Clonazepam
Klonopin
0.5
18â€“50
85.4
Unclear
Yes
Diazepam
Valium
10
20â€“70
98.7
1.1
Yes
Estazolam
ProSom
2.0
8â€“31
93
0.5
No
Flunitrazepam[a]
Rohypnol
1.0
16â€“35
80
1.0â€“1.4

Yes
Flurazepam
Dalmane
30
2.3
97.2
3.4
Yes
Lorazepam
Ativan
2.0
9â€“19
90
1â€“1.3
None
Midazolam
Versed
â€”
3â€“8
95
0.8â€“2
Yes
Oxazepam
Serax
30
5â€“15
Unclear
Unclear
No
Temazepam
Restoril
30
10â€“16
97

0.75â€“1.37
No
Triazolam
Halcion
0.25
1.5â€“5.5
90
0.7â€“1.5
Yes
Nonbenzodiazepine agents active mainly at the type I (Ï‰1) benzodiazepine site
Eszoplicone
Lunesta
?
6
55
1.3
No
Zaleplon
Sonata
20
1.0
92
0.54
No
Zolpidem
Ambien
20
1.7
92
0.5
No
Barbiturates
Amobarbital

Amytal
â€”
8â€“42
Unclear
Unclear
Unclear
Aprobarbital[a]
Alurate
â€”
14â€“34
Unclear
Unclear
Unclear
Butabarbital
Butisol
â€”
34â€“42
Unclear
Unclear
Unclear
Barbital[a]

â€”
6â€“12
25
Unclear
Unclear
Mephobarbital
Mebaral
â€”
5â€“6
40â€“60
Unclear
Yes

Methohexital
Brevital
â€”
3â€“6
73
2.2
Unclear
Pentobarbital
Nembutal
100
15â€“48
45â€“70
0.5â€“1.0
Unclear
Phenobarbital
Luminal
30
80â€“120
50
0.5â€“0.6
No
Primidone
Mysoline
â€”
3.3â€“22.4
19
Unclear
Yes
Secobarbital
Seconal
â€”
15â€“40
52â€“57
Unclear

Unclear
Thiopental
Pentothal
â€”
6â€“46
72â€“86
1.4â€“6.7
Unclear
Other
Chloral hydrate
Aquachloral
NA
4.0â€“9.5
35â€“40
0.6â€“1.6
Yes
Ethchlorvynol[a]
Placidyl
NA
10â€“25
30â€“40
4
Unclear
Etomidate
Amidate
NA
2.9â€“5.3
98
2.5â€“4.5
Unclear
Glutethimide[a]
Doriden
NA
5â€“22

47â€“59
2.7
Unclear
Methprylon[a]
Nodular
NA
3â€“6
60
0.97
Unclear
Meprobamate[a]
Miltown
NA
6â€“17
20
0.75
Unclear
Methaqualone[a]
Quaalude
NA
19
80â€“90
5.8â€“6.0
Yes
Paraldehyde[a]
Paral
NA
7
Unclear
0.9
Unclear
Propofol
Diprivan
NA

4â€“23
98
2â€“10
No
NA = not applicable comparison.
[a] Not presently available in the United States.
[b] This table is an approximation of equipotent doses of drugs affecting the benzodiazepine receptor and several barbiturates. All of the full agonist benzodiazepines have similar amnestic, anxiolytic, sedative, and hypnotic effects. These effects are a reflection of dose and plasma concentration. There can be significant variation of these effects according to age and gender.

Trade Name	Equipotent Dosing Oral Dose (mg)[b]	Plasma $t_{1/2}$	Protein Binding (%)	Vd (L/kg)	Active Metabolite Important

TABLE 72-1. Pharmaceutical Sedative-Hypnotics

Pharmacology

All of the sedative-hypnotics produce central nervous system (CNS) depression. Most clinically effective sedative-hypnotics produce their physiologic effects by enhancing the function of GABA-mediated chloride channels. The presence of sedative-hypnotics alters the receptor and affects the function of the chloride channel. These alterations include increasing the frequency of opening or the duration of opening.[4] The varying effects of the sedative-hypnotics can be explained further by their action on the various GABA receptor subtypes. Different sedative-hypnotics have variable affinities for certain GABA receptors with specific subunits (Chap. 14).

$GABA_A$ receptors are the primary mediators of inhibitory neurotransmission in the brain. The $GABA_A$ receptor is a pentameric structure composed of various polypeptide subunits associated with a chloride channel on the postsynaptic membrane. These subunits are classified into 3 families (Î±, Î², Î³). Variations in the 5 subunits of the GABA receptor confer the potency of its sedative, anxiolytic, hypnotic, amnestic, and muscle-relaxing properties. The most common $GABA_A$ receptor in the brain is composed of $Î±_1$ $Î²_2$ $Î³_2$ subunits. Almost all sedative-hypnotics bind to $GABA_A$ receptors containing the $Î±_1$ subunit. One possible exception is etomidate, which produces sedation at the $Î²_2$ unit and anesthesia at the $Î²_3$ subunit.[30 , 122 , 142 , 172] Low doses of benzodiazepines are effective only at $GABA_A$ receptors with the $Î³_2$ subunit. Even within the classes of sedative-hypnotics, there are varying affinities for different subunits.[40 , 106]

Many sedative-hypnotics have activity at multiple different receptor sites. Not only do sedative-hypnotics increase the effects of GABA-mediated inhibitory neurotransmission, many sedative-hypnotics, such as trichloroethanol, decrease the effects of glutamate-mediated excitatory neurotransmission.[35 , 132 , 149] Barbiturates, benzodiazepines, etomidate, and propofol interact with *N* -methyl-D-aspartate (NMDA) and AMPA/kainate receptor function. Barbiturates and propofol markedly attenuate the excitatory effects of glutamate.[24 , 48 , 130 , 190] Benzodiazepines inhibit adenosine metabolism and reuptake, thereby potentiating both A_1 -adenosine (negative dromotropy) and A_2 -adenosine (coronary vasodilatation) receptor-mediated effects.[118 , 157] Benzodiazepines interact with serotonergic pathways. Diazepam modulates morphine analgesia via serotonergic pathways, and the anxiolytic effects of clonazepam can be partially explained by upregulation of serotonergic receptors, specifically 5-HT_1 and 5-HT_2 .[8 , 119 , 180]

Pharmacokinetics/Toxicokinetics

Most sedative-hypnotics are rapidly absorbed in the gastrointestinal (GI) tract, with the rate-limiting step consisting of dissolution and dispersion of the drug. Barbiturates and benzodiazepines are primarily absorbed in the small intestine. Clinical effects are determined by the relative ability of these drugs to penetrate the bloodâ€“brain barrier. Drugs that are highly lipophilic penetrate most rapidly. The ultrashort-acting barbiturates are clinically active in the most vascular parts of the brain (gray matter first), with sleep occurring within 30 seconds of administration.

After initial distribution, many of the sedative-hypnotics undergo a redistribution phase as they are dispersed to other body tissues, specifically fat. Drugs that are redistributed, such as the lipophilic (ultrashort-acting) barbiturates and some of the benzodiazepines (diazepam, midazolam), may have a brief clinical effect as the early peak concentrations in the brain rapidly decline. The clinical activity of many of these drugs is determined by their rapid distribution and redistribution (alpha phase) and not by their elimination (beta phase) (Chap. 9).

Many of the sedative-hypnotics are metabolized to pharmacologically active intermediates. This is particularly true for chloral hydrate and some of the benzodiazepines. Benzodiazepines can be demethylated, hydroxylated, or conjugated with glucuronide in the liver. Glucuronidation proceeds rapidly with the production of inactive metabolites. Benzodiazepines, such as diazepam, undergo demethylation that yields active intermediates with a more prolonged therapeutic half-life than the parent compound. Because of the individual pharmacokinetics of sedative-hypnotics and the production of active metabolites, there often is no correlation between the therapeutic half-life and the biologic half-life.

The majority of sedative-hypnotics, such as the highly lipid-soluble barbiturates and the benzodiazepines, are highly protein bound. These drugs are poorly filtered by the kidney, and elimination occurs principally by hepatic metabolism. Chloral hydrate and meprobamate

are notable exceptions. Drugs with a low lipid-to-water partition coefficient, such as meprobamate and the longer-acting barbiturates, are poorly protein bound and more subject to renal excretion. Renal elimination can be increased by manipulation of urinary pH (Chap. 10). Phenobarbital is a classic example of a drug whose elimination can be manipulated with this technique. Most other drugs are not amenable to pH manipulation.

Toxicodynamics

Overdoses of combinations of sedative-hypnotics can be more toxic than overdoses of a single xenobiotic because multiple xenobiotics can produce synergistic clinical effects mediated by interactions on the GABA receptor (Chap. 14). For example, both barbiturates and benzodiazepines act on the GABA site, but barbiturates prolong the opening of the chloride ionophore, whereas benzodiazepines increase the frequency of ionophore opening.[159] Various sedative-hypnotics may increase the affinity of another xenobiotic at their respective binding sites. For example, pentobarbital increases the affinity of Î³-hydroxybutyrate (GHB) for its non-GABA binding site.[161] Propofol potentiates pentobarbital's effect on chloride influx at the GABA receptor.[168] Propofol also increases the affinity and decreases the rate of dissociation of benzodiazepines from their site on the GABA receptor.[21 , 144] These actions increase the clinical effect of each xenobiotic and may lead to deeper CNS and respiratory depression.

Another mechanism of synergistic toxicity is the alteration of metabolism. The combination of ethanol and chloral hydrate, historically known as a â€œMickey Finn,â€• has additive CNS depressant effects. Chloral hydrate competes for alcohol dehydrogenase, thereby prolonging the half-life of ethanol. The metabolism of ethanol generates the reduced form of nicotinamide adenine dinucleotide NADH, which is needed as a cofactor for the metabolism of choral hydrate to trichloroethanol, an active metabolite. Finally, ethanol inhibits the conjugation of

trichloroethanol, which in turn inhibits the oxidation of ethanol (Figure 72-1).[154 , 155]

Because of the great variety of drugs, multiple drugâ€“drug interactions can occur that may prolong the half-life of many sedative-hypnotics and significantly increase their potency. For example, the half-life of midazolam, which undergoes hepatic metabolism via cytochrome CYP3A4, can increase dramatically in the presence of certain drugs that compete for metabolism.[124] Specifically, the half-life of midazolam rises 400-fold when coadministered with itraconazole.[7]

Tolerance

Ingestions of relatively large doses may not have the predicted effects in patients who chronically use sedative-hypnotics. These patients often develop *tolerance* , defined as the progressive diminution of effect of a particular drug with repeated administrations that results in a need for greater doses to achieve the same effect. Tolerance can be secondary to pharmacodynamic or pharmacokinetic

factors. However, in the majority of cases, tolerance to sedative-hypnotics is caused by pharmacodynamic changes[160] (Chap. 15).

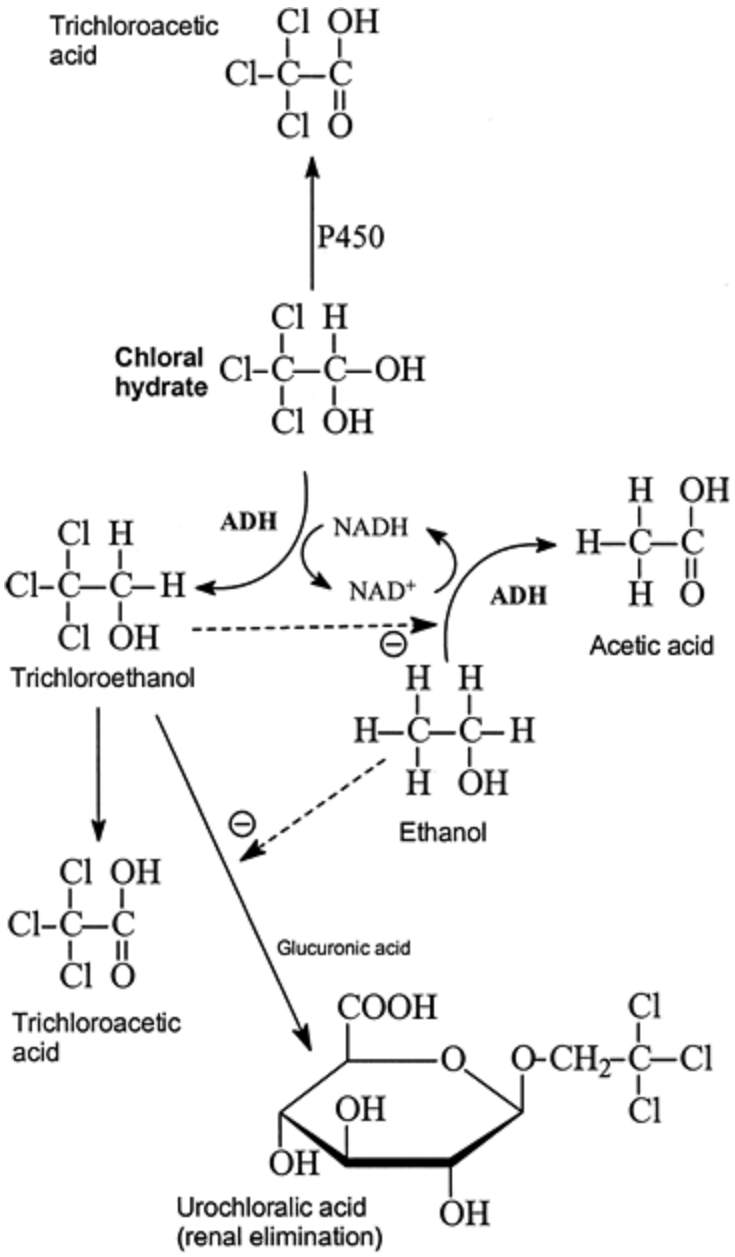

Figure 72-1. Metabolism of chloral hydrate and ethanol, demonstrating the interactions between chloral hydrate and ethanol metabolism. Note the inhibitory effects *(dotted lines)* of ethanol on trichloroethanol metabolism and the converse. *(Adapted from Sellers EM, Lang M, Koch-Weser J, et al: Interaction of chloral hydrate and ethanol in man. I. Metabolism. Clin Pharmacol Ther 1972;13:40.)*

Pharmacodynamic tolerance occurs when adaptive neural and

receptor changes (â€œplasticityâ€•) occur after repeated exposures. These changes include a decrease in the number of receptors (â€œdownregulationâ€•), reduction of firing of receptors (â€œreceptor desensitizationâ€•), structural changes in receptors (â€œreceptor shiftâ€•), and reduction of coupling of sedative-hypnotics and their respective $GABA_A$ -related receptor site. In this setting, a drug has a decreased effect even though drug concentrations do not change significantly. For example, benzodiazepine-dependent patients have decreased $GABA_A$ receptor density and sensitivity.[52, 136] Chronic benzodiazepine administration in rats causes uncoupling of the benzodiazepine receptor and the chloride channel in the GABA receptorâ€“chloride channel complex.[3, 137] Pharmacodynamic tolerance secondary to receptor changes can occur quickly, even during short-term use.[69] With certain xenobiotics, tolerance develops within minutes.[31, 71] In one study using IV infusions of thiopental at variable rates and a specific EEG pattern, rapidly increasing thiopental concentrations were needed to produce a constant state of anesthesia.[17]

The â€œMellanby effectâ€• describes the development of acute tolerance such that, at a given serum concentration, a greater clinical effect occurs when serum concentrations are rising than when they are declining. This effect, initially described for alcohol, may also apply to all sedative-hypnotics drugs.[31, 72, 90, 104] Acute tolerance may not follow a linear pattern, and increasing tolerance may occur at certain thresholds. In a study in which rats were infused with propofol at variable rates and monitored by EEG, acute tolerance occurred only at certain times.[72] Thus, pharmacodynamic tolerance can occur rapidly and have a nonlinear relationship to dose.

Pharmacokinetic tolerance occurs when metabolic changes cause decreasing concentrations of a chronically administered drug. For example, repeated use of phenobarbital induces hepatic microsomal enzyme expression, thereby decreasing its own half-life. Increasing doses of phenobarbital may be required to achieve the same steady-

state concentration.

Cross-tolerance readily exists among the sedative-hypnotics. For example, chronic use of benzodiazepines not only decreases the activity of the benzodiazepine site on the GABA receptor but also decreases the binding affinity of the barbiturate sites.[4, 68] Diazepam-tolerant mice are tolerant to the sedative-hypnotic properties of isoflurane.[50]

After therapy is terminated, tolerance can be lost as the desensitized target receptors return to their original level of function. The rate at which this process occurs is governed by the biologic half-life of the particular sedative-hypnotic and any biologically active intermediates produced. Tolerance persists for a period of time after the active xenobiotics are eliminated.[147]

Dependence and Withdrawal

Physical drug dependence refers to a condition of physiologic withdrawal induced by sudden termination of a drug. All sedative-hypnotics produce dependence and withdrawal. Approximately one third of chronic benzodiazepine users experience withdrawal when benzodiazepine use is suddenly decreased or discontinued.[85] Factors that contribute to the severity of withdrawal include shorter half-life of the agent, higher daily dosage, and underlying medical and psychological illness (Chap. 15).

Other areas of concern are unrecognized development of dependence and iatrogenic precipitation of withdrawal. Potent, fast-acting, short-lived sedatives are commonly used in the critical care setting. However, these same characteristics increase the potential for dependence. Rapid weaning from these medications or use of flumazenil may precipitate withdrawal. Delayed presentation of withdrawal after extubation and cessation of sedation occurs often with rapid weaning.[19, 164] Approximately one third of intensive care unit patients who were mechanically ventilated for >1 week suffered

from acute withdrawal when opioids or sedative-hypnotic agents were discontinued.[25]

Clinical Manifestations

Patients with significant sedative-hypnotic overdoses manifest slurred speech, ataxia, and incoordination, a syndrome similar to ethanol intoxication. Patients with moderate to severe toxicity are stuporous or comatose. In the most severe cases, all neurologic responses may be lost. In most instances, respiratory depression parallels CNS

depression. Hypoventilation produces respiratory acidosis and contributes to cardiovascular depression.

Hypothermia
Barbiturates, bromides, ethchlorvynol
Unique odors
Chloral hydrate, ethchlorvynol
Cardiac dysrhythmias
Meprobamate
  Bradycardia
GHB
  Tachydysrhythmias
Chloral hydrate
Muscular twitching
GHB, methaqualone, propofol, etomidate
Acneiform rash
Bromides
Fluctuating coma
Glutethimide, meprobamate
GI bleeding
Chloral hydrate, methaqualone
Discolored urine
Propofol (green/pink)

Anticholinergic signs
Glutethimide

Clinical Signs Sedative-Hypnotics

TABLE 72-2. Clinical Findings of Sedative-Hypnotic Overdose

Although the physical examination rarely identifies particular sedative-hypnotics, it can give clues to the class of sedative-hypnotics (Table 72-2). Hypothermia has been described with most of the sedative-hypnotics but may be more pronounced with barbiturates.[74 , 148 , 183] Barbiturates may cause fixed drug eruptions that often are bullous and appear over pressure-point areas. However, this phenomenon is not specific to barbiturates and has been documented with other xenobiotics, including carbon monoxide, methadone, imipramine, glutethimide, and benzodiazepines. Methaqualone can cause muscular rigidity and clonus.[1] Glutethimide can present with anticholinergic signs and symptoms.[59] Chloral hydrate may present with vomiting, gastritis, and cardiac dysrhythmias.[58 , 93 , 123 , 171]

Large intravenous doses of sedative-hypnotics are associated with toxicities that are independent of the characteristics of the sedative-hypnotic but rather are associated with their diluents. Propylene glycol inducing hypotension, hyperosmolar states, and metabolic acidosis occur in patients with prolonged use of lorazepam and etomidate.[87 , 96 , 105 , 143 , 170] In one study, two thirds of critical care patients given high doses of lorazepam (0.16 mg/kg/h) for more than 48 hours had significant accumulations of propylene glycol as manifested by hyperosmolar anion gap metabolic acidosis.[6] Fatal reactions are associated with the carrier base of intravenous propofol.[139]

Diagnostic Testing

In the undifferentiated comatose patient without a clear history and when overdose is a primary concern, laboratory testing, including electrolytes, liver enzymes, thyroid function tests, blood urea nitrogen (BUN), creatinine, glucose, venous or arterial blood gas analysis, and cerebrospinal fluid analysis, may be useful to exclude metabolic abnormalities. Diagnostic imaging studies, such as head CT scans, may be warranted on a case-by-case basis.

Routine laboratory screening for â€œdrugs of abuseâ€• generally are not helpful in the management of undifferentiated comatose adult patients, although they may be useful for epidemiologic purposes in a particular community. These tests vary in type, sensitivity, and specificity. The majority of sedative-hypnotics, including the most common class, benzodiazepines, typically are not included or detected on drug-abuse screens (Chap. 7).

The typical benzodiazepine screen identifies metabolites of 1,4-benzodiazepines, such as oxazepam or desmethyldiazepam. Many benzodiazepines that are metabolized to alternative compounds remain undetected. Benzodiazepines that are 7-amino analogs, such as clonazepam and flunitrazepam, may not be detected because they do not have a metabolite with a 1,4-benzodiazepine structure. Alprazolam and triazolam are not detected because they undergo minimal metabolism.[44]

Specific laboratory concentrations (eg, alcohol or phenobarbital) may be helpful to confirm or disprove overdoses of a xenobiotic. However, specific concentrations of sedative-hypnotics other than phenobarbital are not routinely performed in most hospitals. Abdominal radiographs may detect GI chloral hydrate because of its radiopacity (Chap. 6).

Although immediate identification of a particular sedative-hypnotics agent may be helpful in predicting the length of toxicity, it rarely affects the acute management of the patient. Phenobarbital may be the exception, for which urinary alkalinization may alter management.

Management

Historically, analeptics and other nonspecific arousal agents (Antiquated Antidotes in Depth) were used, but their use is to be condemned. Deaths secondary to sedative-hypnotic overdose result from cardiorespiratory collapse. Therefore, careful attention should focus on monitoring and maintaining adequate airway, oxygenation, and hemodynamic support. Supplemental oxygen, respiratory support, and prevention of aspiration are the cornerstones of treatment. Hemodynamic instability, although often a secondary or a delayed manifestation of sedative-hypnotic poisoning typically following respiratory collapse, should be approached with volume expansion. Vasopressors should be used only when patients do not respond to intravenous fluids or when evidence of volume overload is present. Patients with chloral hydrate overdoses classically present with both respiratory depression and cardiac toxicity, including lethal ventricular dysrhythmias, resulting from its active halogenated metabolite trichloroethanol. In the setting of cardiac dysrhythmias, judicious use of Î²-adrenergic antagonists is proposed.[16 , 58 , 181]

Decontamination

All clinically stable patients with significant ingestions should receive activated charcoal. Multiple-dose activated charcoal (MDAC) increases phenobarbital elimination by 50â€“80%.[10 , 11 , 15 , 181] However, in the only controlled study, no difference could be demonstrated in outcome measures (time to extubation and length of hospitalization) in intubated, phenobarbital-poisoned patients who were randomized to single-dose activated charcoal versus MDAC.[135] Although inconclusive, after ensuring an adequately protected airway, activated charcoal has potential benefits that outweigh any risk (Antidotes in Depth: Activated Charcoal).

Although the efficacy of delayed orogastric lavage is controversial, orogastric lavage should be considered in patients who overdose with xenobiotics that may slow GI motility or may develop concretions, specifically phenobarbital and meprobamate.[78 , 152]

No antidotes counteract all sedative-hypnotic overdoses. Flumazenil, a competitive benzodiazepine antagonist, rapidly reverses the sedative effects of benzodiazepines. However, use of flumazenil has a poor risk-to-benefit ratio in patients who present with a depressed mental status and have an undifferentiated overdose (Antidotes in Depth: see Flumazenil).

Patients with sedative-hypnotic overdose require invasive therapy for few situations other than respiratory support. Hemodialysis should be considered in patients with chloral hydrate overdose who develop life-threatening cardiac manifestations and patients who ingest extremely large quantities of phenobarbital and meprobamate and require prolonged intubation times.

Because the lethality of sedative-hypnotics is associated with their ability to cause respiratory depression, asymptomatic patients can be downgraded to a lower level of care after a period of observation. Patients who have been monitored for a period of time (8â€“12 hours) without signs or respiratory depression can be transferred to a general medical floor. Patients with symptomatic overdoses of long-acting drugs, such as meprobamate and clonazepam, or drugs that can have significant enterohepatic circulation, such as glutethimide, will require 24 hours of observation (Chap. 11).

Specific drugs

Barbiturates

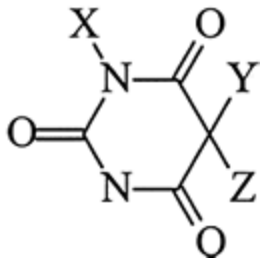

Figure. No Caption Available.

Barbital became the first commercially available barbiturate in 1903. Although many other barbiturates subsequently were developed, their popularity has greatly waned since the introduction of benzodiazepines. Barbiturates are derivatives of barbituric acid (2,4,6-trioxo-hexa-hydropyrimidine), which itself has no CNS depressant properties. Various side chains at the X, Y, and Z sites (see barbiturate chemical structure) influence lipophilicity, potency, and rate of elimination. Barbiturates with long side chains tend to have increased properties in all three areas. However, the observed clinical effects also depend on absorption, redistribution, and the presence or absence of active metabolites. For this reason, the duration of action of barbiturates (like those of benzodiazepines) do not correlate well with their biologic half-lives.

After ingestion, barbiturates are preferentially absorbed in the small intestine and are eliminated by hepatic and renal mechanisms. Longer-acting barbiturates tend to be more lipid soluble and more protein bound, have a high pK_a , a more rapid onset and shorter duration of action, and are metabolized almost completely in the liver. Renal excretion of unchanged drug is significant for phenobarbital. Elimination of phenobarbital, a long-acting barbiturate with a relatively low pK_a (7.24), can be influenced by manipulation of urinary pH. Alkalinization of the urine with sodium bicarbonate to maintain a urinary pH of 7.5â€“8.0 can increase the amount of phenobarbital excreted by 5- to 10-fold. This procedure is not effective for the short-acting barbiturates because they have higher pK_a values, are more protein bound, and are primarily

metabolized by the liver with very little excretion by the kidneys (Chap. 10).

Barbiturates (especially the shorter-acting barbiturates) can accelerate their own hepatic metabolism by enzyme autoinduction. Barbiturate use results in a marked increase in the enzyme content of the hepatic smooth endoplasmic reticulum and an increased rate of metabolism of a number of xenobiotics. Phenobarbital is a nonselective inducer of hepatic cytochromes, with the greatest effect on CYP2B1, CYP2B2, and CYP2B10.[80] Not surprisingly, a variety of drug interactions are reported following the use of barbiturates. Clinically significant interactions as a result of enzyme induction lead to increased metabolism of Î²-adrenergic antagonists, corticosteroids, doxycycline, estrogens, phenothiazines, quinidine, and theophylline.

Similar to other sedative-hypnotics, patients with significant barbiturate overdoses present with CNS and respiratory depression. Hypothermia and cutaneous bullae are often present.[12 , 43] These two signs are also described for other patients with sedative-hypnotic overdoses, but they may be more pronounced with barbiturates.[74 , 148] Early deaths caused by barbiturate ingestions result from respiratory arrest and cardiovascular collapse, whereas delayed deaths result from acute renal failure, pneumonia, acute lung injury, cerebral edema, and multiorgan system failure.[2 , 60]

Benzodiazepines

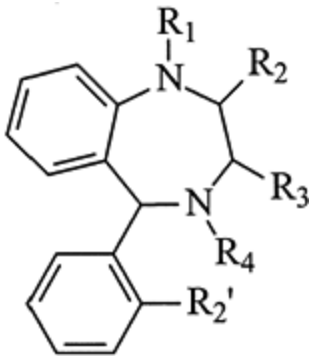

Figure. No Caption Available.

The commercial use of benzodiazepines began with the introduction of chlordiazepoxide for anxiety in 1961 and shortly thereafter of diazepam for seizures in 1963.[50] Benzodiazepines are used principally as sedatives. Temazepam and triazolam are exceptions; they are used as hypnotics to produce sleep. Clonazepam is the only benzodiazepine approved for use as a chronic anticonvulsant agent. Benzodiazepines rarely causes paradoxical psychological effects, including nightmares, delirium, psychosis, and transient global amnesia.[2,13,14,46,115] The incidence and intensity of CNS adverse events increases with age.[112]

The benzodiazepines are organic bases with a benzene structure and a 7-member diazepine moiety. Similar to barbiturates, various side chains at R1, R2, R2â€², R3, R4, R5, and R7 influence potency, duration of action, metabolites, and rate of elimination. Benzodiazepines tend to be highly protein bound and lipophilic. They passively diffuse into the CNS, their main site of action. Because of their lipophilic nature, benzodiazepines are extensively metabolized via oxidation and conjugation in the liver prior to their renal elimination.

Benzodiazepines have a unique distribution and subtypes of receptor sites. Benzodiazepines associated with GABA receptors tend to bind at specific areas in the CNS. Two structurally different â€œcentralâ€• benzodiazepine receptors are found in the brain: type I ($Ï‰_1$) and type II ($Ï‰_2$). Type I receptors tends to be located throughout the brain and contain the $GABA_A$ Î± subunit.[40] They are hypothesized to affect anxiety, sleep, and amnesia. Type II receptors are concentrated predominantly in the hippocampus, striatum, and the spinal cord. They are hypothesized to affect muscle relaxation and dependence.

Benzodiazepines are also active at certain types of benzodiazepine receptors that are not associated with the GABA receptor.

These receptors differ structurally, pharmacologically, and physiologically from GABA-associated benzodiazepine receptors. The function and structure of these receptors are not well defined, so attempts to classify them are not satisfactory. These receptors are located predominantly on the outer membrane of the mitochondria, but they also are present in erythrocytes that lack mitochondria.[125, 126, 131] Although presently termed *peripheral*, they also are located in the brain. Peripheral benzodiazepine receptors are found throughout the body, with the greatest concentrations in steroid-producing cells in the adrenal gland, anterior pituitary gland, and reproductive organs. The exact endogenous ligands that bind to these receptors are not clearly elucidated. Several types of endogenous benzodiazepinelike substances, endozepines, anthralin, porphyrins, and diazepam-binding inhibitor are proposed to bind to these receptors.[54]

The exact role of these receptors is unclear, but benzodiazepines are postulated to influence basic cellular functions such as mitochondrial respiratory control, cell growth, and cell differentiation. Peripheral benzodiazepine receptors appear to affect several biologic systems designed to cope with stress, such as the hypothalamic-pituitary system, sympathetic nervous system, renin-angiotensin system, and neuroendocrine-immune system.[54, 188] They may have a â€œneurosteroidâ€• effect by modulating steroidogenesis.[39, 101, 121]

Peripheral benzodiazepine receptors may be significant in modulating pathologic conditions such as hepatic encephalopathy, anxiety disorders, and abnormal immune function. Peripheral benzodiazepine receptors are markedly decreased after neurotoxic insults caused by the excitatory amino acid domoic acid and the neurotoxins soman and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).[82, 83, 88] These peripheral receptors are increased in encephalopathies caused by hepatic failure and thiamine deficiency.[23, 91, 94, 95] Cardiac benzodiazepine receptor sites are linked to calcium channels

(specifically to dihydropyridine sites) in animal tissues.[92, 107, 108, 109, 110, 111] This mechanism may theoretically support the use of benzodiazepines for treatment of the cardiac toxicity of xenobiotics such as chloroquine, cocaine, and other sympathomimetics.[9, 75, 99, 116]

Another unique property of the benzodiazepines is their relative safety even after substantial ingestion, which probably results from their GABA receptor properties.[40, 127] Unlike many other sedative-hypnotics, benzodiazepines do not open GABA channels independently at high concentrations. Benzodiazepines are not known to cause any specific systemic injury, and their long-term use is not associated with specific organ toxicity. Deaths resulting from benzodiazepine ingestions alone are extremely rare. Most often deaths are secondary to a combination of alcohol or other sedative-hypnotics.[61, 156] Supportive care is the mainstay of treatment.

Tolerance to the sedative effects of the benzodiazepines occurs more rapidly than does tolerance to the antianxiety effects.[100, 146] Abrupt discontinuation following long-term use of benzodiazepines may precipitate benzodiazepine withdrawal, which is characterized by autonomic instability, changes in perception, paresthesias, headaches, tremors, and seizures. Withdrawal from benzodiazepines is common, manifested by almost one third of long-term users.[85] Alprazolam and lorazepam are associated with more severe withdrawal symptoms and more frequent recurrent symptoms compared with chlordiazepoxide and diazepam,[85, 86] drugs that may protect the user because of the effects of their active metabolites. Withdrawal can occur when a chronic user of a particular benzodiazepine is switched to another benzodiazepine that has different receptor activity.[102]

Chloral Hydrate

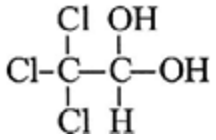

Figure. No Caption Available.

Chloral hydrate belongs to one of the oldest classes of pharmaceutical hypnotics, the chloral derivatives. Chloral hydrate was introduced in 1832. It still is used most commonly in children, although its use has substantially decreased.

Chloral hydrate is well absorbed but is irritating to the GI tract. It has a wide tissue distribution, rapid onset of action, and rapid hepatic metabolism by alcohol dehydrogenase. Trichloroethanol, the first active metabolite, is lipid soluble and is responsible for chloral hydrate's hypnotic effects. Chloral hydrate is metabolized by hepatic alcohol dehydrogenase (Figure 72-1). Trichloroethanol has a plasma half-life of 4â€“12 hours and is metabolized to inactive trichloroacetic acid by alcohol and aldehyde dehydrogenases. It is also conjugated with glucuronide and excreted by the kidney as urochloralic acid. Less than 10% is excreted unchanged.

Metabolic rates in children vary widely because of variable development and function of hepatic enzymes.[41] The elimination half-life of chloral hydrate and trichloroethanol is markedly increased in children younger than 2 years. The half-life of trichloroethanol ranges between 27.8 Â± 21.3 hours in newborns and between 9.7 Â± 1.7 hours in toddlers. Several comprehensive studies of clinical and pharmacologic characteristics of chloral hydrate use in neonates and infants suggest that even single-dose administration results in prolonged chloral hydrate, trichloroethanol, and trichloroacetic acid half-lives.[103 , 140] This latter metabolite still could be detected 6 days after administration in infants. These factors may be of concern in neonates and in infants exposed to repetitive doses.

Acute chloral hydrate poisoning is atypical of the other sedative-

hypnotics. Cardiac dysrhythmias appear to be the main cause of death.[58] Chloral hydrate and its metabolites reduce myocardial contractility, shorten the refractory period, and increase myocardial sensitivity to catecholamines.[18,26,166,181] Persistent cardiac dysrhythmias (ventricular fibrillation, ventricular tachycardia, torsades de pointes) are common terminal events.[58] Standard antidysrhythmics often are ineffective. A Î²-adrenergic antagonist currently is considered the drug of choice for treatment of most dysrhythmias secondary to chloral hydrate toxicity.[16,18,186] Chloral hydrate can also cause GI toxicity. Overdoses can produce vomiting, hemorrhagic gastritis, and rarely gastric and intestinal necrosis, leading to perforation and esophagitis with stricture formation.[93,123,171] Chloral hydrate is radiopaque and occasionally is detected on radiographs. Few hospital-based laboratories have the ability to rapidly detect chloral hydrate or its metabolites.

Ethchlorvynol

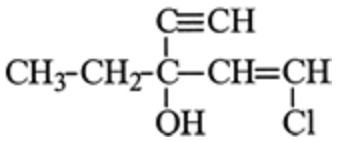

Figure. No Caption Available.

Ethchlorvynol was introduced in 1955 as a substitute for barbiturates. It is no longer legally available in the United States. It is rapidly absorbed and primarily metabolized by the liver, with a half-life of approximately 25 hours after a single use. However, it is readily

stored in adipose tissue because of its high lipophilicity, and its half-life can exceed 100 hours following overdoses. Whether its major metabolite ethynyl 3,4-diol is active is unclear. Because of the

drug's formulation, stomach contents often reveal a pink-tinged (500-mg capsules) or green-tinged (750-mg capsules) content. Extraction of the compound and intravenous injection is an alternative route of abuse. Acute lung injury often occurred rapidly afterward.[34] Symptoms and signs of ethchlorvynol overdoses can resemble barbiturate overdoses, including prolonged coma, hypothermia, and bullous lesions. Prolonged coma and a pungent plastic or vinyl odor on the breath are characteristics of ethchlorvynol poisoning.[163]

Glutethimide

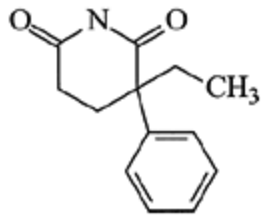

Figure. No Caption Available.

Glutethimide was introduced in 1954 as a substitute for barbiturates. It is no longer legally available in the United States. It is poorly water soluble and is slowly and erratically absorbed from the GI tract. Absorption may be significantly enhanced by coingestion of ethanol. It concentrates in fat-containing tissues because of its lipophilic nature. It is metabolized in the liver. More than 14 metabolites are identified, some of which are biologically active and may contribute to its toxicity.[36] High lipid solubility and delayed absorption may explain the cyclic variation in CNS depression that occurs in patients with acute overdoses. The enterohepatic circulation of metabolites may explain the fluctuating clinical course that occurs in severely intoxicated patients. Active metabolites include 2-phenylglutarimide and Î³-butyrolactone (a precursor of GHB). Unlike many of the other sedative-hypnotic agents, glutethimide can cause anticholinergic symptoms.[59] It reportedly

produces thick and tenacious bronchial secretions with impairment of ventilation.[28] Psychosis, seizures, cerebellar ataxia, and peripheral neuropathy are associated with prolonged use of glutethimide.[28]

Methaqualone

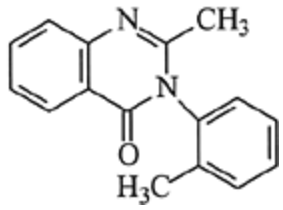

Figure. No Caption Available.

Methaqualone was introduced in 1956 as another substitute for barbiturates. It has anticonvulsant, anesthetic, antihistaminic, and antispasmodic characteristics. Its effects as a mood â€œelevatorâ€• led to extensive abuse and its subsequent withdrawal from the US market. The drug is rapidly and completely absorbed from the GI tract within 2â€“3 hours. It is highly protein bound (70â€“90%) and almost exclusively metabolized in the liver to 4-hydroxymethaqualone and numerous other hydroxy metabolites.[20, 73] Unlike many of the other sedative-hypnotics, hyperreflexia, clonus, and significant muscular hyperactivity can occur. Paresthesias and polyneuropathies can be residual effects after overdoses.[1]

Methyprylon

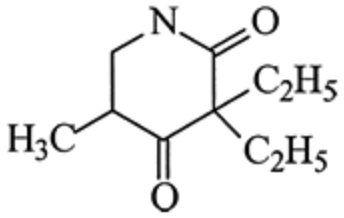

Figure. No Caption Available.

Methyprylon was introduced in the 1950s and is used only as a hypnotic. It is no longer legally available in the United States. It is rapidly absorbed in the GI tract and is metabolized almost entirely in the liver by oxidation and dehydrogenation. Because methyprylon is water soluble, hemodialysis was used in severe cases but was rarely indicated.[32 , 134]

Meprobamate/Carisoprodol

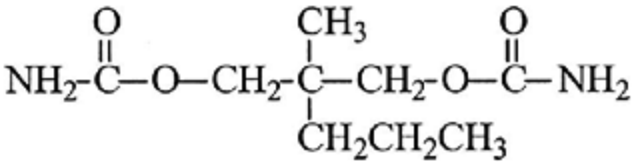

Figure. No Caption Available.

Meprobamate was introduced in 1950 and was used for its muscle-relaxant characteristics. Carisoprodol, which was introduced in 1955, is metabolized to meprobamate. These propanediol carbamates have pharmacologic effects on the $GABA_A$ receptor similar to those of the barbiturates. Like barbiturates, meprobamate can directly open the GABA-mediated chloride channel and may inhibit *N* -methyl-D-aspartate (NMDA) receptor currents.[145] They both are rapidly absorbed from the GI tract. The drug is metabolized in the liver to inactive hydroxylated and glucuronidated metabolites that are excreted almost exclusively by the kidney. Of all the nonbarbiturate tranquilizers, meprobamate most likely will produce euphoria.[76 , 77] Large masses or bezoars of pills have been noted in the stomach at autopsy.[152] Thus, orogastric lavage with a large-bore tube and MDAC may be indicated for significant meprobamate ingestion. Whole-bowel irrigation may be helpful if multiple pills or small concretions are noted. Because patients can experience recurrent toxic manifestations as a result of concretion formation and delayed absorption, careful monitoring of the clinical course is essential even

after the patient shows initial improvement.

Bromides

Bromides were previously used as â€œnerve tonics,â€• headache remedies, and anticonvulsants. Although pharmaceutical bromides have largely disappeared from the US pharmaceutical market, bromide toxicity still occurs because of the availability of bromide salts of common drugs, such as dextromethorphan.[120] Cases occur in immigrants and travelers from other countries where bromides are still therapeutically used.[51] The drug is irritating to the GI tract and is difficult to ingest. A sufficient amount is retained to achieve a toxic concentration without vomiting. Bromide has a long plasma half-life (12 days), and toxicity typically occurs over time as concentrations accumulate in tissue. Bromide and chloride ions have a similar distribution pattern in the extracellular fluid. It is postulated

that because the bromide ion moves across membranes slightly more rapidly than the chloride ion, it is more quickly reabsorbed in the tubules from the glomerular filtrate than the chloride ion. Although osmolar equilibrium persists, CNS function is progressively impaired by a poorly understood mechanism, with resulting inappropriateness of behavior, headache, apathy, irritability, confusion, muscle weakness, anorexia, weight loss, thickened speech, psychotic behavior, tremulousness, ataxia, and eventually coma.[27 , 187] Delusions and hallucinations can occur. Bromide can lead to hypertension, increased intracranial pressure, and papilledema. Chronic use of bromides can lead to dermatologic changes, with the hallmark characteristic of a facial acneiform rash.[65 , 167] Toxicity with bromides during pregnancy may lead to accumulation of bromide in the fetus.[133] A spurious hyperchloridemia may result from bromide's interference with the chloride assay on older analyzers[184] (Chap. 17).

Zolpidem/Zaleplon

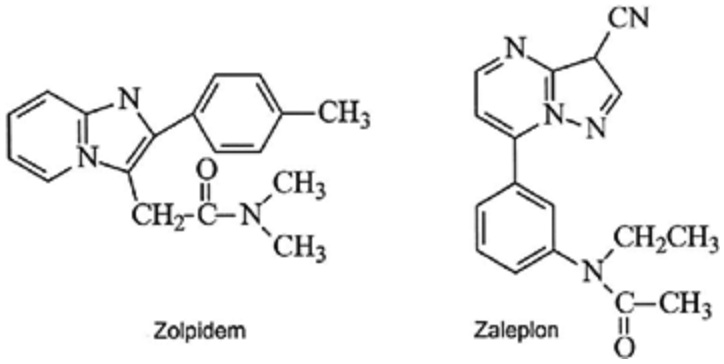

Figure. No Caption Available.

Zolpidem is an imidazopyridine hypnotic. Zaleplon is a pyrazolopyrimidine hypnotic. These xenobiotics have supplanted benzodiazepines as the most commonly prescribed hypnotics.[47] Although zolpidem and zaleplon are structurally unrelated to the benzodiazepines, they bind preferentially to the type I ($Ï‰_1$) benzodiazepine receptor subtype in the brain, specifically the $GABA_A$ $Î±_1$ subunit.[40] Zolpidem and zaleplon have a lower affinity for type II ($Ï‰_2$)receptors than benzodiazepine hypnotics, so they have potent hypnotic effects and less addiction potential.[40,64] Unlike benzodiazepines that prolong the first 2 stages of sleep and shorten stages 3 and 4 of rapid eye movement (REM) sleep, zolpidem and zaleplon have little effect on the stages of sleep. Because of their selectivity, they appear to have minimal effect at other sites on the GABA receptor that mediate anxiolytic, anticonvulsant, or muscle-relaxant effects.[89,173] Both drugs are hepatically metabolized. In isolated overdoses, drowsiness and CNS depression are common, but coma and respiratory depression are exceptionally rare. Even at 40 times the therapeutic dose, no biologic or electrocardiographic abnormalities have been reported.[53] Flumazenil can reverse the effects of both agents.[97,179] Withdrawal is documented with abrupt discontinuation but typically is mild.[62,177] Deaths have resulted when zolpidem was taken in large amounts with other CNS

depressants.[53]

Propofol

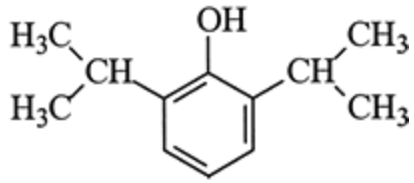

Figure. No Caption Available.

Propofol is a rapid-acting intravenous sedative-hypnotic that is a postsynaptic $GABA_A$ agonist. It induces presynaptic release of GABA.[117] Propofol also interacts with dopamine release at various sites. It promotes nigral dopamine release possibly via $GABA_B$ receptors[128 , 153] and has partial agonist properties at dopamine (D_2) and NMDA receptors.[151] It is used for either induction or maintenance of general anesthesia. Propofol is highly lipid soluble, so it crosses the bloodâ€“brain barrier rapidly. Onset of anesthesia usually occurs in less than 1 minute, with duration of action after short term dosing of 3â€“8 min because of its rapid redistribution from the CNS.

Propofol use is associated with various adverse outcomes. Acutely, propofol causes dose-related respiratory depression. Transient apnea may occur. The drug may decrease systemic arterial pressure and cause myocardial depression. Although propofol does not typically cause dysrhythmias or myocardial ischemia, atropine-sensitive bradydysrhythmias have been noted, specifically sinus bradycardia and Mobitz type I atrioventricular block.[165 , 176 , 185] Prolonged infusions for more than 48 hours at rates of 5 mg/kg/h are associated with acidosis, cardiac, and skeletal muscle injury.[79] Propofol is suggested to induce disruption of mitochondrial free fatty acid metabolism, causing a syndrome similar to other mitochondrial myopathies.[29 , 158] Case reports associate propofol with lactic

acidosis and fatal myocardial failure in children and young adults.[129] Cases of metabolic acidosis may be associated with an inborn disorder of acylcarnitine metabolism.[182] However, a direct cause-and-effect relationship remains unproven.

The unique nature of the carrier base, a milky soybean emulsion formulation, is associated with multiple adverse events. It is a fertile medium for many organisms, such as enterococcal, pseudomonal, staphylococcal, streptococcal, and candidal strains. In 1990, the Centers for Disease Control and Prevention (CDC) reported an outbreak of *Staphylococcus aureus* associated with contaminated propofol. This carrier base also impairs macrophage function and causes[29] hypertriglyceridemia,[45 , 84 , 98] abnormalities in blood coagulability, platelet function,[5 , 38 , 66] and histamine-mediated anaphylactoid reactions.[42 , 81]

Etomidate

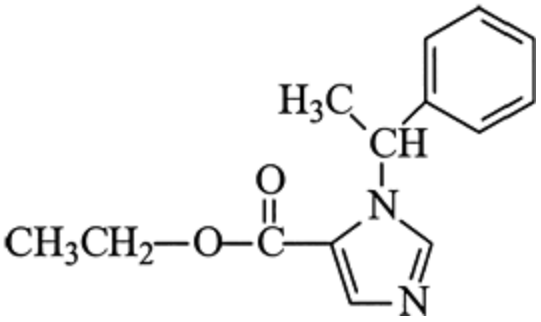

Figure. No Caption Available.

Etomidate is a nonbarbiturate, hypnotic agent primarily used as an anesthesia induction agent. It is active at the $GABA_A$ receptor, specifically the $Î²_2$ and $Î²_3$ subunits.[122 , 142] Only the intravenous formulation is available in the United States. The onset of action is less than 1 minute and its duration is less than 5 minutes.

Etomidate is commercially available as a 2 mg/mL solution in a 35% propylene glycol solution (Amidate).[169] The propylene glycol is

implicated in the development of a hyperosmolar metabolic acidosis.[105, 169, 170] Etomidate has minimal effect on cardiac function, but rare cases of hypotension are reported.[55, 56, 57, 63, 162] It has proconvulsant and anticonvulsant properties.[33, 138] Involuntary muscle movements are common during induction. They may be caused by etomidate interaction with glycine receptors at the spinal cord level.[37, 113, 114]

Etomidate depresses adrenal production of cortisol and aldosterone even after a single dose.[150, 174, 175] This effect is suggested to increase mortality with long-term etomidate use.[178]

Summary

Sedative-hypnotics in combination with alcohol and other respiratory depressants are among the most common drugs implicated in deaths resulting from poisoning. Patients with sedative-hypnotic overdoses often present with the primary manifestation of CNS depression; however, death typically results from respiratory depression. Careful monitoring and supportive care are the cornerstones of treatment. Specific antidotes such as flumazenil and treatments such as hemodialysis are rarely indicated.

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Antidotes in Depth

Flumazenil

Mary Ann Howland

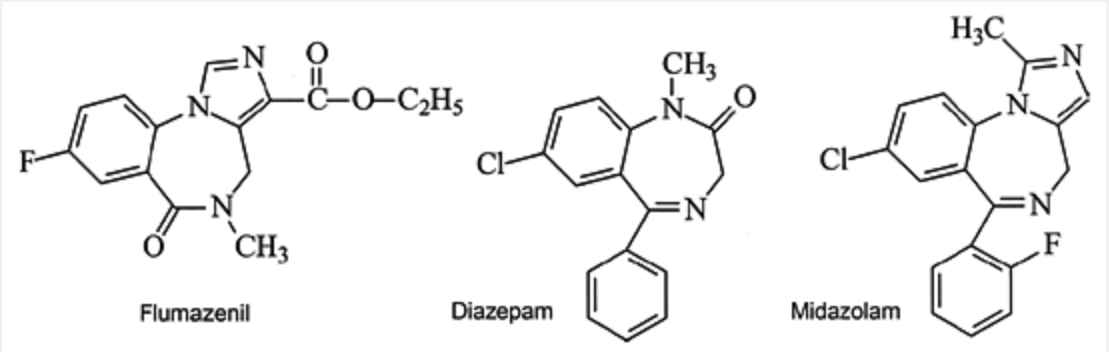

Figure. No Caption Available.

Flumazenil is a competitive benzodiazepine receptor antagonist. It has no role in cases of unknown overdose because seizures and dysrhythmias may occur when the effects of a benzodiazepine are

reversed in a mixed overdose. Flumazenil also has the potential to induce benzodiazepine withdrawal symptoms, including seizures in patients who are benzodiazepine dependent. Flumazenil does not reliably reverse the respiratory depression induced by intravenous benzodiazepines but does reverse central nervous system (CNS) depression.[50] Flumazenil is ideal for the few patients who are naive to benzodiazepines and who overdose solely on a benzodiazepine. Because the duration of effect of flumazenil is shorter than that of most benzodiazepines, repeat doses may be necessary and vigilance is warranted. Flumazenil has no role in the management of ethanol intoxication but may be considered for patients with hepatic encephalopathy. However, further study is needed before its routine use can be recommended.[3] Case reports raise the possibility of a role for flumazenil in patients with paradoxical reactions to therapeutic doses of midazolam. Flumazenil is not expected to be effective in overdoses such as baclofen in which a benzodiazepine receptor is not involved.[13] Flumazenil is effective for overdoses of zolpidem and zaleplon, nonbenzodiazepines that interact with Ï‰1 receptors, a subclass of central benzodiazepine receptors.[36,46,47]

History

Haefely and Hunkeler's initial work on chlordiazepoxide synthesis[62] led to an attempt to develop benzodiazepine derivatives that would act as antagonists.[27] This endeavor initially was unsuccessful, so they investigated the promising Î³-aminobutyric acid (GABA) hypothesis of benzodiazepine mechanism of action. In 1977, the then-new technique of radioligand binding identified specific high-affinity benzodiazepine binding sites. Other investigators simultaneously isolated a product produced by a *Streptomyces* species that had the basic 1,4-benzodiazepine structure. Synthetic compounds subsequently were derived from this molecule to act as potential tranquilizers. Hunkeler attempted to produce benzodiazepines with potent anxiolytic and

anticonvulsant activity and diminished sedative and muscle-relaxing properties. Testing revealed these derivatives had high in vitro binding affinities but lacked in vivo activity. An inability to enter the CNS was considered an explanation for the discordance. During an experiment that attempted to demonstrate CNS penetration of these derivatives, diazepam given to incapacitate the animals had a surprisingly weak effect. This lack of potency led to the discovery of a benzodiazepine antagonist. Further modifications led to the synthesis of flumazenil (Ro 15-1788).[18,48]

Pharmacology

Flumazenil is a water-soluble benzodiazepine analog with a molecular weight of 303 daltons. It is a competitive antagonist at the benzodiazepine receptor, with very weak agonist properties in animal models and in humans.[45] The benzodiazepine receptor modulates the effect of GABA on the $GABA_A$ receptor by increasing the frequency of Cl^- channel opening, leading to hyperpolarization. Agonists such as diazepam stimulate the benzodiazepine receptor to produce anxiolytic, anticonvulsant, sedative, amnestic, and muscle-relaxant effects at low doses and hypnosis at high doses.[28] Inverse agonists bind the benzodiazepine receptor and result in the opposite effects of anxiety, agitation, and seizures. Antagonists, such as flumazenil, competitively occupy the benzodiazepine receptor without causing any functional change and without allowing an agonist or inverse agonist access to the receptor. The zero set point of intrinsic activity may be influenced by the activity of the GABA system or by chronic treatment with benzodiazepines.[20] Positron emission tomography investigations reveal that 1.5 mg flumazenil leads to an initial receptor occupancy of 55%, whereas 15 mg causes almost total blockade of benzodiazepine receptor sites.[53]

The structures of flumazenil, diazepam, and midazolam are shown in the figure. Table A21-1 summarizes the physiochemical and

pharmacokinetic properties of flumazenil.[32]

TABLE A21-1. Physicochemical and Pharmacologic Properties of Flumazenil

pK_A	Weak base
Partition coefficient at pH 7.4	14 (octanol/aqueous PO_4 buffer)
Volume of distribution	1.06 L/kg
Distribution half-life ($t_{1/2}\hat{I}\pm$)	â‰¤5 minutes
Metabolism	Hepatic: three inactive metabolites
	High clearance
Elimination	First order
Protein binding	54â€“64%
Elimination half-life ($t_{1/2}\hat{I}^2$)	53 minutes

Onset of action	1â€“2 minutes
Duration of action	Dependent on dose and elimination ofbenzodiazepine, time interval, dose offlumazenil, and hepatic function

Volunteer Studies

Volunteer studies demonstrate the ability of flumazenil to reverse the effect of benzodiazepines.[16] Reversal is dose dependent and begins within minutes. Peak effects occur within 6â€“10 minutes.[50] Most individuals achieve complete reversal of benzodiazepine effect with a total IV dose of 1 mg.[4,12] A 3-mg IV dose produces similar effects that last approximately twice as long as the 1-mg dose.

Conscious Sedation

A number of studies evaluated patients undergoing conscious sedation for endoscopy or cardioversion who received diazepam or midazolam.[5,11,12,34,35] When a benzodiazepine is given for conscious sedation during a procedure, flumazenil appears safe and effective for reversal of sedation and partial reversal of amnesia and cognitive impairment.[22] Most patients respond to total doses of 0.6â€“1 mg. Administering flumazenil slowly at a rate of 0.1 mg/min minimizes the disconcerting symptoms associated with rapid arousal, such as confusion, agitation, and emotional lability. Resedation occurs within 20â€–120 minutes, depending on the dose and pharmacokinetics of the benzodiazepine and the dose of flumazenil. For this reason, patients must be carefully monitored and subsequent doses of

flumazenil given as needed. Because the amnestic effect of benzodiazepines and the cognitive and psychomotor effects are not fully reversed, posttreatment instructions should be reinforced in writing and given to a responsible caretaker accompanying the patient.[16,22] Because of the risk of resedation, many practitioners elect not to use flumazenil routinely.

Two cases of patients undergoing endoscopy who developed seizures following benzodiazepine reversal are reported.[57] One patient had a history of seizures, and the other had no obvious etiology. Both patients recovered uneventfully.

Use for Paradoxical Reaction to Midazolam

Paradoxical reactions to benzodiazepines are uncommon.[24,41] The mechanism is unclear and has been attributed to a disinhibition reaction.[19] Management strategies include administering higher doses of the benzodiazepines, adding other drugs such as opioids or droperidol, stopping the procedure, and using flumazenil.[31,49,58,59] Three patients undergoing endoscopy were premedicated with meperidine, droperidol, and midazolam in doses up to 10 mg.[17] Each patient exhibited paradoxical agitation and restlessness. Following flumazenil 0.5 mg IV, the patients became calm and sedated, allowing successful completion of endoscopy. A satisfactory explanation has not been established.

Effects on Benzodiazepine-Induced Respiratory Depression

Flumazenil has not consistently reversed benzodiazepine-induced respiratory depression and is not approved for this use.[50,55] If respiratory depression is mediated through the benzodiazepine receptor, then flumazenil should be effective as a reversal agent,

but this effect does not occur consistently.[14,25,39,43,55] The effect of IV midazolam on respiratory depression was examined using oxygen saturation measurements and plethysmography to determine minute ventilation volumes in patients undergoing endoscopy.[14] Flumazenil awakened patients rapidly but failed to affect minute ventilation and had little effect on oxygen saturation. When a benzodiazepine was used concomitantly with an opioid, the effects on ventilation were even more confusing.[63,65] Rebound respiratory depression and prolonged hypoxic episodes were documented. Flumazenil may even have a slight respiratory depressant effect when combined with an opioid.[63] Clinical assessment of respiratory rate is inadequate for detecting hypoxia. Benzodiazepine-induced apnea should be managed with standard procedures such as supplemental oxygen, airway stabilization, bag-valve-mask ventilation, and endotracheal intubation, if indicated.

Use in the Overdose Setting

Use of flumazenil in the overdose setting is controversial. The first argument against flumazenil use is the rare morbidity and mortality associated with benzodiazepine use. An analysis of 702 patients who had taken benzodiazepines alone or in combination with ethanol or other drugs and were admitted to a medical intensive care unit (ICU) over a 14-year period revealed a 0.7% fatality rate (5 deaths) and 9.8% complication rate (69 patients).[30] In comparison, the fatality rate for patients with nonbenzodiazepine-related overdoses was 1.6% (55/3430 patients). In the pure benzodiazepine group, 2 patients died and 18 (12.5%) of 144 patients had complications, mostly aspiration pneumonitis and decubitus ulcers. Proponents of flumazenil therapy suggest that some of the 29 diagnostic procedures used in the patients were unnecessary, and some of the complications could have been prevented. Opponents of flumazenil therapy suggest that many of the cases of aspiration pneumonitis occurred

prior to hospital admission and that the patients also suffered from trauma and infectious disease, making most diagnostic procedures necessary.

In an effort to develop indications for safe and effective use of flumazenil, overdosed comatose patients were retrospectively assigned to either a low-risk or nonâ€“low-risk group.[26] Low-risk patients had CNS depression with normal vital signs, no other neurologic findings, no evidence of ingestion of a tricyclic antidepressant by history or electrocardiogram (ECG), no seizure history, and absence of an available history of chronic benzodiazepine ingestion. All other patients fell into the nonâ€“low-risk category. Of 35 consecutive comatose patients, 4 patients were assigned to the low-risk group. Flumazenil caused complete awakening in 3 patients and partial awakening in the fourth patient in the low-risk group, with no adverse effects. In the nonâ€“low-risk group of 31 patients, flumazenil caused complete awakening in 4 patients and partial awakening in 5 patients. Seizures occurred in 5 patients, of whom 1 had a history of seizures, 5 were long-term benzodiazepine

users, 4 had abnormal vital signs, and 3 had evidence of hyperreflexia or myoclonus. Therefore, although flumazenil use probably was safe and effective in the low-risk group, few patients met the criteria for inclusion in that risk group. The risk of seizures is substantial in the nonâ€“low-risk group.

TABLE A21-2. Indications for Flumazenil Use in the Overdose Setting

Pure benzodiazepine overdose in a nontolerant individual who has

- CNS depression
- Normal vital signs, including SaO_2
- Normal ECG
- Otherwise normal neurologic examination

In conclusion, the risks of flumazenil usually outweigh the benefits in overdose patients.[54] When nonâ€“benzodiazepine-dependent patients ingest benzodiazepines alone in overdose, as rarely occurs in adults but might be expected in children, the risks associated with flumazenil use may be limited.[68] Table A21-2 summarizes the indications for flumazenil use in the overdose setting.

Adverse Effects and Safety Issues

Flumazenil has been studied in more than 3500 patients worldwide, including healthy volunteers and overdosed or consciously sedated patients. The safety of flumazenil in healthy volunteers is well established, with no discernible objective or subjective effects. However, precipitation of seizures in benzodiazepine-dependent patients, unmasking of dysrhythmias in patients who coingest benzodiazepine with a prodysrhythmic drug, and resedation within 20â€“120 minutes in patients receiving benzodiazepine for conscious sedation are recognized adverse effects associated with flumazenil administration.

The ability of flumazenil to precipitate acute benzodiazepine withdrawal seizures in a more controlled environment than the overdose setting was demonstrated by reversal of long-term benzodiazepine sedation in the ICU. A study of 1700 patients revealed that 14 patients developed adverse drug reactions, probably half related to abrupt arousal.[5] Two patients with a history of epilepsy developed tonic-clonic seizures, and 1 patient developed myoclonic seizures.[5] Dose-dependent induction of withdrawal reactions is suggested. Small doses of flumazenil (<1 mg) may allow sufficient occupation of the benzodiazepine receptor sites by benzodiazepines so that abrupt withdrawal seizures are uncommon.

In a study of 12 patients receiving midazolam sedation for 4 Â± 3 days, 0.5 mg flumazenil was administered as a rapid bolus. Norepinephrine and epinephrine plasma concentrations rose within 10 minutes, returned to baseline within 30 minutes, and correlated with increased heart rate, blood pressure, and myocardial oxygen consumption.[33]

Flumazenil causes a significant overshoot in cerebral blood flow and may cause a large increase in intracranial pressure in patients who received midazolam for severe head injury.[70]

Thirty published case studies involving 758 patients with drug overdoses were reviewed.[21] In total, 387 patients participated in double-blind study protocols and 371 patients in open-label studies.[21] Fifty percent of cases were mixed overdoses. The doses of flumazenil ranged from 0.2â€“5 mg. Five cases of seizures were temporally related to flumazenil administration, all after large bolus doses. In 3 of the 5 patients, high concentrations of tricyclic antidepressants were present in the blood. The seizures resolved without treatment or following administration of a small dose of a benzodiazepine. Dysrhythmias developed in 2 patients given small doses of flumazenil, both presumably associated with the presence of a tricyclic antidepressant. Of 497 patients enrolled in two

clinical US studies sponsored by the manufacturer,[21] 6 patients developed seizures (5 had coingested tricyclic antidepressants) and 1 patient who had taken a tricyclic antidepressant and carbamazepine had a junctional tachycardia, which normalized after several minutes. Thus, in reviewing 1255 patients, 11 patients had seizures and 3 developed dysrhythmias, for an incidence of approximately 0.9%. The consensus report was that (a) flumazenil is not a substitute for primary emergency care; (b) hypoxia and hypotension should be corrected before flumazenil is used; (c) small titrated doses of flumazenil should be used; (d) flumazenil not be used in patients with a history of seizures, evidence of seizures or jerking movements, or evidence of a cyclic antidepressant overdose; and (e) flumazenil should not be used by inexperienced clinicians.

An analysis of all seizures associated with flumazenil gathered from previously published cases or reports to the manufacturer was published.[57] Forty-three patients had seizures and 6 patients died, but the author believed that none of the deaths were attributable to flumazenil.[57] Four patients developed status epilepticus; 2 were presumed to be caused by concomitant tricyclic antidepressant exposure, and the other 2 patients had received benzodiazepines to treat status epilepticus prior to flumazenil therapy. In 6 of 43 seizure episodes, the relationship to flumazenil use was believed to be inadequately defined. The remaining 37 patients were stratified into 5 categories. In category 1, 7 patients were given flumazenil after they had received a benzodiazepine for treatment of a seizure disorder. Six of these 7 patients received >1 mg flumazenil. In category 2, 20 patients received flumazenil for reversal of a benzodiazepine in a mixed-drug overdose. Many of these patients had coingested tricyclic antidepressants. Thirteen of these patients received >1 mg flumazenil. Two of the patients in this group developed status epilepticus and died, possibly secondary to a severe tricyclic antidepressant overdose. Category 3 included 5 patients who received benzodiazepines for

suppression of nonâ€“drug-induced seizures. Two of these 5 patients received >1 mg flumazenil. Category 4 included 3 patients with acute benzodiazepine overdoses in the presence of chronic benzodiazepine dependence. Category 5 included 2 patients who received a benzodiazepine for conscious sedation. Therefore, flumazenil use may place the patient at risk for seizures by unmasking a toxic effect in mixed overdose, by removing the protective anticonvulsant effect in a patient with nonâ€“drug-induced seizures, or by precipitating acute benzodiazepine withdrawal.

The risks of flumazenil appear to greatly outweigh the potential benefits of reversal when benzodiazepines are used chronically or acutely to treat a seizure disorder. Flumazenil is best avoided in the overdose setting when evidence indicates ingestion of a drug capable of causing seizures or dysrhythmias. For example, any indication that theophylline, carbamazepine, chloral hydrate, chloroquine, and/or chlorinated hydrocarbons was ingested is a contraindication to flumazenil use.[66] Flumazenil should not be used when involvement of a cyclic antidepressant is strongly suggested based on history, clinical findings, or ECG findings (prolonged QRS complex).[29,38,44,66] In the event of flumazenil-induced seizures, a therapeutic dose of a benzodiazepine such as diazepam should be effective. Flumazenil is a competitive antagonist; higher doses of benzodiazepines will reverse higher doses of flumazenil. Table A21-3 summarizes the contraindications to flumazenil use.

TABLE A21-3. Contraindications to Flumazenil Use

- Prior seizure history or current treatment of seizures
- History of ingestion of a xenobiotic capable of provoking seizures or cardiac dysrhythmias
- Long-term use of benzodiazepines
- ECG evidence of cyclic antidepressants (terminal rightward 40 msec axis, QRS or QTc prolongation)
- Abnormal vital signs; hypoxia

Dosing

Slow IV titration (0.1 mg/min) to a total dose â‰¤1 mg seems most reasonable. Extravasation should be avoided because of the risk of local irritation. Resedation may occur at 20â€“120 minutes, and readministration of flumazenil may be necessary. Although not approved by the FDA, continuous IV infusion of flumazenil 0.1â€“1.0 mg/h in 0.9% sodium chloride solution or 5% dextrose in water has been used following the loading dose.[36,67,69]

Availability

Flumazenil is available as Romazicon in a concentration of 0.1 mg/mL with parabens in 5-mL and 10-mL vials.

Role in Nonbenzodiazepine Toxicity

Hepatic Encephalopathy

Hepatic encephalopathy is considered a reversible metabolic

encephalopathy characterized by a spectrum of CNS effects. Symptoms may progress from confusion and somnolence to coma. The current hypothesis implicates an increase in GABAergic tone in the development of encephalopathy.[6,56]

Animal studies of hepatic encephalopathy secondary to galactosamine or thioacetamide (hepatotoxins) demonstrate an increase in GABA effect, which is antagonized by flumazenil, bicuculline (a GABA-receptor antagonist), and isopropylbiclophosphate chloride (a calcium channel blocker).[6] Cerebrospinal fluid (CSF) from these animals contained a benzodiazepine receptor ligand with agonist activity. Rat studies involving hepatic encephalopathy resulting from acute liver ischemia showed only a slight response to flumazenil but significant improvement after administration of a partial inverse agonist.[10,64]

Human studies have detected benzodiazepine-binding activity in the CSF, but not in serum, of patients with hepatic encephalopathy. One group identified 4â€“19 peaks representing benzodiazepine-binding ligands from the frontal cortex of 11 patients who died of hepatic encephalopathy.[9] Two of the peaks were identified as diazepam and *N*-desmethyldiazepam. Brain concentrations of these substances were 2â€“10 times higher than normal in 6 of the patients and were normal in 5 patients. Patients with idiopathic recurring stupor who have measurable â€œendozepinesâ€• (endogenous benzodiazepine ligands) in serum and CSF are reported.[51,61]

Flumazenil improves the clinical and electrophysiologic responses of patients with hepatic encephalopathy and idiopathic recurring stupor.[7,17,51,61] Some patients with encephalopathy have improved from stage IV to stage II encephalopathy after IV flumazenil. Maximal improvement after flumazenil lasts approximately 1â€“2 hours and gradually dissipates within 6 hours. The response rate in a meta-analysis averaged

approximately 30%.[23] The proposed explanations for the unresponsiveness include cerebral edema, hypoxia, other systemic diseases or complications, and irreversible CNS damage.

Animal and human data convincingly support the concept that increased GABAergic tone is responsible for hepatic encephalopathy. Evidence for endogenous benzodiazepine ligands that enhance GABA action also are demonstrated but controversial.[1,2] The source of these benzodiazepine receptor agonists is unclear, but diet and/or production by gut bacteria is postulated.[6] Most authorities believe endogenous de novo synthesis is unlikely and propose prior benzodiazepine exposure and persistence as an explanation. Neurosteroids and hemoglobin metabolites are also implicated in the pathophysiology of hepatic encephalopathy.[2,52]

Flumazenil can lead to improvement of the clinical condition of a subgroup of patients with hepatic encephalopathy and may prove useful as an addition to conventional therapy.[8] Additional research is necessary to identify prospective responders, dosing considerations, and adverse effects.

Ethanol Intoxication

Animal studies indicate that many of the actions of ethanol are mediated through GABA neurotransmission.[60] Acute ethanol administration appears to enhance GABA transmission and inhibit *N*-methyl-D-aspartate (NMDA) excitation. Chronic ethanol administration leads to downregulation of the GABA system. Ethanol enhances $GABA_A$-induced chloride influx in a dose-dependent fashion without a direct effect on chloride. Flumazenil does not influence this action of GABA. Chronic ethanol use selectively increases the sensitivity to inverse benzodiazepine agonists, invoking a change in coupling or conformation of the receptor. These changes may explain the development of tolerance and the kindling and production of seizures that occur on

withdrawal.

Two double-blind studies in patients with benzodiazepine or ethanol overdose evaluated the response to flumazenil. In one study of 13 patients with suspected ethanol intoxication, 6 had no response to placebo when it was given first, whereas all 13 patients responded to 5 mg flumazenil.[42] Improved consciousness occurred after 15 minutes, and respiratory rates increased from 14 to 16 breaths/min. Heart rate and blood pressure were not affected. The 5-mg dose of flumazenil was selected because no improvement in mental status or vital signs was observed when 1 mg flumazenil was administered to 4 patients.

Another comparable study demonstrated similar results.[37] Flumazenil (1 mg) administered to 9 ethanol-intoxicated patients produced the same effects as placebo. Subsequent administration of 2â€“5 mg flumazenil in the open part of the study produced a clear improvement in the modified Glasgow coma scale in 5 of 11 patients. However, a closer inspection of phase 1 of the study reveals that an arousal reaction occurred in 7 of 9 patients after the flumazenil dose and in 5 of 9 patients following placebo administration. It is conceivable that the improvement in phase 2 was a continuation of the arousal reaction.

One case report indicates that ethanol-induced respiratory depression was reversed by flumazenil,[40] but whether the actual data support the authors' conclusions is unclear.

A randomized, double-blind, crossover study of 8 male volunteers given IV ethanol to achieve a constant serum ethanol concentration

of 160 mg/dL was conducted.[15] Once stabilized, the volunteers were given either placebo or 5 mg flumazenil. Subjective and objective psychomotor tests were conducted, with no differences noted between volunteers given flumazenil and volunteers given placebo. The probability of ethanol reversal at the suggested doses

appears unlikely.

Based on this information, flumazenil likely does not have a significant effect on ethanol intoxication. Low doses of flumazenil (<1 mg) have no effect. The 5-mg doses reportedly produce favorable changes in sensorium, but these findings may be the result of confounding factors. Because we would never administer 5 mg flumazenil in the overdose setting due to the increased risk of adverse effects at this dose, flumazenil cannot be recommended for reversal of ethanol intoxication.

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Chapter 73
Amphetamines

William K. Chiang

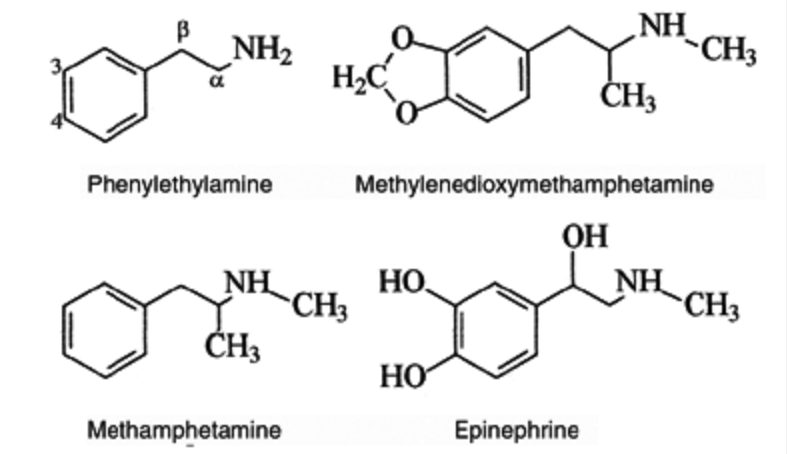


Figure. No Caption Available.

A 25-year-old woman was brought to the emergency department (ED) by ambulance from a dance club. The paramedics reported that

the patient had become agitated in the club and had a generalized seizure. They also reported that the patient had used â€œecstasyâ€• during the night. The woman was delirious, agitated, hallucinating, and paranoid. At times she was exceedingly hyperactive, jumping repeatedly on and off the stretcher. Frequently, she appeared to be involved with her hallucinations.

The physical examination revealed a blood pressure of 170/100 mm Hg; pulse of 120 beats/min and regular; respiratory rate of 18 breaths/min; rectal temperature of 102.7Â°F (39.3Â°C); and a pulse oximetry reading of 97% on room air. The patient appeared to be of normal habitus, acyanotic, and anicteric, but diaphoretic. Her head was normocephalic. Her pupils were dilated to 6 mm bilaterally, and they reacted slowly to light. The conjunctivae, extraocular movements, and the fundi were normal. Her neck was supple, exhibiting no thyromegaly. Examination of her heart was unremarkable, except for tachycardia. Her lungs were clear. The abdomen was soft, nontender, and without hepatomegaly; bowel sounds were normal. The extremities were normal, without any evidence of track marks, bruises, swelling, or rash. The patient moved all her extremities spontaneously and had normal symmetric deep-tendon reflexes with plantar flexion.

A rapid bedside glucose was 95 mg/dL. She was treated with a total of 20 mg of diazepam IV (given in 10-mg increments) for sedation and attached to a continuous cardiac monitor. She was given 1.5 L of 0.9% sodium chloride solution over 60 minutes. External cooling with ice packs around the axillae and groin was initiated. She became calm and less paranoid. Her rectal temperature decreased to 100Â°F (37.7Â°C) within 15 minutes.

Her complete blood count was remarkable for an elevated white blood cell count of 15,000 cells/mm^3. The serum electrolytes were

remarkable for: sodium, 109 mEq/L; potassium, 3.6 mEq/L; chloride, 81 mEq/L; bicarbonate, 20 mEq/L; blood urea nitrogen (BUN), 10

mg/dL; creatinine, 1.1 mg/dL; and glucose, 105 mg/dL. The liver enzymes were normal. The urinalysis was negative for blood and protein, and the urine osmolality was 497 mOsm/kg. The chest radiograph was normal. The electrocardiogram (ECG) revealed a sinus tachycardia. A noncontrast head computed tomography (CT) scan was normal.

Further therapy consisted of the administration of 3% sodium chloride solution at 50 mL/h for 6 hours with frequent serum sodium concentration monitoring. The repeat serum sodium concentration after 6 hours was 123 mEq/L. The patient's mental status improved and she had no further seizures. At this time, the patient was placed on free water restriction and her sodium slowly improved to 130 mEq/L by 24 hours. By that time, the patient's mental status had completely normalized. Her liver enzymes, renal function, and urinalysis remained normal. The patient was discharged from the hospital after 4 days without any sequelae.

Amphetamine is the trivial name and acronym for racemic Î²-phenylisopropylamine or Î±-methylphenylethylamine and belongs in the family of phenylethylamines. Numerous substitutions of the phenylethylamine structure are possible, resulting in different amphetaminelike compounds. Commonly, these compounds are referred to as amphetamines or amphetamine analogs, although phenylethylamines is more precise. For the purposes of this chapter, the term *amphetamines* refers to amphetamine analogs, and *amphetamine* specifically refers to Î²-phenylisopropylamine.

Since the initial marketing of amphetamines, continued abuse and misuse have been substantial.[17,101,184] Amphetamines have been advocated by the medical communities for the treatment of depression, obesity, enuresis, postencephalitic parkinsonism, coma, ADHD, and even alcoholism.[101,138] By 1970, the legal annual production of amphetamines was more than 10 billion tablets, with the majority diverted for illicit usage.[101]

Currently, there are very few medical indications for amphetamines,

including narcolepsy, attention deficit hyperactivity disorder, and short-term weight reduction.[122] The prescriptive amphetamines include methylphenidate, pemoline, phentermine, phendimetrazine, amphetamine, dextroamphetamine, and methamphetamine. Because of structural differences, some amphetamines are marketed as nonamphetamine products in their package inserts. Despite the controlled status of amphetamines, there has been a resurgence of amphetamine abuse, particularly with methamphetamine and methylenedioxymethamphetamine (MDMA).[47,99,208,210,265,272]

History and Epidemiology

Edeleano first synthesized amphetamine (racemic Î²-phenylisopropylamine) in 1887. However, it was not rediscovered until the 1920s, when there was significant concern about the supply of ephedrine for asthma therapy. In the search for the synthesis for ephedrine, Alles from UCLA rediscovered dextroamphetamine and Ogata from Japan discovered methamphetamine (*d*-phenylisopropylmethylamine hydrochloride).[101] Amphetamine was marketed as Benzedrine inhaler, a nasal decongestant, by Smith, Kline, and French in 1932.[17] Amphetamine tablets were available in 1935 for the treatment of narcolepsy, and were advocated as anorexiants in 1938. The stimulant and euphoric effects of amphetamines were widely recognized, resulting in diverse forms of abuse and misuse. Amphetamine abuse was reported as early as 1936.[138] Benzedrine inhalers, each containing 250 mg of amphetamine, were widely abused, leading to a ban by the FDA in 1959. Propylhexedrine (Benzedrex) inhalers, a less-potent amphetaminelike substance marketed in 1949, supplanted Benzedrine inhalers.[7] Propylhexedrine was also significantly misused.[6]

Both amphetamine and methamphetamine were supplied as stimulants for soldiers and prisoners of war in World War II.[17,185] Widespread methamphetamine abuse in Japan persisted for more

than a decade after the war. From 1950 to the 1970s, there were sporadic periods of widespread amphetamine use and abuse in the United States. In the 1960s, various amphetamine derivatives such as methylenedioxyamphetamine (MDA) and *para*-methoxyamphetamine (PMA) were popularized as hallucinogens. Until 1971, only a small proportion of the amphetamines produced by pharmaceutical companies was used for legitimate medical problems.[101,187] The Controlled Substance Act of 1970 placed amphetamines in Schedule II to regulate the diversion of pharmaceutical amphetamines for nonmedicinal uses.[52] Amphetamine abuse subsequently declined in the 1970s.[38,148,187]

In the 1980s, the so-called designer amphetamines (Table 73-1), mostly methylenedioxy derivatives of amphetamine and methamphetamine, came into vogue, as a mechanism of circumventing existing regulations. The most well known substances were MDMA and 3,4-methylenedioxyethamphetamine (MDEA), but more than 200 different derivatives are known.[62,248] Before 1986, the Controlled Substances Act classified drugs as illegal only after they were synthesized and formally recognized by their structure, effects, or illegal usage. During this period, any analogs (such as these â€œdesigner drugsâ€•) not yet formally classified could be sold legally. In 1986, the standard became prospective for any agent that was used as a stimulant, hallucinogen, or depressant, and for any agent designed as such.[26] In effect, this amendment eliminated the legal loophole that allowed the designer drug industry to flourish. Although the meaning of the term â€œdesigner drugsâ€• has changed and is no longer legally relevant, many of these analogs are still widely illicitly available.[117,130,177]

From the late 1980s to the 1990s, a dramatic resurgence of methamphetamine abuse spread throughout much of the United States. A high purity preparation of methamphetamine hydrochloride was marketed in a large crystalline form termed â€œiceâ€• by abusers.[9,42,65,184] In fact, methamphetamine surpassed cocaine and became the primary substance of abuse among those seeking care in

the drug treatment programs of San Diego and San Francisco counties in the 1990s.[99,114] From 1991 to 1994, the number of methamphetamine-related deaths in the United States reported by medical examiners tripled from 151 to 433, with a disproportional distribution from the Los Angeles, San Diego, San Francisco, and Phoenix metropolitan areas. The number of methamphetamine-related emergency department visits also increased from 4900 in 1991 to 17,400 in 1994.[99] The number of methamphetamine-related emergency department visits has remained stable since the mid-1990s despite significant local geographical changes.[71] Recently, methamphetamine use has become particularly prevalent among men having sex with men in New York City.[106] Although the initial source of methamphetamine was from Pacific Rim countries such as Korea and Taiwan, currently the majority is produced in the United States.[43,78,265] Methamphetamine is the most common illicit drug produced by clandestine laboratories in the United States at this time. Because of the ease and low cost of methamphetamine synthesis, the end user cost of methamphetamine is less than one-third

that of cocaine.[78] Methamphetamine production in United States was primarily located in California and Oregon in the late 1990s, but it has spread through every state, although it remains particularly prevalent in the midwest and western United States.[265] The number of clandestine methamphetamine laboratory seizures nationally increased from 327 in 1995 to 15,994 in 2004.[125] Both the cost and the prolonged duration of effect may contribute to the increased popularity of methamphetamine.[99,150,265]

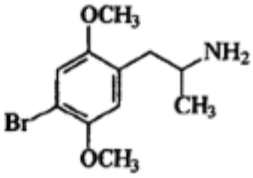
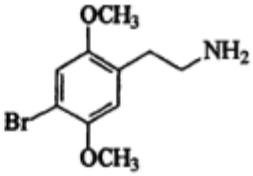
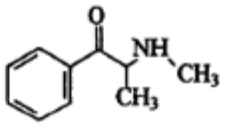
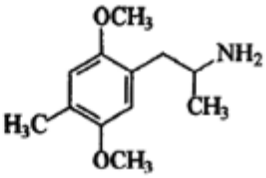
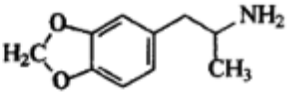
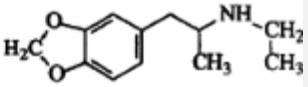
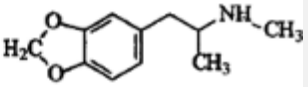
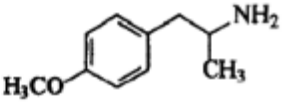
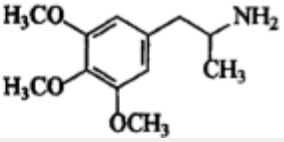
Xenobiotic	Clinical Manifestations	Structure
4-Bromo-2,5-dimethoxy-amphetamine (DOB)	Marked psychoactive effect potency >mescaline Sold as impregnated paper, like LSD Delayed onset of action, peak 3–4 h Fantasy, mood altering for 10 h, resolution 12–24 h Agitation, sympathetic excess	
4-Bromo-2,5-methoxyphenyl-ethylamine (2CB, MFT)	Relaxation Sensory distortion Agitation Hallucination Potency >mescaline	
Methcathinone (cat, Jeff, Khat, ephedrone)	Comparable to hallucinogenic and sympathetic effects of methamphetamine	
4-Methyl-2,5-dimethoxyamphetamine (DOM/STP) (serenity, tranquility, peace)	Narrow therapeutic index Euphoria, perceptual distortion Hallucinations, sympathetic stimulation	
3,4-Methylenedioxyamphetamine (MDA, love drug)	Empathy, euphoria Agitation, delirium, hallucinations, death associated with sympathetic excess	
3,4-Methylenedioxyethamphetamine (MDEA, Eve)	Comparable to MDMA Sympathetic excess	
3,4-Methylenedioxymethamphetamine (MDMA, Adam, ecstasy, XTC)	Psychotherapy "facilitator" Euphoria, empathy Nausea, anorexia Anxiety, insomnia Sympathetic excess	
para-Methoxyamphetamine (PMA)	Potent hallucinogen Marked stimulant effect	
2,4,5-Trimethoxyamphetamine	Similar to mescaline	

TABLE 73-1. Designer Amphetamines

Beginning in the mid-1990s, MDMA became and remains the amphetamine most widely used by college students and teenagers. MDMA is used by this population in large gatherings, known as â€œraveâ€• or â€œtechnoâ€• parties in England, Australia, and the United States.[215,216,272] MDMA use is prevalent in parties and clubs worldwide. Other MDMA-like analogs are often used or sold as MDMA in these gatherings.[10,272] Despite the popularity of MDMA, recent data in the United States demonstrates a decline in its past year use from 3.2 million in 2002 to 2.1 million in 2003.[259]

Reports of methcathinone (a Khat-derived substance) use in the midwestern United States,[94,282] and a resurgence of 4-bromo-2,5-methoxyphenylethylamine (2CB) in dance clubs occurred in the 1990s.[75,88] Fortunately, the fear for the widespread use of these agents never materialized. Although the trend of a particular amphetamine analog waxes and wanes, use and abuse of amphetamines in general is likely to continue to be consequential.

Pharmacology

The pharmacologic effects of amphetamines are complex but the primary mechanism of action is the release of catecholamines, particularly dopamine and norepinephrine, from the presynaptic terminals. Although there are conflicting mechanistic models of amphetamine induction of catecholamine release, the variable results may be directly correlated with the different concentrations of amphetamines used in experimental models. The best models to study the mechanism of action of amphetamines are based on dopaminergic neurons; similar mechanisms are invoked for norepinephrine and serotonin. Two storage pools exist for dopamine in the presynaptic terminals: the vesicular pool and the cytoplasmic pool. The vesicular storage of dopamine and other biogenic amines is maintained by the acidic environment inside the vesicles and the persistence of a stabilizing electrical gradient with respect to the cytoplasm. This environment is maintained by an adenosine

triphosphate (ATP)-dependent active proton transport system.[243] At low doses, amphetamines release dopamine from the cytoplasmic pool by exchange diffusion at the dopamine uptake transporter site in the membrane. At moderate doses, amphetamines diffuse through the presynaptic terminal membrane and interact with the neurotransmitter transporter on the vesicular membrane to cause exchange release of dopamine into the cytoplasm. Dopamine is subsequently released into the synapse by reverse transport at the dopamine uptake site.[243,261] At high doses, an additional mechanism is invoked as amphetamine diffuses through the cellular and vesicular membranes, alkalinizing the vesicles, permitting dopamine release from the vesicles and delivery into the synapse by reverse transport.[261,262] Binding selectivity to the neurotransmitter transporters largely determine the range of pharmacologic effects for the particular amphetamine. The MDMA affinity for serotonin transporters is 10 times greater than that for dopamine and norepinephrine transporters, hence producing primarily serotonergic effects.[97]

Amphetamines may also block the reuptake of catecholamines by competitive inhibition.[102,122] However, the effects of this mechanism are considered to be minor. At higher doses, amphetamines can cause the release of serotonin (5-hydroxytryptamine [5-HT]) and affect central serotonin receptors. Certain amphetamines, such as MDMA and 4-bromo-2,5-dimethoxyamphetamine (DOB), have more significant serotonergic effects.[85,122] Amphetamines are structurally similar to nonhydrazine amine-derivative monoamine oxidase inhibitors such as phenelzine and tranylcypromine, and most also have weak monoamine oxidase-inhibiting activities, the clinical significance of which is unclear.[212]

The most identifiable effects of amphetamines are those caused by catecholamine release and the resultant stimulation of peripheral Î±- and Î²-adrenergic receptors. In the central nervous system, increased norepinephrine at the locus caeruleus mediates the anorectic and alerting effects, and also some locomotor

stimulation.[101] The increase in central dopamine (particularly at the neostriatum) mediates stereotypical behavior and some of the other locomotor activities.[51,92,102,140] The activity of dopamine in the neostriatum appears to be linked to glutamate release and inhibition of GABAergic efferent neurons.[92,139,140] Stimulation of the glutamatergic system contributes significantly to the stereotypical behavior, locomotor activities, and neurotoxicity of amphetamines.[18,24,139,140,256,257] The effects of serotonin and dopamine on the mesolimbic system alter perception and cause psychotic behavior.[92,121] Because amphetamines directly interact with neurotransmitter transporters, minor modifications of the molecule may significantly alter its pharmacologic profile.[128] The Î±-methyl group in the amphetamine structure introduces chirality to the molecule. Except for MDMA and certain MDMA analogs, the *d*-enantiomers are much more potent (typically 4â€“10 times) than the *l* forms of amphetamines. Substitution at different positions of the phenylethylamine molecule alters general clinical effects of amphetamines, as demonstrated by animal discrimination studies and human observations. Compounds with methyl substitution at the Î± carbon, such as amphetamine and methamphetamine, possess strong stimulant, cardiovascular, and anorectic properties.[91,196] Large group substitution at the Î± carbon reduces the stimulant and cardiovascular effects, but retains the anorectic properties (such as in phentermine).[12] Substitution at the *para* position of the phenyl ring enhances the hallucinogenic or serotonergic effects of amphetamines (such as in *para*-chloroamphetamine and MDMA).[12,82,181] Although some of these generalizations enable scientists to understand the effects of amphetamines, there are many exceptions, and such generalizations may not apply when large doses of a particular molecule are ingested.[72] In terms of the spectrum of activities, methamphetamine has the most potent cardiovascular effects, and DOB has the most potent hallucinogenic or serotonergic effects.[91,196]

Pharmacokinetics and Toxicokinetics

In general, amphetamines are relatively lipophilic and hence they can readily cross the bloodâ€“brain barrier. They have large volumes of distribution, varying from 3â€“5 L/kg for amphetamine and 3â€“4 L/kg for methamphetamine and phentermine, to 11â€–33 L/kg for methylphenidate. Pemoline is the exception as it has a small volume of distribution (0.2â€–0.6 L/kg).[11] Amphetamines differ from catecholamines in that they lack the catechol structure (hydroxyl groups at the 3 and 4 positions of the phenyl ring) and are resistant

to metabolism by catechol-*O*-methyltransferase (COMT).[122] The addition of an Î±-methyl group in amphetamines confers resistance to metabolism by monoamine oxidase. These characteristics permit better oral bioavailability and longer duration of effects.[196]

Amphetamines are eliminated via multiple pathways, including diverse routes of hepatic transformations, and by renal elimination. For MDMA and its analogs, *N*-dealkylation, hydroxylation, and demethylation are the dominant hepatic pathways.[43,44,172] Depending on the particular substance, active metabolites of secondary amphetamines and ephedrine derivatives may be formed.[11,43] *N*-demethylation of methamphetamine and MDMA result in the formation of amphetamine and MDA, respectively.[43] Dealkylation and demethylation are mainly performed by cytochrome P450 (CYP) isozymes, including CYP1A2, CYP2D6, and CYP3A4, but they are also performed by flavin monooxygenase (FMO).[172] Polymorphism of CYP2D6 in humans was discovered as a result of decreased *p*-hydroxylation of amphetamine in certain individuals. Since its discovery, CYP2D6 polymorphism has been implicated in drug toxicity, substance use and abuse, and lack of drug efficacy in selected individuals.[246] Increased amphetamine toxicity is a potential concern in patients with decreased CYP2D6 activity. Although animals with CYP2D6 deficiency are more susceptible to MDMA toxicity,[49] limited studies in humans do not demonstrate an association of

mortality and CYP2D6 deficiency.[86,199] In general, because multiple enzymes and pathways (including renal) are involved in amphetamine eliminations, it is less likely that CYP2D6 polymorphism or drug interactions with CYP3A4 alone will significantly increase toxicity. However, it is unclear if toxicity is enhanced when multiple mechanisms for altering drug metabolism and renal dysfunction are present simultaneously.

Renal elimination is substantial for amphetamine (30%), methamphetamine (40â€“50%), MDMA (65%), and phentermine (80%). Amphetamines are relatively strong bases with a typical pK_a range from 9â€“10, and renal elimination varies depending on the urine pH.[11] The half-life of amphetamines varies significantly: amphetamine, 8â€–30 hours; methamphetamine, 12â€–34 hours; MDMA, 5â€–10 hours; methylphenidate, 2.5â€–4 hours; and phentermine, 19â€–24 hours.[11,43] Repetitive administration, which occurs typically during binge use, may lead to drug accumulation and prolongation of the apparent half-life and duration of effect.[132]

Clinical Manifestations

The clinical effects of amphetamines are largely related to the stimulation of central and peripheral adrenergic receptors. These clinical manifestations and complications are similar to those from cocaine use and may be indistinguishable except for the duration of effect of amphetamines, which tends to be longer (up to 24 hours).[65]

Compared to cocaine, amphetamines are less likely to cause seizures, dysrhythmias, and myocardial ischemia. This may be related to the sodium channel-blocking effects and to the thrombogenic effect of cocaine.[93] Psychosis appears to be more likely with amphetamines than cocaine, which may be related to the more prominent dopaminergic effects of amphetamines.[8,92] Tachycardia and hypertension are the most common manifestations of cardiovascular toxicity. Most patients present to the emergency department, however, because of the CNS manifestations.[65,129,276]

These patients are anxious, volatile, aggressive, and may have life-threatening agitation. Visual and tactile hallucinations, as well as psychoses, are common.[21,66,67,112,164,226,239] Other sympathetic findings include mydriasis, diaphoresis, and hyperthermia (Table 73-2).[66,70]

Death from amphetamine toxicity most commonly results from hyperthermia, dysrhythmias, and intracerebral hemorrhage.[39,61,79,135,142,163,206,227] Direct CNS effects may result in seizures. Tachycardia, hypertension, and vasospasm may lead to cerebral infarction,[95,153,231] intraparenchymal and subarachnoid hemorrhage,[57,110,126,141,258,281] myocardial ischemia or infarction,[81,207,269] aortic dissection,[57,69] acute lung injury,[29,193,194] obstetrical complications, fetal death,[162] and ischemic colitis.[16,119,133] Dysrhythmias vary from premature ventricular complexes to ventricular tachycardia and ventricular fibrillation.[135,165] Agitation, increased muscular activity, and hyperthermia can result in metabolic acidosis, rhabdomyolysis,[54] acute tubular necrosis (acute renal failure), and

coagulopathy.[70,87,134,143] Unless these systemic signs and symptoms are rapidly reversed, multiorgan failure and death ensue.

TABLE 73-2. Amphetamine Toxicity

Acute Toxicity
Cardiovascular system
Hypertension
Tachycardia
Dysrhythmias
Myocardial ischemia
Aortic dissection
Vasospasm

- Central nervous system
  - Hyperthermia
  - Agitation
  - Seizures
  - Intracerebral hemorrhage
  - Headache
  - Euphoria
  - Anorexia
  - Bruxism
  - Choreoathetoid movements
  - Hyperreflexia
  - Paranoid psychosis
- Other sympathetic symptoms
  - Diaphoresis
  - Tachypnea
  - Mydriasis
  - Tremor
  - Nausea
- Other organ systems
  - Rhabdomyolysis
  - Muscle rigidity
  - Acute lung injury
  - Ischemic colitis

Chronic toxicity

- Vasculitis
- Cardiomyopathy
- Pulmonary hypertension
- Aortic and mitral regurgitation
- Permanent damage to dopaminergic and serotonergic neurons

Laboratory abnormalities

- Leukocytosis
- Hyperglycemia
- Hyponatremia

Elevated CPK
Elevated liver enzymes
Myoglobinuria

Amphetamine users seeking intense â€œhighsâ€• may go on â€œspeed runsâ€• for days to weeks. Because of the development of acute tolerance, they use increasing amounts of amphetamines during these periods, usually without much sustenance or sleep, attempting to achieve their desired euphoria.[17,52,155,252,263] Acute psychosis resembling paranoid schizophrenia may occur during these binges and has contributed to both amphetamine-related suicides and homicides.[73,151] Return to a normal sensorium occurs within a few days after discontinuation of the drug. Once an amphetamine user experiences psychosis, it is likely to be recurrent, even after prolonged abstinence, which may be related to a kindling phenomenon.[17,204,263] Amphetamine-induced psychosis has contributed to the understanding of dopamine's function in schizophrenia. Typically after such binges, patients may sleep for prolonged periods, feeling hungry and depressed when awake. During this period of depression or withdrawal, the patient continues craving amphetamines.[112,152,158]

There are some direct neurologic effects of amphetamines. Compulsive repetitive behavior patterns are reported in humans and animals. Individuals may constantly pick at their skin, grind their teeth (bruxism), or perform repetitive tasks, such as constantly cleaning their house or car.[17] MDMA users often carry pacifiers to relieve bruxism. Choreoathetoid movements, although uncommon, are reported with acute and chronic amphetamine usage.[149,167,171,219,238,251] The etiology of the choreoathetoid movements may be related to increased dopaminergic activity at the striatal area.

Necrotizing vasculitis is associated with amphetamine abuse.[19,46] Angiography typically demonstrates beading and narrowing of the

small and medium-size arteries (see Fig. 6-25).[233,258] Progressive necrotizing arteritis[57] can involve multiple organ systems, including the central nervous, cardiovascular, gastrointestinal, and renal systems. Complications include cerebral infarction and hemorrhage, coronary artery disease, pancreatitis, and renal failure.[46,109,166,233,258,258,281] The etiology of the arteritis remains unclear. Although various contaminants associated with parenteral drug use were postulated as potential etiologies, oral and IV amphetamine use in animal models are also associated with vasculitis, suggesting that this is a direct amphetamine effect.[234,235,266] Cardiomyopathy is also reported with acute and chronic amphetamine abuse.[19,123,200,254] Excessive catecholamine exposure in patients with pheochromocytomas and chronic cocaine use may be responsible for their associated cardiomyopathies; amphetamine-induced cardiomyopathy may be produced by similar mechanisms.[101,137,275]

Primary pulmonary hypertension, a rare and potentially fatal disease, is reported with chronic methamphetamine and propylhexedrine use.[6,68,156,241] However, substantial epidemiologic risk for primary pulmonary hypertension is demonstrated only with fenfluramine and aminorex (2-amino-5-phenyl-2-oxazoline).[23,103,249] Pulmonary hypertension was associated with the use of aminorex as an anorectic agent in Europe from 1965 to 1968.[104] In 1996, a case-controlled study substantiated the increased risk of pulmonary hypertension with the use of amphetamine appetite-suppressant drugs, particularly with fenfluramine.[1] The risk of pulmonary hypertension was increased 23-fold when the cumulative use of anorectic agents totaled more than 3 months.[1] Pulmonary hypertension may develop following exposure to anorectic agents that may be as brief as 3 weeks.[103] The exact cause of the pulmonary hypertension is unclear. Increased serotonin or direct effects of 5-HT_{2B} receptors in the pulmonary vasculature is postulated to result in pulmonary vasoconstriction and endothelial proliferation.[120,193,229] Interestingly, although fenfluramine is a

weak agonist for 5-HT_{2B} receptors, its metabolite norfenfluramine is a potent agonist for 5-HT_{2B} receptors and may be responsible for causing pulmonary hypertension.[124] Pulmonary hypertension that develops following the use of anorectic drugs may be partially reversible after withdrawal of the agent; however, the median survival of patients studied during the European aminorex epidemic was 3.5 years from the time of diagnosis.[103] With current advances in therapy, improved survival is expected.[232]

Valvular heart disease is also associated with the use of the appetite-suppressants fenfluramine, dexfenfluramine, and phentermine, particularly if the duration of therapy is greater than 4 months.[50,83,131,145,273] The initial reports, in 1997, implicated significant aortic and mitral regurgitation with the use of these drugs and the prevalence was as high as 32%.[37] These reports resulted in the withdrawal of fenfluramine and dexfenfluramine. Subsequent studies demonstrated mostly mild aortic regurgitation and possible mitral regurgitation; the overall prevalence varies from study to study, ranging from 0.14% to 22.7%.[83,131,145,271] The highest risks appear to be in patients taking combination therapy with fenfluramine and phentermine, and those who used the drug for prolonged periods (>4 months).[131] The dramatic differences in the overall prevalence rate in these studies may be related to differences in patient population, duration of therapy, and the timing of echocardiography (ie, during therapy or after the cessation of therapy). The most recent meta-analysis demonstrated a 12% prevalence rate of valvular regurgitation (mostly aortic) with more than 90-day use of the appetite-suppressants, compared to 5.9% in the unexposed group. There was no difference when the appetite-suppressants' use was less than 90 days.[236] Echocardiographic findings of the valvular dysfunctions typically improve following cessation of these drugs.[118] The exact etiology of the valvular disease is postulated to be related to increased serotonin or direct effects on 5-HT_{2B} receptors. Similar valvular disorders are recognized in patients exposed to persistently increased serotonin

levels with conditions such as malignant carcinoid syndrome; its unclear why carcinoid syndrome predominately affects right-sided valves versus primarily left-sided valves for these drugs.[228]

Although the chronic administration of MDMA and its analogs are better publicized, chronic administration of various amphetamines, including amphetamine and methamphetamine, to animals, alters dopamine and serotonin transporters functions, depletes dopamine and serotonin in the neuronal synapses, and produces irreversible destruction of those neurons.[15,85,222,223,225,242,278] The etiology of neuronal toxicity may be related to the generation of free oxygen radicals, resulting in the generation of toxic dopamine and serotonin metabolites and neuronal destruction.[85,157,244,278,279] Based on animal models, dose, frequency and duration of exposure, and ambient temperature can affect neurologic injuries. Intact dopamine or serotonin transporters are necessary to produce neurologic injury. Drugs that inhibit transporter functions may prevent neurologic injuries in animals.[97] Significant differences are also noted across species; mice are typically resistant to MDMA-induced neurologic injury.[175] Although not as well-studied as MDMA, recent studies of former methamphetamine users demonstrated impaired memory and psychomotor functions, as well as corresponding dopamine transporter dysfunction and abnormal glucose metabolism on PET scans.[245,267,268] However, we still do not understand the difference in species susceptibility to neurologic injuries, the duration of effects in primates and humans, and functional

consequences of neurotoxicity in humans. The potential for permanent neurologic effects associated with chronic amphetamine use in humans requires further study. Despite the first report of neurologic injuries from methamphetamine in animals in 1976, many questions remain unanswered.

Finally, multiple medical complications can result from parenteral drug use and from the associated contaminants. Contamination with infectious agents may result in HIV infection, hepatitis, and malaria.

Bacterial and foreign-body contamination may result in endocarditis, tetanus, wound botulism, osteomyelitis, and pulmonary and soft-tissue abscesses.[41]

Diagnostic Testing

Diagnosis by history is rarely reliable as patients often do know the exact drug they have used.[148] Also, there is no readily available drug-specific serum analysis. Qualitative urine immunoassay testing for amphetamines is available, but it is not valuable in the acute overdose setting. Typically, the turnaround time for the test result is at least several hours, which is far too long to be clinically useful. Both false-positive and false-negative results are common. Many cold preparations contain structurally similar substances (such as pseudoephedrine) that may cross-react with the immunoassay.[48,55,80,213] Likewise, selegiline, a selective monoamine oxidase type B (MAO-B) inhibitor used for the treatment of parkinsonism, is metabolized to amphetamine and methamphetamine. Patients taking selegiline will react positively with most amphetamine-testing techniques.[138] Even a true-positive result only means the patient has used an amphetamine analog within the last several days. In addition, most immunoassays do not react with all amphetamines, resulting in false-negative results. For example, MDMA frequently goes unrecognized on standard urinary drug testing.[16,48] Although newer, rapid, serum qualitative drug screens are available, false-positive and false-negative results remain common and may be misleading. The gold standard for drug testing, gas chromatographyâ€“mass spectrometry analysis, can misidentify isomeric substances such as *l*-methamphetamine, which is present in nasal inhalers, with *d*-methamphetamine, if performed by inexperienced personnel.[253] In summary, the suspicion of amphetamine toxicity cannot be confirmed rapidly with a high level of reliability by the laboratory.

The physical and psychological assessment is nonspecific, and

polydrug abuse is quite common. As such, the prevalence of amphetamine abuse in the local geographic region should heighten the suspicion of amphetamine toxicity in patients with an appropriate presentation. Management decisions must be determined by the clinical manifestations and impressions.

Blood specimens should be sent for glucose, BUN, and electrolyte assays. Hyponatremia should be considered for any patient with an altered sensorium and suspected MDMA usage (Chap. 17). An ECG should be obtained to exclude ischemia, hyperkalemia, and drug toxicity (cyclic antidepressant), and continuous cardiac monitoring should be initiated. A complete blood count, urinalysis, coagulation profile, chest radiograph, CT of the head, and lumbar puncture may be necessary, depending on the clinical presentation.

Management

Table 73-3 summarizes the therapeutic approach to a patient with amphetamine toxicity. The initial medical assessment of the agitated patient must include the vital signs and a rapid complete physical examination. An often-neglected vital sign is the rectal temperature.

TABLE 73-3. Management of Patients with Amphetamine Toxicity

Agitation
Benzodiazepines (usually adequate for the cardiovascular manifestations)
Diazepam 10 mg (or equivalent) IV, repeat rapidly until the patient is calm (cumulative dose may be >100 mg of diazepam)
Seizures
Benzodiazepines
Barbiturates
Propofol
Hyperthermia
External cooling
Control agitation rapidly
Gastric decontamination and elimination
Activated charcoal for oral ingestions
Hypertension
Control agitation first
Î±-Adrenergic receptor antagonist (phentolamine)
Vasodilator (nitroprusside, nitroglycerin)
Delirium or hallucinations with abnormal vital signs
If agitated: benzodiazepines
Delirium or hallucinations with normal vital signs
Consider haloperidol or droperidol (consider risk/benefit)

Hyperthermia, a frequent and rapidly fatal manifestation in patients with drug-induced delirium, requires immediate interventions to achieve cooling.[87,134,143] Some patients will require physical restraint to gain clinical control and prevent personal harm to themselves or others. Because agitation and resistance against physical restraint may lead to rhabdomyolysis and continued heat generation, intravenous chemical sedation should be instituted immediately. Blood specimens should be sent for glucose, BUN, and electrolyte assays. Hyponatremia should be considered for patients

with altered sensorium and suspected MDMA usage (Chap. 17). Intravenous (IV) glucose ($D_{50}W$, 0.5â€“1 g/kg) and thiamine 100 mg should be given as indicated.

Because the clinician cannot accurately distinguish the diverse etiologies of drug-induced delirium, the choice of chemical sedation should be safe and effective regardless of the etiology. The most appropriate choice of sedation is a benzodiazepine because these drugs have a high therapeutic index and good anticonvulsant activity. They are effective for the treatment of delirium induced by acute overdose of cocaine, amphetamines, and other drugs, and the delirium associated with ethanol and sedative-hypnotic withdrawal.[63,66,93,205] The dose of benzodiazepine should be titrated rapidly intravenously until the patient is calm. In our clinical experience, cumulative benzodiazepine dosages required in the initial 30 minutes to achieve adequate sedation frequently exceeds 100 mg of diazepam or its equivalent. Antipsychotics, particularly potent dopamine antagonists such as haloperidol and droperidol, are frequently recommended by others for amphetamine-induced delirium. Antipsychotics may actually antagonize some of the effects of amphetamines via dopamine blockade.[63,64,76] In animal models, haloperidol may be

superior to diazepam in preventing mortality from amphetamine toxicity.[34,59,63,64] In clinical experience, however, the benzodiazepines appear to be as efficacious as the antipsychotics in the management of amphetamine toxicity.[66] Antipsychotics may lower the seizure threshold, alter temperature regulation, may cause acute dystonia and cardiac dysrhythmias, and do not interact with the benzodiazepineâ€“Î³-aminobutyric acid (GABA)â€“chloride channel receptor complex. All of these effects may worsen the clinical outcomes related to occult or concomitant cocaine toxicity and ethanol withdrawal.[93,98,205]

Rhabdomyolysis from amphetamine toxicity usually results from agitation and hyperthermia.[82,143] Sedation prevents further muscle

contraction and heat production. External cooling should be instituted for significant hyperthermia. Adequate IV hydration and cardiovascular support should maintain urine output of 1â€“2 mL/kg/h. Although urinary acidification can significantly increase the elimination and decrease the half-lives of amphetamine and methamphetamine,[11,13,14,58] this pH manipulation does not decrease toxicity, and, in fact, may increase the risk of renal compromise and acute tubular necrosis from rhabdomyolysis by precipitating ferrihemate in the renal tubules.[54] Patients with acute renal failure, acidemia, and hyperkalemia will likely require urgent hemodialysis.

Amphetamine body packers should be treated similarly to those who transport cocaine (Chap. 74). Any sympathomimetic symptom suggesting leakage of the packets requires surgical intervention.[270] Fluids, benzodiazepines, intubation, and external cooling may be necessary to stabilize these patients.

Individual Xenobiotics

Methamphetamine

Methamphetamine abuse in the United States is not new. From the 1950s to the 1970s, there were multiple epidemics of methamphetamine abuse.[17] Methamphetamine was and sometimes still is referred to as â€œcrack,â€• â€œspeed,â€• â€œyaba,â€• and â€œgo.â€• The pharmacologic profile of methamphetamine is quite similar to amphetamine, although the effects on the central nervous system are more substantial.[42] â€œIce,â€• the common name for methamphetamine in the 1990s because of the crystal forms, does not differ pharmacologically from other forms of methamphetamine. Methamphetamine is readily absorbed by the oral, parenteral, and inhalational routes. Because of a prolonged half-life of 19â€“34 hours, the duration of its acute effects can be greater than 24 hours.[42,65,66]

Since the 1990s, the activity and purity of methamphetamine available on the street is substantially higher than previous epidemics because of the method of synthesis.[160] Methamphetamine is now typically greater than 80â€“90% pure and almost exclusively in the dextroisomer form, which is most active on the CNS.

Methamphetamine is easily synthesized with the proper chemicals and minimal equipment.[84] The primary ingredient of methamphetamine synthesis is ephedrine, which can be hydrogenated into methamphetamine. The ephedrine method, using pharmaceutical grade L-ephedrine, produces a product with few contaminants that is stereochemically pure.[65,214] The production of the large crystal is possible by creating a supersaturated solution of methamphetamine hydrochloride.[65] Nonprescription sales of ephedrine are now restricted and monitored in many states.[265] Phenyl-2-propanone (P2P), as an alternative ingredient, can be methylated into ephedrine and then into methamphetamine.[28] Because of the strict control of ephedrine and P2P, illicit chemists use phenylacetic acid to synthesize P2P.[28,56] Lead acetate, which is used as a substrate for the reaction, resulted in an epidemic of lead poisoning associated with methamphetamine abuse in Oregon.[3,40] Lead levels reported in drug users were as high as 513 Âµg/dL, and some samples of illicitly manufactured methamphetamine had lead contents as high as 60% by weight.[40] Mercury contamination was also documented, although clinical mercury toxicity has not been reported.[26] The number of potential chemicals involved in the methamphetamine manufacturing process is significant, and without any legal monitoring, contamination of the product and the environment is inevitable.[4,28,127,154] In fact, 20â€“30% of the illicit methamphetamine manufacturing sites discovered were discovered because of laboratory explosion.[78,125] In California's San Bernardino County alone in 1995, 360 methamphetamine laboratories were identified and closed by drug enforcement agents.[78] These makeshift methamphetamine laboratories pose a significant health risk to law enforcement officers and the general public, causing respiratory and

eye irritation, headaches, and burns.[35] Currently, sale of other potential amphetamine synthesis ingredients, such as hydrochloric acid, hydrogen chloride gas, anhydrous ammonia, red phosphorus, and iodine, are also monitored and restricted in the United States.[28,36,265]

3,4-Methylenedioxymethamphetamine

MDMA was first synthesized in 1912, and was rediscovered in 1965 by Shulgin.[26] It is currently one of the most widely abused amphetamines by college students and teenagers.[47,208,272,276] It is commonly known as â€œecstasy,â€• â€œE,â€• â€œAdam,â€• â€œXTC,â€• â€œM&M,â€• and â€œMDM.â€• Other structural relatives of MDMA, MDEA (â€œEveâ€•) and MDA (â€œlove drugâ€•), are also used or distributed as MDMA in areas of MDMA use. These xenobiotics have similar clinical effects and acute and chronic toxicity. Recently, other MDMA-related substances are also found in â€œraveâ€• scenes, 2CB, 2,4-dimethoxy-4-(*n*)-propylthiophenylethylamine (2C-T7), and *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB).[33,75,88,146] The term, â€œecstasyâ€• may be used for all of these substances. Typically, MDMA is available in colorful and branded tablets that vary from 50 mg to 200 mg. MDMA and similar analogs are so-call entactogens (meaning touching within), capable of producing euphoria, inner peace, and a desire to socialize.[177,255] In addition, some psychologists used MDMA to enhance psychotherapy until the Controlled Substances Act of 1986.[195] People who use MDMA report that it enhances pleasure, heightens sexuality, and expands consciousness without the loss of control.[26,100,177] Negative effects reported with acute use included ataxia, restlessness, confusion, poor concentration, and memory problem.[255] MDMA has about one-tenth the CNS stimulant effect of amphetamine. Unlike amphetamine and methamphetamine, MDMA is a potent stimulus for the release of serotonin.[30,60,102] The concentration of MDMA required to stimulate the release of serotonin is 10 times less than that required for the

release of dopamine or norepinephrine. In animal models, the stereotypic and the discriminatory effects of MDMA and its congeners can be distinguished from those of other amphetamines.[31,195]

The sympathetic effects of MDMA are mild in low doses. However, when a large amount of MDMA is taken, the clinical presentation is similar to that of other amphetamines and deaths can result from abuse.[70,116,117,191,276] Those patients at greatest risk develop dysrhythmias, hyperthermia, rhabdomyolysis, and disseminated

intravascular coagulation.[70,117,250] Significant hyponatremia has been well reported with MDMA use.[2,113,173,197] MDMA and its metabolites increase the release of vasopressin (antidiuretic hormone) and may be related their serotonergic effects.[77,115] Furthermore, large free-water intake combined with sodium loss from physical exertion (in dance clubs) may be crucial to the development of hyponatremia.

A major concern with MDMA usage is its long-term effects on the brain. In numerous animal models, acute administration of MDMA leads to the decrease in serotonin reuptake transporter (SERT) function and numbers. Recovery in SERT function may take several weeks. Repetitive administration of MDMA ultimately leads to permanent damage to serotonergic neurons, typically causing injury to the axons and the terminals while sparing the cell bodies.[174,178,180,201,220,222] Some regeneration of synaptic terminals can occur even with neuronal damage, but functional recovery is not complete. Intact SERT function is necessary for MDMA-induced neurotoxicity. Xenobiotics that inhibit the uptake of serotonin prevent MDMA-induced neurotoxicity in animals. Animal data suggest that MDMA induces hydroxyl free-radical generation and decreases antioxidants in serotonergic neurons.[224,247] MDMA does not directly cause neurotoxicity, but its metabolites 3-Î±-methyldopamine and *N*-methyl-Î±-methyldopamine do produce neurotoxicity in animals.[186] When sufficient antioxidants are depleted, neuronal damage may occur.

The evidence for these potential neurotoxic effects in humans is less clear. Indirect evidence of serotonergic effects in humans includes lower concentrations of 5-hydroxyindoleacetic acid (5-HIAA) in the cerebral spinal fluid (CSF) of MDMA users than in controls.[221] Case reports and studies of MDMA users demonstrate alteration in mood, sleep, anxiety, cognition, memory, and impulse controlâ€”all functions that are believed to be affected by serotonin.[5,176,179,181,185] Either single-photon emission tomography (SPECT) or positron emission tomography (PET) demonstrates decreased SERT function in MDMA users, even after prolonged abstinence.[27,202,218] Memory deficits appeared to persist even in abstinent MDMA users.[96,190] A major deficit in human studies is finding comparable control groups; it is possible that people with psychiatric problems are more likely to be MDMA users.[182] MDMA users are also associated with other drug use. Currently, there are no human histopathologic (postmortem) data for MDMA users.[147] Further studies are required to address the long-term neuropsychiatric effects of MDMA.

Propylhexedrine

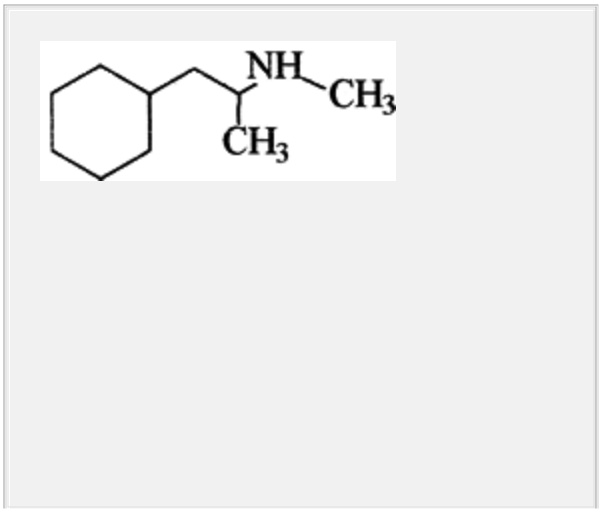


Figure. No Caption Available.

Smith, Kline, and French introduced propylhexedrine in 1949 as the primary active ingredient in Benzedrex nasal inhaler, to replace amphetamine in nasal inhalers because of the widespread abuse.[7,82] Propylhexedrine is an alicyclic aliphatic sympathomimetic amine that is structurally similar to amphetamine, with a local vasoconstrictive effect and approximately 10% of the CNS stimulatory effect of amphetamine.[7] Propylhexedrine abuse became prevalent after the removal of amphetamine from nasal inhalers. The abusers disassembled the inhaler and ingested the cotton pledget vehicle of propylhexedrine itself, diluted it in beverages, or reconstituted the drug for intravenous injection. Numerous effects were reported with propylhexedrine abuse, including sudden death, myocardial infarction, cardiomyopathy, pulmonary hypertension, and acute psychosis.[6,7,53,68,82,161,169,170,274] Although propylhexedrine in nasal inhalers has largely been replaced by safer sympathomimetic agents (Chap. 50), the drug is still readily available and is abused as an inexpensive, legal â€œhigh.â€•

Khat, Cathinone, and Methcathinone

Khat (also known as quat and gat), the fresh leaves and stems from the *Catha edulis* shrub, is a commonly used drug in eastern and central Africa, and in parts of the Arabian peninsula. Attention to khat was highlighted in the early 1990s by the media coverage of war in Somalia and Ethiopia. Khat is sold in small bundles of leaves in the local markets of these countries. The leaves and the tender stems are chewed or occasionally concocted into tea. Khat chewing has a significant role at social gatherings in these countries.[168] There is a trend of increasing khat consumption and binges among adolescents in these countries.[203] When the dried leaves and stems were studied, the primary active ingredient was thought to be

cathine (norpseudoephedrine), present as 0.1â€“0.2% of the dried material. Cathine has about one-tenth the stimulant effects of D-amphetamine. Numerous other amphetaminelike compounds are also isolated, but occur in minute quantities.[136] When the fresh leaves are analyzed, however, cathinone (benzylketoamphetamine), a more potent psychoactive compound, was demonstrated to be the primary active agent.[89,105,136] As the leaves age, cathinone is degraded into cathine, which also explains why dried khat is neither popular nor widely distributed. Imported fresh khat must be consumed within a week, before it loses much of its potency. The primary effects of khat are increased alertness, insomnia, euphoria, anxiety, and hyperactivity. Increased khat consumption is linked to psychosis. Significant adrenergic complications are much less frequent than those associated with amphetamine abuse.

Methcathinone, the methyl derivative of cathinone, chemically synthesized from ephedrine, has been abused in Russsia and other former members of the Soviet Union for many years. The potency of methcathinone is comparable to that of methamphetamine.[90,280] Methcathinoneâ€”also termed ephedrone, or sold under the street names of â€œcatâ€• or â€œJeffâ€•â€”currently remains widely abused in Russia. Methcathinone abuse was first reported in Michigan in the early 1990s and is now reported in other states as well.[74]

Ephedrine or Ma-Huang Herbal Products

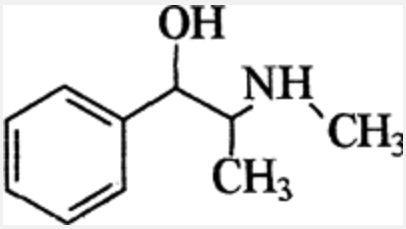


Figure. No Caption Available.

Ephedrine is commonly found in nonprescription cold preparations. Ephedrine is also the active substance in the Chinese plant ma-huang, which has been used for centuries for the treatment of asthma. Although ephedrine is much less potent than amphetamine, when combined with other catecholamine-stimulating xenobiotics or when taken in large quantities, significant toxicity may occur.[25,32,209,240] In the United States, numerous ephedrine products, such as â€œgo,â€• â€œultimate xphoria,â€• â€œup your gas,â€• and â€œherbal ecstasy,â€• are marketed primarily to teenagers. Some of these products

contain more than 500 mg of ephedrine, which may be combined with pseudoephedrine, phenylpropanolamine, and caffeine; other products contain the plant extract ma-huang.[159,209,211] Many of these products are marketed as legal stimulants or safe herbal stimulants for a natural â€œhigh.â€• Similarly, ma-huang is also widely marketed as a â€œsafeâ€• herbal weight-reducing product. Sales appeared to increase when it was recognized that phenylpropanolamine was associated with brain hemorrhage in women.[144] Unfortunately, these products are linked to numerous

deaths and adverse reactions.[107,108,192,211,264,277,282] Because these products are sold as food supplements, they are not regulated by the FDA unless a product can be demonstrated to be unsafe (Chap. 43). In 2004, the FDA finally banned the use of ephedra products. In April 2005, a federal judge in Utah reversed the ban of ephedra sales in Utah, illustrating the difficulty of the FDA in the regulation of herbal products.[111] Herbal products with *Citrus aurantium* (bitter orange), contain a number of adrenergic amines, including synephrine, have now supplanted ephedra products. *Citrus aurantium* has similar pharmacologic effects and toxicity as ephedra.[20,198]

Summary

Amphetamine usage is increasing dramatically throughout the United States. Similarly, ED visits and morbidity and mortality related to amphetamines parallel amphetamine usage. Many of these complications are similar to those of cocaine, such as agitation, hyperthermia, rhabdomyolysis, myocardial ischemia, and cerebral infarction. Physicians, more than ever, must understand the pathophysiology of amphetamines and be ready to diagnosis and treat its toxicity. The chronic effects of amphetamines as demonstrated in animal models pose serious concerns for humans, particularly as amphetamine usage becomes more prevalent; further studies are required to achieve prevention and management.

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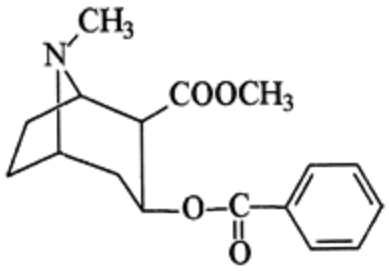
Chapter 74
Cocaine

Robert S. Hoffman



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A 54-year-old man called 911 because of chest discomfort that had begun about 4 hours earlier. The patient had a history of cigarette smoking, daily cocaine use, and a questionable history of hypertension. He stated that shortly following the use of 1 g of cocaine, he developed midsternal chest pressure that radiated to the back, was worse with exertion, and was associated with nausea and three episodes of vomiting. When emergency medical services (EMS) technicians arrived they gave him oxygen, 162 mg of aspirin, and sublingual nitroglycerin spray. The pain resolved by

the time he arrived to the hospital.

On arrival at the hospital the patient was alert and in no distress and his vital signs were as follows: blood pressure, 145/95 mm Hg; pulse, 114 beats/min; respirations, 20 breaths/min; temperature, 96.8Â°F (37Â°C). His oxygen saturation while breathing room air was 97% by pulse oximetry, and a rapid reagent glucose test was normal. Physical examination was remarkable for normal pupils, the absence of diaphoresis, normal chest auscultation, and normal heart sounds. The patient was neurologically and cognitively intact.

The patient was attached to a continuous cardiac monitor, given high flow oxygen, an ECG was obtained (Fig. 74-1), and a chest radiograph was ordered. An intravenous line was inserted and blood samples were obtained and sent for electrolytes, glucose, cardiac enzymes, and a complete blood count analysis. Additionally, about 1 hour after arrival, 10 mg of diazepam was given IV for continued tachycardia. Following that, his repeat vital signs were: blood pressure, 141/93 mm Hg; pulse, 115 beats/min. Another 5 mg of diazepam was administered IV but resulted in no change in the patient's vital signs. The chest radiograph was unremarkable.

Approximately 2 hours after admission to the emergency department, the troponin I was reported as positive at 1.5 ng/mL and the patient was given 325 mg of aspirin and an intravenous loading dose of heparin, followed by a continuous heparin infusion. Two doses of metoprolol (2.5 mg each) were administered IV 10 minutes apart, for persistent tachycardia. Within 10 minutes of the second dose the patient complained of severe crushing substernal chest pain, and became diaphoretic and nauseated. Shortly thereafter his systolic blood pressure dropped to 50 mm Hg. The patient was intubated and resuscitative attempts included administration of atropine, epinephrine, vasopressin, and glucagon. A bedside ultrasonogram showed global akinesis of the

heart and the patient died about 3 hours after presentation.

After review of the case an adverse drug event report was filed with the hospital's drug safety committee citing a probable interaction between cocaine and metoprolol.

History and Epidemiology

Cocaine is a natural alkaloid contained in the leaves of *Erythroxylum coca* , a shrub that grows abundantly in Columbia, Peru, Bolivia, the West Indies, and Indonesia. As early as the 6th century the inhabitants of Peru chewed or sucked on the leaves for social and religious reasons. In the 1100s, the Incas used cocaine-filled saliva as local anesthesia for ritual trephinations of the skull.[69]

In 1859, Albert Niemann isolated cocaine as the active ingredient of the plant. By 1879 Vassili von Anrep demonstrated that cocaine could numb the tongue.[114] However, Europeans knew little

about cocaine until 1884, when the Austrian ophthalmologist Karl Koller introduced cocaine as an effective local anesthetic for eye surgery and Koller's colleague, Sigmund Freud, wrote extensively on the psychoactive properties of cocaine.[57] Following these revelations, Merck, Europe's main cocaine producer increased production from less than 0.75 pounds in 1883 to more than 150,000 pounds in 1886.[109]

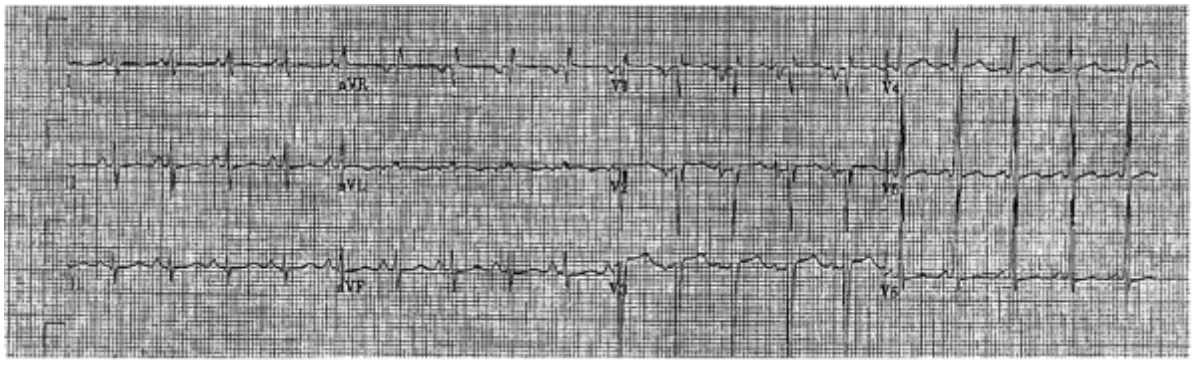

Figure 74-1. The ECG from the 54-year old man with cocaine-associated chest pain described in the case. The ECG shows 1â€“2 mm elevations of the ST segments in the anterior leads (V_2 , V_3).

Nearly simultaneously, reports of complications resulting from the therapeutic use of cocaine began to appear. In 1886, a 25-year-old man had a â€œpulselessâ€• syncopal event after cocaine was applied to his eye to remove a foreign body.[220] By 1887 more than 30 cases of severe toxicity were reported,[189] and by 1895 at least 8 fatalities resulting from a variety of doses and routes of administration were summarized in one article.[59] Recreational cocaine use was legal in the United States until 1914, when it was restricted to medical professionals. It was not until 1982, however, that the first cocaine-associated myocardial infarction was reported in the United States.[28]

Today, cocaine remains an approved pharmaceutical, primarily used either for topical anesthesia of cutaneous lacerations or as both a vasoconstrictor and topical anesthetic for otolaryngology procedures. Multiple factors, including severe complications despite the use of approved doses, complicated regulatory standards for storage, record keeping requirements, and comparable available alternatives have fostered a decline in the medicinal use of cocaine.[19 , 65 , 135] Unfortunately, the recreational use of cocaine remains a significant problem. Although drug use statistics are always questionable, recent estimates suggest that almost 34 million Americans have used cocaine at least once, with just over 2 million being current regular users.[41]

Pharmacology

The alkaloidal form of cocaine (benzoylmethylecgonine) is extracted from the leaf by mechanical degradation in presence of a hydrocarbon. The resultant product is converted into a hydrochloride salt and extracted into an aqueous phase, which is

subsequently evaporated to yield a white powder (cocaine hydrochloride). Cocaine hydrochloride can be insufflated or applied to other mucous membranes, dissolved in water and injected, or ingested, but it rapidly degrades during pyrolysis. Smokeable cocaine (crack) is formed by dissolving cocaine hydrochloride in water and adding a strong base. A hydrocarbon solvent is added, the cocaine base is extracted into the organic phase, and then evaporated. The term free-base refers to the use of cocaine base in solution. Typically a tobacco or marijuana cigarette is dipped into the free-base solution and allowed to dry prior to smoking.

Cocaine is rapidly absorbed following all routes of exposure; however, when applied to a mucous membrane or ingested its vasoconstrictive properties slow the rate of absorption and delay the peak effect. Whereas bioavailability exceeds 90% with intravenous and smoked cocaine, it is only approximately 80% following nasal application.[105] Data for ingested cocaine and application to other mucus membranes such as the urethra, vagina, or rectum are inadequately documented. Table 74-1 lists the typical onsets and durations of action for various uses of cocaine.

Following absorption cocaine is approximately 90% bound to plasma proteins. Although binding to both albumin and Î±$_1$ -acid glycoprotein are reported, it appears that albumin binding is less important.[174] Based on human volunteer studies, the volume of distribution is reported to be about 2.7 L/kg.[105] It is unclear if the volume of distribution changes with overdose.

Peak levels were determined in nonnaive human volunteers by administering intravenous, nasal, or smoked doses that were selected to produce approximately the same subjective peak effects.[105] The resultant peak levels were as follows: after intravenous injection of 20.5 mg, 180 Â± 56 ng/mL; after nasal administration of 95 mg, 220 Â± 39 ng/mL; and after smoking of 40 mg, 203 Â± 88 ng/mL. In this same study, the terminal

elimination half-life of cocaine was on the order of 1 hour.

Intravenous
<1
3â€“5
30â€“60
Nasal insufflation
1â€“5
20â€“30
60â€“120
Smoking
<1
3â€“5
30â€“60
Gastrointestinal
30â€“60
60â€“90
Unknown

Route of Exposure	Onset of Action (min)	Peak Action (min)	Duration of Action (min)

TABLE 74-1. Pharmacology of Cocaine

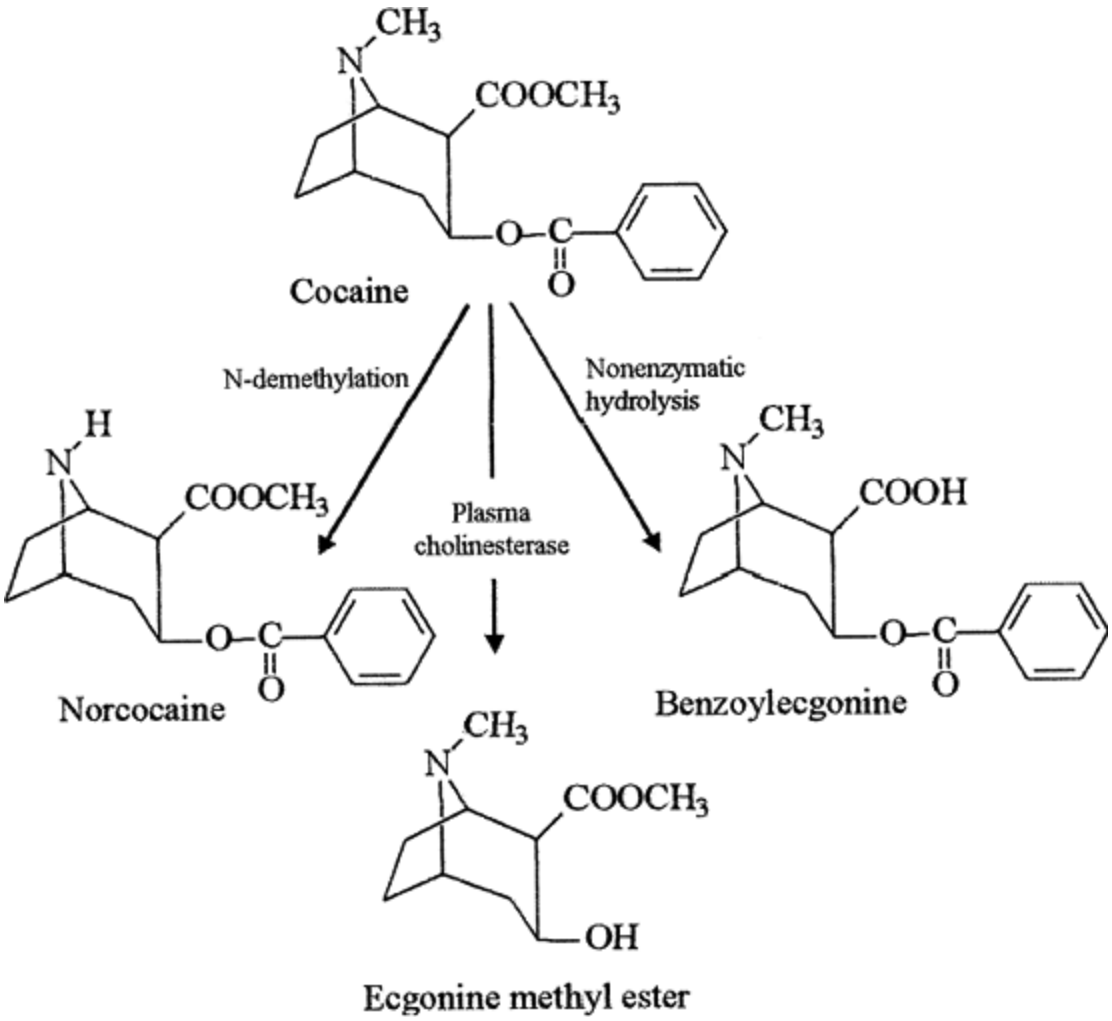

Figure 74-2. Metabolism of cocaine. The three principle metabolic pathways of cocaine are depicted.

The metabolism of cocaine is very complex and dependent on both genetic and acquired factors. Three major pathways of cocaine metabolism are well described (Fig. 74-2). Cocaine undergoes *N* -demethylation in the liver to form norcocaine, a minor metabolite that rarely accounts for more than 5% of drug.[101 , 129 , 212 , 213] However, norcocaine readily crosses the bloodâ€“brain barrier and produces clinical effects in animals that are quite similar to cocaine.[13 , 34 , 108 , 150 , 151 , 157 , 198 , 201 , 235] Nearly half of a

dose of cocaine is both nonenzymatically[213] and enzymatically hydrolyzed[39] to form benzoylecgonine (BE). In vitro, BE has little or no effect on cardiac sodium or potassium channels,[34 , 49] and when injected into animals, it is virtually inactive.[150 , 151 , 157 , 198 , 208] When either injected directly into the cerebral ventricles[151 , 201] or applied to the surface of cerebral arteries,[138] BE is a potent vasoconstrictor. These effects should not be discounted even though BE crosses the bloodâ€“brain barrier poorly in relationship to cocaine,[151] as some BE is probably formed from cocaine that has already entered the CNS. Other studies demonstrate that intravenous BE can produce cerebral vasoconstriction[32] and seizures.[117 , 150] Finally, plasma cholinesterase (PChE) and other esterases metabolize cocaine to ecgonine methyl ester (EME). In normal individuals, between 32 and 49% of a given dose of cocaine is metabolized to EME.[4 , 101] Like BE, EME crosses the bloodâ€“brain barrier poorly[151] and its biologic effects remain a source of debate. Although many authors accept that EME has little or no pharmacologic activity,[34 , 49 , 150 , 151 , 198] diverse animal models demonstrate contradictory results, concluding that EME is a vasodilator,[138 , 172 , 199] sedative, an anticonvulsant,[201] and protective metabolite against lethal doses of cocaine.[84]

The role of genetic or acquired alterations in PChE activity has been of interest for many years. Early in vitro studies showed that cocaine was poorly metabolized in isolated serum samples from patients with succinylcholine sensitivity (low PChE activity). Although these findings led many authors to speculate that patients with low PChE activity would be exquisitely sensitive to cocaine, evidence to support this contention lagged behind by more than 10 years. In several studies and case series, patients with low PChE activity demonstrate increased sensitivity to cocaine,[43 , 82 , 166] findings which are corroborated in multiple animal models.[20 , 21 , 83 , 136 , 147 , 214 , 239]

Multiple other metabolites of cocaine are well characterized.[30]

Some deserve mention because of their clinical or diagnostic importance. In 1990, a unique metabolite was identified in patients who smoke cocaine, which has subsequently come to be known either as anhydroecgonine methyl ester (AEME) or methylecgonide.[103] The presence of this compound and its metabolite, ecgonidine, can be used to help determine the route of administration in cocaine users. Additionally, AEME has demonstrable agonism at the muscarinic (M_2) receptors, which may have important clinical implications.

Ethanol has a unique pharmacologic interaction with cocaine. A transesterification reaction between the two drugs produces a unique agent, benzoylethylecgonine, which is also called ethyl cocaine or cocaethylene.[14] In human volunteers, given cocaine and ethanol, cocaethylene accounted for approximately 17% of the metabolites, producing a decrease in the amount of BE and an increase in the amount of EME formed.[73] Cocaethylene has a relatively long duration of action and like cocaine, it is neurotoxic, cardiotoxic, and dysrhythmogenic.

Pathophysiology

General Effects

Cocaine blocks the reuptake of biogenic amines. Specifically, these effects are described on serotonin and the catecholamines dopamine, norepinephrine and epinephrine. Several innovative animal investigations have helped to elucidate the particular roles of each neurotransmitter. Mice lacking the dopamine transporter are relatively insensitive to the locomotor effects of cocaine.[61] Tachycardia emanates from adrenally derived epinephrine, whereas hypertension results from neuronally derived norepinephrine.[218 , 219] Serotonin is an important modulator of dopamine and has a role in cocaine addiction and reward and seizures.[71 , 127 , 146 , 163]

Whereas much emphasis has been placed on the reuptake blockade of these biogenic amines, it is clear that this effect is insufficient to account for the clinical manifestations of cocaine toxicity. First, other xenobiotics that block the reuptake of biogenic amines, such as cyclic antidepressants, produce quite distinct clinical manifestations (Chap. 71).[219] Also, xenobiotics that block the effects of dopamine, epinephrine, and norepinephrine not only fail to protect against toxicity, they actually exacerbate it.[24 , 67 , 122 , 194] Although this may, in part, result from an unopposed Î±-adrenergic effect, hypertension and vasospasm fail to explain the increase in psychomotor agitation, hyperthermia, and seizures that result.[24 , 67] These effects most likely result from an interaction between cocaine and excitatory amino acids. Cocaine increases excitatory amino acid concentrations in the brain.[207] Excitatory amino acid antagonists prevent both seizures and death in experimental animals.[15 , 185] Finally, because experimental evidence in animals[24 , 67 , 202] and clinical experience in humans demonstrate that sedation treats both the central effects of cocaine and the peripheral effects of biogenic amines, a newer model was proposed (Fig. 74-3). This model emphasizes the necessity of diffuse central nervous system agitation as a prerequisite for cocaine toxicity, explains experimental and clinical observations, and provides insight into a pharmacologic approach to acute toxicity.

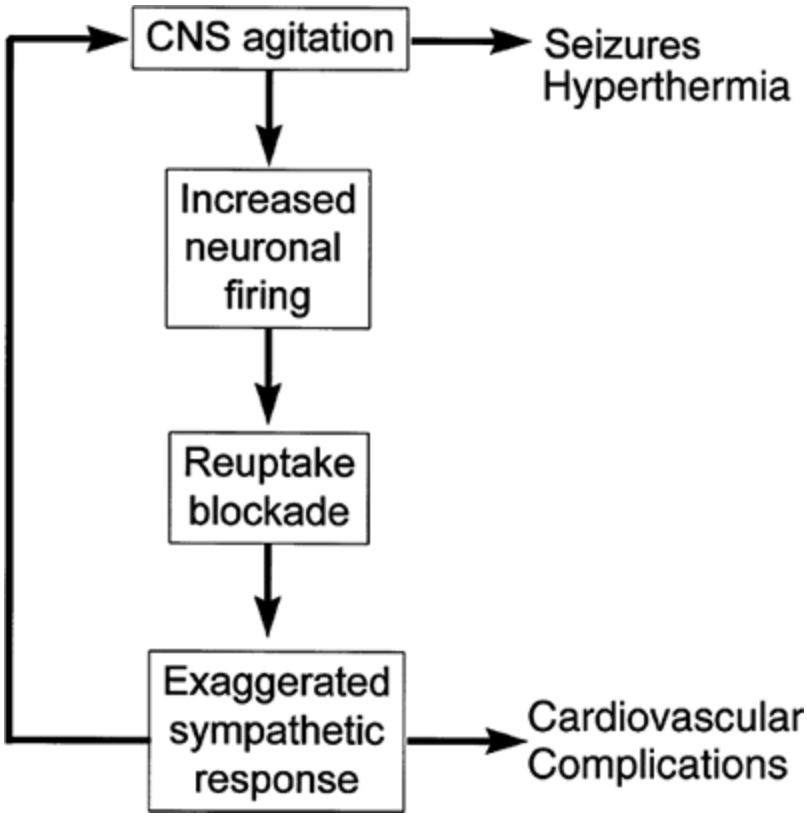

Figure 74-3. Cocaine-induced CNS effects modulate peripheral events.

Specific Organ System Effects

Atherogenesis, Coagulation, and Ischemic Cardiac Events

Cocaine use is associated with cardiac ischemia and infarction in young people, and may account for as much as 25% of myocardial infarctions in patients younger than 45 years old.[181] One simple mechanisms is that hypertension and tachycardia increase myocardial oxygen demand. Although this may be sufficient in some individuals, it is clear that cocaine also produces profound vasoconstriction. Although evidence suggests that cocaine-induced

vasoconstriction is mediated through neuronal norepineprhine,[123, 137] benzoylecgonine has a direct effect on vessels that appears to be calcium mediated.[137] The simultaneous use of nicotine (common in substance users) has additive, if not synergistic, effects with cocaine.[156] Additional contributory factors include effects on atherogenesis and coagulation.

Rabbits fed a normal diet do not develop atherosclerotic vascular disease. However, when that diet includes cocaine and cholesterol, rabbits develop classic atherosclerotic lesions.[115, 125, 126] Experiments with human endothelial cells demonstrate that cocaine directly increases the permeability to lipids by altering tight junctions.[116] This probably promotes the formation of subendothelial atherosclerotic plaques.

Enhanced coagulation and impaired thrombolysis compound the effects of accelerated atherogenesis and vasospasm. In both in vitro and in vivo experiments, cocaine activates human platelets and causes Î±-granule release, resulting in platelet aggregation.[76, 121] Thus even in the absence of endothelial injury, cocaine can initiate a thrombotic cascade while simultaneously enhancing the activity of plasminogen activator inhibitor type 1 (PAI-1), thereby impairing clot lysis.[155]

It is reasonable, although unstudied, to assume that any or all of these effects described in the cardiovascular system can produce ischemia or infarction in other tissues as well (see Clinical Manifestations below).

Dysrhythmias

Like other local anesthetics (Chap. 64) cocaine blocks neuronal sodium channels, thereby preventing saltatory conduction. Because of homology between neuronal and cardiac sodium channels, cocaine also inhibits the rapid inward Na^+ current responsible for phase 0 depolarization of the cardiac action potential (Chaps. 5 , 23 , and 71). Experimental evidence

suggests that cocaine enters the sodium channel and binds on the inner membrane.[34, 114, 180] Like many sodium channel-blockers, binding is both pH and use dependent (ie, binding increases as pH falls or heart rate increases; Chap. 61).[35, 229] Furthermore, although norcocaine has a greater affinity for inactivated sodium channels, it has a much more rapid offset of action than cocaine.[34] Consequently, cocaine can be characterized as a Vaughn-Williams type I antidysrhythmic agent (Chap. 61). Cocaine-induced QRS prolongation, as might be expected, is exacerbated by Vaughn-Williams type IA antidysrhythmic agents,[236] and ameliorated by lidocaine or hypertonic sodium bicarbonate.[8, 66, 173] Another effect of sodium channel blockade, the Brugada pattern, is also associated with cocaine use.[134, 168] In addition to its sodium channel-blocking properties, cocaine also blocks cardiac potassium channels (Chaps. 5 and 23). This results in QTc prolongation[177, 217, 229] and even can produce torsade de pointes.[200]

Pulmonary

Despite what is now well accepted as an association between cocaine use and asthma,[187] this relationship was not recognized until smoked cocaine became prevalent.[47] Furthermore, experiments in human volunteers demonstrate that only smoked cocaine (not intravenous cocaine) produces bronchospasm.[216] Although it is possible that bronchospasm results from direct administration of cocaine to the airways, inhaled contaminants of cocaine, or thermal insult, AEME (the unique pyrolytic metabolite of cocaine that acts as a muscarinic agonist) produces bronchospasm in experimental animals.[26]

Clinical Manifestations

Many clinical manifestations of toxicity develop immediately following cocaine use. These are typically associated with the sympathetic overactivity and their duration of effect is predictable

based on the pharmacokinetics of cocaine use. Other manifestations, such as those associated with tissue ischemia, may present in a delayed fashion, with a clinical latency of hours to even days after last cocaine use. The reasons for this delay are not entirely apparent but may relate to anesthesia and an altered sensorium associated with acute cocaine use, changes in receptor regulation,[159] or affects on platelets, coagulation, and thrombolysis, which incite a slow cascade leading to thrombosis.

Vital sign abnormalities that develop during cocaine toxicity are characteristic of the sympathomimetic toxidrome. Thus, varying degrees of hypertension, tachycardia, tachypnea, and hyperthermia occur. Although any of these vital signs can be life-threatening, experimental and clinical evidence suggests that hyperthermia is the most critical.[24,67,143] Initially, with typically used doses, and at any time with a massive dose, apnea, hypotension, and bradycardia can result, all from direct suppression (anesthesia) of brainstem centers.[113,148] These effects are fleeting and rarely noted when patients present to healthcare as either the sympathetic overdrive rapidly ensues, or sudden death results. Additional sympathomimetic findings include mydriasis, diaphoresis, and neuropsychiatric manifestations.

Cocaine produces end-organ toxicity in virtually every organ system in the body. These events result from vasospasm, hemorrhage secondary to increased vascular sheer force (dP/dT), or enhanced coagulation. Each organ system is discussed separately in the following sections.

Central Nervous System

Seizures, coma, headache, focal neurologic signs or symptoms, or behavioral abnormalities that persist longer than the predicted duration of effect of cocaine should alert the clinician to a potential catastrophic adverse CNS event. Hemorrhage can occur

at any anatomic site in the CNS. Subarachnoid, intraventricular, and intraparenchymal bleeding are all well described in association with cocaine use.[37, 130, 142, 182, 203] Although the early discussions suggested that patients with these events were predisposed because of the presence of arteriovenous malformations or congenital aneurysms,[238] subsequent larger studies failed to support this analysis, suggesting that effects can occur independently of preexisting disease.[2, 161] Presumably CNS bleeding is simply a manifestation of abnormal sheer force. Spontaneous extraaxial bleeding is also associated with cocaine use.[193]

Both vasospastic (bland) infarction and transient ischemic attack (TIA) are also reported in association with cocaine use.[37, 38, 130] In one epidemiologic study, women younger than age 45 years who had strokes were 7 times more likely to report cocaine use than controls.[178] Patients can present with any of the classic physical findings associated with thrombotic or embolic stroke. Although these initial clinical symptoms may resemble hemorrhagic infarction, the pathophysiology is distinct. Vasospasm can also produce consequential injury to the spinal cord, resulting in paralysis from an anterior spinal artery syndrome.[37, 154]

Seizures are commonly provoked by cocaine.[87, 158] Although an underlying seizure focus is not a prerequisite, it is clear that cocaine use can serve as a trigger in patients with epilepsy.[118]

Headache is also well described in cocaine users. While the exact mechanism is unclear, hypertension, vasospasm, or dysregulated neurotransmitters might all be contributory. In addition to typical tension headache, classic migraine and cluster headaches are also reported.[176, 195]

Eyes, Nose, and Throat

Sympathetic excess produces mydriasis through stimulation of the

dilator fibers of the iris. Although often quite large, these pupils characteristically retain their ability to respond to light. Like other mydriatics, cocaine can produce acute angle closure glaucoma.[72] Vasospasm of the retinal vessels can produce both unilateral and bilateral loss of vision.[85, 132] Additionally, although cocaine produces excellent corneal anesthesia, it is highly toxic to the corneal epithelium. Following both intentional and unintentional application of cocaine to the eye, the superficial corneal layer is shed, resulting in pain and decreased acuity.[183] This technique was formerly used as a therapeutic modality for the removal of retained foreign bodies. The loss of eyebrow and eyelash hair from thermal injury associated with smoking crack cocaine is called madarosis.[215]

Chronic cocaine use can produce perforation of the nasal septum. This finding most likely results from repeated ischemic injury with resultant tissue loss. Although this ischemia is usually asymptomatic and necrotic tissue is sloughed, at least 1 case of wound botulism (Chap. 46) presumably resulted from the accumulation of necrotic tissue in the nose, which served as a culture medium for *Clostridia botulinum* .[120]

Angioedema and oropharyngeal burns are associated with smoking crack cocaine.[22, 111, 149] Even esophageal burns are associated with cocaine use.[27] These effects are mostly likely the result of either inhaling or swallowing superheated fumes or hot liquid (from the smoking apparatus) rather than direct toxicity from cocaine.

Pulmonary

Pneumothorax, pneumomediastinum, and pneumopericardium are reported following both intranasal cocaine use and smoking crack.[139, 196, 221, 225] These findings do not represent direct drug toxicity per se; rather, they are epiphenomenon related to the mechanism of drug use. Following insufflation or inhalation,

the user performs a classic Valsalva maneuver in an attempt not to release the drug. Bearing down against a closed epiglottis increases intrathoracic pressure and an alveolar bleb ruptures against the pleural, mediastinal or pericardial surfaces.

Cocaine use exacerbates reversible airway disease and it is common for patients to present with shortness of breath and wheezing.[47 , 169 , 187 , 188] Like so many manifestations of cocaine toxicity, it is unclear whether this is a direct effect of cocaine or related to inhalation of some contaminant of the drug. However, as discussed above, the muscarinic (M2) agonistic effects of the pyrolysis metabolite AEME might be contributory. Another cause for cough and shortness of breath has been termed crack lung, which refers to hemorrhagic alveolitis resulting from cocaine use.[55 , 112] Although hemorrhagic alveolitis may be related to pulmonary hypertension, the presence of fever, elevated IgE, and a clinical response to corticosteroids suggests a possible immune-mediated illness.

Vasospasm and subsequent thrombosis of the pulmonary artery or its branches can produce pulmonary infarction.[40] Patients present with shortness of breath and pleuritic chest pain characteristic of a pulmonary embolus. Clinical signs and symptoms of ventilationâ€“perfusion (V/Q) mismatch (Chap. 22), as well as abnormalities on arterial blood gas analysis, are noted.

Cardiovascular

Chest pain or discomfort is a common emergency department complaint in cocaine users.[17] Although myocardial infarction is a common concern, only approximately 5% of patients with complaints referable to the heart will manifest biochemical evidence of myocardial injury.[92 , 230] Many will have an ischemic cardiac event, but for the remainder the differential diagnosis is broad.[124] Entities to consider include the pulmonary and esophageal etiologies described above, referred abdominal

symptoms (see Abdominal below), chest wall injury,[64] aortic dissection,[100, 131, 171, 184] coronary artery dissection,[11, 211] and dysrhythmia. No single sign or symptom or combination of signs and symptoms reliably identifies cardiovascular injury from among the discussed differential diagnosis.[92]

Chronic cocaine use is associated with a dilated cardiomyopathy,[78, 124, 167, 233] the etiology of which is presumed to be the result of repeated subclinical ischemic events. Patients may present with signs and symptoms of congestive heart failure or pulmonary edema. The pathologic finding of contraction band necrosis also suggests that there may be some direct catecholamine toxicity as this finding only commonly occurs with cocaine and amphetamine use, pheochromocytoma, and in patients receiving high-dose vasopressor agents.[52, 228]

Abdominal

Abdominal pain, or other gastrointestinal complaints also suggest a broad differential diagnosis. Cocaine users have a disproportionate incidence of perforated ulcers.[128, 175, 205] The etiology has not been elucidated, but may be related to local ischemia of the gastrointestinal tract or increased acid production associated with sympathetic activity. Vasospasm produces ischemic colitis that can present with abdominal pain or bloody stools.[133, 160] More severe or

persistent vasospasm, with or without thrombosis, can lead to intestinal infarction[58, 79, 97, 170] with attendant hypotension and metabolic acidosis. Signs and symptoms of bowel obstruction such as vomiting or distension might suggest body packing (gastrointestinal drug smuggling). Although less common, splenic[42, 162] and renal infarctions[44, 152, 192] may also occur. Spontaneous hemoperitoneum was also reported, although occult trauma could not be definitively excluded.[9]

Animals frequently develop hepatotoxicity following cocaine administration. In human cocaine users, minor abnormalities of liver enzymes are common and rarely associated with symptoms.[119] When more severe liver injury occurs, it is usually associated with multisystem organ dysfunction from hyperthermia or another injury.[5] Isolated hepatic injury from cocaine is distinctly uncommon and may result from differences in metabolic pathways, as animals are known to make a hepatotoxic metabolite of cocaine that has not been described in humans.[227]

Musculoskeletal

Rhabdomyolysis is common in all conditions that produce an agitated delirium with or without associated hyperthermia, and cocaine is no exception.[31 , 99 , 190] Unlike most other toxicologic disorders, however, psychomotor agitation is not a prerequisite for cocaine-associated rhabdomyolysis.[241] Muscle injury may result from vasospasm or some yet-to-be-described direct muscle toxin. Patients with cocaine toxicity can present with a spectrum of illness that ranges from asymptomatic enzyme and electrolyte abnormalities characteristic of rhabdomyolysis, to localized or diffuse muscle pain, to frank compartment syndrome and renal failure.[45 , 53]

Traumatic injury is also fairly common in the setting of cocaine use. Clinicians should be aware of the possibilities of occult fractures or other injuries that may be masked by the anesthetic properties of cocaine.[144 , 145]

Neuropsychiatric

The neuropsychiatric effects of cocaine are most likely dose dependent. Low-dose administration produces alertness, exhilaration, hypersexual behavior, and other â€œdesiredâ€• effects. These effects rarely bring users to healthcare facilities. As

the cocaine dose increases, agitation, aggressive behavior, confusion, disorientation, and hallucinations can develop.

Other possible manifestations include a variety of movement disorders that most likely result from depletion or dysregulation of dopamine. Patients may develop acute dystonias[23, 50, 226] or choreoathetoid movements that are also termed crack-dancing. Following binge use of cocaine, a â€œwashed-outâ€• syndrome occurs that is best described by dopamine depletion.[210, 222] Patients complain of anhedonia, want to sleep, and have trouble initiating and sustaining movement. However, they are arousable with minimal stimulation and usually remain cognitively intact.

EMIT (enzyme-mutiplied immunoassay technique)
Urine
X
â€”
200â€“300 ng/mL
RIA (radioimmunoassay)
Urine/serum
X
X
50â€“100 ng/mL
TLC (thin-layer chromatography)
Urine
X
â€”
1000 ng/mL
GC (gas chromatography)
Serum/urine
X
X
200â€“300 ng/mL
HPLC (high pressure liquid chromatography)
Serum/urine

X
X
200â€“300 ng/mL
GC-MS (gas chromatography-mass spectrometry)
Serum/urine
X
X
200â€“300 ng/mL
X = detectable.

Laboratory Assay Specimen BE Cocaine Cut-Off Value

TABLE 74-2. Laboratory Assays for Cocaine and Benzoylecgonine (BE)

Obstetrical

The majority of obstetrical findings associated with cocaine use involve developmental issues in the fetus and newborn that probably result from a combination of chronic vascular insufficiency from cocaine-induced spasm of the uterine artery or distal vessels and other risk factors, such as poor maternal nutrition, cigarette smoking, and a lack of prenatal care. These events are extensively reviewed elsewhere.[25 , 48 , 179] Acute cocaine use during pregnancy is associated with abruptio placentae, causing patients to present with abdominal pain and vaginal bleeding.[1 , 54] The remaining maternal and fetal complications comprise every possible complication described in nonpregnant patients.

Diagnostic Testing

Cocaine and benzoylecgonine, its principle metabolite, can be detected in blood, urine, saliva, hair, and meconium. Routine

drug-of-abuse testing relies on urine testing using a variety of immunologic techniques (Chap. 7). Although cocaine is rapidly eliminated within just a few hours of use, benzoylecgonine is easily detected in the urine for 2â€“3 days following last use.[4] When more sophisticated testing methodology is applied to chronic users, cocaine metabolites can be identified for several weeks following last use.[232] Table 74-2 lists a variety of methods used to identify cocaine and BE, as well as their cut-off values.

Urine testing, even using rapid point-of-care assays, offers little to clinicians managing patients with presumed cocaine toxicity because it cannot distinguish recent from remote cocaine use. In addition, whereas a negative test usually excludes cocaine use, false-negative testing can result either when there is a large quantity of urine in the bladder and the cocaine use was very recent or when the urine was intentionally diluted by increased fluid intake.[29] Regardless of the cause, although there is cocaine in the urine, its urine concentration is below the cut-off value for the test, and therefore interpreted as negative. Under these circumstances, repeat testing is almost always positive. While false-positive tests do occur, they are more common with hair testing than urine or blood because of the increased risk of external contamination.[29 , 186] Because of the very low rate of false-positive results, confirmation of a positive urine is unnecessary for medical indications (Chap. 7).

The greatest usefulness for cocaine testing is in cases of unintentional poisoning or suspected child abuse and neglect. Here

confirmation of a clinical suspicion is essential to support a legal argument. In addition, there may be some usefulness for urine testing of body packers, especially when the concealed substance is unknown.[223] While many body packers will have negative urine throughout their hospitalization, a positive urine test is suggestive of the concealed drug, and possibly more importantly, a conversion from a negative study on admission to a positive study

not only confirms the substance ingested, but also suggests packet leakage, which could be a harbinger of life-threatening toxicity. Another indication for urine testing for cocaine occurs in young patients with chest pain syndromes where the history of drug use is not forthcoming.[88]

Routine diagnostic tests such as a bedside rapid reagent glucose, electrolytes, renal function tests, and markers of muscle and cardiac muscle injury are more likely to be useful than urine drug testing. An ECG may show signs of ischemia or infarction, or dysrhythmias that require specific therapy. However, in the setting of cocaine-associated chest pain, the ECG has neither the sensitivity nor the specificity necessary to permit exclusion or confirmation of cardiac injury.[95] Cardiac markers are therefore always required adjuncts when considering myocardial ischemia or infarction. Because cocaine use is associated with diffuse muscle injury, assays for troponin are preferred over myoglobin or myocardial band enzymes of creatine phosphokinase (CPK-MB).[94] Additionally, a chest radiograph may be useful to exclude certain etiologies in patients with chest discomfort, or to identify free air under the diaphragm when gastrointestinal perforation is suspected. Supplemental diagnostic studies, such as CT scans of the head, chest, or abdomen and functional cardiac imaging, should be guided by the clinical condition of the patient.

Management

General Supportive Care

As in the case of all poisoned patients, the initial emphasis must be on stabilization and control of the patient's airway, breathing, and circulation. If tracheal intubation is required, it is important to recognize that cocaine toxicity may be a relative contraindication to the use of succinylcholine. Specifically, in the setting of rhabdomyolysis, hyperkalemia may be exacerbated by

succinylcholine administration, and life-threatening dysrhythmias may result (Chap. 66). Additionally, it is essential to recognize that PChE metabolizes both cocaine and succinylcholine.[104] Thus their simultaneous use could either prolong cocaine toxicity or paralysis, or both. Human data are insufficient to predict which interaction is more likely to occur. If hypotension is present, the initial approach should be an intravenous bolus of 0.9% sodium chloride solution as many patients are volume depleted as a result of poor oral intake and excessive fluid losses from uncontrolled agitation, diaphoresis, and hyperthermia.

In the setting of cocaine toxicity it is important to recognize that both animal[24 , 67] and human[143] experience suggests that hyperthermia is a critical vital sign abnormality, such that a determination of the core temperature is an essential element of the initial evaluation, even when patients are severely agitated. When hyperthermia is present, immediate rapid cooling with ice water immersion, or the combined use of mist and fan, is required to achieve a rapid return to normal core body temperature (Chap. 16). It may be necessary to sedate or paralyze and intubate the patient in order to facilitate the rapid cooling process. Pharmacotherapy including antipyretics (acetaminophen or salicylates), drugs that prevent shivering (chlorpromazine or meperidine), and dantrolene[56] are not indicated as they are inefficient or ineffective and have the potential for adverse drug interactions.

Sedation remains the mainstay of therapy in patients with cocaine-associated agitation. It is important to remember that cocaine use is associated with hypoglycemia and that many of the peripheral findings of hypoglycemia are the result of a catecholamine discharge.[16 , 153] Consequently, a rapid reagent glucose test should be obtained, or hypertonic dextrose should be empirically administered if indicated, prior to or while simultaneously achieving sedation. Both animal models[24 , 67] and extensive clinical experience in humans support the central role of

benzodiazepines. Although the choice among individual benzodiazepines is not well studied, an understanding of the pharmacology of these drugs allows for rational decision making. The goal is to use parenteral therapy with a drug that has a rapid onset and a rapid peak of action, making titration easy. Using this rationale, midazolam and diazepam are preferable to lorazepam, because lorazepam's significant delay to peak effect often results in oversedation when it is dosed rapidly, or in prolonged agitation when the appropriate dosing interval is used. Drugs should be administered in initial doses that are consistent with routine practices and increased incrementally based on an appropriate understanding of their pharmacology. For example, if using diazepam, the starting dose might be 5â€“10 mg, which can be repeated every 3â€“5 minutes and increased if necessary. Large doses of benzodiazepines may be necessary (on the order of 1 mg/kg of diazepam). This may result from cocaine-induced alterations in benzodiazepine receptor function.[62 , 63 , 107]

On the rare occasion when benzodiazepines fail to achieve an adequate level of sedation, either a rapidly acting barbiturate or propofol should be administered. Controlled animal experience clearly contraindicates the use of phenothiazines and butyrophenones.[24 , 67 , 237] In animal models, these drugs enhance toxicity (seizures) or lethality, or both. Additional concerns regarding these drugs include their ability to interfere with heat dissipation, exacerbate tachycardia, prolong the QTc interval, and induce torsades de pointes, or precipitate dystonic reactions.

Once sedation is accomplished, often no further therapy is required. Specifically, hypertension and tachycardia usually respond to sedation and volume resuscitation. In the uncommon event that hypertension and or tachycardia persist, the use of a Î²-adrenergic antagonist or a mixed Î±- and Î²-adrenergic antagonist is absolutely contraindicated. Again, in both animal models and human reports, these drugs increase lethality and fail

to treat the underlying problem.[12 , 24 , 67 , 122 , 194] The resultant unopposed Î±-adrenergic effect may produce severe and life-threatening hypertension or vasospasm. A direct-acting vasodilator like nitroglycerin or nitroprusside or an Î±-adrenergic antagonist (such as phentolamine) may be considered. Other nonspecific therapies for rhabdomyolysis should be considered.

Decontamination

The majority of patients who present to the hospital following cocaine use will require no gastrointestinal decontamination as the most popular methods of cocaine use are smoking and intravenous and intranasal administration. If the nares contain residual white powder presumed to be cocaine, gentle irrigation with 0.9% sodium chloride solution will help remove adherent material. Less commonly, patients may ingest cocaine in an attempt to conceal evidence during an arrest (body stuffing) or transport large quantities

of drug across international borders (body packing). These patients may require intensive decontamination, possibly including surgery.

Specific Management

End-organ manifestations of vasospasm that do not resolve with sedation, cooling, and volume resuscitation should be treated with a vasodilator (such as phentolamine). When possible it is preferable to deliver direct intraarterial administration into the affected vascular bed. Because this approach is not always feasible, systemic therapy is indicated. Phentolamine can be dosed intravenously in increments of 1â€“2.5 mg, repeated as necessary until symptoms resolve or systemic hypotension develops.

Acute Coronary Syndrome

A significant amount of animal, in vitro, and in vivo human experimentation has been directed at defining the appropriate approach to a patient with presumed cardiac ischemia or infarction. In some instances an approach that is similar to the treatment of atherosclerotic heart disease (ASHD) is indicated, although there are certain notable exceptions. An overall approach to care is available in the American Heart Association guidelines and a number of reviews.[3 , 96 , 124]

High-flow oxygen therapy is clearly indicated as it may help overcome some of the supplyâ€“demand mismatch that occurs with coronary insufficiency. Likewise, based on experience with ASHD and given that cocaine induces platelet aggregation, it is reasonable to administer aspirin. In addition, there is probably a role for administration of morphine as it has been directly demonstrated to relieve cocaine-induced vasoconstriction[191] and offers the same theoretical benefits of preload reduction and reduction of catecholamine release in response to pain that provides its advantage in patients with ASHD.

At this point, the treatment of patients with cocaine-induced chest pain begins to deviate from the standard accepted approach to patients with ASHD. Nitroglycerin is clearly beneficial in that it reduces cocaine-induced coronary constriction of both normal and diseased vessels and relieves chest pain and associated symptoms in patients with cocaine-associated chest pain.[18 , 91] However, in several clinical trials, benzodiazepines are at least as effective or superior to nitroglycerin.[7 , 98] Although the reasons for this are unclear, possible etiologies include blunting of central catecholamines or direct effects on cardiac benzodiazepine receptors. Either or both drugs can be used in standard dosing.

Over the last decade, the benefits of Î²-adrenergic antagonism are continually demonstrated in patients with ASHD. In contrast, Î²-adrenergic antagonism increases lethality in cocaine-toxic

animals[24,67] and in humans, exacerbates cocaine-induced coronary vasoconstriction,[122] and produces severe paradoxical hypertension.[194] Similarly, with regard to coronary constriction, labetalol is no better than placebo.[12] Thus in the setting of cocaine use, Î²-adrenergic antagonism is absolutely contraindicated. If, after the measures mentioned above have been initiated, hypertension or vasospasm is still present and treatment is indicated, phentolamine is preferred based on its demonstrable experimental and clinical results.[90,123] If tachycardia does not respond to accepted therapies above, then a small dose of a diltiazem can be administered and titrated to effect.[10] Prior to administering any drug with strong negative inotropy, it is essential to confirm that the tachycardia is not compensatory for a low cardiac output that results from global myocardial dysfunction. Noninvasive methods of assessment of cardiac function have been used successfully in patients with cocaine-related acute coronary syndromes.[6]

There are no data on the use of either unfractionated or low-molecular-weight heparins, glycoprotein IIb/IIIa inhibitors, or clopidogrel. The decision whether or not to use any of these agents should be based on a risk-to-benefit analysis with a consideration of whether the patient might have underlying atherosclerotic heart disease. When acute thrombosis is likely, thrombolytic therapy should be considered. Mechanistically, cocaine inhibits endogenous thrombolysis through augmentation of the inhibitor of tissue plasminogen activator. Additionally, there is sufficient clinical evidence to support the safety of thrombolytic therapy in patients with cocaine-associated myocardial infarction.[81,89] Even though the number of patients treated with thrombolytic therapy is insufficient to demonstrate efficacy in terms of mortality, evidence of revascularization is encouraging. Similar to patients with ASHD, it is preferable to provide a mechanical approach to revascularization, especially given that spasm may be a fairly common etiology of cocaine-induced

infarction.[204] When cardiac catheterization facilities are unavailable, thrombolysis is an acceptable alternative, given contraindications such as persistent hypertension, dissection, trauma, and altered mental status have been addressed.

Dysrhythmias

Most patients present with sinus tachycardia that resolves following sedation, cooling, rehydration, and time to metabolize the drug. Similarly, other dysrhythmias should also be treated with benzodiazepines, cooling, and rehydration as they will often spontaneously revert because of the short duration of effect of cocaine. However, cocaine use is associated with atrial, supraventricular, and ventricular dysrhythmias, some of which may require additional pharmacotherapy.[102 , 124] Even torsades de pointes is reported.[200] Most notably, wide complex tachycardias result from sodium channel blockade. When approaching patients with cocaine-associated dysrhythmias, there are several important points to consider. The first is that Î²-adrenergic antagonism is absolutely contraindicated. Furthermore, classic types IA and IC antidysrhythmics are also contraindicated because of their ability to exacerbate cocaine-induced sodium and potassium channel blockade.[124 , 236] Additionally, although popular in many advanced cardiac life support dysrhythmia algorithms, the effects of amiodarone are largely unknown in the setting of cocaine toxicity. Because of the lack of data demonstrating a benefit for amiodarone, and because of concerns about its Î²-adrenergic antagonist effects, the use of this drug cannot be recommended. At this time finally, although adenosine and synchronized cardioversion may transiently help convert narrow complex tachycardias, if a substantial amount of cocaine is not metabolized, the patient will likely revert back to his or her original rhythm as these therapeutic interventions have short durations of effect. Thus for rapid atrial fibrillation and narrow complex reentrant tachycardias, a calcium channel blocker such as

diltiazem is preferred. For wide-complex dysrhythmias a trial of hypertonic sodium bicarbonate has demonstrable usefulness analogous to treating patients with tricyclic antidepressant overdose (see Antidotes in Depth: Sodium Bicarbonate).[110 , 173 , 229 , 236] When the use of hypertonic sodium bicarbonate fails to treat the dysrhythmia, lidocaine can be used. Although lidocaine blocks sodium channels, its fast-on, fast-off properties allow it to antagonize the effects of cocaine. The benefits and safety of lidocaine were demonstrated in multiple animal models[77 , 236] and in humans with cocaine-associated myocardial infarction.[206]

Disposition

Patients who present to healthcare facilities with classic sympathomimetic signs and symptoms that resolve spontaneously or with minimal sedation and no signs of end-organ damage can be safely discharged after short periods of observation. Once hyperthermia, rhabdomyolysis, or other signs of end-organ damage are evident, hospital admission is usually required.

For patients with chest pain, a specific management algorithm has been derived based on substantial clinical experience. Those patients with clearly diagnostic or evolving ECGs suggestive of ischemia or infarction, positive cardiac markers, dysrhythmias other than sinus tachycardia, congestive heart failure, or persistent pain require admission. Patients who become pain free and whose ECGs are stable are candidates for discharge if a single cardiac marker obtained at least 8 hours after the onset of chest pain is negative.[231] For all patients it is essential to provide a referral for detoxification, as repeated cocaine use is the greatest risk factor for future cardiovascular complications.[93 , 231]

Special Situations: Body Packers and

Body Stuffers

Cocaine body stuffers ingest drug in an attempt to avoid detection or prosecution. The drug is normally unwrapped or wrapped for transport, and therefore often readily available for gastrointestinal absorption. Although detection may be possible using diagnostic imaging studies,[33, 80] the sensitivity and specificity are presumed to be poor.[46, 81] If symptoms of cocaine toxicity develop, they are usually manifest within a few hours of ingestion,[209] although the onset of toxicity may be more delayed with crack-vial ingestion.[80] Although it is generally accepted that life-threatening toxicity is uncommon as a result of delayed and incomplete absorption of a relatively small dose, serious toxicity and death are reported.[51, 75, 106, 141, 168]

Decontamination with multiple-dose oral activated charcoal therapy should be sufficient in most cases as cocaine is very well adsorbed to activated charcoal.[140] Whole-bowel irrigation (WBI) with polyethylene glycol electrolyte lavage solution (PEG-ELS) can also be considered. Clinical toxicity should be managed as described above.

In contrast, body packers ingest large amounts (often 0.5â€“1 kg) of well-wrapped drug in an attempt to smuggle cocaine across international borders. Although rigorous data are not available, the majority of these packets do not open. However, when they rupture, the amount of drug per packet exceeds the lethal dose of cocaine, and numerous fatalities are reported.[60] The assessment and management of body packers has been extensively reviewed.[223] The presence of mechanical bowel obstruction or *any* sign of packet rupture is considered an absolute indication for surgery. In asymptomatic patients, WBI with PEG-ELS is initiated and dosed in a standard fashion (see Antidotes in Depth: Whole-Bowel Irrigation and Other Intestinal Evacuants). Single- or multiple-dose activated charcoal therapy may also be considered. Although it may be beneficial to have activated charcoal in the gut

should a packet rupture, activated charcoal can be detrimental if it spills into the peritoneal cavity during surgery. These relative risks and benefits should be assessed in each patient.

Although plain abdominal radiography may underestimate the number of packets present, it is usually positive initially, and can be used sequentially to assess the efficacy of WBI. Often patients will require antiemetics and or promotility agents to facilitate WBI.[224]

When plain abdominal radiography is negative, a confirmatory study, such as oral contrast abdominal radiography or an oral contrast-enhanced CT scan, should be ordered.[86] Because these diagnostic imaging studies are not infallible,[70] it is generally prudent to feed and observe the patient for 24 hours after the chosen study is negative. Figure 74-4 presents an algorithm to help clarify these issues.

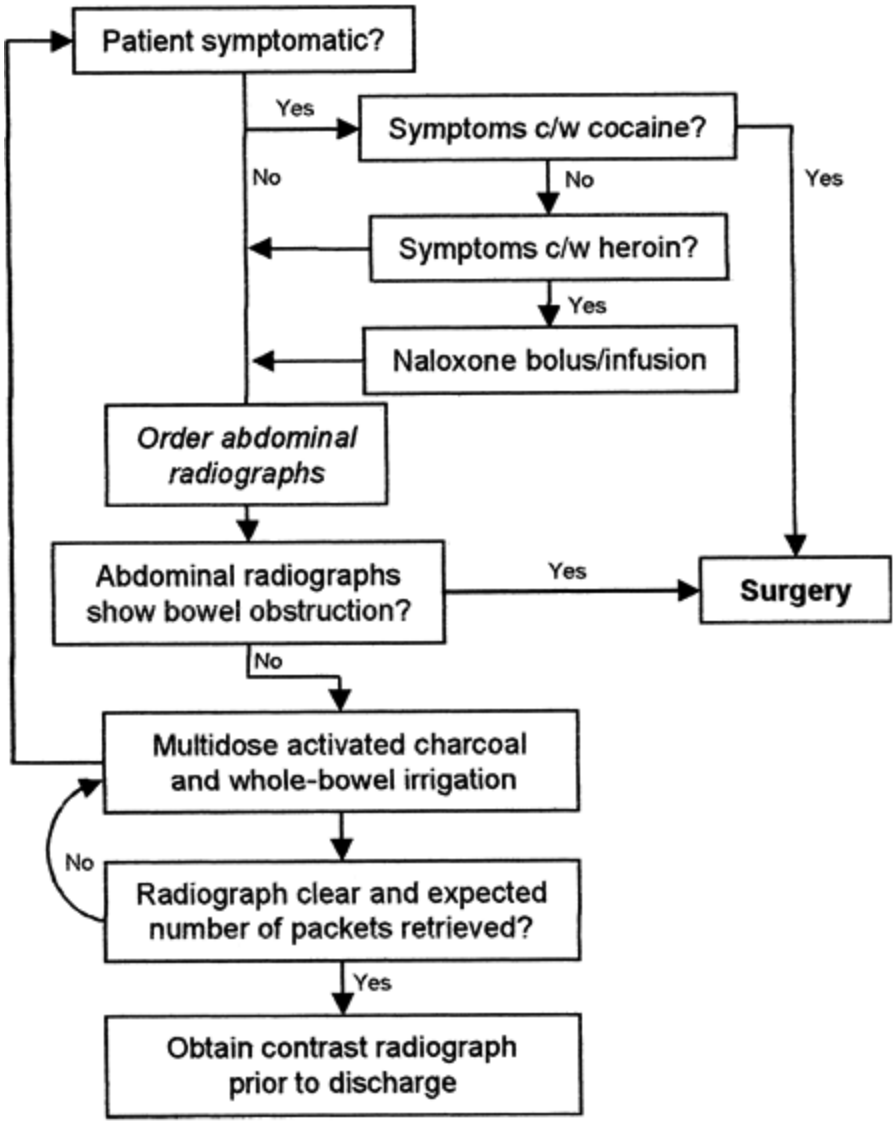

Figure 74-4. Algorithm for managing cocaine or heroin body packers. c/w = Consistent with.

Summary

Cocaine is a unique drug that combines local anesthetic, vasoconstrictive, and neuropsychiatric properties. Although its legitimate pharmaceutical use has diminished because of its high abuse potential, it remains a prevalent recreational drug of abuse. Cocaine produces the prototypical agitated delirium that

characterizes the sympathomimetic toxic syndrome. Most patients can be treated with sedation and cooling, but others require more intensive individualized care. The most essential and difficult aspect of care is providing access to programs that support cocaine detoxification.

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Chapter 75
Ethanol

Luke Yip

A 44-year-old man was found comatose in a homeless shelter. The paramedics were told that the patient had a long history of alcoholism and that he was drinking heavily until 1â€“2 days prior to coming to the shelter. Since then the patient had repeated bouts of vomiting and no significant oral intake. The initial assessment by the paramedics was notable for: blood pressure, 100/72 mm Hg; pulse, 120 beats/min; respiratory rate, 32 breaths/min. The patient was placed on high-flow oxygen, an intravenous (IV) line was inserted with 0.9% NaCl solution infused at 150 mL/h, and blood samples were obtained for analysis. The patient was given 2 mg of naloxone, 25 g of dextrose, and 100 mg of thiamine IV without clinical response, and was transported to the emergency department (ED).

On arrival at the ED, the patient's vital signs were unchanged from the prehospital values; his rectal temperature was 100.4Â°F (38Â°C) and pulse oximetry was 100% on high-flow oxygen. His head was atraumatic, sclera were anicteric, and his pupils were 3 mm in size, equal, round, and reactive to light, with a normal funduscopic

examination. His mucous membranes were dry, and his gag reflex was present. There was no characteristic odor to the patient's breath. There was no meningismus. Chest and abdominal examinations were normal except for a liver edge, which was palpable 3 finger breadths below the costal margin. Rectal tone was normal, stool was dark and negative for occult blood, and there was no bowel or bladder incontinence. The patient was comatose, and the remainder of the neurologic examination was nonfocal.

A rapid bedside glucose test was 120 mg/dL. His ECG revealed a sinus tachycardia with normal intervals and without ectopy. A portable chest radiograph showed haziness over both lung bases. A complete blood cell count (CBC) revealed a leukocytosis, 16,000/mm^3, without a left shift; hematocrit, 52%; platelets, 150,000/mm^3. Blood chemistries were remarkable for sodium, 148 mEq/L; potassium, 2.9 mEq/L; chloride, 108 mEq/L; bicarbonate, 9 mEq/L; glucose, 130 mg/dL; BUN, 50 mg/dL; creatinine, 1.6 mg/dL; aspartate aminotransferase (AST), 168 U/L; alanine aminotransferase (ALT), 80 U/L; and an elevated Î³-glutamyl transpeptidase (GGTP) and alkaline phosphatase. The serum lactate was 2.2 mEq/L (0.6â€“1.7 mEq/L). The prothrombin and partial thromboplastin times, serum lipase, and serum ammonia were normal. Blood ethanol concentration was undetectable. Urinalysis was remarkable for a specific gravity of 1.030, 1â€“2 (+) ketones, and no crystals. His arterial blood gas was remarkable for: pH, 7.08; PCO_2, 12 mm Hg; and PO_2, 110 mm Hg.

The intravenous fluid was changed to dextrose 5% in 0.9% sodium chloride solution (D_5NS) with supplemental potassium, thiamine, folate, and multivitamins. Intravenous ceftriaxone 2 g and gentamicin 490 mg were administered for a presumed aspiration pneumonitis. The patient was given an intravenous loading dose of ethanol followed by an ethanol infusion, while investigations focused on the patient's altered mental status and anion gap metabolic acidosis. A CT scan of the patient's head was remarkable for cerebral atrophy. Analysis of the cerebrospinal fluid from a lumbar puncture

was unremarkable, and specimens were sent for cultures. Investigation into the causes of an anion gap metabolic acidosis was unrewarding (Chaps. 17 and 103). The patient was admitted to the intensive care unit where hemodialysis was performed because of persistent acidâ€“base derangement in spite of supportive care. The patient made a gradual recovery. The patient's blood was later confirmed to be negative for a toxic alcohol as well as formate and glycolate, suggesting the probable diagnosis of alcoholic ketoacidosis.

History and Epidemiology

Ethanol, or ethyl alcohol, is commonly referred to as alcohol. This term is somewhat misleading because there are numerous other alcohols to which a patient may be exposed (Chap. 103). However, ethanol is probably the most commonly used and abused drug in the world. Its use is pervasive among adolescents and adults of all socioeconomic groups, and represents a tremendous financial and social cost.

The ethanol content of alcoholic beverages is expressed by volume percent or by proof. Proof is a measure of the absolute ethanol content of distilled liquor, and is calculated by determining its specific gravity at an index temperature. In the United Kingdom, the Customs and Excise Act of 1952, declared proof spirits (100 proof) as those in which the weight of the spirits is 12/13 the weight of an equal volume of distilled water at 11Â°C (51Â°F). Thus, proof spirits are 48.24% ethanol by weight, or 57.06% by volume. Other spirits are designated over- or underproof, with the percentage of variance noted. In the United States, a proof spirit (100 proof) is one containing 50% ethanol by volume. The derivation of proof comes from the days when sailors in the British Navy suspected that the officers were diluting their rum (grog) ration and demanded â€œproofâ€• that this was not the case. They achieved this by pouring a sample of grog on black granular gunpowder. If the

gunpowder ignited by match or spark, the rum was up to standard, 100% proof that the liquor was 50% ethanol. This became shortened to 100

proof (Table 75-1). In addition to beverages, ethanol is present in hundreds of medicinal preparations, used as a diluent or solvent in concentrations ranging from 0.3% to 75%.[26,39,48,144,148,186] Mouthwashes may have up to 75% ethanol (150 proof), and colognes typically contain 40â€“60% ethanol (80â€“120 proof).[15,87,148,157] These products occasionally cause intoxication, especially when unintentionally ingested by children.[28,44,76,187]

Ethanol MW: 46 daltons
Specific gravity: 0.7939 (~0.8) g/mL
Volume of distribution (Vd): 0.6 L/kg

$$\text{Serum ethanol concentration (mg/dL)} = \frac{\text{dose (mg)}}{\text{Vd (L/kg)} \times \text{body weight (kg)} \times 10}$$

$$\text{mmol} = \frac{\text{mg}}{\text{MW}} = \frac{\text{mg}}{46}$$

$$\text{mmol/L} = \frac{\text{mg/dL}}{4.6}$$

For a 70-kg individual:

Dose of ethanol	Blood ethanol concentration
10 mL/kg of 10% (20 proof)	167 mg/dL (36.30 mmol/L)
3 mL/kg of 10% (20 proof)	50 mg/dL (10.87 mmol/L)
1.5 mL/kg of 10% (20 proof)	25 mg/dL (5.43 mmol/L)
150 mL (5 "shots") of 40% (80 proof)	143 mg/dL (31.09 mmol/L)
30 mL (1 "shot") of 40% (80 proof)	27 mg/dL (5.87 mmol/L)

Blood concentration consistent with legal intoxication = 10.87–17.39 mmol/L (50–80 mg/dL or 0.05–0.08 g/dL [%])

Average reduction in blood ethanol level (elimination phase):
Nontolerant adult: 3.26–4.35 mmol/L/h (15–20 mg/dL/h, 100–125 mg/kg/h)
Tolerant adult: 6.52–8.70 mmol/L/h (30–40 mg/dL/h, 175 mg/kg/h)

TABLE 75-1. Basic Information and Calculations

Veisalgia, â€œalcohol hangover,â€• comes from the Norwegian *kveis*, â€œuneasiness following debaucheryâ€• and the Greek *algia*, â€œpain.â€• The â€œhangoverâ€• syndrome is attributed to congeners, substances that appear in alcoholic beverages in addition to ethanol and water.[24,29,30] Congeners contribute to the special characteristics of taste, flavor, aroma, and color of a beverage. The combinations and exact amounts of congeners vary with the type of beverage, ranging from 33 mg/L in vodka, to averages of 500 mg/L in some whiskies, and as much as 29,000 mg/L in specially aged whiskies or brandies.[24,29,30] The conventional listing of congeners includes fusel oil (a mixture containing amyl, butyl, propyl, and methyl alcohol), aldehydes, furfural, esters, low-molecular-weight organic acids, phenols, and other carbonyl compounds, tannins, solids, and a relatively large number of additional organic and inorganic compounds, usually in trace amounts.[24,30]

Consumption of illicitly produced ethanol (â€œmoonshineâ€•) has resulted in methanol, lead, or arsenic poisoning.[41,62,84,103,109,128,145] Incidental lead contamination is also reported in draught beers or wine contained in lead-capped bottles.[161,162] Of historic interest is the addition of cobalt salts to beer to stabilize the â€œheadâ€• (foam) leading to outbreaks of congestive cardiomyopathy among heavy beer drinkers in Canada and Belgium in the 1960s (Chap. 89). The clinicopathologic pattern of this disease is distinct from the classical alcoholic cardiomyopathy.[120,122]

Alcoholism is the leading cause of morbidity and mortality in the United States. The prevalence of alcohol dependence in the United States has been relatively stable, at around 6% for men and 2% for women.[23] The overall estimated annual cost of health expenses related to ethanol is $185 billion.[135] More than 70% of the estimated

costs are attributed to lost productivity, most of which result from alcohol-related illness or premature death. Most of the remaining estimated costs are expenditures for healthcare services to treat alcohol-induced disorders (14.3%), property and administrative costs of ethanol-related motor vehicle crashes (8.5%), and criminal justice system costs of ethanol-related crime (3.4%). More than 200,000 Americans die annually of alcoholism, far more than those who die of all illicit drugs of abuse combined. Ethanol is the leading cause of mortality in people 15â€“45 years of age. In 2003 there were 15,281 ethanol-related traffic fatalities in the United States, which accounted for 40% of total traffic fatalities.[133] Among 16â€–20-year-old male drivers, an increase of 20 mg/dL in blood ethanol concentration is estimated to more than double the relative risk of a fatal single-vehicle crash injury, compared with sober drivers of the same age and gender.[198] When the blood ethanol concentration is between 80 and 100 mg/dL (17.39 and 21.74 mmol/L), between 100 and 150 mg/dL (21.74 and 32.61 mmol/L), and greater than 150 mg/dL (32.61 mmol/L), the relative risk is 52, 241, and 15,560, respectively.

The Global Burden of Disease Study identified three effects of alcohol: harmful effects in relation to injuries; harmful effects in relation to disease; and the protective effect in relation to ischemic heart disease.[135] Overall, alcohol accounted for 3.5% of mortality and disability, 1.5% of all deaths, 2.1% of all life years lost, and 6% of all the years lived with disability.[135] In the United States, according to National Highway Traffic Safety Administration (NHTSA) information, as of August 2005, all 50 states plus the District of Columbia and Puerto Rico had laws establishing a blood alcohol concentration of â‰¥80 mg/dL (17.39 mmol/L) as

illegal per se.[134] The term *illegal per se* refers to state laws that make it a criminal offense to operate a motor vehicle at or above a specified ethanol (or drug) concentration measured in the blood, breath, or urine. In nontolerant individuals, blood ethanol

concentration as low as 20 mg/dL (4.35 mmol/L) impairs driving-related skills.[135,199] Gross motor control and orientation may be significantly affected at concentrations of 50 mg/dL (10.87 mmol/L).[126] Clinical ethanol intoxication is usually apparent at blood ethanol concentration of 50 mg/dL (10.87 mmol/L). However, ethanol-tolerant patients may not exhibit impairment even at concentrations greater than 300 mg/dL (65.22 mmol/L).[1] There appears to be a doseâ€“response relationship between alcohol consumption and risk of death in men 16â€“34 years of age and in women 16â€–54 years of age. The consumption at which the risk is lowest increases with age, reaching 64â€–80 g/wk in men older than age 65 years and 24â€–30 g/wk in women older than age 65 years. The consumption at which the risk is increased by 5% above this minimum is 40â€–50 g/wk in men ages 16â€–24 years and 64â€–80 g/wk in women ages 16â€–24 years, increasing to 272â€–340 g/wk and 160â€–200 g/wk in men and women older than age 65 years, respectively.[192] Meta-analysis of aggregate data from epidemiologic doseâ€“response ethanol and mortality cohort studies suggests that the level of alcohol consumption at which all-cause risk is lowest is approximately 5 g/d, and that alcohol exerts a protective effect (J-shaped doseâ€“response curve) up to a daily intake of approximately 45 g.[8] Responsible drinking limits of ethanol for men are 8â€–10 g/d up to age 34 years; 16â€–20 g/d between 34 and 44 years of age; 24â€–30 g/d between 44 and 54 years of age; 32â€–40 g/d between 54 and 84 years of age; and 40â€–50 g/d for men older than age 85 years. Women are advised to limit their drinking to 8â€–10 g/d up to age 44 years; to 16â€–20 g/d between 44 and 74 years of age; and to 24â€–30 g/d for women older than age 75 years.[192] However, no safe level of prenatal ethanol exposure has been established. The combination of a national tolerance of drinking and heavy advertising of ethanol makes it especially appealing to young people. In a society that is increasingly concerned with drug abuse, the excessive use of alcohol constitutes a serious and pervasive problem, as well as a major health issue.

Pharmacology

Ethanol is a colorless, odorless, volatile, liquid hydrocarbon. It is fully miscible in water and is lipid soluble. It readily diffuses across lipid membranes, accounting for its ubiquitous multiorgan effects.

Despite ethanol's long history of use and study, no specific receptor for ethanol has been identified and the mechanism of action leading to intoxication remains the subject of debate.[147] Ethanol affects a large number of membrane proteins that participate in signaling pathways, including neurotransmitter receptors, enzymes, and ion channels,[132,183] and there is extensive evidence that ethanol interacts with a variety of neurotransmitters.[45,179,180] The major actions of ethanol involve enhancing the inhibitory effects of Î³-aminobutyric acid (GABA) at $GABA_A$ receptors and blockade of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate, an excitatory amino acid (EAA) receptor.[33,92,93,183] Animal studies indicate that the acute effects of ethanol result from competitive inhibition of glycine's binding to the NMDA receptor, resulting in disruption of excitatory glutamatergic neurotransmission. Persistent glycine antagonism and attenuation of glutamatergic neurotransmission by chronic ethanol exposure results in tolerance to ethanol by enhancing EAA neurotransmission and NMDA receptor upregulation.[77,131,175,179,180] The latter appears to involve selective increases in NMDA R2B subunit levels and other molecular changes in specific brain loci.[3] The abrupt withdrawal of ethanol thus produces a hyperexcitable state that leads to the ethanol withdrawal syndrome and excitotoxic neuronal death.[16,33,180] Chronic ethanol administration also results in tolerance, dependence, and an ethanol withdrawal syndrome, mediated, in part, by desensitization and or downregulation of $GABA_A$ receptors. GABA-mediated inhibition, which normally acts to limit excitation, is eliminated in the absence of ethanol during ethanol withdrawal syndrome, and further intensifies this excitation. Augmentation of excitatory neurotransmission may lead to enhanced oxidative stress, which, in concert with reduced

inhibitory neurotransmission, may contribute to ethanol withdrawal-associated neurotoxicity in humans.[16,33,77,179,180] In addition, NMDA receptors function to inhibit the release of dopamine in the nucleus accumbens and mesolimbic structures, which modulates the reinforcing action of addictive agents like ethanol.[18,19,165] By inhibiting NMDA receptor activity, ethanol could increase dopamine release from the nucleus accumbens and ventral tegmental area, and could thus create dependence (Chap. 14).

Pharmacokinetics and Toxicokinetics

Ethanol is rapidly absorbed from the gastrointestinal (GI) tract, with approximately 20% absorbed from the stomach and the remainder from the small intestine.[137] Factors that enhance absorption include rapid gastric emptying, ethanol intake without food, the absence of congeners, dilution of ethanol (maximum absorption occurs at a concentration of 20%), and carbonation. Under optimal conditions for absorption, 80â€“90% of an ingested dose is fully absorbed within 60 minutes. Factors that delay or decrease ethanol absorption include high concentrations of ethanol (by causing pylorospasm), presence of food, coexistence of GI disease, coingestion of drugs (eg, aspirin and *N*-butylscopolamine),[85,142] time taken to ingest the drink, and individual variation. Any of these factors and individual variation may delay absorption for 2â€“6 hours.

Alcohol dehydrogenase (ADH), the principal enzyme responsible for ethanol oxidation, is an intracellular enzyme that is also present in the stomach and the liver.[106] It is an inducible enzyme, and there is a functional polymorphism of the ADH gene.[43] Class IV ADH (Ï*f*-ADH) is the major ADH expressed in human gastric mucosa and oxidizes a small proportion of the ingested ethanol, thus reducing the amount available for absorption. This effect is more pronounced in men than in women, and in nonalcoholics than in alcoholics.[10,53] Ï*f*-ADH is usually present in non-Asians, whereas in a majority of Pacific Rim Asians, the enzyme activity is either low or undetectable.[10,11,37] The

predominant hepatic ADH is class I ADH and it contains the isozymes ADH1, ADH2, and ADH3. The atypical ADH, ADH2*2, is responsible for an unusually rapid conversion of ethanol to acetaldehyde and is present in 90% of Pacific Rim Asians.

As a result of decreased first-pass metabolism caused by inhibition of the activity of alcohol dehydrogenase in the gastric mucosa,[35] histamine-2 (H_2) receptor antagonists, cimetidine and ranitidine, slightly increase the bioavailability of imbibed ethanol.[6,20,22,47] In alcoholics and those persons with higher ethanol concentrations, cimetidine may also delay ethanol clearance by inhibiting the microsomal ethanol oxidizing system (MEOS) (cytochrome

P450 [CYP] 2E1).[70] However, the increase in blood ethanol concentration from such an interaction is of questionable clinical significance.[5,6,20,21]

In the liver, ADH metabolizes ethanol to acetaldehyde, which is converted to acetate by mitochondrial nicotinamide-adenosine dinucleotide (NAD)-dependent aldehyde dehydrogenase (ALDH). Twelve ALDH genes (ALDH1 to ALDH10, succinic dehydrogenase, and methylmalonate semialdehyde dehydrogenase) are identified in humans. There is a functional polymorphism of the mitochondrial ALDH2 gene, and expression of an inactive form of the ALDH2 results in impaired acetaldehyde metabolizing capacity. The variant allele ALDH2*2 encodes a protein subunit that confers low activity to the enzyme, resulting in marked differences in the steady-state kinetic constants, which appears to be most prevalent in Pacific Rim Asians.[2,27,64,170,171] Homozygous ALDH2*2 individuals are strikingly sensitive to a small dose of ethanol (0.2 g/kg), as evidenced by the intense flushing, pronounced cardiovascular hemodynamic effects, and subjective perception of general discomfort.[43,64,146,176,181] This effect may also be associated with the ADH2*2 and ADH3*1 alleles, and is similar to that induced by disulfiram (Chap. 77). The alcohol-induced flushing response may involve prostaglandin and histamine release. Both prostaglandin antagonists (aspirin)[178] and

antihistamines (H_1 and H_2)[123,166,173] may attenuate this response.

For a typical 70-kg person, a â€œstandard drinkâ€• (15 g of ethanol), defined as 1 oz (30 mL) of 100 proof liquor, about a 4-oz (120-mL) glass of wine (12% ethanol), or about a 10-oz bottle (300-mL) of beer (5% ethanol), could raise blood ethanol concentration by 43 mg/dL (9.35 mmol/L). However, this is the theoretical maximum ethanol concentration, based on instantaneous and complete ethanol absorption and no distribution or metabolism following a â€œstandard drinkâ€• by a typical 70-kg person.

Following complete distribution, ethanol is present in body tissues in a concentration proportional to that of the tissue water content. The concentration in the blood is maintained by back diffusion, which occurs whenever the concentration in the blood falls below that of the tissues. Ethanol freely passes through the placenta, exposing the fetus to ethanol concentrations comparable to that achieved in the mother.

Ethanol is primarily (>90%) eliminated by the liver via enzymatic oxidation, with 5â€“10% excreted unchanged by the kidneys, lungs, and sweat. Ethanol is metabolized via at least three different pathways: the aforementioned alcohol dehydrogenase (ADH) pathway, located in the cytosol of the hepatocytes; the MEOS (CYP2E1), located on the endoplasmic reticulum; and the peroxidaseâ€“catalase system, associated with the hepatic peroxisomes (Fig. 75-1.).[137]

The ADH system is both the main pathway for ethanol metabolism in the body and is the rate-limiting step. ADH is a zinc metalloenzyme that uses oxidized nicotinamide adenine dinucleotide (NAD^+) as a hydrogen ion acceptor to oxidize ethanol to acetaldehyde. In this process, a hydrogen ion is transferred from ethanol to NAD^+, converting it to its reduced form, NADH. Subsequently, a hydrogen ion is transferred from acetaldehyde to NAD^+. Under normal conditions acetate is converted to acetylcoenzyme A (acetyl-CoA), which enters the Krebs cycle and is metabolized to carbon dioxide

and water. The entry of acetyl-CoA into the Krebs cycle is dependent on thiamine (Antidotes in Depth: Thiamine Hydrochloride).

The MEOS (CYP2E1) is responsible for very little ethanol metabolism in the uninitiated drinker, but becomes more important as the ethanol concentration rises or as ethanol use becomes chronic (Fig. 75-1.). CYP2E1 uses oxidized nicotinamide adenine dinucleotide phosphate ($NADP^+$) as an electron acceptor to oxidize ethanol to acetaldehyde.[95] In this process, electrons are transferred from ethanol to $NADP^+$, converting it to its reduced form, NADPH. Subsequently, acetaldehyde is further oxidized to acetate, as a hydrogen ion is transferred from acetaldehyde to $NADP^+$. Ethanol's ability to induce the MEOS forms the basis for the well-established interactions between ethanol and a host of other xenobiotics metabolized by this system.[36,52]

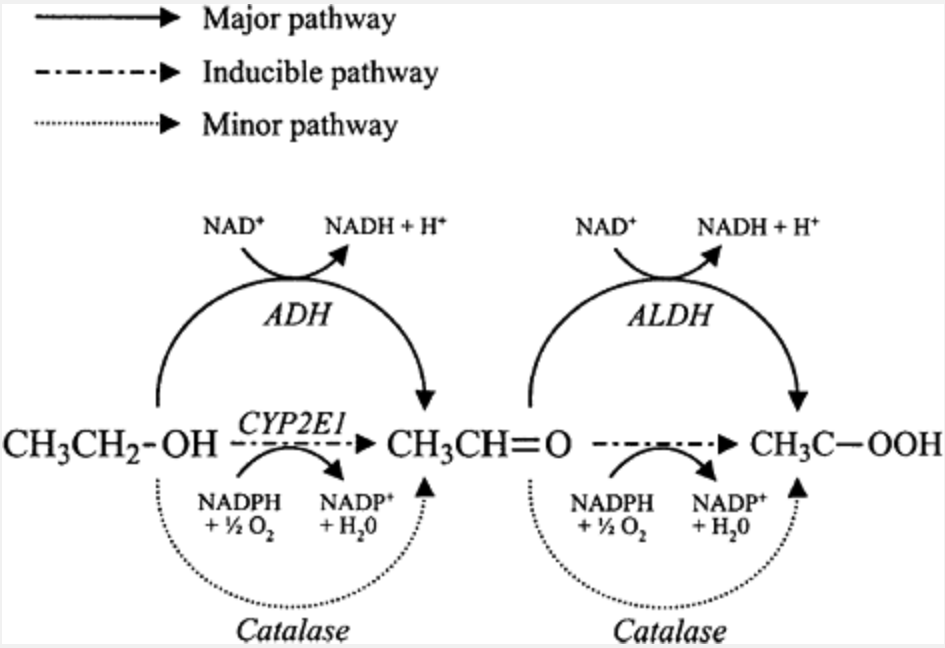

Figure 75-1. Ethanol oxidation. The major, minor, and inducible pathways used for ethanol metabolism.

ADH is saturated at relatively low blood ethanol concentrations. As the system is saturated, ethanol elimination changes from first-order to zero-order kinetics (Chap. 9). In adults, the average rate of ethanol metabolism is 100â€“125 mg/kg/h in occasional drinkers and up to 175 mg/kg/h in habitual drinkers.[17,63] As a result, the average-sized adult metabolizes 7â€“10 g/h and the blood ethanol concentration falls 15â€–20 mg/dL/h (3.26â€–4.35 mmol/L/h). Tolerant drinkers, by recruiting CYP2E1, may increase their clearance of ethanol to 30 mg/dL/h (6.52 mmol/L/h).[17,63] Studies of ethanol-intoxicated patients indicate that although the average ethanol clearance rate is about 20 mg/dL/h (4.35 mmol/L/h), there is considerable individual variation (standard deviation of about 6 mg/dL/h [1.30 mmol/L/h]).[17,63]

Xenobiotic Interactions

Ethanol interacts with a variety of xenobiotics (Table 75-2.).[186] The most frequent interactions occur as a result of an ethanol-induced increase in hepatic xenobiotic-metabolizing enzyme activity. In contrast, acute ethanol use may inhibit metabolism of other xenobiotics, which may be a result of decreased hepatic enzyme activity or blood flow. The interaction between ethanol and disulfiram (Antabuse) is well described, and it can be life-threatening (Chap. 77).

Acute intoxication with ethanol can transiently prolong the elimination of certain xenobiotics, such as phenytoin, because of competition for shared metabolic pathways; an increase in the MEOS (CYP2E1) with chronic ethanol ingestion leads to accelerated metabolism and shortens the half-lives of drugs such as phenytoin, methadone, isoniazid, and warfarin.[83]

Ethanol has additive sedative effects when ingested with antihistamines, cyclic antidepressants, phenothiazines, opioids, and other sedative-hypnotics such as benzodiazepines, barbiturates,

glutethimide, and chloral hydrate (â€œMickey Finnâ€•). Ethanol also potentiates the pharmacologic effects of vasodilators and oral hypoglycemic agents, and may enhance the antiplatelet action of aspirin.

TABLE 75-2. Ethanol Xenobiotic Interactions

Xenobiotics	Adverse Effects
Antihistamines (H_1)	Enhanced CNS depression
Carbamates	Disulfiramlike effect
Cephalosporins[a]	Disulfiramlike effect
Chloral hydrate	Enhanced CNS depression
Chloramphenicol	Disulfiramlike effect
Chlorpropamide	Disulfiramlike effect
Cocaine	Formation of cocaethylene
Coprinus mushrooms	Disulfiramlike effect
Disulfiram (Antabuse)	Nausea, vomiting, abdominal pain, flushing, diaphoresis, chest pain, headache, vertigo, palpitations

Griseofulvin	Disulfiramlike effect
Heroin	Enhanced CNS depression
Isoniazid	Increased incidence of hepatitis; increased metabolism[b]
Methadone	Increased methadone metabolism[b]
Metronidazole	Disulfiramlike effect
Nitrofurantoin	Disulfiramlike effect
Phenytoin	Increased phenytoin metabolism
Ranitidine, cimetidine	Increased ethanol concentration
Sedativeâ€“hypnotics	Enhanced CNS depression
Thiram derivatives	Disulfiramlike effect
Warfarin	Increased warfarin metabolism[b]

[a]Those containing a *N*-methylthiotetrazole side chain.
[b]Effect possibly associated with chronic alcohol consumption.

Concomitant use of cocaine and ethanol leads to the formation of an active metabolite, cocaethylene, through transesterification of

cocaine by the liver.[152] Cocaethylene has a longer half-life than cocaine itself (2 hours vs. 48 minutes), which might explain some of the delayed cardiovascular effects attributed to cocaine use.[7,193] Both ethanol and cocaethylene inhibit the metabolism of cocaine, thereby prolonging the elimination of cocaine and enhancing its effect (Chap. 74).[143]

Case reports and retrospective case series suggest that chronic ethanol consumption may predispose a person to acetaminophen (APAP) hepatotoxicity (Chap. 34)[42,113,119,158,202] even when APAP has been taken according to the manufacturer's recommended dosage of not more than 4 g daily.[201] Because ethanol induces cytochrome P450, the enzyme involved in the metabolism of acetaminophen to its hepatotoxic intermediate, *N*-acetyl-*p*-benzoquinoneimine (NAPQI), a theoretical basis for this association exists. However, in a double-blind placebo-controlled study, where confirmed alcoholics were given acetaminophen 4 g daily or placebo for 3 consecutive days, there were no differences between the two groups with regard to liver enzymes or to coagulation profiles.[94] Recent fasting, common in alcoholics, was also associated with a predisposition to acetaminophen hepatotoxicity, likely as a consequence of depletion of glutathione (Chap. 34).[191] However, in a retrospective study, heavy drinkers did not develop more severe hepatoxicity following APAP overdose when compared to nondrinkers.[114]

Pathophysiology

Ethanol affects practically every organ system in the body (Table 75-3); the relationships between ethanol use, nutrition, and liver disease are reviewed elsewhere.[105] In addition to the harmful effects of ethanol itself (eg, impairment of protein synthesis), its metabolite, acetaldehyde, is inherently toxic to biologic systems.[100,107,182,200] Acetaldehyde directly impairs cardiac contractile function, disrupts cardiac excitationâ€“contractile coupling, inhibits myocardial protein

synthesis, interferes with phosphorylation, causes structural and functional alterations in mitochondria and hepatocytes, and inactivates coenzyme A. Acetaldehyde can also react with intracellular proteins to generate adducts. Acetaldehyde adducts are believed to play an important role in the early phase of alcoholic liver disease, and in advanced liver disease they contribute to the development of hepatic fibrosis.

Ethanol metabolism through the hepatic CYP2E1 pathway generates highly reactive oxygen radicals, including the hydroxyethyl radical (HER) molecule. Elevated oxygen radical levels generate a state of oxidative stress, which leads to cell damage. Oxygen radicals can also initiate lipid peroxidation, resulting in reactive molecules such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE). These reactive molecules react with proteins or acetaldehyde to form adducts, which contribute to the development of alcoholic liver injury.

Oxidation of ethanol generates an excess of reducing potential in the cytosol in the form of NADH, with the ratio of NADH to NAD^+ being dramatically increased. This ratio, also known as the redox potential, determines the ability of the cell to carry on various oxidative processes. The unfavorable change in redox potential as a consequence of ethanol metabolism contributes to the development of metabolic disorders (eg, impaired gluconeogenesis, alterations in fatty acid metabolism, fatty liver, hyperlipidemia, hypoglycemia, lactic acidemia, hyperuricemia [gouty attacks]), increased collagen and scar tissue formation associated with alcoholism, and a clinical syndrome of alcoholic ketoacidosis.

Recent studies in alcoholic liver disease have focused on Kupffer cell activation by endotoxin that is released by intestinal bacteria. When Kupffer cells are activated, they produce regulatory nuclear factor-kappa B (NF-Î´B) and generate significant amounts of superoxide radicals (O_2^-) and cytokines (tumor necrosis factor and interleukin-8), which are an essential factor in the injury to hepatocytes

associated with alcoholic liver disease.[118,190]

Clinical Features

Ethanol is a selective CNS depressant at low doses and a general depressant at high doses. Initially, it depresses those areas of the brain involved with highly integrated functions. Cortical release leads to animated behavior and the loss of restraint. This paradoxical CNS stimulation is caused by disinhibition. In cases of mild intoxication, the signs of ethanol inebriation are quite variable. The patient may be energized and loquacious, expansive, emotionally labile, and increasingly gregarious, or may appear to have lost self-control, exhibit antisocial behavior, and be ill-tempered. As the degree of intoxication increases, there is successive inhibition and impairment of neuronal activity. The patient may become irritable, abusive, aggressive, violent, dysarthric, confused, disoriented, or lethargic. With severe intoxication, there is loss of airway protective reflexes, coma, and increasing risk of death from respiratory depression. An ethanol-naive adult with a blood ethanol concentration >250 mg/dL (54.35 mmol/L) is usually comatose.[1]

The acute effects of ethanol ingestion also depend on the habituation of the drinker. This is mainly a result of the development of

tolerance, which has both a metabolic (pharmacokinetic) and a functional (pharmacodynamic) component.[169] Metabolic tolerance to ethanol is based on enhanced elimination by the ADH enzyme and CYP2E1 system. Functional tolerance (resistance to the effects of ethanol at the cellular level) is a more important determinant of habituation and may be mediated through alterations in serotonergic and adrenergic neurons.[88,89,168] Acute alcohol tolerance may be demonstrated by the Mellanby effect, which involves the comparison of physiologic responses or behavioral effects at the same blood ethanol concentration on the ascending and descending limbs of the blood ethanol curve. Impairment is greater at a given blood ethanol

concentration when the blood ethanol concentration is increasing, than for the same blood ethanol concentration when the blood ethanol concentration is falling.[136,185] Although individuals who are acutely intoxicated move through a progressive sequence of events, the association of a particular aspect of intoxication with a specific blood ethanol concentration is not usually possible without knowing the pattern of ethanol use of the patient. Acute ethanol intoxication occurs in habitual drinkers when they raise their ethanol concentration an equivalent amount above baseline, and specific clinical manifestations of inebriation typically occur in habitual drinkers at a significantly higher blood ethanol concentration than in nontolerant individuals. Regardless, the absolute change above baseline may be important.

TABLE 75-3. Systemic Effects Associated with Alcoholism

Cardiovascular
Cardiomyopathy
â€œHoliday heartâ€• (dysrhythmias)
â€œWetâ€• beriberi (thiamine deficiency)
Endocrine and metabolic
Hypoglycemia
Hypophosphatemia
Hypokalemia
Hypomagnesemia
Hypothermia
Hypertriglyceridemia
Hyperuricemia
Metabolic acidosis
Malnutrition
Gastrointestinal
Mouth
Cancer of the mouth, pharynx, larynx

- Cheilosis
- Nutritional stomatitis
- Esophagus
  - Boerhaave syndrome
  - Cancer of the esophagus
  - Diffuse esophageal spasm
  - Esophagitis
  - Mallory-Weiss tear
- Stomach and duodenum
  - Gastritis
  - Chronic hypertrophic gastritis
  - Diarrhea
  - Hematemesis
  - Malabsorption
  - Peptic ulcer
- Liver
  - Steatosis
  - Hepatitis
  - Cirrhosis
- Pancreas
  - Pancreatitis (acute or chronic)

Genitourinary

- Hypogonadism
- Impotence
- Infertility

Hematologic

- Coagulopathy
- Folate, B_{12}, iron-deficiency anemias
- Hemolysis (Zieve syndrome, stomatocytosis, spur-cell anemia)
- Leukopenia
- Thrombocytopenia

Neurologic

- Alcohol amnestic syndrome

Alcoholic hallucinosis
Alcohol withdrawl
Central pontine myelinolysis
Cerebral atrophy (dementia)
Cerebellar degeneration
CVA (SAH, infarction)
Wernicke encephalopathy
Korsakoff psychosis
Intoxication
Marchiafava-Bignami disease
Myopathy
Polyneuropathy
Pellagra

Ophthalmic

Tobaccoâ€“ethanol amblyopia

Psychiatric

Animated behavior
Loss of self-restraint
Manic-depressive illness
Suicide and depression

Respiratory

Atelectasis
Pneumonia
Respiratory depression
Respiratory acidosis

A patient may present with obvious signs and symptoms consistent with ethanol intoxication that include flushed facies, diaphoresis, tachycardia, hypotension, hypothermia, hypoventilation, mydriasis, nystagmus, vomiting, dysarthria, muscular incoordination, ataxia, altered consciousness, and coma. However, an ethanol-intoxicated patient may present to the ED with a broad range of diagnostic possibilities and should prompt the physician to carefully evaluate the patient for a variety of covert clinical and metabolic disorders. A

meticulous and systematic approach to the evaluation and management of an inebriated patient will help the clinician avoid potential pitfalls in such a situation.[56] The presence or absence of an odor of ethanol on the breath is an unreliable means of ascertaining whether a person is intoxicated or whether ethanol was recently consumed.[130] Diplopia, visual disturbances, and nystagmus may be evident, which may be caused by the toxic effects of ethanol or may represent Wernicke encephalopathy. Hypothermia may be exacerbated by environmental exposure, from malnutrition and loss of carbohydrate or energy substrate, and from ethanol-induced vasodilation. Ethanol intoxication can impair cardiac output in patients with preexisting cardiac disease.[66] Dysrhythmias, such as atrial fibrillation and nonsustained ventricular tachycardia, as well as atrioventricular block, are documented in binge drinkers.[40,67,68] The association between ethanol use and cardiac dysrhythmias, particularly supraventricular tachydysrhythmias in apparently healthy people, is called â€œholiday heart syndrome.â€•[90,96,121] The syndrome was first described in people with heavy ethanol consumption, who typically presented on weekends or after holidays, and it may also occur in patients who binge, but who usually drink little ethanol. The most common dysrhythmia is atrial fibrillation, which usually reverts to normal sinus rhythm within 24 hours. Although the syndrome may recur, the clinical course is benign in patients without anatomic cardiac pathology, and specific antidysrhythmic therapy is usually not warranted.[54,68]

Acute heavy ethanol drinking may precipitate silent myocardial ischemia in patients with stable angina pectoris.[155] Variant angina is reported to occur in patients following ethanol ingestion at a time when the blood ethanol concentration has decreased almost to zero.[49,82,116,124,141,156,172] Acute altered mental status in an alcoholic patient can be the result of a variety of causes, including acute ethanol or toxic ethanol intoxication; hypoglycemia; therapeutic or illicit drug overdose; Wernicke-Korsakoff syndrome;

head trauma; a postictal condition; infection; an intracranial hematoma (acute or chronic); hepatic encephalopathy; an electrolyte or acidâ€“base disorder; or ethanol withdrawal. Ethanol-induced seizures are reported in adults, but are more frequent in children. Sometimes they are associated with hypoglycemia.[28,76] Patients presenting with acute ethanol intoxication commonly have decreased serum ionized magnesium concentrations, although their total serum magnesium concentration is within the normal range.[197] Total body magnesium may be depleted because of poor dietary intake, decreased GI absorption secondary to ethanol, and renal wasting as a consequence of the ethanol-related diuresis.[50,81,154,160,167]

Diagnostic Tests

There are numerous qualitative and quantitative assays for ethanol in biologic fluids and exhaled breath. Immunoassay or gas chromatography is commonly used for determination of ethanol in liquid specimens in most hospitals. Hospital laboratory analysis of blood samples for ethanol content is usually based on serum (liquid portion of whole blood after the cellular components and clotting factors are removed), rarely on plasma (acellular liquid portion of whole blood), and forensic ethanol concentration is defined in whole blood. Serum contains slightly more water than does plasma and whole blood, and will have a slightly higher ethanol concentration. The median ratio of serum to whole blood ethanol concentration is 1.15 (range: 0.88â€“1.59:1)[151] and the mean ratio of plasma to whole blood ethanol concentration is 1.10 (range: 1.03â€“1.24:1).[80] As a result, a serum ethanol concentration of 88â€“159 mg/dL (19.13â€“34.57 mmol/L) is equivalent to a whole-blood ethanol concentration of 100 mg/dL (21.74â€“39.75 mmol/L).

The excretion of ethanol by the lungs is first order and obeys the Henry law: The ratio between the concentration of ethanol in the alveolar air and the blood is constant. Although the alveolar air-to-blood constant is quite low and very little ethanol is excreted by this

route, the fixed relationship forms the basis for the sampling of a person's breath to estimate their blood ethanol concentration. The mean breath-to-blood ratio is 1:2300 during the postabsorptive phase of ethanol kinetics and a ratio of 1:2100 is used in forensic casework.[137] There are individual and interindividual variations in the normal blood-to-breath ethanol ratio, and log-transformation of the values is used to calculate means and confidence intervals.[69,79,97] Breath ethanol analyzers make use of electrochemical sensors for ethanol oxidation or infrared spectral analysis for ethanol determination.[137] They are widely available and are routinely used by law enforcement agencies as ethanol-screening devices. In the ED, they have been shown to accurately predict serum ethanol levels.[188] However, the unconscious or uncooperative patient may be unable to comply with the proper use of the breath alcohol analyzer. Breath-ethanol devices adapted with mouth cups and nasal tubes, to sample the breath of unconscious patients, produce results that correlate fairly well with serum ethanol concentrations.[46,61] Breath-ethanol concentration may not always reflect the concentration of ethanol in blood. Potential sources of interference include recent use of ethanol-containing products, belching or vomiting of gastric ethanol contents, inadequate exhalation, obstructive pulmonary disease, mouth ethanol retained in the bridges or periodontal spaces, and poor technique.[4,101,177] Multidose inhalers (eg, Tornalate [bitolterol mesylate with 38% ethanol], Bronkometer [isoetharine mesylate with 30% ethanol], Primatene Mist [adrenaline with 34% ethanol], and salbutamol) and mouthwashes (eg, Listerine [26.9% alcohol], Scope [18.9% alcohol], and Lavoris [6.0% alcohol]) may contain significant concentrations of ethanol and can cause elevations of breath ethanol above the legal criteria for intoxication.[12,65,110,125] However, these effects are transient and may be prevented by a 10â€“15-minute interval between the use of multidose inhaler or mouthwash and breath-ethanol testing.[65,110,125]

Ethanol-saliva testing is a promising alternative to breath ethanol analysis in the rapid assessment of blood ethanol levels in patients,

regardless of their mental status.[31,163] Fatty acid ethyl esters (FAEEs) may be a highly sensitive test for recent ethanol use.[14,38,164] Because FAEEs remain in the system for at least 24 hours, they may have a role as a marker of recent ethanol use, even after ethanol is completely metabolized. However, their availability is limited and their place in patient management is undefined.

Blood tests that should be considered for patients with ethanol intoxication or alcoholic ketoacidosis include CBC, electrolytes, BUN, creatinine, ketones, acetone, lipase, liver enzymes, a prothrombin time, ammonia, calcium, and magnesium. Patients with an anion gap metabolic acidosis should have urine ketones and serum lactate concentration analysis (Chaps. 17 and 103). High serum acetone concentrations may be indicative of isopropanol intoxication, whereas elevated serum or urinary ketones concentrations may be indicative of alcoholic ketoacidosis, starvation ketosis, or diabetic ketoacidosis. Because the laboratory nitroprusside reaction detects only ketones (acetoacetate and acetone) and not Î²-hydroxybutyrate, the assay for urinary ketones in patients with alcoholic ketoacidosis may be only mildly positive.

A blood ethanol concentration analysis should be included in the initial laboratory studies.[75] If the blood ethanol concentration is inconsistent with the patient's clinical condition, prompt reevaluation of the patient is indicated to elucidate the etiology of the altered mental status, including toxicâ€“metabolic, trauma-related, neurologic, and infectious etiologies. Comatose patients with concentrations below 300 mg/dL (65.22 mmol/L), and those with values in excess of 300 mg/dL (65.22 mmol/L) who fail to improve clinically during a limited period of close observation, should have a head CT scan, followed by a lumbar puncture if warranted. Because chronically ethanol-tolerant patients are prone to trauma and coagulopathies, both of which can cause intracerebral bleeding, the threshold for head CT scanning should be low.

Management of the Intoxicated Patient

Ethanol is rapidly absorbed from the gastrointestinal tract. In situations where recent ingestion (within 1 hour of presentation), delayed absorption, and concomitant ingestions are under consideration, gastrointestinal decontamination may be considered. Occasionally, the extremely intoxicated or comatose patient may have severe respiratory depression, necessitating endotracheal intubation and ventilatory support.

Any patient presenting to the ED with an acute altered mental status mandates immediate investigation and treatment of reversible etiologies such as hypoxia, hypoglycemia, and opioid intoxication. In addition, Wernicke encephalopathy should be considered. Supplemental oxygen should be administered if the patient is hypoxic; intravenous dextrose (0.5â€“1.0 g/kg), thiamine 100 mg, and naloxone should be administered as clinically indicated. Abnormal vital signs should be addressed and stabilized. Patients who are combative and violent should be both physically and then chemically restrained with a benzodiazepine. Caution should be taken because of additive effects of ethanol and benzodiazepine on respiratory depression. Attempts by those who are clinically intoxicated to sign out against medical advice, or attempt to leave, should also be prevented (Chap. 135). The patient's fluid and electrolyte status should be assessed and abnormalities corrected. Multivitamins with folate, thiamine, and magnesium may be added to the maintenance IV solution.

A variety of techniques and xenobiotics have been advocated, either to reverse the intoxicating effects of ethanol or to enhance its elimination. Neither coffee nor caffeine itself counteracts the impaired psychomotor functions that occur with acute intoxication (Antiquated Antidotes in Depth).[138] Earlier anecdotal reports suggested a role for naloxone in reversing ethanol intoxication, but these reports could not be reliably reproduced.[139] The specific

benzodiazepine antagonist flumazenil has no predictable effect on ethanol intoxication.[51] It is unlikely that a specific ethanol antagonist will be discovered because ethanol's mechanisms of action are complex and are not apparently mediated by a single receptor. Rapid intravenous saline (1 L) loading does not accelerate ethanol clearance in intoxicated patients.[104] Hemodialysis is an effective means of enhancing the systemic elimination of ethanol because of the small volume of distribution and low molecular weight of ethanol. In severe ethanol poisoning that results in respiratory failure or coma, hemodialysis may be an adjunct treatment to supportive care. However, this is rarely indicated or necessary.

Indications for Hospitalization

A patient with uncomplicated ethanol intoxication can be safely discharged from the ED after a careful observation and social service or psychiatric counseling. An individual should not be discharged while still clinically intoxicated. However, consideration may be given to a situation where the intoxicated patient is discharged to a protected environment under the supervision of a responsible, not intoxicated, adult. In this case, the clinical assessment of the patient is more important than the blood ethanol level. Indications for hospital admission include persistently abnormal vital signs; persistently abnormal mental status, with or without an obvious cause; a mixed overdose with other concerning xenobiotics; concomitant serious trauma; consequential ethanol withdrawal, and an associated serious disease process, such as pancreatitis or gastrointestinal hemorrhage.

Chronic alcoholism leads to an organic brain syndrome that is irreversible. The patients' socioeconomic condition and their ability to comply with a treatment plan are critical in making a disposition. Alcoholics requesting ethanol detoxification can be admitted for rehabilitation. Inpatient detoxification programs differ substantially from outpatient programs, but their most consequential advantages

may be that they enforce abstinence, provide more support and structure, and separate the patient from the social surroundings associated with drinking.[135] For patients who are not admitted, a referral should be offered to Alcoholics Anonymous or another suitable ethanol rehabilitation program.

Ethanol-Induced Hypoglycemia

Mechanism of Ethanol-Associated Hypoglycemia

Hypoglycemia associated with ethanol consumption is believed to occur when ethanol metabolism provides a high cellular reduction-to-oxidation (redox) ratio. This redox state favors the conversion of pyruvate to lactate, diverting pyruvate from gluconeogenesis (Fig. 75-2.).[74] Hypoglycemia typically occurs when there is a reduced caloric intake and only after the hepatic glycogen stores are depleted, as in an overnight fast. The mechanism by which hypoglycemia is associated with ethanol consumption in the well nourished individual is less well defined.

Population at Risk

Although the conditions that cause hypoglycemia in adults may also be present in infants and children, children with their smaller livers have less glycogen stores than adults and are more likely to develop hypoglycemia. Hypoglycemia associated with ethanol consumption usually occurs in malnourished chronic alcoholics and children (Chap. 48). It may also occur in binge drinkers who do not eat. A 22% incidence of hypoglycemia was reported in one retrospective study of children with documented ethanol ingestion.[102] In another retrospective study of pediatric and adolescent patients, there was a 3.4% incidence of hypoglycemia (serum glucose concentration <67 mg/dL [3.72 mmol/L]).[44] Ethanol-intoxicated children younger than 5

years of age have an increased risk of developing hypoglycemia, and it is the most common reported clinical abnormality related to ethanol ingestion in this age group.[98,99]

Clinical Features

Patients with ethanol-associated hypoglycemia usually present with an altered consciousness 2â€“10 hours following ethanol ingestion. Other physical findings include hypothermia and tachypnea. Laboratory findings, in addition to hypoglycemia, usually include a positive blood ethanol concentration, ketonuria without glucosuria, and mild acidosis. Management of ethanol-induced hypoglycemia is similar to other causes of hypoglycemia (Chap. 48).

Alcoholic Ketoacidosis

The development of alcoholic ketoacidosis (AKA) requires a combination of physical and physiologic events to occur, and each of these conditions may be independent of the others. The normal response to starvation and depletion of hepatic glycogen stores is for amino acids to be converted to pyruvate. Pyruvate serves as a substrate for gluconeogenesis by being converted to acetyl-CoA, which enters the Krebs cycle, or undergoes conversion to fatty acids. As described earlier, ethanol metabolism generates NADH, resulting in an excess of reducing potential. This high redox state favors the conversion of pyruvate to lactate, diverting pyruvate from being a substrate for gluconeogenesis. To compensate for the lack of normal metabolic substrates, the body mobilizes fat from adipose tissue and increases fatty acid metabolism as an alternative source of

energy. This response is mediated by a decrease in insulin and an increased secretion of glucagon, catecholamines, growth hormone, and cortisol. Fatty acid metabolism results in the formation of acetyl-CoA, and it combines with the excess acetate that is generated from ethanol metabolism to form acetoacetate (Fig. 75-3).[74] Most of the

acetoacetate is reduced to Î²-hydroxybutyrate as a consequence of the excess reducing potential or low redox state of the cell. Volume depletion interferes with the renal elimination of acetoacetate and Î²-hydroxybutyrate and contributes to the acidosis. Lactic acidosis caused by hypoperfusion or infection may coexist with the underlying ketoacidosis.

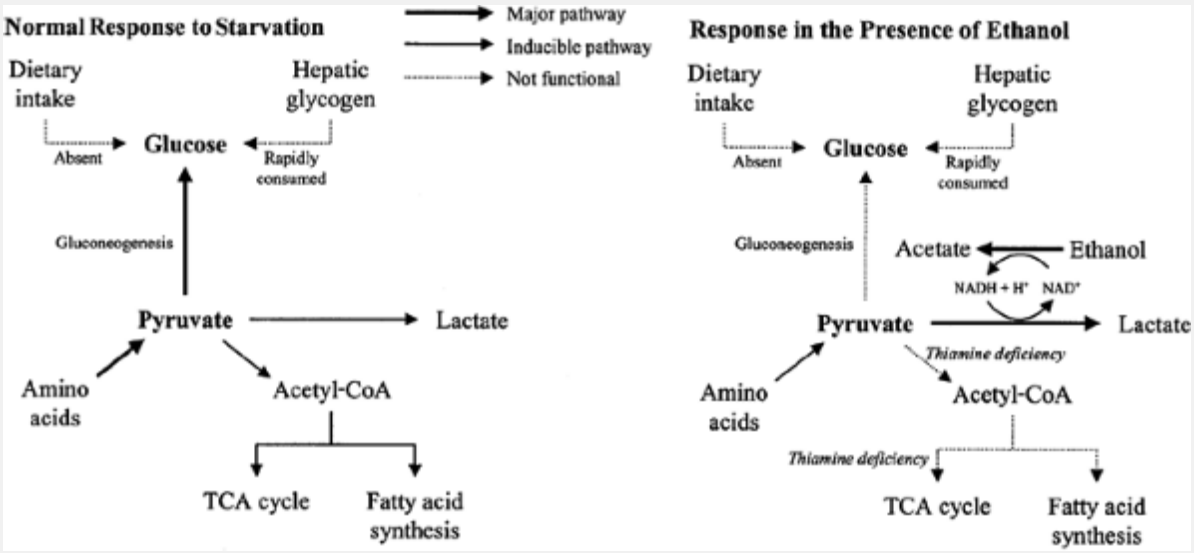

Figure 75-2. Central role of pyruvate in ethanol-induced hypoglycemia. TCA cycle = tricarboxylic acid cycle. *(Modified, with permission, from Hoffman RS, Goldfrank LR: Ethanol-associated metabolic disorders in Endocrine Metabolic Disorders. Emerg Med Clin North Am 1989;7:945.)*

Clinical Features

Patients with AKA are typically chronic ethanol users, presenting after a few days of â€œbingeâ€• drinking, who become acutely starved because of cessation in oral intake as a consequence of binging itself, or because of nausea, vomiting, abdominal pain from

gastritis, hepatitis, pancreatitis, or a concurrent acute illness.[56,57,59] The patient may appear acutely ill with dehydration, tachypnea, tachycardia, and hypotension. Underlying medical conditions such as sepsis, meningitis, pyelonephritis, or pneumonia may be present, and alcohol withdrawal may develop, all of which should be considered and systematically excluded. The diagnosis of AKA is a diagnosis of exclusion.

The blood ethanol concentration is usually low or undetectable because ethanol intake ceased substantially earlier in the clinical course. The hallmarks of AKA include an elevated anion gap metabolic acidosis with a serum lactate concentration insufficient to account for the gap. However, some patients will have a normal arterial pH or be alkalemic because of an associated primary metabolic alkalosis caused by vomiting and a compensatory respiratory alkalosis (Chap. 17).[55] When patients with AKA were compared

with patients with diabetic ketoacidosis (DKA), those with AKA tended to have a higher blood pH, lower serum potassium and chloride concentrations, and a higher serum bicarbonate concentration.[58] The anion gaps in patients with AKA and DKA are very similar, with Î²-hydroxybutyrate being the primary anion contributor and lactate having a less-consequential role.[58]

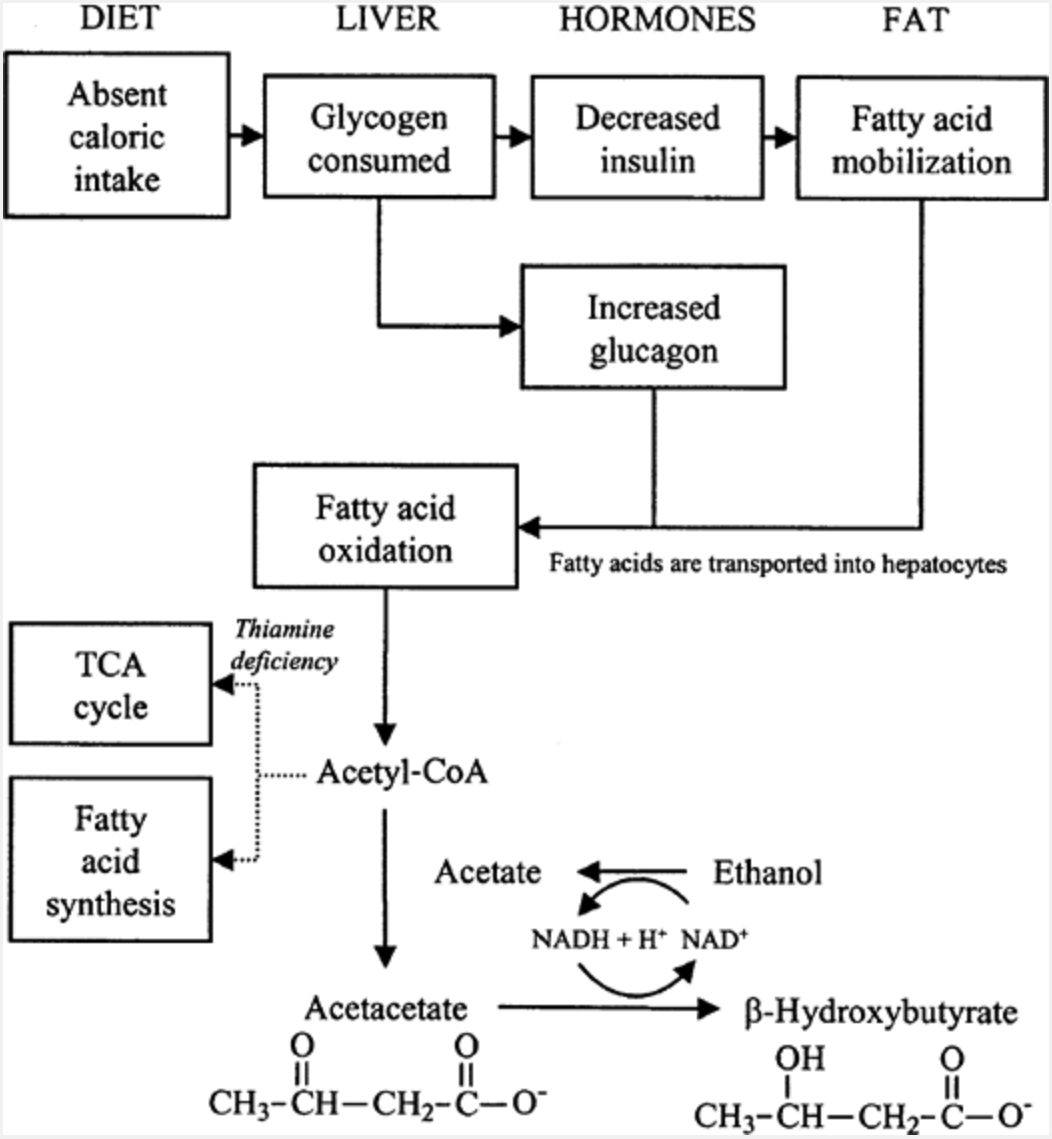

Figure 75-3. Mechanism of alcoholic ketoacidosis. TCA cycle = tricarboxylic acid cycle. *(Modified, with permission, from Hoffman RS, Goldfrank LR: Ethanol-associated metabolic disorders in Endocrine Metabolic Disorders. Emerg Med Clin North Am 1989;7:952.)*

The nitroprusside test used to detect the presence of ketones in

serum and urine may be negative or mildly positive in patients with AKA because the nitroprusside reaction only detects molecules containing ketone moieties. This includes acetone and acetoacetate but not Î²-hydroxybutyrate. Reliance on the nitroprusside test alone may underestimate the severity of ketoacidosis. Specific assays for Î²-hydroxybutyrate may be performed, but are not readily available in most hospital laboratories. The blood glucose may be low or mildly elevated. It is postulated that ethanol-induced hypoglycemia occurs first, causing increased levels of cortisol, growth hormone, glucagon, and epinephrine; this may correct the hypoglycemia and mobilize fatty acids, which are converted to ketones.[32] Therefore, alcoholic hypoglycemia and alcoholic ketoacidosis may be sequential events of the same process, depending on the point in this process at which the patient is evaluated.

Management

Treatment should begin with adequate crystalloid fluid replacement, dextrose, and thiamine. Supplemental multivitamins, potassium, and magnesium should be instituted on an individual basis. The administration of dextrose will stimulate the release of insulin, decrease the release of glucagon, and reduce the oxidation of fatty acids. Exogenous glucose also facilitates the synthesis of adenosine triphosphate (ATP), which reverses the pyruvate-to-lactate and NAD^+-to-NADH ratios. The provision of thiamine facilitates pyruvate entry into the Krebs cycle, thus increasing ATP production. Volume replacement restores glomerular flow and improves excretion of organic acids. Administration of either insulin or sodium bicarbonate in the management of AKA is usually unnecessary.[59]

During the recovery phase of AKA, Î²-hydroxybutyrate is converted to acetoacetate. As this process occurs, the nitroprusside test may become more positive because of higher levels of acetoacetate, resulting in a transient hyperketonemia that actually represents improvement of the metabolic status.

Mortality is rare from either ethanol-induced ketoacidosis or hypoglycemia. However, these patients may succumb to other precipitating or coexisting medical or surgical disorders[56] such as occult trauma, pancreatitis, gastrointestinal hemorrhage or hepatorenal dysfunction, and infections.

TABLE 75-4. The Brief Michigan Alcoholism Screening Test

Question	Circle Correct Answer		Points
1. Do you feel you are a normal drinker?	Yes	No	N2
2. Do friends or relatives think you are a normal drinker?	Yes	No	N2
3. Have you ever attended a meeting of Alcoholics Anonymous?	Yes	No	Y5
4. Have you ever lost friends or girlfriends/boyfriends because of drinking?	Yes	No	Y2
5. Have you ever gotten into trouble at work because of drinking?	Yes	No	Y2
6. Have you ever neglected your obligations, your family, or your work for 2 or more days in a row because	Yes	No	Y2

you were drinking?			
7. Have you ever had delirium tremens (DTs) or severe shaking, or heard voices, or seen things that weren't there after heavy drinking?	Yes	No	Y2
8. Have you ever gone to anyone for help about your drinking?	Yes	No	Y5
9. Have you ever been in a hospital because of drinking?	Yes	No	Y5
10. Have you ever been arrested for drunk driving after drinking?	Yes	No	Y2
Score 6 = Probable diagnosis of alcoholism.			
Reprinted, with permission, from Pokorny AO, Miller BA, Kaplan HB: The brief MAST: A shortened version of the Michigan Alcoholism Screening Test. Am J Psychiatry 1972;129:342â€“345.			

Alcoholism

Alcoholism is traditionally defined as a chronic, progressive disease characterized by tolerance and physical dependence to ethanol and pathologic organ changes. Alcoholism is a multifactorial, genetically influenced disorder,[27,71,135,146,153,159,174] and should be suspected in any patient who presents to the ED with unexplained trauma, seizures, or inappropriate behavior. Physical findings associated with

long-term alcoholism include flushed facies, parotid enlargement, gynecomastia, cardiomyopathy, hepatomegaly, stigmata of cirrhosis, testicular atrophy, palmar erythema, Dupuytren contractures, peripheral neuropathy, nutritional deficiencies, and recurrent infections.

Concern for early detection and intervention led to attempts to create reliable diagnostic screening systems. The brief Michigan Alcoholism Screening Test (MAST) (Table 75-4)[149] and the CAGE (cut down, annoyance, guilt, eye-opener) questions (Table 75-5)[117,189] represent two such tools. As can be seen from these screening tools, the presence of physical tolerance and/or dependence is not essential for a diagnosis of alcoholism. Emphasis instead is placed on the social and behavioral concomitants of heavy drinking.[129] In the ED setting, questions concerning the patient's ability to function physically and psychologically are just as appropriate as quantifying the amount of ethanol consumed per day.

Alcoholism is commonly associated with affective disorders, especially depression.[127,150] There is a higher rate of alcoholism amongst patients with bipolar disorder than in the general population, and there may be a genetic relationship between alcoholism and depression.[86,140,194,195] Ethanol affects mood, judgment, and self-control, creates a clinical condition conducive to violence directed at

self and others, and is an important risk factor for suicide. Although many people drink in an attempt to ameliorate their depression, all available evidence suggests that alcoholism adversely affects mood and cognitive ability. Research indicates an increased incidence of alcoholism in families, and twin studies suggest that a tendency to drink is partly under genetic control.[9,86,91,108] Chromosomal linkage analysis has implicated chromosomes 9, 15, and 16 in the genetic predisposition to alcoholism.[13,34,112] Genetic epidemiologic studies strongly suggest that expression of polymorphism in ADH and ALDH genes may be markers for risk of alcoholism.[25,27,43,174,176] The

ADH2*2 and ADH3*1 alleles that encode for high ADH activity (eg, rapid conversion of ethanol to acetaldehyde), and the variant ALDH2*2 allele that encodes for inactive gene product (eg, slow conversion of acetaldehyde to acetate), are associated with a reduced risk of alcoholism. The combined ADH2*2/*2-ALDH2*2/*2 (homozygous) genotype appears to offer virtual absolute protection against alcoholism. The incidence of both ADH2*1/*1 and ALDH2*1/*1 was significantly higher in patients with ethanol dependence and in patients with alcoholic liver disease.

TABLE 75-5. The CAGE Questions

1. Have you ever felt you should cut down on your drinking?
2. Have people annoyed you by criticizing your drinking?
3. Have you ever felt bad or guilty about your drinking?
4. Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (eye-opener)?

Two or more affirmatives = probable diagnosis of alcoholism.

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Although it is a serious disease with important health and economic consequences, alcoholism remains underdiagnosed and remains a treatment challenge.[115,196] In general, healthcare providers tend to have an overly pessimistic view of the benefits of treating alcoholism. Particularly problematic is the apparent inability of most healthcare workers to effectively deal with the problem when it

affects their colleagues. Successful efforts to combat alcoholism will require increased public education and greater acceptance of alcoholism as a medical illness amenable to treatment.

Various strategies are employed to treat alcoholism, including psychosocial and pharmacologic interventions. A review of the evidence regarding the pharmacologic treatment of ethanol dependence focusing on 5 categories of drugsâ€”the opioid antagonists naltrexone and nalmefene; acamprosate; disulfiram; various serotonergic agents; and lithiumâ€”found as follows:[60] Naltrexone reduces the risk of relapse to heavy drinking and the frequency of drinking compared with placebo, but does not substantially enhance abstinence. Acamprosate reduces drinking frequency, although its effects on enhancing abstinence or reducing time to first drink are less clear. Controlled studies of disulfiram reveal a mixed outcome pattern; some evidence suggests that drinking frequency is reduced, but minimal evidence exists to support improved continuous abstinence rates. There is limited data on serotonergic agents and the data is not encouraging. However, most studies are confounded by high rates of comorbid mood disorders. Lithium lacks efficacy in the treatment of primary ethanol dependence. Topiramate is a drug used to treat partial and generalized tonicâ€“clonic seizures. Clinical evidence suggests topiramate may aid chronic drinkers to wean themselves off alcohol and may ameliorate alcohol withdrawal symptoms.[78] The nonpharmacologic treatment for alcoholism may also be successful. Data derived from several studies and membership surveys indicate that recovery rates of 40â€“80% can be achieved in treatment programs based on the 12-step approach of Alcoholics Anonymous.[72,73,184] This approach appears to be more effective with patients who have social network support.[111]

Summary

Ethanol is widely used in our society, and ethanol use problems

impose a staggering personal, social, and economic burden. Most people are responsible drinkers of ethanol. However, some people drink alcohol in ways that are detrimental to themselves or others. Domestic violence, child abuse, fires, falls, rape, and other crimes, such as robbery and assault, and medical conditions, such as cancer, liver disease, and heart disease, are all associated with ethanol misuse. An interesting area for future study in ethanol research is the finding that genetics may be an important determinant in vulnerability to alcohol dependence. This finding suggests a biologic basis of alcoholism.

Acute ethanol intoxication and chronic alcoholism are among the most common and complex toxicologic and societal problems. These patients may present with a diversity of clinical problems that challenge clinicians to be meticulous and systematic in their evaluation and management of these patients.

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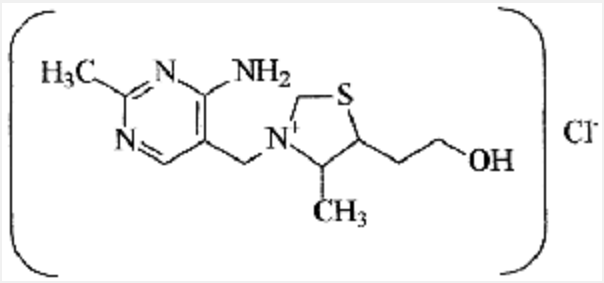
Antidotes in Depth

Thiamine Hydrochloride

Robert S. Hoffman

Biochemistry



Vitamin B_1 (Thiamine Hydrochloride)

Thiamine (vitamin B_1) is a water-soluble vitamin that is essential in the creation and utilization of cellular energy. As a coenzyme in

the pyruvate dehydrogenase complex, thiamine diphosphate, the active form of thiamine, accelerates the conversion of pyruvate to acetylcoenzyme A (acetyl-CoA). This reaction occurs at thiamine's C2 atom, which is located between the nitrogen and sulfur atoms on the thiazolium ring.[21] In the protein-rich environment of the enzyme complex, this C2 atom is deprotonated to form a carbanion that rapidly attaches to the carbonyl group of pyruvate, thereby stabilizing it for decarboxylation.[28] In a series of subsequent reactions, the hydroxyethyl group that remains bound to thiamine diphosphate is transferred to lipoamide, where an acetyl group is later broken off and attached to coenzyme A (CoA). This overall process links anaerobic glycolysis to the Krebs cycle, where subsequent aerobic metabolism produces the equivalent of 36 moles of adenosine triphosphate (ATP) from each mole of glucose (Fig. A22-1). When pyruvate cannot be converted to acetyl-CoA because of thiamine deficiency, for example, only 2 moles of ATP can be generated by anaerobic metabolism from each mole of glucose. Thiamine is also required as a cofactor for Î±-ketoglutarate dehydrogenase, a second enzyme in the Krebs cycle, and for transketolase, an enzyme in the pentose phosphate pathway, in which nicotinamide adenine dinucleotide phosphate (NADPH) is formed for subsequent use in reductive biosynthesis. In addition, thiamine is important in maintaining normal neuronal conduction.[61,76]

Thiamine is available from natural sources, such as organ meats, yeast, eggs, and green leafy vegetables, in a basic form composed of a substituted pyrimidine ring and a substituted thiazole ring connected by a methylene bridge. This connection between the two rings is weak, and the molecule is unstable in an alkaline milieu and in a high temperature environment. In addition, thiamine is highly water soluble, allowing it to leach out of foods that are washed or cooked in water for prolonged times. However, thiamine, which is synthesized as a hydrochloride salt is usually quite stable. Thiamine requirements are determined by total

caloric intake and energy demand, with a minimum daily requirement of 0.5 mg/1000 calories.[61]

Pharmacology

Thiamine is well absorbed from the human gastrointestinal tract by a complex process.[34,53] At low concentrations, thiamine absorption occurs through a saturable mechanism, that is most effective in the duodenum, with absorption occurring to a lesser degree in the large bowel and stomach. As thiamine concentrations increase, however, the majority of absorption occurs through simple passive diffusion. Although more recently synthesized analogs such as thiamine propyl disulfide, benfotiamine, and fursultiamine have enhanced bioavailability, their use remains largely experimental.[21,69] Chronic liver disease, folate deficiency, steatorrhea, and other forms of malabsorption all significantly decrease thiamine's absorption. This malabsorption has even greater clinical relevance in alcoholics.[4,68] In experimental studies, when healthy volunteers were given small amounts of ethanol, a 50% reduction in gastrointestinal thiamine absorption resulted.[68]

Thiamine is eliminated from the body largely by renal clearance, which consists of a combination of glomerular filtration, flow-dependent tubular secretion, and saturable tubular reabsorption.[74] In an animal model, furosemide, acetazolamide, chlorothiazide, amiloride, mannitol, and salt loading all significantly increased urinary elimination of thiamine.[39] This nonspecific flow-dependent elimination was confirmed in humans given small doses of furosemide.[52] Additionally, both furosemide and digoxin appear to inhibit thiamine uptake into myocardial cells.[79]

Thiamine Deficiency

Pathophysiology

Mice develop signs of encephalopathy 10 days after being rendered thiamine deficient. Immunohistochemistry in these animals demonstrates a breakdown of the blood-brain barrier with resultant extravasation of albumin.[24] Similarly, rats develop symptoms after 10 days of thiamine deficiency, and subsequently demonstrate deterioration of the bloodâ€“brain barrier with hemorrhage into the mammillary bodies and other areas of the brain.[11] This pattern is similar to findings described in humans with Wernicke encephalopathy.[49]

The exact cause of Wernicke encephalopathy is unclear. In human autopsy studies, brain samples from alcoholic patients with Wernicke-Korsakoff syndrome demonstrate decreased levels of pyruvate dehydrogenase, Î±-ketoglutarate dehydrogenase, and transketolase when compared to controls.[10] However, a similar decrease in enzyme activity of neuronal tissue was demonstrated in alcoholics who died from hepatic coma without ever manifesting signs of Wernicke encephalopathy.[38] Likewise, the activity of thiamine-requiring Kreb cycle enzymes is reduced in thiamine-replete patients with neurodegenerative diseases.[7] Thus, while thiamine deficiency produces deficits in critical enzymes in humans, it is

unclear whether these deficits are either necessary or sufficient to produce clinical disease.

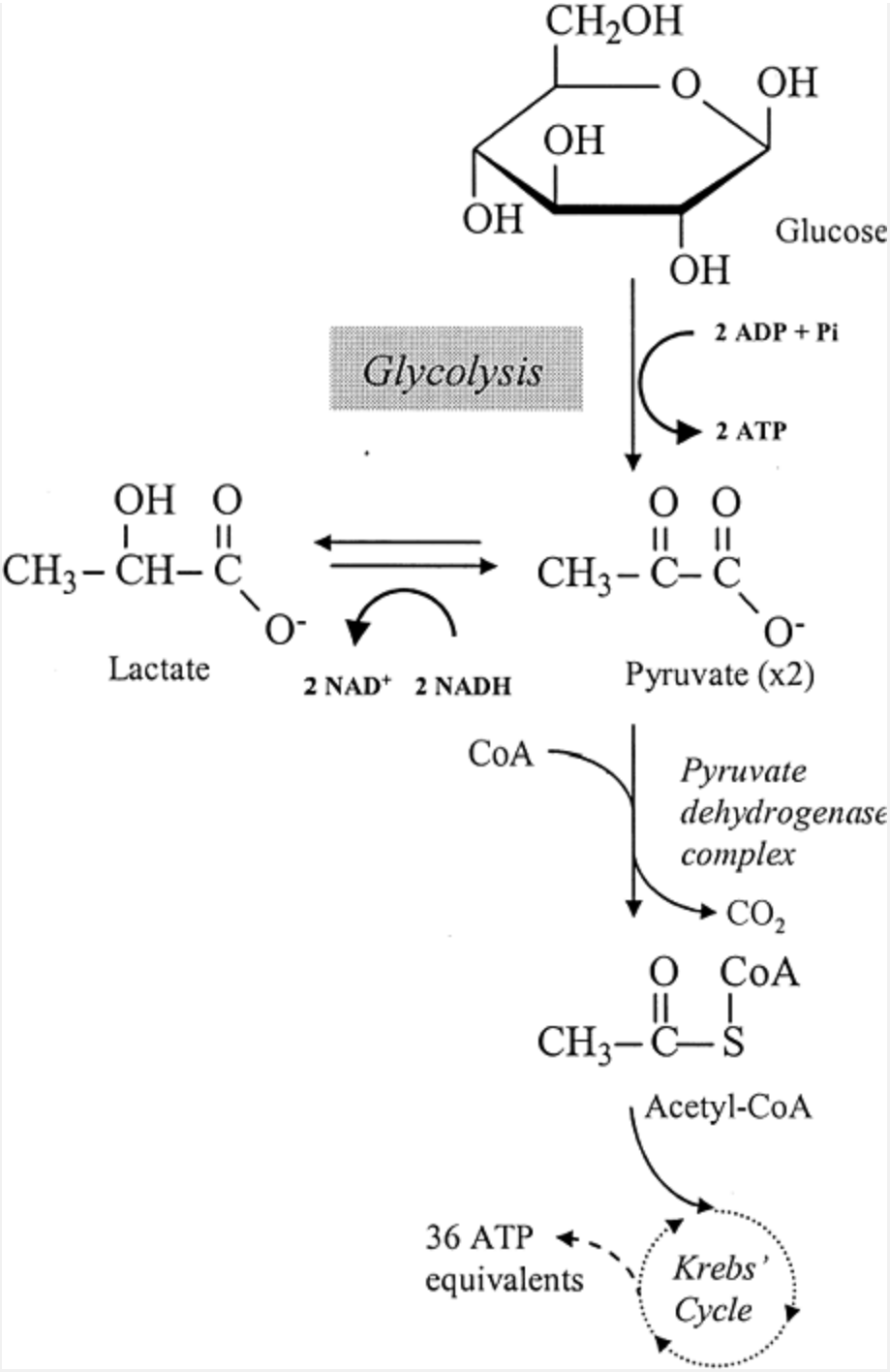


Figure A22-1. Thiamine links anaerobic glycolysis to the Krebs cycle. Anaerobic glycolysis only yields 2 moles of ATP as each mole of glucose is metabolized to 2 moles of pyruvate. To

obtain the 36 additional ATP equivalents that can be derived as the Krebs cycle converts pyruvate to CO_2 and H_2O, pyruvate must first be combined with CoA to form acetyl-CoA and CO_2. This process is dependent on the thiamine-requiring enzyme system known as pyruvate dehydrogenase complex.

Animal models offer insight into the mechanisms involved in developing thiamine-deficient neurologic injury. While the exact chain of events leading to these structural abnormalities is unclear, several models demonstrate key portions of the pathway. Thiamine deficiency in rats produces 200â€“640% increases in levels of glutamate, an excitatory amino acid.[37] This excess of glutamate presumably results from blockade of Î±-ketoglutarate dehydrogenase, which shunts Î±-ketoglutarate, a natural precursor of glutamate away from the Krebs cycle. Rats subsequently develop increases in lactate in vulnerable regions of the brain marked by the induction of the protooncogene c-fos. Both the histochemical lesions and the gene induction can be blocked by the administration of the calcium channel blocker nicardipine.[42] This suggests a strong role for excitatory amino acid-induced alterations in calcium transport in the genesis of thiamine-deficient encephalopathy. In other animal models of thiamine deficiency, neuronal tissues are also directly injured by oxidative stress and lipid peroxidation.[12] Additional lines of investigations demonstrate roles for triggered mast cell degranulation,[20] histamine,[36] and nitric oxide[31] in the generation of neuronal injury. The final common pathway is localized cerebral edema, which may result from altered expression of aquaporin.[16]

Clinical Manifestations

When thiamine is completely removed from the human diet, clinical manifestations of thiamine deficiency typically develop within 2â€“3 weeks, although tachycardia, the first sign of

deficiency, may occur as early as 9 days after cessation of thiamine intake.[76] The clinical symptoms of thiamine deficiency present as two distinct patterns: â€œwetâ€• beriberi or cardiovascular disease, and â€œdryâ€• beriberi, the neurologic disease known as Wernicke-Korsakoff syndrome. Although some patients display symptoms consistent with both disorders, usually either the cardiovascular or the neurologic manifestations predominate. A genetic variant of transketolase activity, combined with low physical activity and low-carbohydrate diet, may predispose to neurologic symptoms, whereas high-carbohydrate diets and increased physical activity lead to cardiovascular symptoms.[6,76] Thus, cardiovascular disease is more common in Asians, and neurologic disease predominates in northern Europeans.

Wet beriberi results from high-output cardiac failure induced by peripheral vasodilation and the formation of arteriovenous fistulae secondary to thiamine deficiency. These patients complain of fatigue, decreased exercise tolerance, shortness of breath, and peripheral edema. The classic triad of oculomotor abnormalities, ataxia, and global confusion defines Wernicke encephalopathy. Other manifestations include hypothermia and the absence of deep-tendon reflexes.[73] Additionally, patients develop a peripheral neuropathy with paresthesias, hypesthesias, and an associated myopathy, all related to axonal degeneration.[61] Laboratory studies may reflect a lactic acidosis brought on by excessive anaerobic glycolysis resulting from blocked entry of substrate into the Kreb cycle.[17,29,30,35,54,73] Korsakoff psychosis, an irreversible disorder of learning and processing of new information characterized by a deficit in short-term memory and confabulation, often occurs together with Wernicke encephalopathy.[71] A 10â€“20% mortality rate is associated with Wernicke encephalopathy, with survivors having an 80% risk of developing Korsakoff psychosis.[51]

Populations at Risk

In the United States, a healthy diet and mandatory thiamine supplementation of numerous food products protect most people from the manifestations of thiamine deficiency. This is, unfortunately, not true in other countries. A survey of the 17 major public hospitals in the Sydney, Australia area, identified more than 1000 cases of either acute Wernicke encephalopathy or Korsakoff psychosis between 1978 and 1993.[40] Similarly, a single Australian hospital identified 32 cases of Wernicke encephalopathy during a 33-month period.[77] In Australia, mandatory supplementation of flour with thiamine in 1991 resulted in a dramatic reduction in hospitalized cases during 1992 and 1993,[40] as well as of those subsequently identified by postmortem studies.[25] Current areas at risk include Ireland and New Zealand where lack of a mandatory supplementation program is correlated with a high prevalence of biochemical evidence of thiamine deficiency.[45]

The alcoholic patient, whose consumption of ethanol is his or her major source of calories, is the best described and most easily recognized patient at risk for thiamine deficiency.[51] Consequential thiamine deficiency is also described in inmates; postoperative patients; in those patients with hyperemesis gravidarum or anorexia nervosa; in those patients receiving parenteral nutrition; in patients with acquired immunodeficiency syndrome (AIDS); in patients with malignancies; in the institutionalized elderly;[34,35] foreign laborers from the Far East; patients

with congestive heart failure on furosemide therapy; and in patients receiving hemodialysis; among others. Thus, despite routine dietary supplementation, many people are still at risk because of dietary limitations, alcohol abuse, or underlying medical conditions.

Thiamine Replacement

Thiamine hydrochloride is included in the initial therapy for any patient with an altered mental status, potentially acting as both treatment and prevention of Wernicke encephalopathy. Many patients with altered levels of consciousness have had or will have a poor nutritional status, or will be hospitalized without oral intake for a number of days because of gastrointestinal disorders or altered mental status. Although thiamine levels can be measured, either directly or functionally, by measuring their erythrocyte transketolase activity at baseline and in response to thiamine diphosphate,[26] these tests are unavailable for clinical use. Likewise, although clinical prediction models have been developed, they are cumbersome and unvalidated.[59] Glucose loading increases thiamine requirements, which can exacerbate marginal thiamine deficiencies or even precipitate coma in the absence of parenteral thiamine supplementation.[51] Although it is commonly believed that acute glucose loading, in the form of a bolus of hypertonic dextrose, can precipitate Wernicke encephalopathy over several hours in normal individuals, there is only evidence to support this effect in patients who already have grave manifestations of thiamine deficiency.[73] Previously healthy patients require prolonged dextrose administration in order to develop Wernicke encephalopathy. Because the morbidity and mortality associated with Wernicke encephalopathy are so severe, and treatment is both benign and inexpensive, thiamine hydrochloride should be included in the initial therapy for all patients who receive dextrose, for all patients with altered consciousness, and for every potential alcoholic or nutritionally deprived individual who presents to the emergency department or other clinical setting.

Initial therapy consists of the immediate parenteral administration of 100 mg of thiamine hydrochloride. This can be given either intramuscularly or intravenously, but the oral route should be

avoided because of its unpredictable absorption. In countries where thiamine propyl disulfide (a lipid-soluble thiamine preparation) is available, the oral route may be considered equally efficacious for the replacement of serious thiamine deficiencies.[4,68,69,2] In some patients, symptoms such as ophthalmoplegia are reported to respond rapidly to as little as 2 mg of thiamine; however, the other neurologic and cardiovascular manifestations of thiamine deprivation may necessitate higher doses and may respond more slowly, if at all. Although virtually every source recommends that daily doses of 100 mg of thiamine are sufficient as preventive therapy, a recent trial suggested improved cognitive function when a daily dose of 200 mg was compared to lower doses.[1] Because of the safety of thiamine hydrochloride, and the urgency to correct the manifestations of thiamine deficiency, up to 1000 mg of thiamine hydrochloride can be used in the first 12 hours if a patient demonstrates persistent neurologic abnormalities.[43]

The practice of requiring the administration of parenteral thiamine prior to hypertonic dextrose in patients with altered consciousness is illogical.[22] Besides the fact that the first dose of dextrose is unlikely to cause thiamine deficiency, thiamine uptake into cells and activation of enzyme systems is slower than that of glucose uptake, which suggests that even pretreatment with thiamine offers little benefit over posttreatment.[66] Despite these limitations it is prudent to administer 100 mg of parenteral thiamine at the time of initial dextrose administration. The biochemical link between dextrose and thiamine is obvious, which demonstrates to the clinician the scientific basis for the administration of thiamine. Although thiamine is unlikely to offer immediate benefits for patients with altered consciousness, it will offer some long-term protection for these individuals at risk and initiate therapy for an uncommon, serious, insidious and easily overlooked disorder.

A supplementary indication for the administration of thiamine hydrochloride occurs in patients with ethylene glycol poisoning. As

shown in Figure 103-2, a minor pathway for the elimination of glyoxylic acid involves its conversion to Î±-hydroxy-Î²-ketoadipate by Î±-ketoglutarate:glyoxylate carboligase, a thiamine and magnesium-requiring enzyme. There are no data to support an increase in Î±-hydroxy-Î²-ketoadipate formation following thiamine administration in ethylene glycol-poisoned animals or humans. However, animal models of primary hyperoxaluria show increases in urinary oxalate during thiamine deficiency, suggesting at least a potential importance of this pathway.[23,65] Because therapy is benign and inexpensive, it is prudent to administer standard doses of thiamine to patients with suspected or confirmed ethylene glycol poisoning. If magnesium supplementation is considered, caution is required because of the potential for renal compromise in ethylene glycol poisoned patients.

Routine thiamine administration should also be considered in patients with congestive heart failure and long-term use of diuretics. Diuretics enhance renal thiamine elimination. In one randomized trial, 200 mg of daily intravenous thiamine was able to increase cardiac ejection fraction by 22% at 7 weeks.[60]

Adverse Events

Very few complications are associated with the parenteral administration of thiamine. The older literature emphasized intramuscular administration because of numerous reports of anaphylactoid reactions associated with intravenous thiamine delivery.[19,50,56,63,75] It is generally believed that these reactions resulted from responses to the vehicle (chlorbutanol) or its contaminants rather than thiamine itself. Despite the availability of purer, aqueous preparations of thiamine, rare adverse reports still occur.[3,41,48,62] Although the intramuscular route is theoretically comparably efficacious in a healthy individual, many patients requiring thiamine may have diminished muscle mass or a

coagulopathy, exacerbating the potential for pain and unpredictable absorption. The safety of thiamine use was evaluated in a large case series in which nearly 1000 patients received parenteral doses of up to 500 mg of thiamine without significant complications.[78] This study suggests that if anaphylaxis to thiamine exists, its occurrence is exceedingly rare, permitting the safe intravenous administration of thiamine to most patients.

Pregnancy Category

Thiamine hydrochloride is listed as pregnancy A and is also considered safe for use in lactating mothers.

Availability

Multiple manufacturers formulate thiamine hydrochloride for intravenous or intramuscular administration. Typical concentrations are either 50 or 100 mg/mL. Although more concentrated solutions are available, their use is usually reserved for preparation of total parenteral nutrition solutions.

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Chapter 76
Ethanol Withdrawal

Jeffrey Gold

Lewis S. Nelson

A 46-year-old man with a seizure disorder arrived in the emergency department requesting his daily phenytoin dose after being in police custody for 18 hours. He denied any physical complaints, and simply wanted to be seen and discharged.

His triage vital signs were: blood pressure, 130/80 mm Hg; respiratory rate, 12 breaths/min; pulse, 105 beats/min, without orthostatic changes; and rectal temperature, 99.9Â°F (37.2Â°C). He was well developed, poorly nourished, and appeared older than his stated age. He was garrulous and somewhat anxious, although alert and oriented to time, place, and person. On physical examination he had fine hand and tongue tremors, scattered spider hemangiomata, and hepatomegaly of 14 cm.

Blood was drawn for a complete blood count, serum chemistries, liver function tests, and blood alcohol and phenytoin concentrations. A bedside rapid reagent blood sugar was 70 mg/dL. One liter of 0.9% sodium chloride was administered at 500 mL/h. Multivitamins and

100 mg of thiamine were given intravenously.

One hour later, the patient began to shout at nursing staff that he was being held against his will and that he must leave. He was unable to remember why he asked to be evaluated or who brought him to the hospital. Repeat vital signs were: blood pressure, 130/80 mm Hg; pulse, 130 beats/min; respiratory rate, 12 breaths/min; room air pulse oximetry, 98% saturation; and rectal temperature, 100.3Â°F (37.9Â°C). The patient was diaphoretic with a coarse tremor. The pupils were 5 mm, equal, and briskly reactive.

The patient's clinical condition was unchanged after two separate doses of diazepam 10 mg IV 15 minutes apart. Diazepam was repeated as 10-mg IV boluses to a total of 100 mg, and the patient was placed in 4-point soft restraints after he began to remove his intravenous line and climb off the stretcher. His diaphoresis and tachycardia continued. He picked at the restraints, scratched his skin, and shouted nonsensical words occasionally.

Diazepam administered to a total dose of 220 mg did not improve the patient's agitation; the pulse was 110 beats/min; respiratory rate, 12 breaths/min; and temperature, 101.0Â°F (38.3Â°C). Phenobarbital was administered as 130-mg boluses over 3 minutes and repeated 4 times (520 mg total), following which the patient was calm, and the heart rate was 100 beats/min. The patient was electively intubated, given thiopental, and attached to a mechanical ventilator for airway protection. The patient remained sedated and required an additional 40 mg of diazepam over the next 24 hours. He developed a right lower lobe infiltrate on day 2 of his hospitalization and was treated with ampicillin plus sulbactam. He recovered uneventfully and was extubated 48 hours later.

History and Epidemiology

The medical problems associated with alcoholism and alcohol withdrawal were first described by Pliny the Elder in the 1st century

B.C. In his work *Naturalis Historia*, the alcoholic and alcohol withdrawal were described as follows: â€œâ€¦drunkenness brings pallor and sagging cheeks, sore eyes, and trembling hands that spill a full cup, of which the immediate punishment is a haunted sleep and unrestful nights. â€¦â€• [63] Initial treatments as described by Osler were focused on supportive care, including confinement to bed, cold baths to reduce fever, and judicious use of potassium bromide, chloral hydrate, hyoscine, and, possibly, opium.[62]

Some of the initial large series of alcohol related complications in the early 20th century describe the alcohol withdrawal syndrome (AWS) as a major public health concern. At Bellevue Hospital in New York City, Jolliffe describes 7000â€“10,000 admissions per year for alcohol-related problems from 1902â€“1935, with an estimated rate of 2.5â€“5 admissions/1000 New York City residents.[42] Moore et al describe similar numbers of admissions to Boston City Hospital, with up to 10% of alcoholics admitted with evidence of delirium tremens (DT). The mortality at the beginning of their study among patients with DT was 52% (1912), and DT was the leading cause of death among admitted alcoholics. Over the ensuing 20 years, this rate declined to approximately 10â€“12%, a decrease believed to be secondary to improved supportive care and nursing.[57]

Though widely recognized that alcoholics had a high incidence of delirium and psychomotor agitation, it remained controversial as to whether this was caused by ethanol use, ethanol abstinence, or coexisting psychological disorders. Isbell and colleagues, in 1955, proved that abstinence from alcohol was the cause of this syndrome when they subjected 9 male prisoners to chronic alcohol ingestion for a period of 6â€“12 weeks followed by 2 weeks of abstinence.[40] During this latter period, 6 of the 9 men developed tremor, elevations in blood pressure, heart rate, diaphoresis, and varying degrees of either auditory or visual hallucinations, consistent with the diagnosis of DT.[40] In addition, 2 of the 9 men developed convulsions, further linking alcohol abstinence to seizures. However, it should be noted that the high rate of development of

DT (67%) is atypical and does not represent the true prevalence found in later epidemiologic studies.[12]

Currently, alcoholism and alcohol withdrawal syndromes still represent a major problem in both the inpatient and outpatient setting. In a 10-year epidemiologic study, the prevalence of self-reported symptoms of alcohol withdrawal, including morning tremors and sweating, in the general population was quite low, with only 1â€“3% of men describing 1 or more symptoms of alcohol withdrawal; rates were even lower among women.[12] However, when the population in this study was enriched by those at risk for alcoholism, with at risk being defined as convicted for driving under the influence, nearly 19% met self-reported *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) (DSM-IV) criteria for alcohol withdrawal. The prevalence was even higher among persons admitted for detoxification, with nearly 80% experiencing 1 or more withdrawal symptom.[12]

Similar results have been obtained in the inpatient setting. Alcohol-related complications accounted for 21% of all medical ICU admissions, with alcohol withdrawal being the most common alcohol-related diagnosis.[54] In one study, 8% of all general hospital admissions, 16% of all postsurgical patients, and 31% of all trauma patients developed AWS.[27,69] The development of AWS in postsurgical and trauma patients can increase the mortality in this population nearly 3-fold.[68,70] Furthermore, alcohol was involved in nearly 86% of homicides, 37% of assaults, and 25â€“35% of nonfatal motor vehicle crashes.[59]

Pathophysiology

Numerous studies over the past 2 decades have provided valuable insight into the mechanism of alcohol withdrawal, allowing for better understanding of both the clinical spectrum of the disorder and potential therapeutic interventions. Alcohol withdrawal is a

neurologic disorder with a continuum of progressively worsening symptoms caused by the effects of chronic ethanol use on the central nervous system, and often exacerbated by the clinical manifestations of alcoholism (eg, nutritional depletion, impaired immunity, anemia, cirrhosis, head trauma).

The effects of chronic alcohol consumption on neurotransmitter function best explains the clinical findings. Persistent stimulation of the inhibitory Î³-aminobutyric acid (GABA) receptor-chloride channel complex by ethanol, leads to downregulation of GABA receptorâ€“chloride channel complex.[11,44] This allows the alcohol user to maintain a relatively normal level of consciousness despite the presence of sedative concentrations of ethanol in the brain. A continued escalation of the steady-state ethanol concentration is required to achieve euphoria (ie, tolerance), which results in progressive desensitization of the GABA receptorâ€“chloride channel complex.[24] The exact mechanism by which this adaptive change occurs is undefined, but may involve substitution of an $\hat{I}\pm_4$ for an $\hat{I}\pm_1$ receptor subunit on the $GABA_A$ receptor (Chap. 15).[13,49] A converse series of events occurs at the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor. Binding by ethanol to the glycine binding site of this receptor inhibits the NMDA function, resulting in compensatory upregulation of these excitatory receptors.[33,38] Thus withdrawal of alcohol is associated with both a decrease in GABAergic activity and an increase glutamatergic activity.[33] This phenomenon of a concomitant increased excitation and loss of inhibition results in the clinical manifestations of autonomic excitability and psychomotor agitation.

Repeated episodes of alcohol withdrawal may lead to poorly understood permanent alterations in neurotransmitters and their receptors. In rats, repeated episodes of alcohol withdrawal leads to persistent and progressive EEG abnormalities, with further episodes of withdrawal becoming increasingly resistant to benzodiazepines. Both clinical observation and in vitro data suggest that repeated episodes of alcohol withdrawal leads to permanent dysregulation of

GABA receptors. This understanding may be an explanation for the â€œkindling phenomena,â€• which is the clinical observation of increasing severity of alcohol withdrawal among individual subjects, and the development of benzodiazepine resistant alcohol withdrawal.[10,30,84]

Clinical Syndromes

Alcohol withdrawal is defined in the DSM-IV as the cessation of heavy or prolonged alcohol use resulting, within a period of a few hours to several days, in the development of 2 or more of the clinical findings listed in Table 76-1.[26] Furthermore, these symptoms must have no other organic etiology. Alcohol withdrawal syndromes can be classified both by timing (early vs. late) and severity (complicated vs. uncomplicated). However, there are no adequate or fully accepted criteria by which to define these categories. Furthermore, the clinical course of AWS can vary widely among patients, and progression of individual patients through these different stages is extremely variable. In fact, some heavy alcohol users experience no withdrawal syndrome following the cessation of alcohol consumption. Recognizing these limitations, this conceptual framework still proves helpful in the clinical management of patients with alcohol withdrawal.

Early Uncomplicated Withdrawal

Alcohol withdrawal begins as early as 6 hours after the cessation of drinking. Early withdrawal is characterized by autonomic hyperactivity including tachycardia, tremor, hypertension, and psychomotor agitation. Although these symptoms are uncomfortable, they are not generally dangerous. Most patients who ultimately develop severe manifestations of AWS initially develop these findings, but this is not universal. At this â€œstageâ€• of AWS, the symptoms are still readily amenable to treatment with ethanol, as is done daily by most heavy alcohol users.

TABLE 76-1. DSM-IV Criteria for Alcohol Withdrawal

A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged.
B. Two (or more) of the following, developing within several hours to a few days after criterion A:
   1. Autonomic hyperactivity (e.g., sweating or pulse rate greater than 100)
   2. Increased hand tremor
   3. Insomnia
   4. Nausea or vomiting
   5. Transient visual, tactile, or auditory hallucinations or illusions
   6. Psychomotor agitation
   7. Anxiety
   8. Grand mal seizures
C. The symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to a general condition and are not better accounted for by another mental disorder.

Alcoholic Hallucinosis

Nearly 25% of patients with AWS will develop hallucinations, and a subset of these patients will develop alcoholic hallucinosis, a syndrome of persistent hallucinations.[75,78] Although classically these hallucinations are tactile or visual, other types of hallucinations are described. Tactile hallucinations include formication, or the sensation of ants crawling on the skin, which can result in repeated itching and

excoriations. However, as opposed to what is observed with DT, alcoholic hallucinosis is associated with a clear sensorium. The presence of alcoholic hallucinosis is neither a positive or negative predictor of the subsequent development of DT.[39]

Alcohol Withdrawal Seizures

Approximately 10% of patients with AWS develop alcohol withdrawal seizures, or â€œrum fits.â€• For many patients, a generalized alcohol withdrawal seizure may be the first manifestation of the AWS.[76] Approximately 40% of patients with alcohol withdrawal seizures have isolated seizures and 3% develop status epilepticus.[76,77] Alcohol withdrawal seizures may occur in the absence of other signs of alcohol withdrawal and are characteristically brief, generalized, tonicâ€“clonic events with a short postictal period. Rapid recovery and normal mental status belie the seriousness of an alcohol withdrawal seizure. However, for approximately one-third of patients with DT, the sentinel event is an isolated alcohol withdrawal seizure. Alcohol withdrawal seizures occurring in the presence of an elevated ethanol concentration may be a poor prognostic indicator for the development of DT because the relative protection against withdrawal of an elevated ethanol concentration will be lost as the concentration drops.[74] Finally, clinicians should be cognizant that many alcoholics are prescribed anticonvulsant medications because they have a preexisting seizure disorder, often related to repetitive brain trauma.[29] Conversely, the use of anticonvulsants does not unequivocally indicate the presence of a preexisting seizure disorder because of the difficulty in differentiating these seizures from those of alcohol withdrawal.

Delirium Tremens

Delirium tremens is the most serious complication of the AWS, and it generally manifests between 48 and 96 hours after the cessation of drinking.[76] Many of the clinical manifestations of DT are similar to

those of uncomplicated early alcohol withdrawal, differing only in severity, and include tremors, autonomic instability (hypertension and tachycardia), and psychomotor agitation. However, unlike AWS, DT, as defined in DSM-IV, is associated with either (a) disturbance of consciousness (such as reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention, delirium, confusion, and frank psychosis, or (b) a change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.[26] Unlike the early manifestations of alcohol withdrawal, which typically last for 3â€“5 days, DT can last for up to 2 weeks (Table 76-2).[76]

TABLE 76-2. Diagnostic Criteria for Substance Withdrawal Delirium

A. Disturbance of consciousness (ie, reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
B. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.
C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
D. There is evidence from the history, physical examination, or laboratory findings that the symptoms in criteria A and B developed during, or shortly after discontinuation of substance use.

Risk Factors for the Development of Alcohol Withdrawal

Factors determining whether an individual will develop AWS are not well identified. The strongest predictor for the development of AWS is a history of prior episodes of AWS/DT and/or a family history.[46] The influence of family history on the development of AWS suggests a strong role for genetic factors. Recent studies document a strong association between the A9 polymorphism of the dopamine transporter and the development of AWS/DT.[31] Whether this finding represents a predisposition to greater ethanol consumption because of an enhanced mesolimbic reward system, or some other underlying pathophysiologic effect, is unclear. Similar results are observed with the C allele of the neuropeptide Y gene.[45] Larger and more varied patient cohorts that include both women and nonwhite ethnic groups are required before any definitive conclusions can be drawn.

Because of the subjective nature of many of these findings, we discourage the use of pure clinical descriptors, such as DT, tremors, rum fits, and the like, to classify the severity of alcohol withdrawal in any given patient. Furthermore, the necessity of having a standardized means of classification has enormous implications for epidemiologic, genetic, and treatment studies. One of the more commonly used means for accurately assessing alcohol withdrawal is the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) score (Fig. 76-1).[72] This scoring system contains 10 clinical categories and requires less than 5 minutes to complete. Scoring systems are not only essential for symptom-triggered therapy, but provide a basis for comparative analysis of clinical trials in ethanol withdrawal. Greater use of CIWA-Ar or a comparable validated scale will be essential for interpretation of both genetic and treatment trials in the future.

Clinical and Biochemical Predictors

Alcohol concentrations, homocysteine concentrations, and liver function tests are often studied and loosely associated with the development of AWS, with frequently contradictory study results.[8,46] Because many studies are based on small numbers of often highly selected subjects, their generalizability is extremely poor.

Numerous attempts have been made to develop biochemical predictors for the presence and/or severity of alcohol withdrawal. Although consistent abnormalities in readily obtained laboratory values are observed in patients with AWS (eg, aminotransferases, magnesium, erythrocyte parameters), their role in predicting the severity of AWS is poorly described. In one study, an alanine aminotransferase (ALT) >50 U/L (odds ratio [OR] 9.0; 3.5â€“24), a chloride <96 mEq/L (OR 61.5; 54.4â€“69.6), and a potassium <3.6 mEq/L (OR 5.7; 2â€“16.4) were all associated with the development of alcohol withdrawal in patients admitted to a detoxification

center.[81] However, the low specificity of these derangements makes it difficult to assess their predictive value, especially when accounting for other clinical characteristics such as prior history and admission CIWA-Ar score. In addition, there is a negative association between the presence of severe alcohol withdrawal and histopathologic cirrhosis, further clouding the usefulness of routine laboratory testing for prognostication.[3]

Clinical Institute Withdrawal Assessment Of Alcohol Scale, Revised (CIWA-Ar)

Patient:_____ Date: _____Time: _____(24 hour clock, midnight = 00:00)

Pulse or heart rate, taken for one minute: _____ Blood pressure:_____

NAUSEA AND VOMITING: Ask "Do you feel sick to your stomach? Have you vomited?" Observation.
0 No nausea and no vomiting
1 Mild nausea with no vomiting
2
3
4 Intermittent nausea with dry heaves
5
6
7 Constant nausea, frequent dry heaves and vomiting

TREMOR: Arms extended and fingers spread apart. Observation.
0 No tremor
1 Not visible, but can be felt fingertip to fingertip
2
3
4 Moderate, with patient's arms extended
5
6
7 Severe, even with arms not extended

PAROXYSMAL SWEATS: Observation.
0 No sweat visible
1 Barely perceptible sweating, palms moist
2
3
4 Beads of sweat obvious on forehead
5
6
7 Drenching sweats

ANXIETY: Ask "Do you feel nervous?" Observation.
0 No anxiety, at ease
1 Mild anxious
2
3
4 Moderately anxious, or guarded, so anxiety is inferred
5
6
7 Equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions

AGITATION: Observation.
0 Normal activity
1 Somewhat more than normal activity
2
3
4 Moderately fidgety and restless
5
6
7 Paces back and forth during most of the interview, or constantly thrashes about

TACTILE DISTURBANCES: Ask "Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?" Observation. 0 none
1 Very mild itching, pins and needles, burning or numbness
2 Mild itching, pins and needles, burning or numbness
3 Moderate itching, pins and needles, burning numbness
4 Moderately severe hallucinations
5 Severe hallucinations
6 Extremely severe hallucinations
7 Continuous hallucinations

AUDITORY DISTURBANCES: Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation.
0 Not present
1 Very mild harshness or ability to frighten
2 Mild harshness or ability to frighten
3 Moderate harshness or ability to frighten
4 Moderately severe hallucinations
5 Severe hallucinations
6 Extremely severe hallucinations
7 Continuous hallucinations

VISUAL DISTURBANCES: Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation.
0 Not present
1 Very mild sensitivity
2 Mild sensitivity
3 Moderate sensitivity
4 Moderately severe hallucinations
5 Severe hallucinations
6 Extremely severe hallucinations
7 Continuous hallucinations

HEADACHE, FULLNESS IN HEAD: Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity. 0 no present
1 Very mild
2 Mild
3 Moderate
4 Moderately severe
5 Severe
6 Very severe
7 Extremely severe

ORIENTATION AND CLOUDING OF SENSORIUM: Ask "What day is this? Where are you? Who am I?"
0 Oriented and can do serial additions
1 Cannot do serial additions or is uncertain about date
2 Disoriented for date by no more than 2 calendar days
3 Disoriented for date by more than 2 calendar days
4 Disoriented for place/or person

Total CIWA-Ar Score: _____

Rater's Initials: _____

Maximum Possible score 67

Figure 76-1. Clinical Institute Withdrawal Assessment.

(Reproduced from Sullivan JT, Sykora K, Schneiderman J, et al: Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA-Ar). Br J Addict 1989;84:1353â€“1357.)

Other investigators have focused on admission ethanol concentration as a predictor for the severity of alcohol withdrawal in at risk subjects. In one study, an admission blood ethanol concentration of >150 mg/dL had a 100% sensitivity and a 57% specificity for the need of acute care for treatment of alcohol withdrawal.[79] At a different treatment facility, an ethanol concentration of >150 mg/dL had an 81% positive predictive value for the need to use more than a single dose of chlordiazepoxide for the treatment of AWS.[79] In addition, admission blood ethanol concentrations in patients with alcohol withdrawal seizures were 2-fold higher than in those without seizures, irrespective of whether or not they had a history of prior withdrawal seizures.[79] However, these results should be interpreted with caution, as other studies yield conflicting results. In one study, an admission ethanol concentration <100 gm/dL was associated with an increased risk of recurrent alcohol withdrawal seizures, and in another study, admission ethanol concentrations failed to predict the development of DT.[18,65] There are many potential explanations, including differences in patient population, differences in cohort size, and the late onset of DT, at a time when ethanol concentrations would be extremely low or nonexistent.[18]

More recently, investigators have looked at the prognostic usefulness of plasma homocysteine concentrations. Numerous reports document hyperhomocysteinemia in alcoholism, presumably caused by a deficiency of dietary folic acid.[21] Furthermore, homocysteine and its metabolites can act as excitatory neurotransmitters at the NMDA receptor and cause seizures and excitatory neuronal death.[51] In one study, plasma homocysteine concentrations were predictive of alcohol withdrawal seizures. However, in this study, there was very

strong correlation (r^2 = 0.7666; P < 0.001) between admission blood ethanol concentrations and homocysteine concentrations, raising doubts as to whether this holds any advantage over blood ethanol concentrations.[8]

Management

Alcohol Withdrawal Seizures

Alcohol withdrawal seizures are perhaps the most rigorously studied complication of AWS. Although alcohol withdrawal seizures are generally self-limited, benzodiazepines are the preferred agent for patients with persistent or recurrent alcohol withdrawal seizures. In a randomized placebo-controlled trial of 229 subjects with alcohol withdrawal seizures, 2 mg of intramuscular lorazepam reduced the risk of recurrent seizure from 24% to 3% (p < 0.001) at 6 hours, and the need for hospital admission from 42% to 29% (p = 0.0222). There is no role for phenytoin in either treatment or prevention of alcohol withdrawal seizures. In multiple trials, phenytoin was ineffective in preventing alcohol withdrawal seizure recurrence.[1,15,64] The most likely explanation for the failure of phenytoin is its inability to regulate GABA or NMDA receptors, the principle mediators of seizures in alcohol withdrawal. One exception to this lack of usefulness occurs in the alcoholic patient with a nonalcohol withdrawal-mediated seizure, or a history of underlying seizure disorders.

Alcohol Withdrawal

In the early stages of alcohol withdrawal, many patients are able to self-medicate with additional ethanol consumption. Among those who seek medical attention, many patients with AWS can be safely managed as outpatients. Outpatient management has significant cost savings with little effect on treatment outcome.[34] In one study, patients who exhibited a lack of intoxication, no history of either DT

or alcohol withdrawal seizures, no comorbid psychiatric or medical disorders, and a CIWA-Ar score of <8, were safely managed as outpatients.[2] Patients not meeting these criteria were referred to inpatient detoxification centers or medical units, depending on the severity of withdrawal and other comorbid conditions.

For all patients with AWS, the initial stages of therapy remain the same, and should include a thorough assessment to identify a coexisting medical, psychiatric, or toxicologic disorder. In particular, an assessment for central nervous system trauma and infection should include the appropriate use of computed tomography and lumbar puncture. Patients with altered cognition and an elevated body temperature should receive antibiotics, pending the results of a lumbar puncture. In concert with this approach, adequate supportive care should be instituted, including maneuvers to normalize any abnormal vital signs such as hyperthermia.

Chronic ethanol consumption leads to severe vitamin and nutritional deficiencies and electrolytes disturbances that should be corrected.[21,37] Specifically, thiamine should be given to all patients to prevent the development of Wernicke encephalopathy. It is generally suggested that thiamine should be given prior to the administration of dextrose to prevent precipitation of Wernicke encephalopathy.[55,80] Although there is little evidence for this approach, the administration of thiamine (see Antidote in Depth: Thiamine Hydrochloride) and dextrose together is a reasonable practice. In addition, there is a high incidence of intravascular volume depletion among alcoholics, so all patients should receive adequate volume resuscitation. Of 39 deaths attributed to DT in which volume status was recorded, all subjects were volume depleted.[57] Finally, for patients with AWS, particularly if severe, prevention of nosocomial complications is paramount for reducing hospital stay. Currently, in addition to adequate volume replacement, we recommend that all patients be kept with the head of the bed elevated to prevent aspiration, and that deep vein thrombosis prophylaxis be given if the patient is bed bound for an extended

period.

The association of severe alcohol withdrawal with severe psychomotor agitation led to early use of sedative hypnotics. One of the first randomized trials compared chlorpromazine to paraldehyde. In both arms there was a 0% mortality, suggesting equivalency of the 2 treatments.[28] Over the ensuing years, numerous trials documented similar efficacy between paraldehyde, benzodiazepines, and antipsychotics.[14,28,73] However, in a landmark study, 547 patients were randomized to 1 of 4 drugs (chlordiazepoxide, chlorpromazine, hydroxyzine, and thiamine) or to placebo for the treatment of alcohol withdrawal.[43] Patients receiving chlordiazepoxide had the lowest incidence of both DT and alcohol withdrawal seizures, establishing benzodiazepines as a first-line agent for treatment of AWS. Of note, use of chlorpromazine, an antipsychotic, was associated with a significant increase in the incidence of seizures in both humans and animal models.[9,43]

Since this study, numerous trials have compared different routes of administration among various sedativeâ€“hypnotic agents, both to each other and to placebo. Because of the historical use noted above, chlordiazepoxide remains widely used in outpatient and inpatient detoxification clinics. Oral benzodiazepine administration is generally effective in patients with early or mild AWS, although initial rapid titration with an intravenous regimen may be more efficient. Benzodiazepines administered intravenously have a rapid onset of action, and have long displaced paraldehyde as the preferred choice for acute control. Among the benzodiazepines, diazepam offers the most rapid time to peak clinical effects, which limits oversedation that may occur following the administration of drugs with slower onset to the peak drug effect, such as lorazepam. Because of the delayed peak clinical effect of lorazepam of approximately 10â€“20 minutes, several doses may be administered in rapid succession with little clinical effect, followed by the appearance of the sedative effect of the cumulative doses. Midazolam may be administered

intramuscularly if intravenous access is not available, but intramuscular injection delays significantly the time to both onset and peak clinical effect. Although no significant differences are observed between benzodiazepines and barbiturates in terms of mortality or the duration of delirium,[2,47] the improved pharmacokinetic profile and ease of administration favor benzodiazepines as the preferred initial agent.

Other pharmacokinetic factors and experience confirm that diazepam is the preferred agent for initial intravenous use in patients with moderate to severe AWS. Diazepam has a long half-life and has an active metabolite (desmethyldiazepam). The prolonged half life (48â€“72 hours) of desmethyldiazepam further extends the effective duration of action of the initial dose of diazepam.[87] A retrospective review reported that the use of a single benzodiazepine rather than multiple benzodiazepines was a marker for treatment success in surgical patients experiencing alcohol withdrawal during surgical admission.[60] These data suggest that it is more important to rapidly sedate the patient with adequate doses of a single benzodiazepine than to use multiple agents in hopes of finding an effective regimen. Finally, it should be noted that in patients with advanced liver disease, the use of diazepam may result in a very prolonged period of sedation because of impaired clearance of the parent compound and its metabolites. Consequently, in these patients, a benzodiazepine without active metabolites, such as lorazepam, may be a better drug.

The initial management of patients with AWS/DT should include rapid titration with intravenous benzodiazepine to achieve sedation. The goal of therapy is to have the patient sedated but breathing spontaneously, with normal vital signs. In many patients, complete sedation may allow for autotitration; that is, as the AWS resolves, the blood concentrations of diazepam and desmethyldiazepam decrease, allowing gradual recovery. In practicality, most patients need periodic redosing with diazepam to maintain adequate sedation. This is particularly important in patients with AWS with an elevated

blood alcohol concentration.

Multiple studies now suggest that if additional doses are required, they should be administered based on symptoms (â€œsymptom triggeredâ€•), as opposed to a fixed dosing schedule. In 2 randomized controlled trials, administration of benzodiazepine in a symptom-triggered fashion reduced both the total amount of benzodiazepine and the duration of treatment.[23,67] In these trials, benzodiazepines were administered every hour as long as the CIWA-Ar score remained >8â€“10. In both trials, symptom-triggered therapy resulted in a 4â€“6-fold reduction in the duration of therapy and a 4â€“5-fold reduction in the total amount of benzodiazepine administered, with no increase in withdrawal seizures or adverse events.[23,67] Symptom-triggered doses in patients with moderate or severe AWS should be diazepam 10â€“20 mg IV or lorazepam 2â€“4 mg.[55] For less-symptomatic patients, oral chlordiazepoxide 50â€“100 mg should be administered. However, it is important to note, that the decision to treat in the symptom-triggered group was made based on CIWA-Ar score (usually >8), which demonstrates the usefulness of standardized scoring and evaluation tools. Finally, it should be noted that in both of these trials, patients had very mild withdrawal symptoms, with mean CIWA-Ar scores of 9â€“11, although experience suggests that this same regimen is also effective in patients with serious withdrawal and/or DT.

Resistant Alcohol Withdrawal and Delirium Tremens

There is a subgroup of patients with AWS who require very large doses of diazepam, or another comparable drug to achieve initial sedation.[50,61,85] This same group often has exceedingly high benzodiazepine requirements to maintain this level of sedation. Subjects with resistant AWS and DT may have benzodiazepine requirements that exceed 2600 mg of diazepam within the first 24 hours, and generally require admission to an intensive care or

stepdown unit.[85] Patients admitted to the Bellevue hospital medical ICU for resistant alcohol withdrawal had very high diazepam requirements, with a mean of 234 mg (range: 10â€“1490 mg) required in the first 24 hours, and individual doses of diazepam that often exceeded 100 mg, to control their agitation. At Bellevue, these patients comprise approximately 5% of all ICU admissions, with nearly 40% of patients requiring mechanical ventilation and a mean ICU length of stay of 5.7 days.

The approach to the management of resistant AWS depends on several factors, including the availability of an intensive care unit bed. In the ICU, despite the perception of failure of high benzodiazepine requirements, we favor administration of benzodiazepines in a symptom-triggered fashion. Patients who receive this therapy generally respond to bolus doses of diazepam ranging from 10â€“100 mg, which results in a brief period of sedation followed by recrudescence of their AWS. This approach was confirmed in a study of patients who developed AWS postoperatively in the ICU.[71] In this study, a symptom-triggered strategy resulted in a shorter length of stay and a lower incidence of mechanical ventilation than did continuous infusion of midazolam.[71] In non-ICU settings, the ability to administer frequent intravenous doses of diazepam is limited, and the use intravenous infusions with secondary sedative agents may be more practical.

In instances of extreme benzodiazepine resistance, patients often receive a second GABAergic drug because of â€œfailureâ€• of benzodiazepine therapy. Phenobarbital, given in combination with benzodiazepine, in intravenous doses of 130 mg, is a reasonable choice. Caution is required to avoid stacking doses of phenobarbital, as the onset of clinical effect takes approximately 20â€“40 minutes.[35,41] Alternatively, propofol in standard doses may be administered. Although propofol has a rapid onset, it is difficult to titrate.[19,56] The main drawback to the use of these drugs is their narrow therapeuticâ€“toxic index, with the potential for profound respiratory depression. This is especially true for propofol, which

should generally only be used in the setting of mechanical ventilation. Both of these agents can act synergistically with benzodiazepines to enhance GABA-induced chloride channel opening. In

addition, propofol uniquely antagonizes NMDA receptors, thus reducing the excitatory component of AWS.

Ethanol

Ethanol consumption is a common and effective means by which alcoholics can self-medicate to treat and/or prevent mild alcohol withdrawal. However, little controlled data exist on the role of ethanol, whether oral or by infusion, for the in-hospital treatment of AWS/DT. In one trial, 39 trauma patients without liver or CNS disease were successfully treated with 10% ethanol infusion for treatment of presumed AWS.[20] Although the authors did not report any adverse effects in this trial, the necessity for frequent blood alcohol monitoring, unpredictable elimination kinetics, potential for significant hepatic complications, and the difficulty in safely administering this therapy makes it inappropriate to recommend this regimen.[25,36,55,82]

Adrenergic Antagonists

Numerous studies have investigated the use of sympatholytics to control the autonomic symptoms of alcohol withdrawal. Both Î²-adrenergic antagonists and clonidine reduced blood pressure and heart rate in randomized, placebo-controlled trials.[4,48,86] However, the inability of these agents to address the underlying pathophysiologic mechanism of AWS, and subsequently control the neurologic manifestations, makes them suboptimal as sole therapeutic agents. There are additional concerns that by altering the physiologic parameters that serve as classic markers for AWS severity, there is a risk of underadministering necessary amounts of

benzodiazepines.[86] Consequently, we do not recommend using these drugs for the treatment of alcohol withdrawal until it becomes clear that other standard therapies have failed.

Magnesium

The benefits of magnesium supplementation are based both on the high prevalence of magnesium deficiency in alcoholics and its usefulness in preventing seizures in other disorders, including eclampsia.[5,37] Furthermore, magnesium deficiency has many clinical similarities to AWS, clouding the differential diagnosis. Numerous studies have evaluated the efficacy of magnesium supplementation. However, in a randomized, placebo-controlled trial, magnesium sulfate had no effect on either severity of alcohol withdrawal or incidence of withdrawal seizures.[83] Consequently, aside from repletion of electrolyte abnormalities, there is no indication for routine administration of magnesium for the treatment of AWS.

Anticonvulsants

Carbamazepine has been used in multiple trials for treatment of mild AWS, more commonly in Europe where an intravenous preparation is available. In animal studies, carbamazepine increases both the central nervous system GABA concentrations and the seizure threshold in alcohol withdrawal.[17] In humans, carbamazepine is superior to placebo and equally efficacious as benzodiazepines for treatment of mild to moderate AWS in both inpatients and outpatients.[7,52,53] Similar data has been obtained with valproic acid, which appears to have a benzodiazepine-sparing effect in patients with mild withdrawal.[66] These drugs may be reasonably recommended as adjuncts, but should not be used as monotherapy.

Newer Agents and Future Directions

There is a constant search for newer agents to treat alcohol

withdrawal, especially for agents that target NMDA receptors. In animal studies, NMDA antagonists have shown benefit in preventing AWS seizure, neurologic damage, and alcohol craving.[6,58] In humans, one NMDA inhibitor, acamprosate, has undergone significant study in the prevention of relapse following alcohol detoxification.[16,32] Its effects on AWS are less clear, although in one study of patients capable of outpatient detoxification, it had no adverse effects on CIWA-Ar scores.[16]

Summary

Alcohol withdrawal is a complex physiologic process involving both enhanced neuronal excitation and reduced inhibition resulting in neuroexcitation. The manifestations of greatest concern are neurologic and include altered mental status and seizure, but the autonomic excess may be clinically consequential. Treatment includes supportive care and sedation with benzodiazepines. When benzodiazepines cannot produce adequate sedation, agents such as phenobarbital or propofol should be added.

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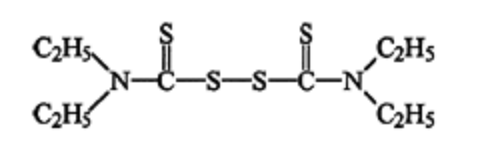
Chapter 77

Disulfiram and Disulfiramlike Reactions

Edwin K. Kuffner



Disulfiram

A 40-year-old woman with a history of depression was found unresponsive by her husband. The husband stated that the patient

had a strange garlic odor on her breath and that she had complained of exhaustion and confusion for several days. The patient's medications included paroxetine, risperidone, and trazodone. The patient also had access to a supply of nonprescription vitamins, herbal preparations, muscle liniments, and an unknown Mexican medication.

Emergency medical personnel transported the patient to the emergency department. Her vital signs were: blood pressure, 178/100 mm Hg; pulse, 56 beats/min; respiratory rate, 32 breaths/min; rectal temperature, 94.8Â°F (34.9Â°C); pulse oximetry on room air, 99%. A bedside rapid reagent blood glucose was 130 mg/dL and therefore dextrose was not administered.

The physical examination revealed an unresponsive patient with a Glasgow Coma Score (GCS) of 6. No evidence of trauma was noted. Pupils were 3 mm and sluggishly reactive to light. Cardiac, pulmonary, and abdominal examinations were unremarkable. Neurologic examination revealed flexion withdrawal to painful stimuli, areflexia, and occasional myoclonic jerks.

The patient's trachea was intubated. Fifty grams of activated charcoal was administered via a nasogastric tube. The 12-lead electrocardiogram (ECG) revealed peaked T waves but was otherwise normal. The serum electrolytes were significant for a bicarbonate of 4 mEq/L, a potassium of 6.0 mEq/L, and an anion gap of 26 mEq/L. The serum lactate was 16.9 mmol/L. Serum blood urea nitrogen (BUN), serum creatinine, and hepatic aminotransferases were normal. Serum acetaminophen, salicylate, and blood ethanol concentrations were undetectable. An arterial blood gas analysis on supplemental oxygen revealed a pH of 7.11, a PCO_2 of 6.7 mm Hg, and a PO_2 of 187 mm Hg. A complete blood count revealed a white blood cell count (WBC) of 15,600/mm^3 (89% neutrophils and 9% lymphocytes) with a normal hematocrit and platelet count. A computed tomography scan of the head, a chest radiograph, and a lumbar puncture were normal.

Blood was sent for determination of ethylene glycol and methanol concentrations and the patient was treated with 50 mg of pyridoxine and 50 mg of folinic acid intravenously. Instead of using fomepizole, which was unavailable, the patient was started on intravenous ethanol. A loading dose of 800 mg/kg of ethanol was followed by a continuous infusion to maintain the blood ethanol concentration between 100 and 120 mg/dL. Shortly after the loading dose of ethanol was administered, the patient developed generalized flushing, tachycardia with a pulse of 120 beats/min, and a systolic blood pressure of 70 mm Hg. The blood pressure did not respond to IV crystalloid, but did respond to norepinephrine. Hemodialysis was performed.

The ethylene glycol and methanol levels were eventually reported as negative. The severe metabolic acidosis was corrected with hemodialysis. Within a few hours of discontinuing the ethanol infusion, the patient's tachycardia and hypotension resolved. Within 24 hours of presentation, the patient's mental status had returned to baseline. The patient later admitted to ingesting a â€œnonprescriptionâ€• Mexican medication for alcoholism that she purchased from a Mexican pharmacist in the United States. The unknown medication was later identified as disulfiram.

A complete understanding of disulfiram toxicity is dependent on understanding the distinction between the different forms of disulfiram toxicity that are associated with acute ingestions, chronic therapy, and disulfiramâ€“ethanol reactions. The preceding case is unique in that it involves both toxicity from an acute overdose of disulfiram and toxicity from an iatrogenic disulfiramâ€“ethanol reaction. This chapter emphasizes the distinctions between these three different forms of disulfiram toxicity.

History and Epidemiology

Disulfiram, tetraethylthiuram disulfide, and related chemicals were used in the rubber industry as catalytic accelerators for the vulcanization (stabilization) of rubber by the addition of sulfur. In the early 1900s, workers exposed to disulfiram were observed to develop adverse reactions when exposed to ethanol, and this suggested that disulfiram might be a useful adjunct in the treatment of alcoholism. In the 1940s, two Danish physicians, Hald and Jacobsen, using disulfiram for its antihelmintic properties became ill after consuming alcohol.[29] Subsequently, disulfiram treatment for alcoholism gained popularity.[3] Although evidence to support the benefit of using disulfiram in a comprehensive alcohol treatment program is equivocal, disulfiram is still prescribed for this purpose today.[36]

Specific epidemiologic information about the three different forms of disulfiram toxicity is difficult to elucidate, even from an analysis of the American Association of Poison Control Centers (AAPCC) (Chap. 130).

Between 1982 and 2003 more than 10,000 patients exposed to disulfiram were reported to the AAPCC. Fewer than 200 of these patients developed major adverse effects. Unlike most xenobiotics reported to the AAPCC, the majority of the disulfiram exposures were in adults. All 12 deaths were adults and most involved a disulfiramâ€“ethanol reaction. In many of the deaths, coingestants other than disulfiram and ethanol were involved.

The best studied and the most commonly reported life-threatening adverse effect of chronic disulfiram therapy is hepatotoxicity. The frequency of disulfiram-related hepatotoxicity is also difficult to determine. As many as 25% of all alcoholics treated with disulfiram develop subclinical elevations in their hepatic aminotransferase levels, and the frequency of disulfiram-induced fatal hepatitis is estimated at 1 in 25,000â€“30,000 patients treated per year.[75]

Pharmacology and Pharmacokinetics of Therapeutic doses of Disulfiram

The effectiveness of disulfiram in discouraging alcohol consumption is aversive in nature, as it is dependent on the patient's fear of developing a disulfiramâ€“ethanol reaction. Disulfiram does not produce central nervous system effects that alter an alcoholic's drinking behavior. Therapeutic doses of disulfiram, used as part of a comprehensive alcohol treatment program, typically range from 125â€“500 mg/d.

Absorption

Disulfiram is highly lipid soluble and very insoluble in water. Following ingestion, disulfiram is either absorbed as the parent compound or converted to diethyldithiocarbamic acid (diethyldithiocarbamate) in the acid environment of the stomach.[13] Diethyldithiocarbamic acid is also very unstable in this acid environment, and either rapidly undergoes absorption and spontaneous decomposition to carbon disulfide and diethylamine, or chelates copper, forming a bis (diethyldithiocarbamate)-copper complex. The bis(diethyldithiocarbamate)-copper complex is more stable than diethyldithiocarbamic acid and also can be absorbed as it passes through the upper gastrointestinal tract. In fact, most disulfiram is absorbed from the small intestine as this bis(diethyldithiocarbamate)-copper complex. Approximately 70â€“90% of an ingested therapeutic dose of disulfiram is absorbed. The bioavailability of disulfiram varies with different preparations. In one study, the mean serum disulfiram concentration in humans following a 250-mg dose was reported to be 0.38 Â± 0.03 Âµg/mL.[22] Peak serum concentrations of disulfiram and its metabolites are achieved 8â€“10 hours following a 250-mg dose.[40]

Distribution

Approximately 96% of disulfiram itself and approximately 80% of disulfiram metabolites are protein bound.[40] Following absorption, disulfiram and its metabolites are uniformly distributed throughout body tissues. A specific volume of distribution for disulfiram is not recognized.

Metabolism

Any absorbed disulfiram is rapidly converted to diethyldithiocarbamic acid by erythrocyte glutathione reductase and endogenous thiols. Diethyldithiocarbamic acid in the blood also reversibly chelates copper, forming a bis(diethyldithiocarbamate)-copper complex. Diethyldithiocarbamic acid is metabolized by a number of different pathways, including glucuronidation, methylation, nonenzymatic degradation, and oxidation. Nonenzymatic degradation of diethyldithiocarbamic acid produces diethylamine and carbon disulfide. Carbon disulfide can be further oxidized to carbonyl sulfide, which, in turn, can be further oxidized to carbon dioxide. Phase II methylation of diethyldithiocarbamic acid, which is mediated by an S-methyltransferase, produces diethyldithiomethylcarbamic acid. Diethyldithiomethylcarbamic acid can be oxidized to diethylthiomethylcarbamic acid. Diethylthiomethylcarbamic acid is further oxidized to sulfoxide and sulfone metabolites and undergoes demethylation to form diethylthiocarbamic acid. Although diethyldithiocarbamic acid can be converted back to disulfiram, and carbon disulfide and diethylamine can be converted back to diethyldithiocarbamic acid, these reactions are not clinically significant[20] (Fig. 77-1).

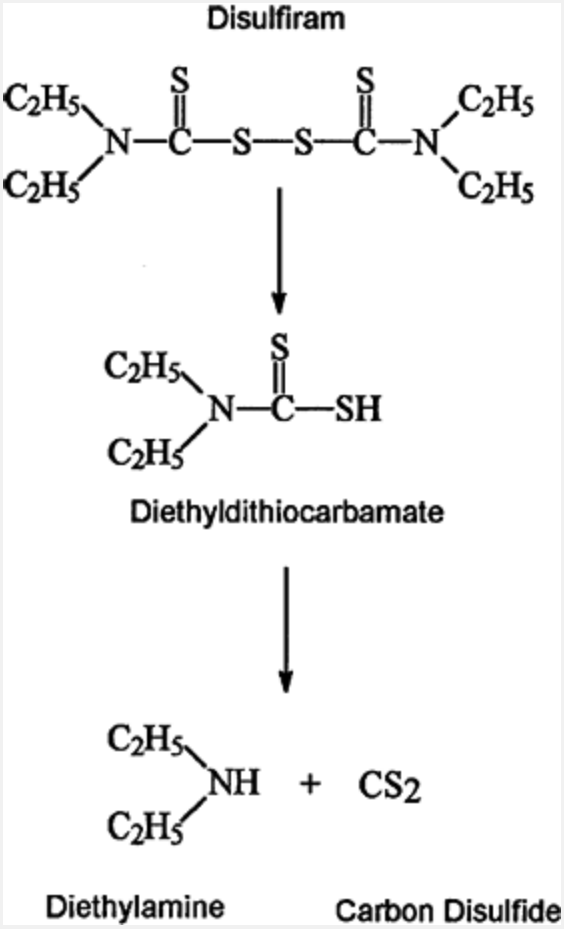


Figure 77-1. Disulfiram metabolism occurs in the liver and in the erythrocyte. The most consequential metabolites are diethyldithiocarbamate and carbon disulfide.

Elimination

Following a 250-mg dose, the half-lives of disulfiram, diethyldithiocarbamate, and carbon disulfide are 7.3 Â± 1.5 hours, 15.5 Â± 4.5 hours, and 8.9 Â± 1.4 hours, respectively. Approximately 20% of disulfiram is excreted unchanged in the

feces and another 20% or more is excreted by the lungs as carbon disulfide. The majority of disulfiram is excreted in the urine as the glucuronidated metabolite of diethyldithiocarbamic acid.[40] At 48 hours after administration of a single 250-mg dose, there is a negligible amount of disulfiram and metabolites detectable in the serum.[22,38]

Disulfiramâ€“Ethanol Reaction

Pharmacology and Pharmacokinetics of Disulfiramâ€“Ethanol Reaction

Understanding the metabolism of ethanol is critical to understanding the mechanism of action of disulfiram as it relates to the disulfiramâ€“ethanol reaction (Fig. 77-2). Disulfiram and its metabolites impair both cytosolic aldehyde dehydrogenase 1 (ALDH 1) and mitochondrial aldehyde dehydrogenase 2 (ALDH 2). The inhibition by disulfiram of ALDH 2 leads to a rise of acetaldehyde levels 5â€“10 times above baseline levels, and a few days of treatment with disulfiram can reduce baseline aldehyde dehydrogenase activity by 50%.[6] Although aldehyde dehydrogenase is present throughout the body, inhibition of hepatic mitochondrial aldehyde dehydrogenase is most important in the disulfiram-ethanol reaction.

The exact mechanism by which disulfiram and its metabolites inhibit ALDH 1 and ALDH 2 is still unclear. Disulfiram may inactivate aldehyde dehydrogenase by causing internal sulfur-sulfur bonds, or by competing for nicotinamide adenine dinucleotide.[97] The metabolites of disulfiram, including diethylthiomethylcarbamic acid and its sulfoxide and sulfone metabolites, may also inhibit aldehyde dehydrogenase.[29,40] Different metabolites may possibly inactivate different isoenzymes of aldehyde dehydrogenase. Diethylthiocarbamic acid is believed to

inactivate ALDH 2. Because aldehyde dehydrogenase inhibition is irreversible, new ALDH must be synthesized to metabolize acetaldehyde.[40] This explains why disulfiram has a longer-lasting effect than would be predicted based upon its half-life.

The duration of the inhibition of aldehyde dehydrogenase by disulfiram is partially dependent on the dose ingested and the route of administration. A 500-mg dose inhibits aldehyde dehydrogenase for up to 4 days, a 1000-mg dose for up to 6 days, and a 1500-mg dose up to 8 days.[29] There are also sustained-release and depot disulfiram preparations, but none are readily available in the United States. A patient reacted to oral ethanol 21 days following the subcutaneous injection of 2 g of disulfiram.[73] Although the severity of the disulfiramâ€“ethanol reaction following subcutaneous disulfiram dosing is reported to be less than that following oral dosing, this has not been proven.

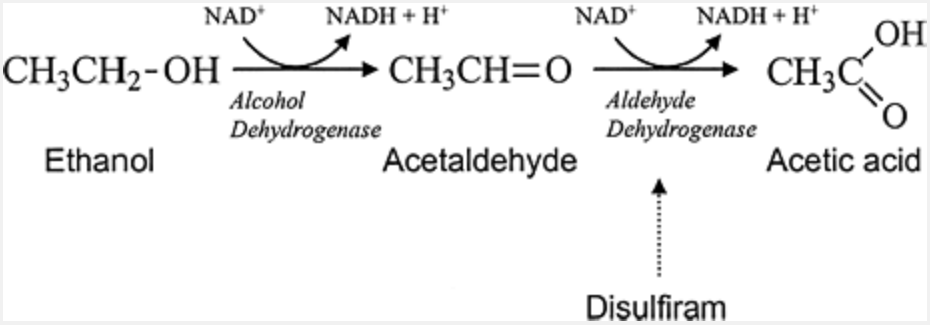


Figure 77-2. The site of action of disulfiram. The irreversible inactivation of aldehyde dehydrogenase results in an increased acetaldehyde level after ethanol is administered.

TABLE 77-1. Common Household Products that Contain Ethanol and May Cause a Disulfiramâ€“Ethanol Reaction

Adhesives
Alcohols: denatured alcohol, rubbing alcohol
Detergents
Foods: liquor-containing desserts, fermented vinegar, some sauces
Nonprescription medications: analgesics, antacids, antidiarrheals, cough and cold preparations, topical anesthetics, vitamins
Personal hygiene products: after-shave lotions, colognes, deodorants, liquid soaps, mouthwashes, perfumes, skin liniments and lotions
Solvents

The accumulation of acetaldehyde, that is normally metabolized rapidly by aldehyde dehydrogenase, is responsible for many of the symptoms produced by the disulfiramâ€“ethanol reaction. In fact, intravenous administration of acetaldehyde to humans produces symptoms similar to those experienced by patients on disulfiram who consume ethanol.[4] Acetaldehyde may increase the release of histamine, which may also be responsible for some of the effects of the disulfiramâ€“ethanol reaction.

Disulfiramâ€“ethanol reactions are reported following exposure to disulfiram by the oral and subcutaneous routes, and to ethanol by any route.[88] Disulfiramâ€“ethanol reactions may follow exposure to the ethanol contained in many products other than alcoholic beverages. Table 77-1 lists some common household products containing ethanol.

Other Enzymes Inhibited by Disulfiram

Disulfiram and its metabolites inhibit other enzymes besides aldehyde hydrogenase, especially those that contain sulfhydryl groups and metalloproteins.[67] Importantly, disulfiram inhibits dopamine Î²-hydroxylase, an enzyme necessary for norepinephrine synthesis.[27,65] The mechanism for this inhibition may be the chelation of copper by diethyldithiocarbamate, which is necessary for dopamine Î²-hydroxylase activity.[81] Disulfiram also decreases urinary concentrations of vanillylmandelic acid in humans.[32] Decreased norepinephrine in the presence of acetaldehyde, a potential vasodilator, may account for the hypotension associated with the disulfiramâ€“ethanol reaction. Increased concentrations of dopamine, as a consequence of dopamine Î²-hydroxylase inhibition, may also explain the psychiatric effects following both acute disulfiram overdose and chronic disulfiram therapy. Although it has been theorized that some of the neurologic effects following both acute disulfiram overdose and chronic disulfiram therapy may be related to the metabolite carbon disulfide, this has not been confirmed in a well-controlled trial.[76]

Disulfiram and the Cytochrome P450 System

Disulfiram and its metabolites are inhibitors of cytochrome P450 (CYP) 2E1.[42] Single doses of disulfiram administered to healthy humans result in 50% inhibition of baseline CYP2E1 activity for at least 3 days, with some inhibition for longer than 1 week.[19,21] Although animal studies suggest that disulfiram alters acetaminophen metabolism, a human study found that disulfiram did not

significantly alter the metabolism of a therapeutic dose of acetaminophen, in either healthy patients or in patients with

alcoholic liver disease.[74] Disulfiram may be an inducer of CYP2B1 and CYP2A1, but it does not appear to affect CYP2C9, CYP2C19, CYP2D6, or CYP3A4 activity.[40,42] Disulfiram inhibits the metabolism and/or decreases the clearance of phenytoin, theophylline and warfarin.[55,67,69,82] The effects of disulfiram on the CYP system may be both dose and time dependent.

Disulfiramâ€“Xenobiotic Interactions

Disulfiram may decrease the clearance of benzodiazepines (chlordiazepoxide, diazepam, and oxazepam),[56] caffeine, phenytoin,[93] theophylline,[14] and some tricyclic antidepressants (desipramine and imipramine).[16] Disulfiram can increase the prothrombin time (international normalized ratio) in patients taking warfarin.[69] Combined therapy of disulfiram with omeprazole can cause catatonia.[28] Isoniazid and metronidazole may potentiate the neuropsychiatric effects of disulfiram, producing confusion and psychosis.[83,100] Patients taking disulfiram therapeutically may develop hypotension following the administration of anesthetic agents.[18] There is a theoretical concern that disulfiram may decrease the metabolism of propylene glycol found in many liquid and parenteral drug formulations, but specific cases of toxicity have not been reported. Although animal studies suggest that disulfiram may increase the carcinogenicity of ethylene dibromide, this has not been substantiated in humans.[103]

Use of Disulfiram as an Antidote

Case reports suggest that disulfiram may be useful for the treatment of nickel dermatitis.[15,41] However, a small double-blind, placebo-controlled study of patients with hand eczema and nickel allergy did not find a clinically significant difference between those treated with disulfiram and those treated with placebo.[41] Because the conditions of some patients have worsened with this therapy,[45] and because some patients treated for nickel dermatitis

have developed disulfiram-induced hepatitis, this therapy is not generally indicated.

Diethyldithiocarbamate, a disulfiram metabolite, is available as the chelator ditiocarb. Although animal data and human case series suggest that diethyldithiocarbamate may be an effective chelator for the treatment of nickel-carbonyl poisoning, no well-controlled human trial has evaluated this therapy. Because disulfiram increases nickel absorption in humans, it is prudent to only use diethyldithiocarbamate in the treatment of nickel-carbonyl poisoning and not for the treatment of elemental or inorganic nickel poisoning.[11,8]

Clinical Manifestations

Most patients taking disulfiram who are exposed to ethanol develop symptoms of the disulfiramâ€“ethanol reaction within 15 minutes. The symptoms usually peak within 30 minutes to 1 hour, and then gradually subside over the next few hours.

Signs and symptoms of a disulfiramâ€“ethanol reaction include facial and generalized body warmth and flushing, conjunctival injection, pruritus, urticaria, diaphoresis, lightheadedness, vertigo, headache, nausea, vomiting, and abdominal pain. Cardiac effects include palpitations, chest pain, and dyspnea. Tachycardia and hypotension, including orthostatic hypotension, are common. Rare complications include shock, myocardial ischemia,[62] hypertension, bronchospasm, and methemoglobinemia.[104] Esophageal rupture and intracranial hemorrhage, secondary to profound vomiting, may occur.[23,64,92,104] Deaths attributed to the disulfiram-ethanol reaction occur but are rare.[5,39,64] There is significant interindividual and intraindividual variation in the intensity and duration of a disulfiramâ€“ethanol reaction.

TABLE 77-2. Xenobiotics Reported to Cause a Disulfiramlike Reaction with Ethanol

Antimicrobials
- Cephalosporins, especially those that contain a methylthiotetrazole (MTT) side chain, such as cefotetan, cefoperazone, cefamandole, and cefmenoxime.
- Metronidazole
- Moxalactam
- Trimethoprim-sulfamethoxazole

Possible reactions with chloramphenicol, griseofulvin, quinacrine, procarbazine, phentolamine, nitrofurantoin

Sulfonylurea oral hypoglycemics
- Chlorpropamide
- Tolbutamide

Chemicals
- Calcium carbimide (citrated)
- Carbon disulfide
- Carbon tetrachloride
- Chloral hydrate
- Dimethylformamide
- Nitrefazole
- Tetraethylthiuram disulfide (disulfiram)
- Tetramethylthiuram disulfide (thiram)
- Thiram analogs (fungicides)
  - Copper, mercuric, and sodium diethyldithiocarbamate
  - Zinc and ferric dimethyldithiocarbamate
  - Zinc and disodium ethylenebis [dithiocarbamate]
- Trichloroethylene

Mushrooms
- *Coprinus* mushrooms including *C. atramentarius, C. insignis, C. variegatus*, and *C. quadrifidus, Boletus luridus, Clitocybe clavipes, Polyporus sulphureus, Pholiota*

squarosa, Tricholoma aurantum, and *Verpa bohemica*

Disulfiramâ€“Ethanollike Reactions

The term *disulfiramlike reaction* is commonly used to describe a presentation similar to the typical disulfiramâ€“ethanol reaction when the patient has not been exposed to both disulfiram and ethanol. Most disulfiramlike reactions involve an exposure to ethanol.[30,51,53,101]

Ingestion of ethanol following ingestion of various *Coprinus* species of mushrooms can cause symptoms of a disulfiramâ€“ethanol reaction (Chap. 113).[80,89]

Many xenobiotics in combination with ethanol also produce symptoms of the disulfiramâ€“ethanol reaction (Table 77-2). Alcohols other than ethanol and organic solvents, including mineral spirits, can also cause symptoms of a disulfiramâ€“ethanol reaction.[87]

Management of Disulfiramâ€“Ethanol Reactions

For most patients experiencing suspected disulfiramâ€“ethanol reactions, it is frequently useful to confirm the presence of ethanol,

either with an exhaled ethanol concentration or by obtaining a blood ethanol concentration. Because only small amounts of ethanol can precipitate a disulfiramâ€“ethanol reaction, some patients, especially those with small ingestions or dermal exposures, may still manifest reactions in the absence of detectable ethanol concentrations at the time of evaluation. Elevated acetaldehyde concentrations in the blood will occur

during a disulfiramâ€“ethanol reaction, but acetaldehyde concentrations are not readily available, and thus are not clinically useful in managing most patients.[31]

Symptomatic and supportive care is the mainstay of treatment. Gastrointestinal decontamination aimed at removing ethanol is unlikely to have any clinically significant effect on limiting the severity or duration of the disulfiramâ€“ethanol reaction, because even small amounts of ethanol can cause toxicity in the presence of disulfiram. Additionally, because nausea and vomiting are common, patients often experience spontaneous gastric emptying. Antiemetics may improve nausea and vomiting, and histamine (H_1) receptor antagonists, such as diphenhydramine, may lesson cutaneous flushing.[91] Most patients with hypotension respond to intravenous crystalloid administration. Symptomatic hypotension refractory to these measures rarely occurs. If hypotension is refractory to crystalloid administration, a vasopressor should be administered. There is a theoretical benefit to administering a direct-acting vasopressor such as norepinephrine, because disulfiram inhibits dopamine Î²-hydroxylase, an enzyme necessary for norepinephrine synthesis. Indirect-acting vasopressors, such as dopamine, that require functioning dopamine Î²-hydroxylase to create a releasable pool of norepinephrine, may be less effective in the setting of disulfiram toxicity. Patients with cardiovascular instability should have an electrocardiogram performed.[62] Most patients with a typical disulfiram-ethanol reaction who have normal vital signs can be safely discharged following resolution of symptoms. More prolonged observation is essential for patients with persistent symptoms, ECG abnormalities, or any potentially life-threatening effect.

Fomepizole, an inhibitor of alcohol dehydrogenase, prevents the metabolism of ethanol to acetaldehyde.[10] Theoretically, by preventing the production of acetaldehyde, fomepizole could limit the effects of the disulfiramâ€“ethanol reaction. A patient on disulfiram experiencing a disulfiramâ€“ethanol reaction was given

fomepizole experimentally, with an almost immediate decrease in the serum acetaldehyde concentration, and a rapid clinical improvement.[54] Fomepizole normalized blood acetaldehyde concentrations and relieved the symptoms of the disulfiramâ€“ethanol reaction in 4 volunteers given calcium carbimide and ethanol.[54] Fomepizole should be considered for patients with life-threatening signs or symptoms of a disulfiramâ€“ethanol reaction who are unresponsive to standard treatment (see Antidotes In Depth: Fomepizole).

Clinical Manifestations

Acute Disulfiram Overdose

Acute overdose of disulfiram is uncommon and typically does not cause life-threatening toxicity. Most patients will develop symptoms within the first 12 hours following ingestion, with resolution of symptoms within 24 hours of ingestion.[79]

Nausea, vomiting, and abdominal pain are common. A spectrum of central nervous system depressionâ€”from drowsiness to comaâ€”may occur.[79] Metabolic acidosis is rare.[57] Dysarthria and movement disorders, including myoclonus, ataxia, dystonia, and akinesia, occur rarely. The movement disorders may be related to direct effects on the basal ganglia.[50,52,57] Sensorimotor neuropathy, subacute weakness, and psychosis are uncommon.[34,44,84,105] Hypotonia may be a prominent feature in children.[6] Persistent neurologic abnormalities, lasting for weeks to months, are reported in both children and adults, but are rare.[11,57,79]

Chronic Disulfiram Therapy

Most of the known adverse effects are derived from case reports. Despite the widespread international use of disulfiram, there are

few well-controlled human trials evaluating chronic disulfiram toxicity. Toxicity from chronic disulfiram therapy correlates poorly with dose, and there is a wide variability in latency period between the time therapeutic dosing is initiated and when symptoms develop. Side effects of chronic disulfiram therapy, unsurprisingly, occur most commonly in alcoholic patients.

Adverse effects most typically involve the liver, the skin, or the central nervous system. Common effects include nausea, drowsiness, dizziness, headache, a metallic taste in the mouth, halitosis, and skin odor described as having a sulfur or garlic smell, decreased libido, impotence, and hypertension.[32,58,98]

Disulfiram therapy causes a spectrum of hepatotoxicity ranging from asymptomatic minor elevations of the aminotransferase levels, to fulminant hepatic failure and death. The hepatotoxicity is clinically indistinguishable from alcoholic hepatitis. The mechanism of disulfiram-induced hepatotoxicity is poorly understood and may be idiosyncratic. Injury may be caused by a hypersensitivity reaction or by direct hepatotoxicity related to a metabolite, or to an immunologic reaction.[25] Histologic patterns of toxicity are predominantly hepatocellular, specifically centrilobular in nature.[8] The onset of hepatotoxicity usually varies from 2 weeks to 6 months after initiation of disulfiram therapy.[8] Although disulfiram-induced hepatotoxicity may be exacerbated by concurrent alcohol consumption, nonalcoholic patients taking disulfiram as a treatment for nickel dermatitis also developed hepatotoxicity.[37,52,43] Elevated aminotransferases are a relative contraindication to disulfiram therapy. They cannot be used to confidently predict which patients will develop disulfiram-induced hepatotoxicity.[86] Dermatoses associated with disulfiram therapy include exfoliative dermatitis, contact dermatitis, urticaria, pruritus, acne, and yellow palms.[59,85] Interestingly, thiram and its analogs, which are found in rubber, are also potent skin sensitizers.[89] Some patients with rubber sensitivity develop localized and generalized dermatitis following ingestion of

disulfiram, whereas other patients can be treated with disulfiram without dermatologic complications.[68,99,101] Disulfiram can also cause exacerbations of nickel and cobalt dermatitis.[45,63] Disulfiram may exacerbate nickel dermatitis because diethyldithiocarbamate complexes with nickel and increases its absorption.[35]

Reported neuropsychiatric side effects include headache, dizziness, confusion,[77] memory impairment,[58] ataxia, parkinsonian symptoms,[52] seizures,[17] optic neuropathy,[1] coma,[58] peripheral neuropathy, psychosis,[7,32] depression, catatonia,[24] and organic brain syndrome.[48,84] Confusion, memory impairment, peripheral neuropathy, and psychiatric diagnoses are common in alcoholic patients who are not taking disulfiram. Alcohol-induced and disulfiram-induced peripheral neuropathy are difficult to distinguish clinically. Disulfiram-induced peripheral neuropathy usually involves motor nerves more than sensory and autonomic nerves, is worse distally, and is usually bilateral. A small prospective study of alcoholics taking therapeutic doses of disulfiram did reveal abnormalities of peripheral

nerve function.[70] Neurologic symptoms may be related to both dose and duration of therapy, but these issues are not well studied.[21] Although case reports suggest an increased incidence of psychiatric complications, one prospective randomized study did not find an increased incidence of psychiatric complications in alcoholic patients taking disulfiram.[12]

Disulfiram therapy may result in increases in serum cholesterol.[60] Although patients with occupational exposures to carbon disulfide, a metabolite of disulfiram, have an increased risk of atherosclerosis and ischemic heart disease, this has not been proven for patients taking disulfiram. One case report suggests that disulfiram may cause thrombocytopenia.[95] Disulfiram is not believed to be teratogenic or carcinogenic.

Diagnostic Testing

Disulfiram serum concentrations are not useful when managing most patients with suspected disulfiram toxicity following an acute overdose, chronic therapy, or a disulfiramâ€“ethanol reaction. When interpreting a disulfiram serum concentration, it is important to note that because of rapid metabolism, only a small proportion of ingested disulfiram appears in the blood as the parent compound. Metabolites of disulfiram, including diethyldithiomethylcarbamic acid and diethylthiomethylcarbamic acid, can also be measured in the serum. Other markers of ingestion of disulfiram include carbon disulfide on the breath and diethylamine in the urine. The activity of hepatic mitochondrial aldehyde dehydrogenase can be determined by liver biopsy, but this is impractical and dangerous. Leukocyte aldehyde dehydrogenase activity correlates most closely with hepatic mitochondrial aldehyde dehydrogenase activity. Decreased erythrocyte ALDH 1 activity and leukocyte ALDH 2 activity are markers of disulfiram exposure, although neither enzyme assay is commonly available.

Chronic Disulfiram Therapy

Monitoring aminotransferase levels, both before the initiation of therapy to establish a baseline and during the course of therapy, is recommended. Unfortunately, no well-controlled trial has specifically addressed the issue of the timing or frequency of routine aminotransferase monitoring. There is indirect evidence that continued use of disulfiram in the face of elevated aminotransferase levels increases the risk of developing life-threatening hepatotoxicity.[25] If an alcoholic patient has increased aminotransferase concentrations from chronic alcohol use, it is appropriate to delay the administration of disulfiram until the aminotransferase concentrations have normalized, as it is never obligatory to emergently initiate therapy. Common, but not

uniform, recommendations for asymptomatic patients include monitoring aminotransferases at 2 weeks following initiation of disulfiram therapy, and at 3â€“6 months intervals thereafter, or as needed.[102] Unfortunately, even conservative monitoring regimens may fail to detect patients who develop hepatitis during the testing intervals, so clinicians should educate patients about the signs and symptoms of hepatitis.

As a method of determining compliance with chronic disulfiram therapy, some authors have advocated using ethanol patch testing to produce cutaneous vasodilation. Studies demonstrate that patch testing is not a reliable measure of compliance with disulfiram therapy. Measuring leukocyte aldehyde dehydrogenase activity, or serum concentrations of disulfiram and/or its metabolites, are better measures of compliance with disulfiram therapy.

Management of Disulfiram Toxicity

Acute Disulfiram Overdose

Symptomatic and supportive care is the mainstay of treatment. There is no antidote for disulfiram toxicity. No studies have specifically addressed gastrointestinal decontamination in the setting of an acute disulfiram overdose. Unless otherwise contraindicated, activated charcoal, 1 g/kg of body weight, should be administered. It would be unusual for a patient with an isolated disulfiram ingestion to require either orogastric lavage or whole-bowel irrigation. Emesis is not indicated, especially because some emetics contain ethanol, which could precipitate a disulfiramâ€“ethanol reaction.

Chronic Disulfiram Toxicity

If a patient on chronic disulfiram therapy develops hepatotoxicity related to disulfiram, the drug should be discontinued. In addition,

patients should be instructed to have their aminotransferase concentrations measured if they develop any signs or symptoms of hepatitis, including anorexia, nausea, vomiting, abdominal pain, generalized weakness, malaise, fever, pruritus, scleral icterus, or jaundice.

If aminotransferase concentrations rise during disulfiram therapy, the drug should be discontinued. Although in some cases rechallenge with disulfiram can confirm the role of disulfiram in causing hepatotoxicity, the benefit is not substantial enough to outweigh the risk.[8] Because the evidence to support the use of disulfiram therapy as part of a comprehensive alcohol treatment program is equivocal using the standards of evidence-based medicine, the risks of continuing disulfiram therapy usually outweigh the benefits. Following discontinuation of disulfiram therapy, hepatic aminotransferase levels usually return to baseline values. Rarely, patients may develop fulminant hepatic failure. Supportive care is the mainstay of treatment for disulfiram-induced hepatic failure. Liver transplantation has been successfully performed for disulfiram-induced hepatic failure.[75]

Summary

Because disulfiram is still used in comprehensive alcohol treatment programs, it is critical to understand the distinction between the different forms of disulfiram toxicity, including toxicity from an acute overdose, from chronic therapy, and from a disulfiramâ€“ethanol reaction. Disulfiram toxicity following an acute overdose is unlikely to be life-threatening unless a massive amount is ingested, an event that usually only occurs in suicidal adults. Although death is reported following disulfiramâ€“ethanol reactions, most patients do not develop life-threatening toxicity. With the recent widespread availability of fomepizole, its role in treating life-threatening disulfiramâ€“ethanol reactions requires further study. The most common adverse effects of disulfiram that

most clinicians, including toxicologists, encounter are secondary to chronic disulfiram therapy. These adverse effects on the liver and the central and peripheral nervous systems are often difficult to distinguish from the effects of chronic alcohol abuse. The effects, including life-threatening disulfiram-induced hepatotoxicity, are rare, and may be limited by closely monitoring patients prescribed disulfiram and by discontinuing disulfiram therapy as soon as any evidence of toxicity develops.

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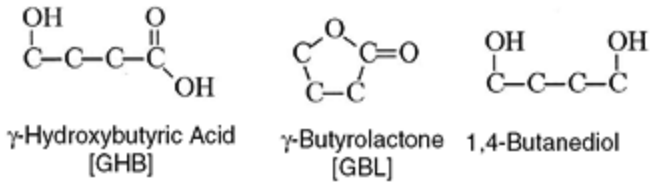
Chapter 78
Î³-Hydroxybutyric Acid

Lawrence S. Quang



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An ambulance was called to provide assistance for a comatose 17-year-old student in a college campus dormitory. The paramedics found the patient completely unresponsive, hypoventilating (4 breaths/min), and lying in a pool of urine and feces. Earlier that same evening the patient had attended a dormitory party where, reportedly, there was â€œheavyâ€• alcohol and â€œliquid Eâ€• consumption.

Physical examination in the emergency department, revealed a minimally responsive young man with the following vital signs: blood pressure, 98/40 mm Hg; pulse, 43 beats/min; respirations, 4 breaths/min; rectal temperature, 95.9Â°F (35.5Â°C). Miosis and intermittent myoclonic

movements of his extremities were also noted. The patient was ventilated by bag-valve-mask. While preparations were made to perform endotracheal intubation, naloxone 0.4 mg IV was administered without effect. The patient was subsequently intubated uneventfully. An electrocardiogram (ECG) demonstrated sinus bradycardia with prominent U waves, and a basic metabolic panel, and serum and urine toxicology screens were unremarkable.

The patient was admitted to the pediatric intensive care unit where he required mechanical ventilation for 4 hours before being extubated. On recovery he admitted to his first experimentation with Î³-hydroxybutyric acid.

Since its scientific discovery as a Î³-aminobutyric acid (GABA) mimetic neurochemical, gamma-hydroxybutyric acid (GHB) has been transformed from an investigational drug with legitimate research applications and lici medical uses to the toxic ingredient in banned nutritional supplements and illicit recreational drugs. GHB and its numerous chemical precursors and structural analogs, most notably Î³-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), represent an emerging group of drugs among the broad class of recreational drugs known as â€œclub drugs.â€• Like most other â€œclub drugs,â€• GHB, GBL, and 1,4-BD are physically and psychologically addictive with acute and chronic toxicity that may be severe or lethal.

GHB, GBL, and 1,4-BD are consumed by a diverse population of acute and chronic abusers, who have misused them as sports supplements with touted anabolic effects; as dietary health supplements, with numerous unsubstantiated â€œnatural health benefitsâ€•, such as sleep and sexua enhancement; or as recreational drugs, with purported euphoriant and psychedelic effects. Despite a federal proscription on GHB since 1990, state and federal legislative efforts to regulate and curb GHB abuse have proven to be more difficult to effect than with other â€œclub drugsâ€• because of the lawful availability of GHB chemical precursors, which are widely used by industry (GBL and 1,4-BD), and because of the unabating supply of alternative GHB analogs that include such drugs as Î³-

valerolactone (GVL), Î³-hydroxyvaleric acid (GHV), and tetrahydrofuran (THF). Perhaps more than any other contemporary drug of abuse, GHB and its analogs heralded the age of electronic drug trafficking, as purveyors exploited the Internet to popularize, market, and distribute GHB and its analogs. Recently, there has been a conspicuous increase in case reports of GHB, GBL, and 1,4-BD use leading to a severe, potentially life-threatening withdrawal syndrome, a clinical feature of toxicity that has not been described with other â€œclub drugs.â€• With the notable exception of ketamine, GHB is one of the only â€œclub drugsâ€• that ha licit medical uses, having recently received approval from the US Food and Drug Administration (FDA) as a therapy for narcolepsy.

History

Before their recent emergence as popular recreational drugs, GHB, GBL, and 1,4-BD had a relatively quiescent history of medical research and lici therapeutic use that spanned more than 6 decades. The toxic effects of GBL were first reported in 1947, when it was noted to completely suppress cortical electroencephalographic

(EEG) activity and cause death from respiratory failure.[35] Simultaneously it was demonstrated that sublethal doses of GBL produced a reversible inhibition of voluntary movements in mice and chickens.

GHB was subsequently discovered in 1960, when it was synthesized as a structural analog of the inhibitory neurotransmitter, GABA, and found to be capable of traversing the bloodâ€“brain barrier after peripheral administration.[53 , 54 , 55] Three years later, GHB was determined to be a naturally occurring neurochemical in the mammalian brain.[5 , 6] In 1966, the first association of the effects of 1,4-BD with GHB were made. Noting the close structural similarity of 1,4-BD with GHB, researchers demonstrated that 1,4-BD could produce an anesthetic response similar t GHB and GBL. In rodents, GHB, GBL, and 1,4-BD all produce anesthesia that is characterized by the loss of voluntary movement, righting reflex, struggle response, and body and limb tone, as well as myoclonic jerking.

EEG tracings of animals treated with GHB, GBL, or 1,4-BD have very similar wave patterns.[95]

As a result of these discoveries, GHB found its first clinical application as an anesthetic in the early 1960s.[53, 54, 55] Several studies in the 1960s, involving a total of 376 patients, confirmed the potential of GHB to serve as an adjuvant to anesthesia.[7, 94] However, those same studies also documented adverse effects, including the occurrence of gross muscular movements when rapidly administered,[7] as well as inadequate analgesia (abrupt rise in systolic and diastolic pressure during surgical incision), emergence delirium, and bradycardia.[94] Although GHB continues to be investigated and used as an anesthetic adjuvant abroad,[50, 51, 52] it has never gained widespread acceptance in the United States for this clinical application.

An important research milestone in GHB history was reached in 1977, when it was reported that GHB use resulted in a significant increase in plasma growth hormone and rapid eye movement sleep in 6 healthy male human subjects.[98] This discovery launched concerted efforts to study and develop GHB as a potential therapeutic agent for sleep disorders such as narcolepsy. However, as an unintended and misappropriated consequence of this and similar studies, GHB became popular as a sports supplement and â€œnaturalâ€• soporific. Subsequently, in the late 1980s, GHB was introduced to the health and dietary supplement market with dubious claims that it could metabolize fat, enhance muscle building, and improve sleep. However, it was quickly associated with severe adverse effects and deaths.[11, 23] Accordingly, the FDA intervened in November 1990 to prohibit further nonprescription sales of GHB in nutritional supplements.[3, 33]

Despite the known dangers from overdoses and FDA regulations, GHB became fashionable and trendy as a recreational drug during the 1990s, as reports of its â€œnaturalâ€• euphoric and hallucinogenic properties popularized its misuse at â€œdance ravesâ€• and nightclubs. The rapid expansion of the Internet during the 1990s helped to fuel the emergence of GHB as a widespread recreational drug. The Internet allowed GHB

purveyors to circumvent the FDA ban on nonprescription sale of GHB-containing products by shifting their distribution from over-the-counter sales to online sales. This FDA ban was further circumvented by substitution of GBL for GHB as the active ingredient in dietary supplements. Soon after its substitution into dietary health supplements, toxic effects similar to GHB, including deaths, were attributed to GBL.[10, 45, 60, 82] Consequently, the FDA issued a voluntary recall of GBL-containing health supplements in February 1999.[31] As was the case with the initial recall of GHB, purveyors of GBL-containing dietary health supplements willingly complied with the FDA order because of the availability of yet another GHB precursor, 1,4-BD. Predictably, the consequences of 1,4-BD misuse and abuse including death were clinically similar to that of GHB and GBL.[14, 24, 87, 90, 110]

In the midst of its emergence as an illicit drug, GHB received both orphan drug and investigational new drug (IND) status from the FDA for clinical trials as a therapeutic drug for narcolepsy. Confounding and nearly preventing its clinical development as a narcolepsy treatment, GHB also developed forensic notoriety as a chemical submission agent used in the commission of drug-facilitated sexual assault. After several highly publicized GHB-related â€œdate rapeâ€• deaths, a federal statute gave GHB dual status as a Schedule III drug for IND use in clinical trials for narcolepsy, and as a Schedule I drug for illicit purposes.[20] Authority was also granted to federal law enforcement agencies to monitor the commercial and industrial sale and distribution of GBL for potential diversionary activity.[19] In response to several deaths in 1999, 1,4-BD was classified by the FDA as a Class I Health Hazard.[31] This FDA categorization recognizes 1,4-BD to be a potentially life-threatening health hazard but does not impose any regulatory actions on its commercial sale or distribution. The current legal status of GHB under federal law has rendered GHB more difficult to obtain, and subsequently increased trafficking and abuse of its chemical precursors and structural analogs.

Epidemiology

Illicit use of GHB and its analogs have primarily occurred in 1 of 4 settings: in the recreational setting of raves or night clubs; in the athletic setting of bodybuilding gyms and fitness centers; in the home consumer setting of individuals seeking its â€œnatural health benefitsâ€•; and in the criminal setting of drug-facilitated sexual assault. Products containing GHB, GBL, or 1,4-BD marketed for these purposes are generally no longer sold because of law enforcement pressure; however, comparable products with similar brand names are available.[31 , 32]

National statistics demonstrate a trend of escalating GHB abuse and poisoning throughout the last decade. In 2002, there were 1386 exposures with GHB and its analogs and precursors reported to the American Association of Poison Control Centersâ€“Toxic Exposure Surveillance System, representing more than a 2-fold increase from approximately 600 GHB cases reported in 1996. Among these, 1181 exposures (85%) required treatment in a healthcare facility and resulted in 272 major outcomes and 3 deaths (Chap. 130).[108] Eighty-five percent of these exposures involved individuals older than age 19 years. According to the Drug Abuse Warning Network, emergency department (ED) mentions related to GHB increased significantly from 1994â€“1999, and GHB mentions increased dramatically from 1997â€“2000.[96] Almost half (46%) of these ED mentions of GHB were attributed to patients age 20 to 25 years, nearly 90% were white, and two-thirds were male. Seventy-four percent of ED visits for GHB toxicity involved another club drug. Alcohol was the most frequently mentioned coingestant in visits with GHB (54%), followed by marijuana (14%) and 3,4-methylenedioxymethamphetamine (ecstasy, 12%). Although most GHB abusers are young adults, adolescents have also abused GHB, and the 2002 â€œMonitoring the Futureâ€• study reported an annual prevalence rate of GHB use of 0.8%, 1.4%, and 1.5% in grades 8, 10, and 12, respectively.[48]

While the illicit use of GHB and its precursors appears to have reached a

plateau in the United States, recent worldwide statistics have reported GHB abuse to be on the rise internationally. For example, in Spain, GHB was responsible for 3.1% of all toxicologic emergencies in an urban publi hospital ED during a 15-month study period, and ranked second in illicit drugs requiring emergency consultation.[72] While European and Asian countries have reported recent rises in acute poisonings from GHB and its chemical precursors and structural analogues, virtually all of the reports of GHB dependence and withdrawal have been from the United States.

Pharmacology

GHB has a dual pharmacologic profile, with the intrinsic neuropharmacology of endogenous GHB being distinct and divergent from that of exogenously administered GHB. The principal difference between their profiles is that the intrinsic neuropharmacologic activity of endogenous GHB appears to be mediated by the GHB receptor, whereas the neuropharmacologic activity of exogenously administered GHB is likel mediated by the $GABA_B$ receptor.

Endogenous GHB

Although the precise physiologic function of endogenous GHB is unknown GHB is a putative neurotransmitter or neuromodulator because it possesses the requisite pharmacologic properties for recognition as such. That is, (a) it has a discrete regional and subcellular distribution in the CNS; (b) it has subcellular systems for synthesis, vesicular uptake, and storage in presynaptic terminals; (c) it is released in a Ca^{2+} -dependent manner following depolarization of neurons; (d) subsequent to neuronal release, GHB binds to GHB-specific receptors and modulates neurotransmitter systems; (e) following neuronal release, GHB activity is terminated by active uptake from the synaptic cleft for metabolism by specific cytosolic and mitochondrial enzymes; and (f) localized applicatior of GHB can produce a response that mimics the action of endogenous GH released by nerve stimulation.

Although GHB is heterogeneously distributed throughout the mammalian CNS, its highest concentrations are found in the hippocampus, basal ganglia, hypothalamus, striatum, and substantia nigra.[64, 66, 103] As shown in Figure 78-1, the subcellular presynaptic synthesis of endogenous GHB involves 3 precursors (GABA, GBL, and 1,4-BD) and 5 enzymes (GABA-transaminase, succinic semialdehyde reductase [SSA reductase], alcohol dehydrogenase [ADH], aldehyde dehydrogenase [ALDH], and serum and peripheral tissue lactonases). The extracellular release of GHB from presynaptic GHB terminals occurs by neuronal depolarization in a Ca^{2+} -dependent manner.[61, 62]

In the early 1980s, three independent studies collectively proposed the existence of a putative GHB-specific receptor.[4, 63, 93] Although the existence of a GHB-specific receptor has been speculated and disputed fo some time, its existence was recently verified by the cloning of a G-proteinâ€“coupled receptor in the rat that is activated by endogenous GHB.[1] This newly cloned receptor exhibits no binding affinity for GABA, baclofen, or glutamate, which have no capacity to displace radioactive GHB from this binding site. In fact, a family of GHB receptors in the brair is now identified.

Activation of the GHB receptor alters second-messenger systems in the hippocampus by increasing cyclic guanosine monophosphate (cGMP) turnover and stimulating inositol phosphate turnover, which subsequently modulate the activity of other neurotransmitter systems.[104] From a toxicologic perspective, perhaps the most important neurotransmitter system altered by GHB binding is the GABA system at the $GABA_B$ receptor. Low-dose GHB inhibits GABA release in the thalamus, which ma implicate a role for GHB in producing absence seizures,[2] and decreases the extracellular GABA concentration in the frontal cortex.[37] However, higher doses of GHB enhance GABA concentrations in the frontal cortex.[3]

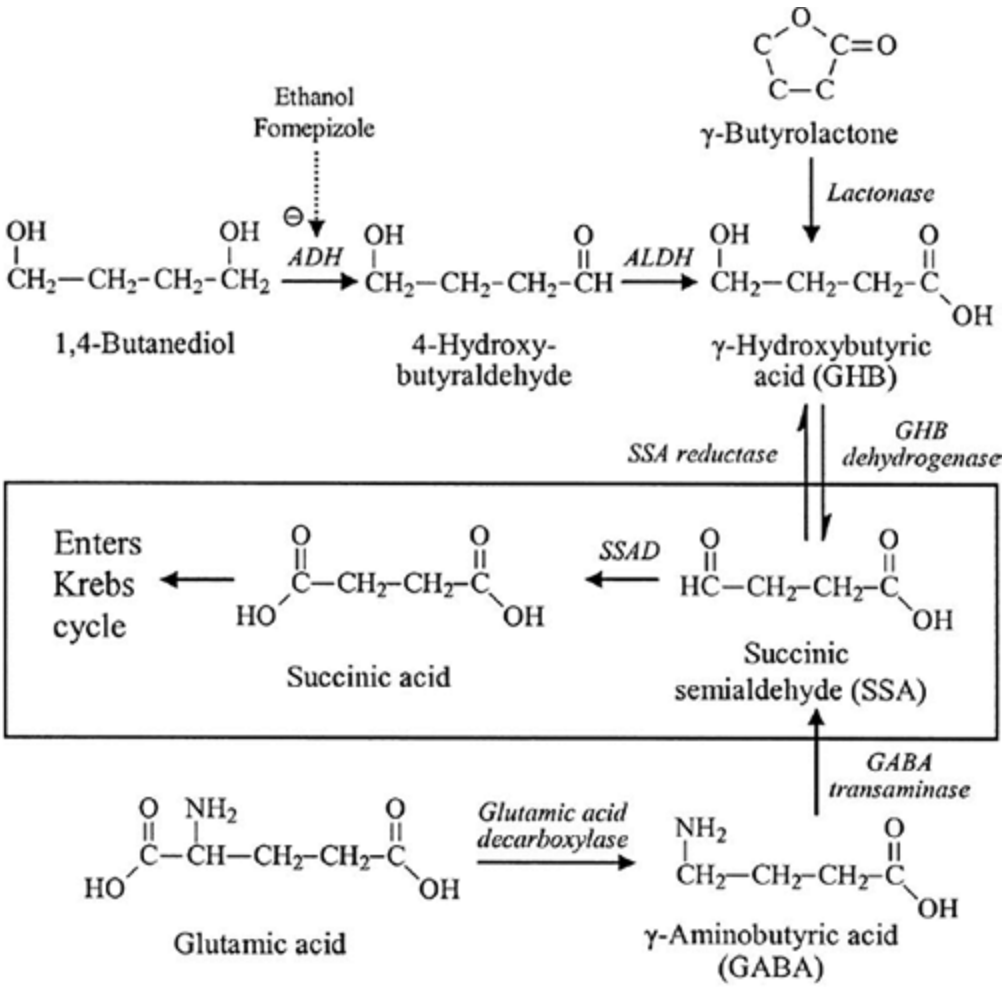

Figure 78-1. The synthesis and metabolism of Î³-hydroxybutyric acid. ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; SSA reductase, succinic semialdehyde reductase; SSAD, succinic semialdehyde dehydrogenase.

GHB also exerts a prominent modulatory effect on dopamine neurotransmission. Acute administration of GHB inhibits dopamine release and results in the accumulation of dopamine in the presynaptic cells. This effect is mediated by GHB inhibition of dopamine neuron firing in the substantia nigra and mesolimbic regions,[41, 47, 84] and the subsequent autoreceptor-mediated stimulation of tyrosine hydroxylase activity, resulting in increased presynaptic dopamine production.[73, 107] The attenuation of dopamine neurotransmission following GHB administration

may be the pharmacologic basis for the loss of locomotor activity in experimental animals and overdose patients.

Other systems modulated by GHB include the serotonin system, cholinergic system, and opioid system. GHB modulates the serotonin system by increasing its turnover rate, without altering total brain serotonin concentrations, likely by elevating presynaptic tryptophan concentrations.[43, 64, 106] GBL, but not GHB itself, increases total brain acetylcholine concentrations by decreasing firing of cholinergic neurons.[3, 56, 89] Such an increase in brain acetylcholine might underlie the pharmacologic basis for the reported analeptic effect of GHB in narcolepsy. Despite having no binding affinity for opioid receptors, GHB increases the release of endogenous opioids in various brain regions.[30, 38, 41, 57] Furthermore, despite naloxone having no affinity for the GHB receptor, administration of the opioid antagonists naloxone and naltrexone can

attenuate or reverse the electrophysiologic and behavioral actions of GHB on dopamine neuron firing and catalepsy in experimental animals.[29, 92]

After its release from GHBergic presynaptic membranes, GHB activity is terminated by an active vesicular uptake system driven by the vesicular inhibitory amino acid transporter (the same transporter that mediates the vesicular uptake of GABA and glycine) or by an active cellular uptake from the synaptic cleft by means of a high-affinity, Na^+ -dependent, transport protein specific for GHB and its analogs.[3, 40, 75] Once within the cell, the degradation of endogenous GHB in the mammalian brain can occur via 4 pathways, leading to succinic acid (SSA) which enters the tricarboxylic acid cycle, GABA, *trans* -4-hydroxycrotonic acid, or 4,5-dihydroxyhexanoic acid. In the first degradative pathway, which is the most significant quantitatively, GHB is oxidized to SSA by the nicotinamide adenine dinucleotide, phosphate-dependent, high K_m SSR (succinic semialdehyde reductase), which is now commonly referred to as GHB dehydrogenase (GHB-DH) (Fig. 78-1).

Exogenous Î³-Hydroxybutyric Acid

Although accumulating evidence favors the role of endogenous GHB as a neuromodulator, the study of the pharmacologic profile of exogenous GHI is still in its infancy. However, current data suggest that the $GABA_B$ receptor is a major component of the neural substrate mediating the pharmacologic, behavioral, clinical, and toxicologic actions of exogenous GHB and its precursors. When the brain GHB concentration exceeds its physiologic concentration by 2â€“3 orders of magnitude, it will saturate GHB-specific receptors and produce $GABA_B$ receptor-mediated brain perturbations.[59] Similarly, only millimolar concentrations of GHB can mimic the postsynaptic electrophysiologic effects of baclofen on the $GABA_B$ receptor, which can be blocked by $GABA_B$ receptor-selective antagonists but not by GHB receptor-selective antagonists such as NCS 382.[26 , 28] It is theorized that under conditions of excess exogenous administration, GHB may act both directly as a partial $GABA_B$ receptor agonist and indirectly through a GHB-derived GABA pool.[42] GHB itself is a weak $GABA_B$ receptor agonist with an affinity in the mmol/L range, which far exceeds the 1â€“4 Âµmol/L physiologic concentrations of GHB in the brain.[18 , 59 , 69] Therefore, the supraphysiologic concentration of GHB that could accumulate after its exogenous administration may exert its effects through a weak, direct agonistic effect on $GABA_B$ receptor-mediated mechanisms.

GHB and Endogenous Analogs

GHB has several *endogenous* structural analogs (GABA, *trans* -4-hydroxycrotonic acid [T-HCA]) and chemical precursors (GBL, 1,4-BD, Î³-crotonolactone [GCL]), as well as several well *synthetic* structural analog (5-hydroxyvaleric acid, Î³-methyl-GHB, Î³-phenyl-GHB, Î³-(*p* -chlorophenyl)-GHB, Î³-(*p* -methoxyphenyl)-GHB, Î³-benzyl-GHB, *R* -Î³-benzyl-GHB, *S* -Î³-benzyl-GHB, Î³-(*p* -methoxybenzyl)-GHB [NCS 435]), and precursors (GVL, THF). Of these analogs, illicit abuse has only been reported with GBL, 1,4-BD, Î³-methyl-GHB, GVL, and THF.

GHB itself usually exists as either a free acid (a colorless liquid) or as a

sodium salt (generally a white powder). The molecular formulas of GHB for its free acid and sodium salt are $C_4 H_8 O_3$ (molecular weight [MW] 104.11 g/mol) and $C_4 H_7 NaO_3$ (MW 126.09 g/mol), respectively. 4-Hydroxybutyric acid is the chemical name for its free acid, and sodium oxybate is the national nonproprietary name for its sodium salt, which is also a prescription drug. Synonyms for its chemical name are important because illicit GHB products often intentionally list obscure alternative chemical synonyms to conceal the identity of GHB. Synonyms include Î³-hydroxybutyric acid, 4-hydroxybutyric acid sodium salt, Î³-hydroxybutyric acid sodium salt, sodium 4-hydroxybutyrate, and 4-hydroxybutanoic acid.

GBL, the lactone ring precursor analog of GHB, is an endogenous substance in the mammalian brain at concentrations of approximately 10% that of GHB.[17] Chemically, it is most commonly referred to as Î³-butyrolactone, but it also has numerous obscure chemical synonyms, which are often intentionally listed on illicit GBL product labels to conceal the identity of GBL, such as 2(3 H)-furanone dihydro; butyrolactone; 4-butyrolactone; dihydro-2(3 H)-furanone; 4-butanolide; 2(3 H)-furanone; tetrahydro-2-furanone; 4-deoxytetronic acid; butyrolactone-Î³; 4-hydroxbutyric acid lactone; Î³-hydroxybutyric acid lactone; butyryl lactone; butyric acid lactone; butyrolactone; hydroxybutanoic acid lactone; tetrahydro-2-furanone; 1,4-butanolide; and 1,4-lactone. Based on behavioral and analytical observations, GBL is best described as a precursor to the pharmacologically active metabolite GHB. 1,4-BD, the other naturally occurring GHB precursor analog, is usually referred to by the chemical name 1,4-butanediol, but it has several additional chemical synonyms, including 1,4-butylene glycol, 1,4-dihydroxybutane, and 1,4-tetramethylene glycol. CNS depression by 1,4-BD is mediated through metabolism to GHB.[85]

Synthetic Analogs

Numerous pharmacologically active synthetic GHB structural analogs have been produced in the laboratory. In general, lengthening of the GHB carbon chain and introduction of functional groups to the Î³-carbon both

can yield potent compounds with respect to affinity for [^{3} H]GHB-labeled binding sites. Although the list of pharmacologically active GHB structura analogs appears to be ever increasing, only GHV (Î³-methyl-GHB) abuse is reported to date. Nevertheless, the possibility exists for future illicit introduction of these GHB structural analogs, as law enforcement pressur continues to increase for GHB, GBL, and 1,4-BD.

Synthetic Precursor Analogs

GVL and THF have been illicitly used as synthetic precursor analogs of GHV and GBL/GHB, respectively. GVL is the structural analog of GBL produced by the methylation of GBL in the Î³ (4-carbon) position. It has the chemical synonyms 4-hydroxypentanoic acid lactone, 4,5-dihydro-5-methyl-2(^{3} H)-furanone, and Î³-methyl-GHB. When administered, GVL undergoes hydrolysis to yield the GHB structural analog GHV.[67 , 77 , 78] Furthermore, GVL is reported to be used in the illicit synthesis of GHV.[22] THF is the cyclic ether structural analog of GBL. THF can serve as the key precursor ingredient in the illicit synthesis of GBL.[80 , 86] Because THF is a widely employed industrial solvent, human toxicity is generally available in the context of occupational exposure and poisoning, where THF causes nausea, headache, blurred vision, dizziness, narcosis, tinnitus, chest pair and coughing.[9 , 81] Acute poisonings and fatalities from THF are rare; only 2 published references are available. In the first case, a 50-year-old man ingested a drink offered by a stranger and abruptly developed abdominal pain, nausea, and vomiting. He was hospitalized 16 hours postingestion, developed hepatorenal syndrome, and died on hospital day 5. THF was detected in the patient's urine by gas chromatography-mass spectrometry (GC/MS).[76] In the second case, a 55-year-old woman intentionally ingested an organic solvent and psychoactive medications, and presented to an ED with

coma. She required endotracheal intubation, and a chest radiograph was consistent with aspiration pneumonitis. She had a complete recovery on hospital day 4 and was discharged after 8 days, without any sequelae. Toxicologic screening by high-performance liquid chromatography (HPLC)

revealed the presence of zolpidem and fluoxetine. Quantitative nuclear magnetic resonance (NMR) analysis was performed, demonstrating THF and GHB in serum and urine at concentrations of 813 and 850 mg/L, and 239 and 2977 mg/L, respectively. A GC/MS method confirmed the NMR observations.[9]

Pharmacokinetics and Toxicokinetics

GHB is rapidly and near completely absorbed from the gastrointestinal tract with an onset of action of about 15 minutes,[105] and reaches its peal effect by 90â€“120 minutes.[46] The steady-state volume of distribution is approximately 0.58 L/kg.[44] GHB is eliminated very rapidly, with a half-life of 30 minutes.[8] Less than 5% of the parent compound is recovered in the urine. In comparison, GBL is more rapidly absorbed and has a longer duration of action, a result of higher lipid solubility. Because 1,4-BD is metabolized by alcohol dehydrogenase (ADH), coingestion with ethanol can prolong its clinical effects because of competitive inhibition of ADH.[79, 87]

Clinical Manifestations

The clinical manifestations of overdose of GHB and related xenobiotics ca be predicted based on known pharmacologic activity and kinetics. Specifically, effects on the GABA and opioid neurotransmitter symptoms seem to predominate. In volunteers undergoing sleep studies, a clear ora doseâ€“response effect for GHB is noted: 30 mg/kg produces CNS depression and myoclonus, 50 mg/kg produces unconsciousness, and 60 mg/kg produces coma.[33, 65] Again, tolerance has the ability to shift this doseâ€“response curve to the right.

These clinical manifestations of overdose are highlighted by a number of well-documented cases.[23, 24, 90, 99, 110] Although the constellation of signs and symptoms are best reported for GHB, the following is most likely applicable to the entire class of xenobiotics. The onset of action is very rapid, with effects noted as early as 15 minutes postingestion. Vital

signs typically reveal hypotension, bradycardia, bradypnea, and hypothermia. Bradypnea is the most consequential of these effects, and apnea is the most likely cause of death. Pupils are typically miotic and poorly responsive to light. Salivation and vomiting are common, especiall when CNS depression is prominent. These effects compound bradypnea and hypoventilation in that they increase the risk for aspiration.

CNS effects can range from hallucinations, disorientation, and agitation t lethargy, followed by stupor and coma. These findings most likely represent disinhibition of higher cortical areas and are consistent with other sedativeâ€“hypnotics such as ethanol. In contrast to ethanol and other sedativeâ€“hypnotics, however, patients with GHB overdose often have a characteristic violent arousal that accompanies attempts to assess their gag reflex or perform intubation, which is somewhat suggestive of a clonidine overdose (Chap. 60).

Motor abnormalities are also common, and there is debate whether they represent seizures, myoclonus or both. In animal models, GHB can produce seizures, yet EEG monitoring in humans suggests that repetitive movements most likely represent myoclonus.[27] Clinically, these events are often called â€œseizuresâ€• because, in the absence of consciousness or EEG monitoring, it is difficult to distinguish these two disorders.

Other findings include prominent U waves on the ECG.[13] Electrolytes, anion gap, and other standard tests are usually normal.

The duration of effect is characteristically short. Many patients will abruptly awaken within a few hours of presentation and appear completely normal. Even those patients who require endotracheal intubation are usually able to be extubated within 8 hours. As long as aspiration and hypoxia have not occurred, most patients suffer no sequelae.

Diagnostic Testing

The presence of GHB and related xenobiotics can be determined,

quantitatively and qualitatively, in both serum and urine, using a variety of analytical techniques.[39 , 102 , 109] The most important caveat is that appropriate cutoff values must be selected to distinguish use and overdose from endogenous levels.[16 , 25 , 49 , 74] In general, unconsciousness occurs when serum concentrations reach 50 Âµg/mL, an levels above 260 Âµg/mL typically produce deep coma.[90] Attempts to relate concentrations to clinical effects in any individual might not be valid because of the potential for tolerance. Due to rapid metabolism and elimination, concentrations return to endogenous values shortly after nontolerant patients become clinically normal. Most clinical hospital laboratories do not routinely test for the presence of GHB and related xenobiotics, and recovery is typically rapid, so results of analytical testin are not useful for clinical care. They may, however, have forensic implications.

Other routine tests that should be obtained in patients with depressed levels of consciousness include a rapid evaluation of blood glucose, an ethanol concentration, and an ECG. When intentional overdose or self-harm is suspected, a determination of acetaminophen concentration is also indicated. Other studies should be obtained based on the clinical condition of the patient.

Treatment

The provision of good supportive care remains the mainstay of therapy. The decision to perform endotracheal intubation should be made at the bedside and based on a clinical assessment of oxygenation and ventilation. Despite deep coma, many patients will have adequate respirations and airway-protective reflexes. Because the duration of unconsciousness is relatively brief, coma, in and of itself, should not be considered an absolute indication for endotracheal intubation. Hypotension usually responds to fluids, and bradycardia rarely requires pharmacologic intervention. Hypothermia is mild and typically responds t passive rewarming.

Dextrose and thiamine should be given, as clinically indicated. Although

no clinically available GHB antagonists exist, both naloxone and physostigmine have been used. A trial of naloxone is often clinically reasonable in the undifferentiated patient, based on the findings of small pupils and CNS and respiratory depression. Although in animal models some of the effects of GHB are reversed by naloxone, naloxone administration to GHB-toxic humans is largely unsuccessful.[58] Likewise, while

anecdotal reports suggest some utility for physostigmine, a systematic review of available data failed to find any convincing supporting evidence.[101]

There is no role for any form of gastrointestinal decontamination. GHB and related xenobiotics are rapidly absorbed and can produce significant airway compromise. It is unlikely that a significant percentage of the ingested dose will be present in the stomach at the time of presentation, and the use of activated charcoal will only increase the risk of vomiting and aspiration. However, if a coingestant is suspected, appropriate decontamination techniques can be used, as long as there are no contraindications.

GHB Withdrawal

Severe and life-threatening manifestations follow abrupt cessation or reduction in intake of GHB or any of its precursors or analogs.[15, 21, 70, 88, 100] Because GHB and related xenobiotics have a short duration of effect, symptoms usually develop very rapidly and are clinically consisten with sedative hypnotic withdrawal. Patients develop agitation, disorientation, hallucinations, hypertension, tachycardia, hyperthermia, tremor, and seizures, often within hours of their last use.[12, 83]

Treatment principles involve sedation, cooling, volume resuscitation, and a search for other medical and traumatic causes of alterations in behavior. Although benzodiazepines appear to be the safest initial pharmacologic agent to control behavior, excessively large doses may be required. When patients appear resistant to benzodiazepines, either

barbiturates or propofol can be given.[91] Endotracheal intubation is often required when barbiturates or propofol are used.

Summary

GHB is a unique xenobiotic in that it is an endogenous neurotransmitter, licensed pharmaceutical, and a drug of abuse. Complex pharmacologic effects with multiple receptors produce rapid coma with hypotension, bradycardia, respiratory depression, and miosis. Treatment is largely supportive, and because the duration of effect is short, there is essentially no value in attempting to antagonize receptors or enhance elimination. Although fatality is possible, most patients recover rapidly, with no long-standing effects.

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Chapter 79
Inhalants

Heather Long

A mother returned home from a parentâ€“teacher conference regarding her 11-year-old daughter; both the parent and the teacher had become concerned about some behavioral changes noted in the girl over the past few months. The mother found her daughter in the bathroom, holding a can of air freshener aerosol spray. Upon discovery, the girl immediately collapsed and lost consciousness. She had some short-lived twitching movements of her extremities that were not rhythmic. On arrival of emergency medical services (EMS), the girl was unresponsive and the electrocardiogram revealed ventricular tachycardia. A white residue was noted around her mouth. EMS initiated resuscitation following the Pediatric Advanced Life Support protocol, which included three stacked, unsynchronized defibrillations at 200, 300, and 360 joules, followed by the administration of intravenous epinephrine (0.01 mg/kg). The patient was endotracheally intubated and given 100% oxygen. Chest compressions were continued throughout transport to the emergency department (ED).

On arrival to the ED, the child was asystolic. Resuscitative efforts,

including chest compressions and the intravenous administration of epinephrine (0.1 mg/kg) and atropine (0.02 mg/kg), were continued in the ED. After approximately 30 minutes, the patient was pronounced dead.

Inhalant abuse is defined as the deliberate inhalation of vapors for the purpose of changing one's consciousness or becoming â€œhigh.â€• It is also referred to as volatile substance abuse and was first described in 1951.[30] Inhalants are appealing to adolescents because they are inexpensive, readily available, and sold legally. Initially, inhalant abuse was viewed as physically harmless, but reports of â€œsudden sniffing deathâ€• began to appear in the 1960s.[6] Shortly thereafter, evidence surfaced of other significant morbidities, including organic brain syndromes and peripheral neuropathy.

Epidemiology

The demographics of inhalant abuse differ markedly from that of other traditional substances of abuse. The 2003 Monitoring the Future Study found that more than 2 million youths between the ages of 12 and 17 years used inhalants at least once in their lifetime.[126] The 2000 National Household Survey on Drug Abuse showed that the number of new inhalan users in the United States increased more than 50%, from 618,000 to 979,000, between 1994 and 2000.[126] Youths ages 12â€“17 years had higher rates of past-year use than did adults ages 18 years and older. Th lifetime prevalence of inhalant use peaked among 8th graders at 15%. The median age of first use is 13 years.[4]

Although long considered to be a problem among boys, there has been a steady increase of inhalant abuse among girls, and their lifetime prevalence now equals that of boys.[8] In the United States, the problem is greatest among children of lower socioeconomic groups; non-Hispanic white adolescents are the most likely and black adolescents the least likely to use inhalants.[80] Although inhalant use is a problem in both urba and rural communities, its prevalence is higher in rural settings.[105] This may relate to the easier access teens in urban areas have to other drugs

of abuse.

Inhalant abuse includes the practices of sniffing, huffing, and bagging. Sniffing entails the inhalation of a volatile substance directly from a container, as occurs with airplane glue or rubber cement. Huffing involves pouring a volatile liquid onto fabric, such as a rag or sock, and placing it over the mouth and/or nose while inhaling. Huffing is the method used by more than 60% of volatile-substance abusers.[80] Bagging refers to spraying a solvent into a plastic or paper bag and rebreathing from the bag several times; spray paint is among the xenobiotics commonly used with this method.

Agents Used

There are myriad xenobiotics abused as inhalants (Table 79-1), most of which are volatile hydrocarbons. Hydrocarbons are organic compounds comprised of carbon and hydrogen atoms and are divided into two basic categories: aliphatic (straight, branched, or cyclic chains) and aromatic. Most of the commercially available hydrocarbon products are mixtures of hydrocarbons; for example, gasoline is a mixture of aliphatic and aromatic hydrocarbons that may consist of more than 1500 compounds. Substituted hydrocarbons contain halogens or other functional groups (eg, hydroxyl or nitrite), other than carbon and hydrogen, that are substituted for hydrogen atoms in the parent structure. Solvents are themselves a heterogeneous group of chemical compounds that are used to dissolve other chemical compounds or provide a vehicle for their delivery.

The most commonly inhaled volatile hydrocarbons are fuels, such as gasoline, and solvents, such as toluene.[105] Other commonly inhaled hydrocarbon-containing products include spray paints, lighter fluid, air fresheners, and glue. In most reported cases of inhalant use, the inhalant is identified not by its chemical name (eg, butane, toluene) but rather by its form (eg, lighter fluid, paint thinner). Because exact components may vary between commercial products, this method is inaccurate and imprecise.

Although volatile alkyl nitrites are technically substituted hydrocarbons, they have pharmacologic and behavioral effects,

as well as patterns of abuse that are distinct from the other volatile hydrocarbons. For this reason, researchers usually classify them as a separate category among abused inhalants. Amyl nitrite is the prototypical volatile alkyl nitrite.[4] Amyl nitrite became popular in the 1960s with the appearance of â€œpoppers,â€• small glass capsules containing the chemical in a plastic sheath or gauze. When crushed, the ampules release the amyl nitrite. When over-the-counter sales of amyl nitrite were restricted in 1968, sex and drug paraphernalia shops began selling small vials of butyl and isobutyl nitrites marketed as room deodorizers or liquid incense.[4 , 75] Because of further restrictions on sales of alkyl nitrites, most of these products now contain chemicals that are not technically alkyl nitrites, such as cyclohexyl nitrite.[4]

Glues/adhesives
Toluene, *n* -hexane, benzene, xylene, trichloroethane, trichloroethylene, tetrachloroethylene, ethyl acetate, methylethyl ketone, methyl chloride
Spray paint
Toluene, butane, propane
Hair spray, deodorants, air fresheners
Butane, propane, fluorocarbons
Cigarette lighter fluid
Butane
Paint thinner
Toluene, methylene chloride, methanol
Gasoline
Aliphatic and aromatic hydrocarbons
Carburetor cleaner
Methanol, methylene chloride, toluene, propane
Dry cleaning agents, spot removers, degreasing agents
Tetrachloroethylene, trichloroethane, trichloroethylene
Typewriter correction fluid
Trichloroethane, trichloroethylene

Nail polish remover
Acetone
Paints, lacquers, varnishes
Trichloroethylene, toluene, n-hexane
â€œPoppersâ€•
Amyl nitrite, isobutyl nitrite
Room deodorizers
Butyl nitrite, isobutyl nitrite, cyclohexyl nitrite
Whipped cream dispensers â€œwhippetsâ€•
Nitrous oxide

Inhalant Chemical

TABLE 79-1. Common Inhalants and the Constituent Chemicals

The most commonly used nonhydrocarbon inhalant is nitrous oxide. Nitrous oxide, or â€œlaughing gas,â€• is used medicinally as an inhalational anesthetic. It is the propellant in supermarket-bought whipped cream canisters, and cartridges of the compressed gas are sold for home use in whipped cream dispensers. These battery-sized metal containers of compressed gas may be used as â€œwhippets,â€• in which the container is punctured using a device known as a â€œcracker,â€• and the escaping gas is either inhaled directly or collected in a balloon and then rebreathed.

Pharmacology

Although chemically heterogeneous, inhalants are generally highly lipophilic and gain rapid entrance into the central nervous system (CNS). Little is known about the cellular basis of the effects of inhalants and it is unclear whether these actually represent a single pharmacologic group. Their effects are probably best represented by the model for ethanol in which multiple different cellular mechanisms explain diverse pharmacologic and toxicologic effects.[4]

Volatile Hydrocarbons

The clinical effects of the volatile hydrocarbons are likely mediated through stimulation of the Î³-aminobutyric acid (GABA) receptor complex the primary system responsible for inhibitory neurotransmission within the CNS. Like ethanol, both toluene and TCE enhance $GABA_A$ receptor-mediated synaptic currents as well as glycine receptor-activated ion function; stimulation of these receptors acts to increase chloride permeability, hyperpolarizing the cell membrane and inhibiting excitability. Despite very different molecular structures, ethanol, enflurane, chloroform, toluene, and 1,1,1-trichloroethane (TCE) compete for binding sites in glycine $Î±_1$ receptors.[9] Additionally, toluene, like ethanol, interferes with glutamate-mediated excitatory neurotransmissior by inhibiting *N* -methyl-D-aspartate (NMDA) receptor-mediated currents i a concentration-dependent manner.[32]

Toluene is the prototypical volatile hydrocarbon and the best studied. In animal models, differences in pharmacologic action are demonstrated between toluene and other alkylbenzenes, and halogenated hydrocarbons such as TCE, and acetone.[17 , 18 , 113] These differences may represent evidence that specific cellular sites for their actions exist. Additionally these differences may explain the variation in their abuse potential or their intoxicating effects.[4] Despite these distinctions, there are marked similarities in the behavioral and pharmacologic effects of the volatile hydrocarbons. Moreover, the clinical effects profile shared by the volatile hydrocarbons, subanesthetic concentrations of general anesthetics, ethanol, and benzodiazepines suggests that they share cellular mechanisms. Shared clinical effects include anxiolytic effects,[19] anticonvulsant effects,[125] impaired motor coordination,[85] and evidence o physical dependence on withdrawal.[36 , 37]

There are scant data on the pharmacokinetics of the inhalants. Most data are derived from studies on occupational and environmental exposures and have limited applicability to the intentional inhalation. More relevant to the understanding of inhalants are the similarities with the inhalationa anesthetic agents, many of which are halogenated hydrocarbons. Factors

determining pharmacokinetic and pharmacodynamic effects of a given inhalational anesthetic include concentration in inspired air; its partition coefficient; interaction with other inhaled substances, alcohol, and drugs; the patient's respiratory rate and blood flow; their percent body fat; and individual variation in drug metabolism (Chap. 65).[46] Whereas the pharmacokinetics of the inhalational anesthetics are extensively studied, the intentional inhalation of variable concentrations of abused inhalants for variable periods of time remains unstudied.

Partition coefficients measure the relative affinity of a gas for two different substances at equilibrium and are used to predict the rate and extent of uptake of an inhaled substance. The blood:gas partition coefficient is most commonly referenced. The higher the number, the more soluble the substance is in blood. Substances with a low blood:gas partition coefficient, like nitrous oxide, are rapidly taken up by the brain and, conversely, are rapidly eliminated from the brain once exposure is ended (Table 79-2).

In a rodent model of inhalation abuse of toluene and acetone,[24] the rapidity of onset and the depth of CNS depression were dependent on the concentration of the solvent inhaled. There was a parallel relationship between brain concentration and pharmacologic effect during induction (inhalation) and postexposure. Brain and liver concentrations dropped rapidly after exposure; concentration in blood decreased at the slowest rate. Elimination was biphasic: rapid elimination during the first step was a result of tissue redistribution,

alveolar ventilation, and metabolic clearance. During the second phase there was a slow decrease in tissue concentrations as a result of the gradual mobilization from adipose tissue with subsequent exhalation or metabolism. Acetone, which is more water-soluble than toluene, is less potent and more slow acting than toluene, but is eliminated much more slowly than toluene and has a much longer duration of action.[24] Positron emission tomography (PET) studies using (^{11}C) radiolabeled toluene in nonhuman primates showed rapid uptake of radioactivity in striatal and frontal regions of the cortex followed by rapid clearance from brain.

Whole-body PET scans in mice showed excretion through the kidneys and liver.[44]

Acetone
243â€“300
Largely unchanged via exhalation 95% and urine 5%
None
n- Butane
0.019
Largely unchanged via exhalation
None
Carbon tetrachloride
1.6
50% unchanged via exhalation; 50% hepatic metabolism and urinary excretion
CYP2E1 to trichloromethyl radical, trichloromethyl peroxy radical, phosgene
n -Hexane
2
10â€“20% exhaled unchanged; hepatic metabolism and urinary excretion
CYP2E1 to 2-hexanol, 2,5-hexanedione, Î³-valerolactone
Methylene chloride
5â€“10
92% exhaled unchanged; hepatic metabolism and urinary excretion
(1) CYP2E1 to CO and CO_2
(2) Glutathione transferase to CO_2 , formaldehyde, and formic acid
Nitrous oxide
0.47
>99% exhaled unchanged
None
Toluene
8â€“16
<20% exhaled unchanged; >80% hepatic metabolism and urinary excretion
CYP2E1 to benzoic acid, then

(1) glycine conjugation to form hippuric acid (68%)
(2) glucuronic acid conjugation to benzoyl glucuronide (insignificant pathway except following large exposure to toluene)
1,1,1-Trichloroethane
1â€“3
91% exhaled unchanged; hepatic metabolism and urinary excretion
CYP2E1 to trichloroethanol, then
(1) conjugated wih glucuronic acid (urochloralic acid) or
(2) further oxidized to trichloracetic acid
Trichloroethylene
9
16% exhaled unchanged; 84% hepatic metabolism and urinary excretion
CYP2E1 to epoxide intermediate (transient); chloral hydrate (transient); trichloroethanol (45%), trichloroacetic acid (32%)

Xenobiotic	Blood:Gas Partition Coefficient (98.6Â°F/37Â°C)	Routes of Elimination	Important Metabolites

TABLE 79-2. Blood: Gas Partition Coefficients, Routes of Elimination and Important Metabolites of Selected Inhalants

The inhalants are eliminated unchanged via respiration, undergo hepatic metabolism or both (Table 79-2). For some the percentage that is metabolized versus eliminated unchanged varies with the exposure dose. Nitrous oxide and the aliphatic hydrocarbons are frequently eliminated unchanged in the expired air. The aromatic hydrocarbons are usually metabolized extensively via the cytochrome P450 (CYP) system, particularly CYP2E1, which has a substrate spectrum that includes a number of aliphatic, aromatic, and halogenated hydrocarbons.[15] Extrahepatic expression of CYP2E1 occurs to a lesser extent but may be of toxicologic significance, particularly in the kidneys and the dopaminergic cells of the substantia nigra.[16 , 56 , 116] In humans, there appears to be no significant gender differences in CYP2E1; however, it is

polymorphic and, as such, allelic distributions vary among different human populations.[15, 103] Moreover, this polymorphism may explain the varying degrees of toxicity exhibited following inhalant abuse.

Although little is known about the cellular actions of the inhalants, even less is known about the reward mechanisms and consequently the abuse potential of inhalants. Animal research on toluene suggests that similar to other drugs of abuse, activation of mesolimbic dopaminergic pathways may play an important role.[13, 44, 96]

Volatile Alkyl Nitrites

Unlike other volatile hydrocarbons, the volatile alkyl nitrites are not thought to have any direct effects on the CNS. Their effects are mediated through smooth muscle relaxation in the central and peripheral vasculature and they share a common cellular pathway with other nitric oxide (NO) donors like nitroglycerin and sodium nitroprusside.[65] A rat model of inhalation of isobutyl nitrite found a half-life of 1.4 minutes with almost 100% biotransformation to isobutyl alcohol. Bioavailability following inhalation was estimated to be 43%.

Nitrous Oxide

The pharmacokinetics and pharmacodynamics of nitrous oxide (N_2O) abuse are derived from its use as an inhalation anesthetic. Anesthetic uptake or induction, as well as emergence with N_2O, is rapid because of its low solubility in blood, muscle, and fat.[107] There is no appreciable metabolism of N_2O in human tissue.[38] An animal study found N_2O significantly inhibited excitatory NMDA-activated currents and had no effect on GABA-activated currents.[57] N_2O is also known to stimulate dopaminergic neurons, but the significance of this in mediating its anesthetic effects remains unclear.[62, 86]

Animal studies suggest the analgesic effects (or more accurately the antinociceptive effects because it refers to animals) of N_2O appear to be mediated through opioid peptide release in the midbrain. These

antinociceptive effects can be reversed by the opiate antagonist naloxone.[12] However, the anesthetic effects are not attenuated by naloxone, and, in humans, the subjective and psychomotor effects of N_2O are not extinguished by even high doses of naloxone.[104, 127]

Clinical Manifestations

Signs and symptoms of inhalant use may be subtle, tend to vary widely among individuals, and generally resolve within two hours

of exposure. Following acute exposure, there may be a distinct odor of the abused inhalant on the patient's breath or clothing. Depending on the inhalant used and the method, there may be discoloration of skin around the nose and mouth. Mucus membrane irritation may cause sneezing, coughing, and tearing. Patients may complain of dyspnea and palpitations. Gastrointestinal complaints include nausea, vomiting, and abdominal pain. After an initial period of euphoria, patients may have residual headache and dizziness.

Volatile Hydrocarbons

The central nervous system is the intended target of the inhalants and is most susceptible to adverse effects. Initial CNS effects include euphoria and hallucinations (both visual and auditory) as well as headache and dizziness. As toxicity progresses, CNS depression worsens and patients may develop slurred speech, confusion, tremor, and weakness. Transient cranial nerve palsies are reported.[111] Further CNS depression is marked by ataxia, lethargy, seizures, coma, and respiratory depression. These acute encephalopathic effects generally resolve spontaneously and associated neuroimaging abnormalities are not reported.[40]

As can be expected given the high lipophilicity of most inhalants, toxicity from chronic use is manifested most strikingly in the central nervous system. Toluene leukoencephalopathy, characterized by dementia, ataxia, eye movement disorders, and anosmia, is the prototypical manifestation

of chronic inhalant neurotoxicity. Patients with toluene leukoencephalopathy display characteristic neurobehavioral deficits reflecting white matter involvement: inattention, apathy, and impaired memory and visuospatial skills with relative preservation of language.[40] Autopsy studies reveal white matter degeneration including cerebral and cerebellar atrophy and thinning of the corpus callosum.[66, 97] On microscopy, there is diffuse demyelination with relative sparing of the axons. Abundant perivascular macrophages containing coarse or laminar myelin debris found in areas of the greatest myelin loss is a characteristic pathologic feature.[40] This targeting of myelin, which is 70% lipid, may be explained by toluene's lipophilicity.[40] As myelination continues at least through the second decade of life, the typical toluene abuser who begins inhaling during adolescence may be particularly susceptible to its toxic CNS effects.[39] Advances in magnetic resonance imaging with gadolinium, which allow enhanced visualization of the cerebral white matter, demonstrate that the extent of white matter injury in the brain directly corresponds to the clinical severity of toluene leukoencephalopathy.[40] It is postulated that reactive oxygen species generated either by toluene or its metabolite benzaldehyde induce lipid peroxidation.[77, 78] Genetic polymorphisms and host susceptibility among chronic abusers are also hypothesized to play a role.[49]

Acute cardiotoxicity associated with hydrocarbon inhalation is manifested most dramatically in â€œsudden sniffing death.â€• In witnessed cases, sudden death occurred when sniffing was followed by some physical activity. Examples include running or wrestling or a stressful situation like being caught sniffing by parents or police.[6] It is thought that the inhalant â€œsensitizes the myocardiumâ€• by blocking the potassium current (I_K), thereby prolonging repolarization.[88] This produces a substrate for dysrhythmia propagation; the activity or stress then causes a catecholamine surge that initiates the dysrhythmia (Chap. 23).[88] Cardiac dysrhythmias following the inhalation of hydrocarbons were documented with the halogenated inhalational anesthetics in the early 1900s, and this association was subsequently confirmed in both animal and human studies.[42, 112] Multiple case reports of ventricular fibrillation follow

intentional inhalation of other hydrocarbons as well, such as butane fuel,[51, 123] Freon (Dupont trade name for fluorinated hydrocarbons), and Glade Air Freshener (SC Johnson), which contains a mixture of short-chain aliphatic hydrocarbons.[71] Although cardiotoxic effects of inhalant abuse are generally acute, dilated cardiomyopathy is reported with chronic abuse of toluene and with trichloroethylene.[81, 124] Microscopy reveals evidence of chronic myocarditis with fibrosis.[124]

The typical clinical presentation of a patient with hydrocarbon cardiotoxicity includes palpitations, shortness of breath, syncope, and ECG abnormalities, including atrial fibrillation, premature ventricular contractions, QTc prolongation, and U waves.

The primary respiratory toxicity complication of inhalational substance abuse is hypoxia, which is either caused by rebreathing of exhaled air, as occurs with bagging, or displacement of inspired oxygen with the inhalant reducing the FiO_2 . Direct pulmonary toxicity associated with inhalants is most often a result of inadvertent aspiration of a liquid hydrocarbon (Chap. 102). Aspiration injury is associated with acute lung injury and the acute respiratory distress syndrome, a continuum of lung injury characterized by increased permeability of the alveolar-capillary barrier and the resulting influx of edema into the alveoli, neutrophilic inflammation, and an imbalance of cytokines and other inflammatory mediators.[119] Reports of asphyxiation initially ascribed to inhalant abuse were later found to be caused by suffocation by a plastic bag, mask, or container pressed firmly to the face, and not specifically by toxicity of the inhaled vapor.[6, 27, 118]

Irritant effects on the respiratory system are frequently transient, but patients may develop chemical pneumonitis. This syndrome is characterized by tachypnea, fever, tachycardia, rales/rhonchi, leukocytosis, and radiographic abnormalities, including perihilar densities bronchovascular markings, increased interstitial markings, infiltrates, and consolidation. Rebreathing of exhaled air, as occurs with bagging, may lead to hypercapnia and hypoxia. Acute eosinophilic pneumonia following abuse of a fabric protector containing 1,1,1-trichloroethane, is also

reported.[63] Barotrauma presents as pneumomediastinum or subcutaneou emphysema.[100]

Hepatoxicity is associated with exposure to halogenated hydrocarbons, particularly carbon tetrachloride, but also chloroform, trichloroethane, trichloroethylene, and toluene.[76] Intentional inhalation of carbon tetrachloride is rarely reported, but its toxic metabolite, the trichloromethyl radical, created by the cytochrome CYP2E1, can covalentl bind to hepatocyte macromolecules and cause lipid peroxidation.[95] The resultant depletion of glutathione and the potentially fatal centrilobular necrosis mimic acetaminophen toxicity and have led to a postulated role for *N* -acetylcysteine (NAC) in preventing carbon tetrachloride hepatoxicity. Animal studies on the efficacy of NAC in preventing carbon tetrachloride-induced hepatoxicity have yielded mixed results.[31 , 33 , 34] There are no clinical trials in humans, but case series suggest a protectiv role for NAC.[98] Two cases of centrilobular hepatic necrosis following inhalation of trichloroethylene are reported. Inhalation of either toluene or one of the many halogenated hydrocarbons is associated with elevated liver enzymes and hepatomegaly that generally return to baseline within weeks of abstinence.[3 , 55 , 60 , 70 , 87 , 89]

Renal toxicity is most frequently described following inhalation of toluene Traditionally, prolonged toluene inhalation was said to cause a distal rena tubular acidosis (RTA), resulting in hypokalemia. However, distal RTA is associated classically with a hyperchloremic metabolic acidosis and a normal anion gap, and

toluene abuse may be associated with an increased anion gap. Production of hippuric acid, a toluene metabolite, plays a more important role in the genesis of the metabolic acidosis than was previously thought.[28] Hippurate excretion, usually expressed as a ratio to creatinine, rises dramatically with toluene inhalation.[82] The excretion of abundant hippurate in the urine unmatched by ammonium mandates an enhanced rate of excretion of sodium and potassium cations. Continued loss of potassium in the urine leads to hypokalemia. Toluene is rapidly metabolized to hippuric acid, and the hippurate anion is swiftly cleared by

the kidneys, leaving the hydrogen ion behind. This prevents the rise in anion gap that would normally occur with an acid anion other than chloride, generating a normal anion gap. In some cases, the loss of sodium causes extracellular fluid volume contraction and a fall in the glomerular filtration rate, which may transform the metabolic acidosis with a normal anion gap into one with a high anion gap caused by the accumulation of hippurate and other anions.[28] Through unclear mechanisms, other renal abnormalities occur with toluene inhalation, including hematuria, albuminuria, and pyuria. Glomerulonephritis associated with hydrocarbon inhalation is also reported and is a result of antiglomerular basement membrane antibody-mediated immune complex deposition.[115 , 128]

Toluene-abusing patients may present with profound hypokalemic muscle weakness. In a study of 25 patients admitted to the hospital following inhalant abuse, 9 presented with muscle weakness. The mean serum potassium concentration was 1.7 mEq/L and 6 of these patients had elevated creatine phosphokinase concentrations, ranging from 118â€“4350 IU/L (normal: <50 IU/L in women and <85 IU/L in men). Four patients were quadriplegic on presentation and of these, 2 were initially diagnosed erroneously with Guillain-BarrÃ© syndrome. The patients had inhaled toluene 6â€“7 hours per day for 4â€“14 days prior to presentation.[108]

Acute dermatologic and upper airway toxicity is associated with the inhalation of Freon, a previously widely used refrigerant. Vesicular lesions resembling frostbite and massive, potentially life-threatening edema of the oropharyngeal, glottic, epiglottic, and paratracheal structures are reported.[1 , 67] This is caused by the cooling of the gas associated with its rapid expansion once it is released from its pressurized container. With chronic abuse of volatile hydrocarbons, patients may develop severe drying and cracking around the mouth and nose as a consequence of a defatting dermatitis known as â€œhuffer's eczema.â€• Other manifestations of chronic irritation include recurrent epistaxis, chronic rhinitis, conjunctivitis, halitosis, and ulceration of the nasal and oral mucosa.[82]

Methylene chloride (dichloromethane), most commonly found in paint removers and degreasers, is unique among the halogenated hydrocarbons in that it undergoes metabolism in the liver by CYP2E1 to carbon monoxide.[90] In addition to acute CNS and cardiac manifestations, inhalation of methylene chloride is associated with delayed onset and prolonged duration of signs and symptoms of carbon monoxide poisoning. The CO metabolite is generated 4â€“8 hours after exposure and its half-life is 13 hours, significantly longer than that of CO following inhalation (Chap. 120).[5 , 109]

Methanol toxicity is reported following intentional inhalation of methanol-containing carburetor cleaners.[43 , 72 , 79] Significant findings may include hyperemic discs on funduscopic examination, metabolic acidosis, and CNS and respiratory depression (Chap. 103). Methanol-containing carburetor cleaners may also contain significant amounts of toluene (43.8%), methylene chloride (20.5%), and propane (12.5%). These xenobiotics may potentiate CNS depression and contribute to the toxicity associated with these products.

Chronic inhalation of the solvent *n* -hexane, a petroleum distillate and a simple aliphatic hydrocarbon found, for example, in rubber cement, can cause a sensorimotor peripheral neuropathy. Toxicity is mediated via a metabolite, 2,5-hexanedione, that interferes with glyceraldehyde-3-phosphate dehydrogenase-dependent axonal transport, resulting in axonal death.[35] Numbness and tingling of the fingers and toes is the most common initial complaint; progressive, ascending loss of motor function with frank quadriparesis may ensue.[29] Sural nerve biopsy shows axonal swelling and axonal loss, with secondary loss of myelin, probably as a result of retraction by axonal swelling, and accumulation of neurofilaments.[68] Nerve conduction studies show marked conduction slowing and conduction block (Chap. 19).[29 , 68]

Reports of polyneuropathy associated with chronic gasoline inhalation date to the 1960s and describe a symmetric, progressive, sensorimotor neuropathy with occasional superimposed mononeuropathies.[25 , 61] Initially these deficits were attributed to the presence of tetraethyl lead

as an â€œantiknockingâ€• agent in gasoline, but cases following abuse of unleaded gasoline are also reported.[25, 101] *n* -Hexane is present in gasoline in concentrations up to 3% and is thought the likely mediator of gasoline neuropathy.[120]

Teratogenicity

Fetal solvent syndrome (FSS) was first reported in 1979.[114] The authors described a 20-year-old primigravida with a 14-year history of solvent abuse defined as â€œdailyâ€• and â€œheavyâ€• who gave birth to an infant exhibiting facial dysmorphia, growth retardation, and microcephaly a constellation of findings that resembles fetal alcohol syndrome (FAS).[10] Since then a number of cases and case series have been reported.[103, 104, 105, 106] A general limitation of these case series is their reliance on self-reporting of substance abuse. In a number of cases included for analysis of teratogenic effects, mothers admit to use during pregnancy of other potential teratogens, including ethanol, cocaine, heroin, and phenobarbital.[104, 105] Cases purported to represent inhalant abuse in the absence of other drug abuse, particularly ethanol, are not verified by laboratory testing. A small study of infants born to mothers with a self-reported history of chronic solvent abuse found 16% had major anomalies, 12.5% had facial features resembling FAS, and 3.6% had cleft palate.[99] Craniofacial abnormalities common to both FAS and FSS include small palpebral fissures, thin upper lip, and midfacial hypoplasia. Features of FSS that distinguish it from FAS include micrognathia, low-set ears, abnormal scalp hair pattern, large anterior fontanelle, and downturned corners of the mouth.[114] Hypoplasia of the philtrum and nose are more characteristic of FAS.[92] Compared to matched controls, infants born to mothers who report inhalant abuse are more likely to be premature, to be low birth weight, to have smaller birth length, and to have small head circumference.[2, 122] Followup studies of these infants show developmental delay when compared to children matched for age, race, sex, and socioeconomic status.[2, 53] A rat model of toluene-abuse embryopathy found a significant reduction in the number of neurons within each cortical layer, as well as abnormal neural migration.[47] In

another animal model of inhalant abuse, mice exposed in utero to either toluene or TCE gained less weight and performed worse on behavioral tests than controls.[58, 59]

Withdrawal

Observed similarities in the acute effects of inhalants compared with other CNS depressants have suggested similar patterns of tolerance and withdrawal. Rodent models of inhalant abuse with toluene and TCE show evidence of physical

dependence that manifest as an increase in handling-induced seizures on cessation of inhalation.[37, 121] Additionally, these studies demonstrate cross-tolerance of the benzodiazepine diazepam with the motor-stimulating effects of TCE and, to lesser degree, with toluene. Inhalant abusers have themselves described tolerance with weekly usage in as little as 3 months.[22, 50] Withdrawal symptoms, including sleep disturbances, nausea, tremor, and irritability, lasting 2â€“5 days after last use are described.[22] Whether this represents a true withdrawal syndrome or residual effects of the inhalant is unclear.

Volatile Alkyl Nitrites

Methemoglobinemia caused by inhalation of amyl, butyl, and isobutyl nitrites is well reported.[20, 48, 74] Nitrites are strong oxidants that may induce hemoglobin oxidation from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state. Patients may present with signs and symptoms of methemoglobinemia including shortness of breath, cyanosis, tachycardia, and tachypnea (Chap. 122). Eye pain and transient increased intraocular pressure are reported following use of amyl nitrite.[91]

Nitrous Oxide

Reported deaths associated with abuse of nitrous oxide (N_2O) appear to be caused by secondary effects of N_2O, including asphyxiation and motor

vehicle collisions while under the influence, and not to direct toxicity.[110] [118] Investigations following deaths associated with N_2O have found many of the dead were discovered with plastic bags over their heads, in an apparent attempt to both prolong the duration of effect and increase the concentration to heighten the effect.[51] Autopsy findings in these cases were consistent with asphyxiation: acute lung injury, cardiac petechiae, and generalized visceral congestion.[110, 118] Laboratory simulation of a reported death in which the victim was found with a plastic bag over his head with a belt fastened loosely around his neck and a spent whipped cream canister within the plastic bag showed nitrous oxide displaces oxygen in a closed space.[118] Additionally, N_2O concentrations in this simulation were greater than 60%; at concentrations of nitrous oxide greater than 50%, the normal hypoxic response is diminished.[118] The combined effects of displaced oxygen and a blunted hypoxic drive may increase the risk of asphyxia.

Chronic abuse of nitrous oxide is associated with neurologic toxicity mediated via irreversible oxidation of the cobalt ion of cobalamin (vitamin B_{12}). Oxidation blocks formation of methylcobalamin, a coenzyme in the production of methionine and *S*-adenosylmethionine, required for methylation of the phospholipids of the myelin sheaths. Additionally, cobalamin oxidation inhibits the conversion of methylmalonyl to succinyl coenzyme A. The resultant accumulation of methylmalonate and propionate can result in synthesis of abnormal fatty acids and their subsequent incorporation into the myelin sheath (Chap. 65).[93] Case reports and small case series in humans following self-reported chronic, heavy abuse of N_2O found development of myeloneuropathy resembling the subacute combined degeneration of the dorsal columns of the spinal cord of classic vitamin B_{12} deficiency.[14, 26, 69, 73, 117] Presenting signs and symptoms reflect varying involvement of the posterior columns, the corticospinal tracts and the peripheral nerves. Numbness and tingling of the distal extremities is the most common presenting complaint. Physical examination may reveal diminished sensation to pinprick and light touch, vibratory sensation and proprioception, gait disturbances, the Lhermitte sign (electric shock sensation with neck flexion), hyperreflexia, spasticity

urinary and fecal incontinence, and extensor plantar response.[26,93] Among reported patients with nitrous oxide-associated neurotoxicity who had documented levels of vitamin B_{12}, approximately 50% had low vitamin B_{12} serum concentrations.[14,26,69,73,106,117] In the few patients who underwent Schilling tests, results were normal.[54,69,106] Nerve conduction studies and electromyography typically revealed a distal, axonal sensorimotor polyneuropathy.[26,54,69,117]

Laboratory and Diagnostic Testing

Routine urine toxicology screens are unable to detect inhalants or their metabolites. Most volatile inhalants can be detected using gas chromatography after exposure; likelihood of detection is limited by the dose, time to sampling, and method of specimen storage. Blood is the preferred specimen, but urinalysis for metabolites and hippuric acid (for toluene) may extend the time until the limit of detection is reached.[23] Specimens should be stored at a temperature between 23Â°F (â€“5Â°C) and 39.2Â°F (4Â°C).[23] Testing is not readily available at most institutions and the need to send the specimen to a reference laboratory limits the clinical usefulness in most situations. A thorough history and physical examination and careful questioning of the patient's friends and family are probably more helpful in cases of suspected inhalant abuse.

Depending on the patient's signs and symptoms, additional diagnostic testing may be indicated, including an electrocardiogram, chest radiograph, serum electrolytes, liver enzymes, and serum pH. The patient's presenting complaint(s) should guide decisions regarding furthe diagnostic testing.

Some inhalants present with unique diagnostic considerations (Table 79-3). The potassium concentration should be analyzed in patients manifestin muscle weakness and decreased deep tendon reflexes for suspected toluene-induced hypokalemia. A carboxyhemoglobin concentration should be determined following methylene chloride exposure. A methemoglobin concentration analysis might be indicated following exposure to amyl, butyl, or isobutyl nitrites. Liver function tests might be indicated followin

exposure to toluene, trichloroethylene, and TCE. A methanol concentration might be indicated following inhalation of methanol-containing carburetor cleaners.

Nerve conduction studies and electromyography can be useful in cases of suspected peripheral neuropathy. Routine laboratory testing, including cerebrospinal fluid analysis, is unremarkable in patients with inhalant-induced leukoencephalopathy. A CT scan of

the head is generally normal until late in the disease, when diffuse hypodensity of white matter becomes evident. T2-weighted magnetic resonance imaging with its superior resolution of white matter is the diagnostic study of choice. Standard MRI does not detect initial changes caused by toluene leukoencephalopathy; measurement of *N* -acetyl aspartate (NAA), a marker of CNS axons, with magnetic resonance spectroscopy (MRS) may assist with earlier detection. A decrease in NAA concentration, usually expressed as ratio of NAA to creatinine (NAA:Cr), may serve as a marker of axonal damage.[40]

Toluene
Hypokalemia; hepatotoxicity; leukoencephalopathy (chronic)
1,1,1-Trichloroethane, trichloroethylene
Hepatotoxicity
Methylene chloride
Carbon monoxide poisoning
Alkyl nitrites (amyl, butyl, isobutyl)
Methemoglobinemia
n -Hexane
Peripheral neuropathy (chronic)
Nitrous oxide
Myeloneuropathy (chronic)

Agent Special Considerations

TABLE 79-3. Inhalants, Common Sources, Special Considerations

Management

Management begins with assessment and stabilization of the patient's airway, breathing, and circulation (the â€œABCsâ€•). The patient should be connected to a pulse oximeter and cardiac monitor. Oxygen should be administered and the patient should be treated with nebulized albuterol i wheezing. Early consultation with a regional poison control center may assist with identification of the xenobiotic and patient management.

Cardiac dysrhythmias associated with inhalant abuse carry a significantly poor prognosis. Sudden death following use is not limited to new users and there appears to be no premonitory signal to the user.[6 , 94] Life-threatening electrolyte abnormalities must be considered early and corrected in the patient presenting with dysrhythmia. Patients with nonperfusing rhythms should be managed following standard managemen with defibrillation. There are no evidence-based treatment guidelines for the management of inhalant-induced cardiac dysrhythmias, but Î²-adrenergic antagonists are thought to offer some cardioprotective effects to the sensitized myocardium.[88] Propranolol and esmolol have both been used successfully in treatment of ventricular dysrhythmias following inhalant abuse.[45 , 84]

Fluid and electrolyte abnormalities should be sought and corrected early. Other complications, including methemoglobinemia, elevated carboxyhemoglobin, and methanol toxicity, should be managed with the appropriate antidotal therapy. Patients with respiratory symptoms that persist beyond the initial complaints of gagging and choking should be evaluated for hydrocarbon pneumonitis and treated supportively (Chap. 102).

With abstinence, behavioral and neuroimaging changes associated with toluene-induced leukoencephalopathy may be partially reversible early on; beyond a poorly defined period, changes are irreversible.[40] Cessation of abuse is the most important therapeutic intervention in patients with *n*-hexaneâ€“induced neuropathy and nitrous oxide-induced

myeloneuropathy; limited anecdotal evidence supports the coadministration of vitamin B_{12} (1000 Âµg intramuscularly) and methionine (1 g orally) in cases of nitrous oxide-induced myeloneuropathy.[26, 106]

Agitation, either from acute effects of the inhalant or from withdrawal, is safely managed with a benzodiazepine. In the vast majority of patients, symptoms resolve quickly and hospitalization is not required. The potential toxicity of inhalants should be reinforced and patients should be referred for counseling. Subsets of users, meeting the criteria for inhalant dependence and inhalant-induced psychosis, require inpatient psychiatric care. Pharmacotherapy with carbamazepine or the antipsychotics haloperidol or risperidone appears beneficial to some patients with an inhalant-induced psychotic disorder.[52, 83] Drug use treatment programs for inhalant abuse are scarce and few providers have special training in this area.[7]

Summary

Inhalants are a heterogeneous group of agents that include the volatile hydrocarbons, the alkyl nitrates, and nitrous oxide. Incidence of abuse is greatest among adolescents. The central nervous system is the intended target for the inhalant users; early effects include euphoria, hallucinations, headache, and dizziness. Acute cardiotoxicity is manifested most dramatically in â€œsudden sniffing death.â€• Unique consideration and toxicity are associated with specific agents (Table 79-3). Diagnosis is largely clinical; further diagnostic testing should be guided by the patient's presenting complaint. Management begins with basic life support and care is generally supportive. Cessation of use is the only known treatment for many manifestations of chronic toxicity.

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Chapter 80 Hallucinogens

Kavita M Babu

Robert P. Ferm

A 17-year-old boy was taken to the emergency department (ED) by his friends because he was acting bizarrely on the way home from school. He told a friend that he had â€œdropped acidâ€• after school and now could not stop staring at the bright lights. He encouraged his friends to enjoy the â€œpeace of the lights.â€• Physical examination revealed that the patient was agitated, and staring at the overhead lights. Vital signs were: blood pressure, 150/100 mm Hg; pulse, 112 beats/min; respiratory rate, 28 breaths/min; oral temperature, 100.4Â°F (38Â°C); and room air pulse oximetry 97%. A rapid bedside blood glucose was 120 mg/dL. His skin was moist and pale. Examination of the eyes revealed slowly reactive 6-mm pupils without nystagmus. He had occasional faint, scattered end-expiratory wheezes. Cardiac auscultation was normal. The abdomen was soft and nontender with hyperactive bowel sounds. There was no clubbing, cyanosis, or edema. Neuropsychiatric examination revealed that the patient was oriented, but was frightened by the visual hallucinations, and was â€œhearing purple and blueâ€• from the overhead lights. The remainder of the

neurologic examination was intact except for the presence of a fine tremor. The patient stated that he had previously taken lysergic acid diethylamide (LSD), although this was the first time that he had used it while alone. He understood that he was experiencing drug effects; however, he was extremely anxious and afraid of â€œlosing his mind.â€• The patient was moved to a quiet location with minimal stimuli and an intravenous line was inserted. He received diazepam 10 mg via slow IV push, and had some subsequent improvement of his anxiety. After approximately 8 hours of observation, the patient returned to his baseline functional status, without hallucinations or anxiety. After obtaining permission from the patient regarding disclosure, the ED staff notified his pediatrician and parents. A referral was made for drug counseling, and the patient was discharged to home with family members.

Epidemiology

Hallucinogens are a diverse group of xenobiotics that alter and distort perception, thought, and mood without clouding the sensorium. They have been used for thousands of years by many different cultures, largely during religious ceremonies. The ancient Indian holy book *Rig-Veda* , written more than 3500 years ago, describes a sacramental xenobiotic called Soma both as a god and as an intoxicating xenobiotic. Although debated for many years, the source of Soma is now believed to be the juice of the mushroom *Amanita muscaria* .[84 , 90] The Aztecs used the psilocybin-containing teonanacatl (flesh of the gods) and Ololiuqui (morning glory species) in their religious ceremonies. To this day, the Native American Church uses peyote in religious ceremonies.

Synthetic hallucinogen use is often said to have begun with the discovery of lysergic acid diethylamide (LSD). The synthesis of LSD resulted from extensive research on the ergot alkaloids derived from the fungus *Claviceps purpurea.* From medieval times through recent years, several large-scale epidemics of vasospastic ischemia, gangrene, and hallucinations (collectively called ergotism) have

resulted from *C. purpurea* contamination of cereal crops.[117] *C. purpurea* is suggested as the cause of the mass hysteria leading up to the Salem Witch trials. Many of these adverse effects after ingestion of *C. purpurea* are attributed to its serotonergic agonist effects.[35]

In 1938, Albert Hofmann, a Swiss chemist, synthesized LSD-25, the 25th substance in a series of lysergic acid derivatives being researched as new arousal, or analeptic, agents. These lysergic acid compounds were based on ergot extracts from *C. purpurea.* Five years later, LSD-25 was â€œtestedâ€• when Hofmann had an unintentional exposure in his laboratory, and subsequently developed hallucinations.[54 , 98] Soon thereafter, Sandoz laboratories began marketing LSD under the trademark name Delysid as an adjunct for analytic psychotherapy. In the 1950s, a small number of psychiatrists began using LSD to release the repressed memories of patients, and as an experimental model for schizophrenia.[103] The Central Intelligence Agency reportedly experimented with using LSD as a tool for interrogating suspected communists and as a mind-control agent.[23 , 98]

In the 1960s, the concept of the â€œfifth freedomâ€• emerged. As individuals explored this â€œrightâ€• to alter their consciousness as they saw fit, LSD (also called â€œacidâ€•) became a fashionable recreational drug. In one of the most famous slogans of the 1960s, Dr. Timothy Leary popularized LSD with the phrase, â€œTune in, Turn on, Drop out.â€•[98] By 1966, federal law banned the use of LSD.[80] Initial reports of LSD-induced chromosomal damage appeared in the 1960s, although further studies of pregnant women who had taken LSD did not demonstrate an increased risk of abortions or birth defects.[29 , 39 , 56 , 64 , 67]

LSD use diminished in the late 1970s and early 1980s, perhaps because of users' concerns regarding potential health risks of brain damage, â€œbad trips,â€• and flashbacks.[83] In the meantime, there was a rise in the use of the â€œdesignerâ€• hallucinogens. Exploiting a loophole in drug enforcement laws, these synthetic tryptamine and amphetamine hallucinogens were chemically similar to, but legally

distinct from, their outlawed counterparts.

A resurgence in LSD use was reported among high school teens in the late 1990s, with more prevalent use in the suburbs than

the inner city.[4,81,91] In 1997, two studies of adolescents showed a lifetime prevalence of LSD use at 13 and 14%.[57,83] However, in 2000, DEA agents seized an LSD-production lab and apprehended two men involved in massive production of LSD in the United States. Their incarceration resulted in a more than 90% decrease in LSD availability nationwide.[107]

The use of contemporary hallucinogens has grown in venues like all-night dance clubs and â€œrave parties.â€•[14] While the impact of these parties and clubs on the growth of hallucinogen use in the United States is unclear, many of the newer hallucinogens have been christened â€œclub drugsâ€• because of this association.[48] In addition, the Internet has developed as a vehicle for the rapid and facile sharing of information on the synthesis of emerging drugs, user experiences, and adverse effects.[21]

Specific Hallucinogens

The term *hallucination* can be defined as false perception that has no basis in the external environment. The term is derived from the Latin â€œto wander in mind.â€• A hallucination is distinct from an illusion, which refers to mental impressions derived from the misinterpretation of an actual experience. Hallucinogenic substances may also have illusogenic effects. Although the term *psychedelic* has been used for years to refer to the recreational and nonmedical effects of hallucinogens, other terms, like entheogen, and entactogen, frequently appear in Internet discussions. Entheogens are â€œsubstances which generate the god or spirit within,â€• whereas entactogens create an awareness of â€œthe touch within.â€•[37]

Hallucinogens can be categorized by their chemical structures, and

further divided into natural and synthetic members of each family (Table 80-1). The major structural classes of hallucinogens include the lysergamides, indolealkylamines (tryptamines), phenylethylamines (amphetamines), arylhexamines, cannabinoids, harmine alkaloids, and the tropane alkaloids. In addition, there are several unique hallucinogens, such as Salvinorin A. This chapter focuses on lysergamides, tryptamines, phenylethylamines, and Salvinorin A. Further discussion of the other classes of hallucinogens can be found in Chaps. 73 and 81 .

Lysergamides

Lysergamides are derivatives of lysergic acid, a substituted tetracyclic amine based on an indole nucleus (Fig. 80-1). Naturally occurring lysergamides are found in several species of morning glory (*Rivea corymbosa* , *Ipomoea violacea*) and Hawaiian baby wood rose (*Argyreia nervosa*).[52] Morning glory seeds contain multiple alkaloids, including lysergic acid hydroxyethylamide and ergonovine. The morning glory seeds were called Ololiuqui in ancient Mexico, where Aztecs and other indigenous populations used them in religious rites.[101] However, in one volunteer study, Ololiuqui use predominantly caused sedation rather than hallucinations.[55]

Lysergamides
- D-Lysergic acid diethylamide (LSD)
- Lysergic acid hydroxyethylamide
  - *Ipomoea violacea* (morning glory)
  - Ololiuqui (South American morning glory)
- Ergine
  - *Argyreia* (Hawaiian baby wood rose)

Indolalkylamines/Tryptamines
- 5-Methoxy-*N,N* -dimethyltryptamine
- *N,N* -Dimethyltryptamine
- Psilocin
- Psilocybin

Phenylethylamines
- Mescaline
- MDMA (3,4-methylenedioxymethamphetamine)
- 2CB
- 2CT-7

Tetrahydrocannabinoids
- Marijuana
- Hashish

Belladonna alkaloids
- Jimsonweed (*Datura stramonium*)
- Henbane (*Hyoscyamus niger*)
- Deadly nightshade (*Atropa belladonna*)
- *Brugmansia* species

Miscellaneous
- *Salvia divinorum*
- *Ketamine*
- Phencyclidine (PCP)

TABLE 80-1. Xenobiotics Classified as Hallucinogens

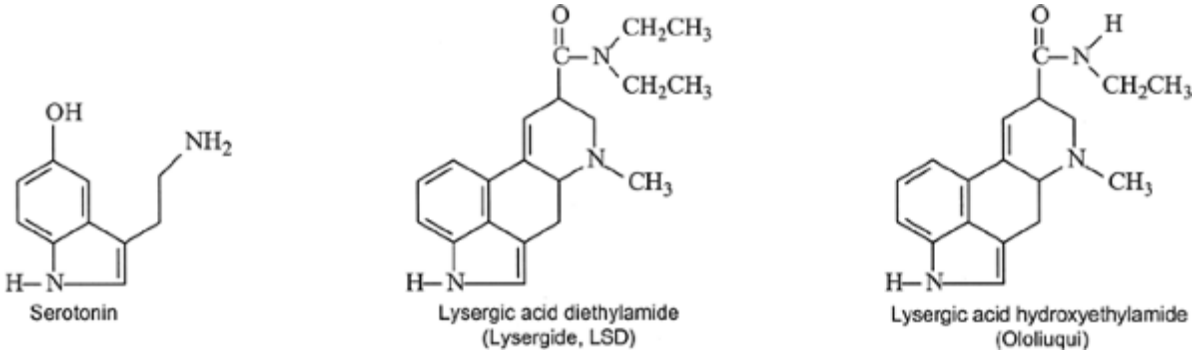

Figure 80-1. Hallucinogens of the lysergamide class and their chemical similarity to serotonin.

Ingestion of 200â€“300 morning glory seeds is required to achieve hallucinogenic effects. Hawaiian baby wood rose seeds contain ergine, and only 5â€“10 seeds are required to produce hallucinations. Ten

seeds may cost as little as 2 dollars. After ingestion of wood

rose seeds, the effects typically last for 6â€“8 hours, and produce tranquility without marked euphoria.[6] Both morning glory and Hawaiian baby wood rose seeds can be purchased legally in garden stores and on the Internet.

The synthetic lysergamide, LSD, is derived from an ergot alkaloid of the fungus *C. purpurea.* Although four LSD isomers exist, only the *d* isomer is active. Lysergic acid diethylamide is a water-soluble, colorless, tasteless, and odorless powder. Currently, LSD is typically sold as liquid-impregnated blotter paper, microdots, tiny tablets, â€œwindow paneâ€• gelatin squares, liquid, powder, or tablets.[91] Although LSD use has been reported via intravenous and intramuscular routes, ingestion of blotter paper is the most common route of abuse. The minimum effective oral dose is 25 Âµg.[60] The Drug Enforcement Administration reports that the current street dose of LSD ranges from 20â€“80 Âµg, which is lower than the 100â€“200 Âµg quantities reported during the 1960s and early 1970s.[32] The onset of effects may occur 30â€–60 minutes after exposure, with a duration of 10â€–12 hours after ingestion. LSD users typically experience heightened awareness of auditory and visual stimuli with size, shape, and color distortions. Auditory and visual hallucinations may occur, as well as synesthesia, a confusion of the senses, where users may describe â€œhearing colorsâ€• or â€œseeing sounds.â€• Other more complex perceptual effects may include depersonalization and a sensation of enhanced insight or awareness. A â€œbad tripâ€• may occur with any dose of LSD, and produce anxiety, bizarre behaviors, and combativeness.

LSD is classified as a Schedule I agent, with a high abuse potential, a lack of established safety even under medical supervision, and no known use in medical treatment.[110]

Indolealkylamines (Tryptamines)

Indolealkylamines, or tryptamines, represent a class of natural and synthetic compounds that structurally share a substituted monoamine group (Fig. 80-2). Endogenous tryptamines include serotonin and melatonin. Naturally occurring exogenous tryptamines include psilocybin, bufotenine, and dimethyltryptamine (DMT). Psilocybin is found in three major genera of mushrooms: *Psilocybe, Panaelous* , and *Conocybe* .[90] Other hallucinogenic mushrooms include *A. muscaria* and *A. pantherina* , which contain ibotenic acid, muscimol, and muscazone.[52] Toxic and hallucinogen mushrooms are discussed at length in Chapter 113 . Psilocybin-containing mushrooms, or â€œmagic mushrooms,â€• grow in the Pacific Northwest and the southern United States, usually in cow pastures. The mushroom may be recognized by a green-blue color that it assumes after bruising, but misidentification is common.[12] In the gastrointestinal tract, psilocybin is converted to psilocin, the active hallucinogen.[50] The effects of psilocin are similar to LSD, but with a shorter duration of action of about four hours.

DMT is a potent short-acting hallucinogen. It is found naturally in the bark of the Yakee plant (*Virola calophylla*), which grows in the Amazon basin and is used by shamans as a hallucinogenic snuff to â€œcommunicate with the spirits.â€•[90] DMT is also found in the hallucinogenic tea, Ayahuasca, which is used by indigenous healers in the Amazon Basin. In Ayahuasca, dimethyltryptamine-containing plants (eg, *Psychotria viridis*) are combined with plants containing harmine alkaloids (eg, *Banisteriopsis caapi*) that inhibit hepatic monoamine oxidases to increase the oral bioavailability of DMT (Chap. 69).[73] For current recreational purposes, DMT is typically smoked, snorted, or injected. By this route, its hallucinogenic effects peak in 5â€“20 minutes, with a duration of 30â€“60 minutes. This short duration of action has earned DMT the nickname â€œbusinessman's trip.â€•

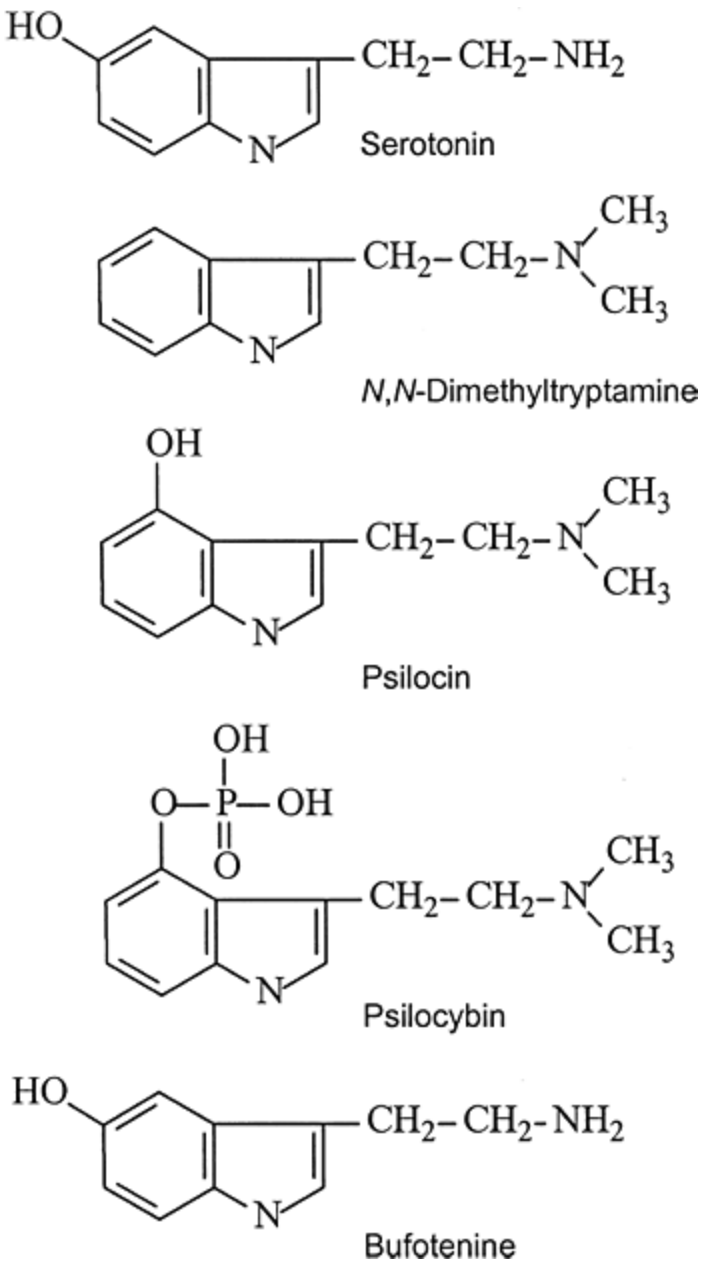

Figure 80-2. Hallucinogens of the indolalkylamine class and their chemical similarity to serotonin.

The use of toads in religious ceremonies and witchcraft dates back thousands of years. All species of the toad genus *Bufo* have parotid glands on their backs that produce a variety of xenobiotics, including dopamine, epinephrine, and serotonin.[70] Many of these toads produce

bufotenine, a tryptamine, which causes hypertension, but does not cross the bloodâ€“brain barrier. Interest in bufotenine grew out of reports of a toad-licking fad in the 1980s, in which individuals would reportedly lick toads for recreational purposes.[69] However, further review suggests that bufotenine is not the hallucinogenic substance found in toad secretions. Instead, 5-methoxydimethyl tryptamine (5-MeO-DMT), has been identified as the psychoactive substance.[116] 5-MeO-DMT is only found in one species of toad, *Bufo alvarius* (Sonoran Desert toad or Colorado River toad).[69] Although bufotenine is currently classified as a Schedule I substance by the United States Drug Enforcement Administration, 5-MeO-DMT is not scheduled.[77 , 105] Like DMT, 5-MeO-DMT is rapidly metabolized by intestinal monoamine oxidase enzymes; licking or ingesting toads skins would thus have limited potential as a route of recreational use.[21] Methods for extracting and drying *B. alvarius* secretions for smoking are available and on the Internet. The toad venom glands also produce cardioactive steroids, called bufadienolides, which may cause cardioactive steroid toxicity (Chap. 62), and in some species, can secrete tetrodotoxin.[75 , 119] Death has resulted from wrongful use of *Bufo* secretions for purposes of aphrodisia.[28 , 49]

Two of the more important synthetic tryptamines include *N,N* -diisopropyl-5-methoxytryptamine (5-MeO-DiPT, Foxy Methoxy), and Î±-methyltryptamine (AMT, IT-290). Since 2001, law enforcement authorities in more than 10 states have seized large amounts of 5-MeO-DiPT and AMT.[106] These xenobiotics are often sold surreptitiously as methylenedioxymethamphetamine (MDMA).

5-MeO-DiPT is usually ingested, but it can be smoked or insufflated. Effects begin 20â€“30 minutes after ingestion, and include disinhibition and relaxation. There is a dose-dependent response and at higher doses symptoms may be similar to LSD or MDMA, with mydriasis, euphoria, auditory and visual hallucinations, nausea, diarrhea, and jaw clenching.[79 , 95] The hallucinogenic effects are reported to last from 3â€“6 hours.[74 , 95 , 106] Other substances, such as sildenafil, Î³-

hydroxybutyrate, benzodiazepines, and marijuana, may be used to heighten or prolong the hallucinogenic effects of 5-MeO-DiPT.[68] 5-MeO-DiPT received Schedule I status in 2004.[109]

AMT is a monoamine oxidase inhibitor that was initially marketed as an antidepressant in the former Soviet Union.[94 , 106] AMT is available as a white powder that can be ingested, smoked, or insufflated. Despite its chemical similarity to DMT, the effects of AMT may last from 12â€“16 hours.[66] AMT was given Schedule I status by the DEA in September 2004.[109]

Phenylethylamines (Amphetamines)

Endogenous phenylethylamines include dopamine, norepinephrine, and tyrosine. Exogenous phenylethylamines are known for their ability to stimulate catecholamine release and cause a variety of physiologic and psychiatric effects, including hallucinations. Substitution on the phenylethylamine structure has important effects on both the hallucinogenic and stimulant potential of the xenobiotic. The presence of a methyl group in the side chain of the phenylethylamines is associated with a higher degree of hallucinogenic effect (Fig. 80-3).[59] MDMA, amphetamine and methamphetamine are well-known members of this family and are discussed in detail in Chap. 73 .

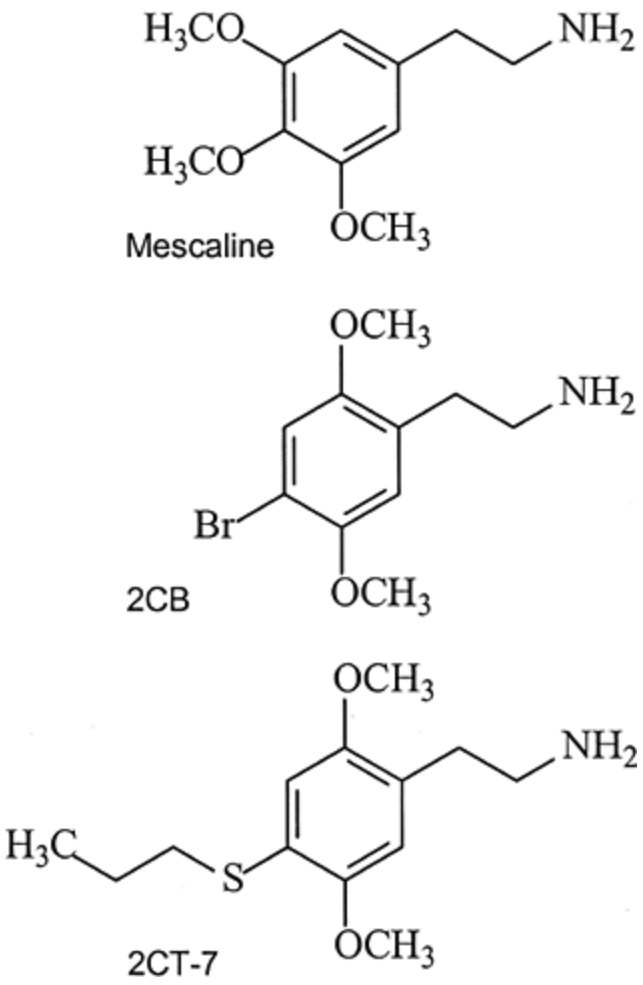

Figure 80-3. Hallucinogens of the phenylethylamine class.

The best recognized of the naturally occurring phenylethylamines is mescaline. Mescaline is found in peyote (*Lophophora williamsii*), a small, blue-green spineless cactus that grows in dry and rocky slopes throughout the southwestern United States and northern Mexico. Peyote buttons are the round, fleshy tops of the cactus that have been sliced off and dried. The bitter-tasting buttons are eaten whole or can be dried and crushed into a powder, which is reconstituted into a tea.[52] Nausea, vomiting, and diaphoresis often precede the onset of hallucinations. Six to 12 peyote buttons, or 270â€“540 mg of mescaline, are commonly required to produce hallucinogenic effects.[89] The legal use of peyote in the United States is restricted to the Native

American Church, where peyote buttons are used in religious ceremonies, and for medical treatment of physical and psychological ailments.[24, 26]

Other nonindigenous cactus species containing significant amounts of mescaline include the San Pedro cactus (*Trichocereus pachanoi*) and Peruvian torch cactus (*Trichocereus peruvianus*). These plants can be purchased in garden stores and on the Internet for ornamental purposes.[52]

However, the synthesis and effects of hundreds of other congeners of amphetamine have been described.[93] The best known of these synthetic hallucinogenic amphetamines are 4-bromo-2,5-dimethoxyphenethylamine (2CB, Nexus, Bromo, Spectrum), and 2,5-dimethoxy-4-*N*-propylthiopheneethylamine (2CT-7, Blue Mystic).

During the 1980s, 2CB gained popularity as a legal alternative to MDMA. When 2CB was given Schedule I status in 1995, 2CT-7 emerged as another legal designer amphetamine.[11] In March 2004, 2CT-7 also received Schedule I status.[31] Low doses of 2CB and 2CT-7 can produce hypertension, tachycardia, and visual hallucinations, while elevated doses are associated with shifts in color perception, enhanced auditory and visual stimulation, and even morbid hallucinations.

Salvia divinorum

Salvia divinorum is a perennial herb classified as a member of the mint family or *Labiatae.* Although there are more than 500 species of *Salvia*, *S. divinorum* is most recognized for its hallucinogenic properties. The plant is characterized by a height greater than 1 m, large green leaves, hollow square stems, and white flowers with purple calyces.[111] *S. divinorum* is a native to areas of Oaxaca, Mexico, and grows well in sunny, temperate climates (Fig. 80-4).

Since the 16th century, the Mazatec Indians have employed *S. divinorum* in religious rites as a means of producing visions.[111] The Mazatecs continue to revere *S. divinorum* as an incarnation of the

Virgin Mary, referring to the plant as Ska Maria Pastora. *S. divinorum* may be chewed, smoked, or ingested as tea. Hallucinations occur immediately after exposure to the xenobiotic and are typically quite vivid. Synesthesia, a confusion of the senses, like hearing colors or smelling sounds, has been reported among *Salvia* users.[33] However, this effect is not specific to *S. divinorum* , and has been reported with multiple other hallucinogens. Hallucinogenic effects after *S. divinorum* use are typically brief, lasting only 1â€“2 hours.

Currently, the Controlled Substances Act does not prohibit use of *S. divinorum* or its active ingredients. Nationwide regulation of this xenobiotic exists in Australia, and there is local legislation in some midwestern towns where use among teenagers is rampant.[108] There is widespread marketing of this hallucinogen on the Internet as a â€œlegal hallucinogen.â€•[33] Plants, leaves, and extracts may be purchased online, and tips for cultivation of plants are easily accessible.

Pharmacokinetics

LSD is the most studied hallucinogen, and there is extensive information about its pharmacokinetics. Ingestion is the most common route of exposure, and the gastrointestinal tract rapidly absorbs LSD. Other routes of administration include intranasal, parenteral, sublingual, smoking, and conjunctival instillation. Plasma protein binding is greater than 80% and volume of distribution is 0.28 L/kg. It is concentrated within the visual cortex, as well as the limbic and reticular activating systems. LSD is metabolized in the liver via hydroxylation and glucuronidation, and excreted predominantly as a pharmacologically inactive compound. LSD has an elimination half-life of about 2.5 hours. Only small amounts are eliminated unchanged in the urine.

Tolerance to the psychological effects of LSD occurs within 3 days with daily dosing, but rapidly dissipates if the xenobiotic is withheld for 2

days. Psychological cross-tolerance among mescaline, psilocybin, and LSD is reported in humans.[15] There is no evidence for physiologic tolerance, physiologic dependence, or a withdrawal syndrome with LSD. Limited tolerance is demonstrated between psilocybin and cannabinoids such as marijuana.[22]

There is little information about 2CB and 2CT-7 in the medical literature. Both drugs may be used via oral, intranasal, and intrarectal routes. Both 2CB and 2CT-7 exert their hallucinogenic effects within 1 hour of use, and physiologic and psychologic effects may persist for 6â€“10 hours. While specific pharmacokinetic data on 2CB and 2CT-7 are not available, the pharmacokinetics of other phenylethylamines may be similar. Amphetamine, methamphetamine, and MDMA are well absorbed through the GI tract. The elimination half-life ranges from 8â€“30 hours for members of this class, and is dependent on urine pH.[13,30] Amphetamines are weak bases, and undergo more rapid elimination in an acidic urine environment.[92] The volume of distribution ranges from 3â€“5 L/kg for amphetamine, 3â€“4 L/kg for methamphetamine, and is likely more than 5 L/kg for MDMA.[13,30,65,92] Elimination of other amphetamines occurs through multiple mechanisms including aromatic hydroxylation, aliphatic hydroxylation, and *N* -dealkylation.[65] Tolerance has been demonstrated in chronic amphetamine users.[61]

Pharmacokinetic data for *S. divinorum* have been described in one volunteer study. Psychoactive effects were typically experienced 5â€“10 minutes after absorption of Salvinorin A via the buccal mucosa, reaching a plateau during the first hour after exposure, and resolving within 2 hours. Vaporization and inhalation of Salvinorin A led to more rapid effects at 30 seconds after exposure. These effects would plateau at 5â€“10 minutes, and typically subside after 20â€“30 minutes. In this study, ingestion of *S. divinorum* leaves did not produce the same effects as buccal or inhalational administration, leading to the theory that gastrointestinal deactivation of Salvinorin A occurs after ingestion.[96] The pharmacokinetic characteristics of hallucinogens are summarized in Table 80-2 .

Ultrashort acting
DMT IV
1 min
5 min
30 min
Short acting
DMT IM
5â€“15 min
15â€“60 min
1â€“2 h
Intermediate acting
Psilocybin
15â€“30 min
1â€“3 h
6 h
Long acting
LSD; Mescaline
30â€–90 min
3â€–5 h
8â€–12 h
Ultralong acting
Ibogaine
2â€–4 h
4â€–8 h
18â€–24 h

Classification	Xenobiotic	Onset	Peak effect	Duration of effect

TABLE 80-2. Pharmacokinetic Classification of Hallucinogens

Pharmacology

Although the lysergamide, indolealkylamine, and phenylethylamine hallucinogens are structurally distinct, the similarities in their effects on cognition have led scientists to postulate a shared mechanism of action. Studies support a common site of action on central serotonin receptors.[5, 20, 25, 53, 102] Serotonin (5-HT) modulates many psychological and physiologic processes, including mood, personality, affect, appetite, motor function, sexual activity, temperature regulation, pain perception, sleep induction, and antidiuretic hormone release. There are more than 14 known 5-HT receptor subtypes; differing affinity for these subtypes occurs based on the structure of the hallucinogen, and may account for the subtle differences between their effects.

Another theory held by hallucinogen researchers was that the common site of action within the brain itself would involve the cerebral cortex, the area of the brain responsible for higher functions like cognition and mood. Alternatively, hallucinogens could affect subcortical areas, like the locus coeruleus found in the upper pons. The locus coeruleus is the part of the brain that responds to new stimuli and has projections throughout the entire cortex which affect cortical functioning.[72]

The lysergamide, indolealkylamine, and phenylethylamine hallucinogens all bind to the 5-HT_2 class of receptors. There is a good correlation between the affinity of both indolealkylamine and phenylethylamine hallucinogens for 5-HT_2 receptors in vitro and hallucinogenic potency in humans in vivo.[5, 46, 82, 102] Of the multiple subtypes of 5-HT_2 receptors, 5-HT_{2A} receptors are found with highest density in the cerebral cortex, making the 5-HT_{2A} receptor the most likely common site of hallucinogen action.[72] This theory is bolstered by an animal study that shows that a selective 5-HT_{2A} antagonist can inhibit the effects of LSD and a phenylethylamine, 2,5-dimethoxy-4-iodo-amphetamine (DOI). The response to high doses of LSD and DOI suggest that both lysergamides and phenylethylamines are partial agonists at cortical 5-HT_{2A} receptors.[47, 72, 87]

Although the majority of investigation has focused on the role of

serotonin for drug-induced hallucinations, other neurotransmitters are involved. Stimulation of 5-HT_{2A} receptors enhances release of glutamate in the cortical layer V pyramidal cells.[5, 10] LSD and other lysergamides stimulate both D_1 and D_2 dopamine receptors.[9, 45, 115] In animal models, LSD and phenylethylamine hallucinogens modulate *N*-methyl-D-aspartate (NMDA) receptor-mediated effects, and may have a protective effect against neurotoxicity secondary to phencyclidine (PCP) and ketamine.[10, 38] Another theory that incorporates these other neurotransmitters revolves around â€œthalamic filtering.â€• The thalamus receives input and output from the cortex and reticular activating system, and functions to filter relevant sensory input. This theory has been explored as an explanation for organic psychosis and the effects of hallucinogens. Multiple neurotransmitters, including dopamine, acetylcholine, Î³-aminobutyric acid (GABA), and

glutamate, exert their actions on the thalamus. Increased excitatory or decreased inhibitory neurotransmitter in this region of the brain may lead to â€œsensory overload,â€• which manifests itself clinically as symptoms of psychosis.[44]

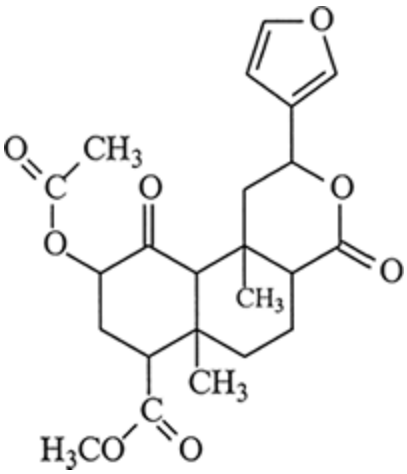

Figure 80-4. Salvinorin A.

The psychological effects of hallucinogens seem to represent a complex and elusive interaction between different neurotransmitters, including

the serotonergic and dopaminergic systems.

Based on this serotonergic mechanism, serotonin syndrome could theoretically occur after the use of any of the lysergamide, indolealkylamine, or phenylethylamine hallucinogens. Animal studies have documented LSD and tryptamine-induced serotonin syndrome.[97, 112] Case reports have linked phenylethylamine use to fatal serotonin syndrome in recreational users.[78, 114]

Salvinorin A, the psychoactive component of *S. divinorum*, is thought to be one of the most potent natural hallucinogens. The effect of Salvinorin A occurs via binding at the Î´ opioid receptor, making it structurally and mechanistically unique (Fig. 80-4).[86, 118] The Î´ opioid receptor is distinct from the Âµ opioid receptor, which generally mediates euphoria and analgesia (Chap. 38).

Clinical Effects

Physiologic changes accompany and often precede the perceptual changes induced by lysergamides, tryptamines, and phenylethylamines. The physical effects may be caused by direct drug effect or by a response to the disturbing or enjoyable hallucinogenic experience. Sympathetic effects mediated by the locus coeruleus include mydriasis, tachycardia, hypertension, tachypnea, hyperthermia, and diaphoresis. They may occur shortly after ingestion and often precede the hallucinogenic effects. Other reported clinical findings include piloerection, dizziness, hyperactivity, muscle weakness, ataxia, altered mental status, coma, and hippus, a rhythmic dilation and constriction of the pupils.[62] Nausea and vomiting often precede the psychedelic effects produced by psilocybin and mescaline.

Potentially life-threatening complications, such as hyperthermia, coma, respiratory arrest, hypertension, tachycardia, and coagulopathy, were described in a report of 8 patients with a massive LSD overdose.[58] Sympathomimetic effects are generally less prominent in LSD ingestion than in phenylethylamine toxicity. Similar sympathetic symptoms have

been described after the use of 2CB and 2CT-7. Three deaths are associated with 2CT-7 use; anecdotal reports suggest that 1 death may have resulted from seizures or aspiration.[31 , 36 , 104]

The vast majority of morbidity from hallucinogen use stems from trauma. Hallucinogen users frequently report lacerations and bruises sustained during their â€œhigh.â€• Additionally, dysphoric reactions may drive patients to react to stimuli with unpredictable, and occasionally aggressive, behaviors. Many Internet sites advise readers to take hallucinogens only while under the supervision of a â€œsitter.â€•

The psychological effects of hallucinogens are dose-related and affect changes in arousal, emotion, perception, thought process, and self-image. The response to the xenobiotic is related to the user's mindset, emotions, or expectations at the time of exposure, and can be altered by the group or setting.[2] A person experiencing the effects of a hallucinogen is usually fully alert, oriented, and aware that he or she is under the influence of a drug. Euphoria, dysphoria, and emotional lability may occur.

Perceptual distortions are common, typically involving distortion of body image and alteration in visual perceptions. Hallucinogen users may display acute attention to details with excessive attachment of meaning to ordinary objects and events. Usual thoughts seem novel and profound. Many people report an intensification of their sensory perceptions such as sound magnification and distortion. Colors often seem brighter with halolike lights around objects. Frequently, hallucinogen users relate a sense of depersonalization and separation from the environment, commonly called an â€œout-of-bodyâ€• experience. Synesthesia, or sensory misperception, occurs frequently and may include â€œhearingâ€• color or â€œseeingâ€• sounds. True hallucinations may occur and can be visual, auditory, tactile, or olfactory.

Acute adverse psychiatric effects of hallucinogens include panic reactions, true hallucinations, psychosis, and major depressive

dysphoric reactions. Acute panic reaction, the most common adverse effect, presents with frightening illusions, tremendous anxiety, apprehension, and a terrifying sense of loss of self-control.[46] These psychiatric effects may cause patients to seek care in the emergency department.

Differential Diagnosis

Hallucinosis is the abnormal organic mental condition of persistent hallucinations. The major causes of hallucinosis can be divided by etiology into structural, infectious, functional, and toxicâ€“metabolic. The diagnosis of hallucinogen exposure often must be established on the basis of history and physical examination alone. The person who has ingested hallucinogens typically is oriented and will often give a history of hallucinogen use. This stands in stark contrast to patients with xenobiotic-induced delirium, in whom orientation is, by definition, altered.

Xenobiotics such as amphetamine, cocaine, PCP, and anticholinergics produce delirium or psychosis at doses capable of producing hallucinations. Psychiatric or â€œfunctionalâ€• causes of perceptual changes, such as schizophrenia, typically present with auditory hallucinations. Patients with central anticholinergic toxicity usually present with disorientation, combative behavior, and incoherent mumbling, and may be unaware that the hallucinations are drug-induced.[60] The presence of marked hyperthermia, uncontrollable behavior, or extreme agitation should suggest phenylethylamine use, or an alternative drug exposure, such as cocaine or PCP.

Evaluation for other causes of altered mental status and hallucinations should include early exclusion of hypoglycemia, meningitis, intracerebral hemorrhage, thyrotoxicosis, sepsis, decompensated

psychiatric disease, withdrawal states and other toxic exposures. A lumbar puncture and computed tomography of the head are adjunctive tests that may be required in a case where the history of hallucinogen

exposure is unclear.

Laboratory

Routine drug-of-abuse screens do not detect LSD or other hallucinogens. Although LSD exposure can be detected by radioimmunoassay, confirmation by high-performance liquid chromatography or gas chromatography is necessary. These tests are rarely used in the clinical setting, but are much more common for forensic matters.[15, 34] False-positive urine testing for LSD has been reported after exposure to several medications including fentanyl, sertraline, haloperidol, and verapamil.[42, 85]

Depending on their structure, phenylethylamines may cause positive qualitative urine testing for amphetamines. However, amphetamine drug testing is associated with numerous false-positive results, particularly after the use of cold medications that contain ephedrine, pseudoephedrine, or phenylpropanolamine.[99] Gas chromatography-mass spectrometry testing methods for detection of 5-MeO-DiPT, DMT, AMT, 2CT-7, and 2CB have been described.[113]

There is currently no information on laboratory drug testing for *S. divinorum.*

Treatment

Most hallucinogen users do not seek medical attention because they experience only the desired effect of the drug. For any hallucinogen user who does present to the ED, initial treatment must begin with attention to airway, breathing, circulation, level of consciousness, and abnormal vital signs. Even when hallucinogen exposure is suspected, the basic approach to altered mental status should include dextrose, naloxone, and oxygen therapy as indicated, along with a vigorous search for other etiologies.

Hallucinogens rarely produce life-threatening toxicity. Sedation with benzodiazepines is usually sufficient to treat hypertension, tachycardia,

and hyperthermia. Benzodiazepines remain the cornerstone of therapy, as the sedating effect can diminish both endogenous and exogenous sympathetic effects.[76] Autonomic instability and hyperthermia may be a feature of phenylethylamine use, as well as tryptamine use or massive LSD overdose.[41 , 58 , 76] Hyperthermia resulting from agitation or muscle rigidity requires urgent sedation with benzodiazepines and rapid cooling. While CNS depression is unlikely to be severe enough to require endotracheal intubation in a patient with a pure hallucinogen exposure, intubation and paralysis may be required in the patient with intractable hyperthermia.[18] Seizures may occur with tryptamine or phenylethylamine use, and can be initially treated with benzodiazepines. Morbidity and mortality typically result from the complications of hyperthermia including rhabdomyolysis and myoglobinuric renal failure, hepatic necrosis, and disseminated intravascular coagulopathy. For the most part, however, hydration, sedation, a quiet environment, and meticulous supportive care will prove adequate to prevent mortality in recreational use or overdose.[27]

The patient with a dysphoric reaction can be placed in a quiet location with minimal stimuli. A nonjudgmental advocate should attempt to reduce the patient's anxiety, provide reality testing, and remind the individual that a drug was ingested and the effect will wear off in a couple of hours.[100] Significant agitation, dysphoria, or a â€œbad trip,â€• combined with signs of autonomic instability, can usually be treated by the administration of a benzodiazepine.[1] The role of antipsychotics in controlling hallucinogen-induced agitation is unclear. Haloperidol, risperidone, and ziprasidone may help control the acutely agitated patient. However, haloperidol and risperidone may worsen panic and visual symptoms, and increase the incidence of hallucinogen persisting perception disorder.[3] The safety of ziprasidone in hallucinogen users has not yet been reported. Although further study on these xenobiotics is required, prolonged psychosis may require treatment with long-term antipsychotic therapy.

Gastrointestinal decontamination with activated charcoal may be considered for asymptomatic patients with recent ingestions, but is

probably not helpful after clinical symptoms appear, and attempts may lead to further agitation. Excessive physical restraint should be avoided out of concern for hyperthermia and rhabdomyolysis.

Serotonin syndrome may occur after hallucinogen use, and has been described after LSD, tryptamine, and phenylethylamine use.[35, 78, 97, 112] Diagnosis begins with early identification of serotonin syndrome based on the constellation of symptoms. Treatment is largely supportive and symptomatic, and includes the avoidance of further administration of serotonergic medications. Specific therapy with agents like cyproheptadine may be warranted (Chap. 70).[19]

In comparison to the other hallucinogens, the high produced by *S. divinorum* is relatively mild. Symptoms severe enough to require treatment in the emergency department are uncommon, but may include agitation and confusion. Gastrointestinal decontamination with activated charcoal may be considered if presentation is early after ingestion or if coingestants are suspected. Agitation may be managed through administration of benzodiazepines. To date, no significant toxicity or death from *S. divinorum* use or overdose has been reported.

Long-Term Effects

Long-term consequences of LSD use include prolonged psychotic reactions, severe depression, and exacerbation of preexisting psychiatric illness.[51, 88] When LSD was initially popularized, some patients were noted to behave in a manner similar to schizophrenia and required admission to psychiatric facilities. In volunteer studies, panic reactions, hallucinogen persisting perception disorder, and extended psychoses were noted. When the xenobiotic was used for alleviation of anxiety and personality abnormalities, flashbacks and extended psychosis were reported.[40] Several authors have suggested that individuals who reacted this way to hallucinogen use may have had preexisting, compensated psychological disturbances.[5, 71]

Flashbacks have been reported in up to 80% of LSD users.[7]

Anesthesia, alcohol intake, and medications can precipitate flashbacks.[43] These abnormal perceptions can be triggered during times of stress, illness, and exercise, and are often a virtual recurrence of the initial hallucinations.

Hallucinogen-persisting perception disorder (HPPD) is a chronic problem associated with LSD abuse. According to the *Diagnostic and Statistical Manual 4th Edition* , the diagnosis of HPPD requires the recurrence of perceptual symptoms that were experienced while intoxicated with the hallucinogen that causes functional impairment and is not caused by a medical condition.[8] The etiology of HPPD is still unknown, and the reported incidence varies widely.

Symptoms are primarily visual, and reality testing is typically intact in HPPD. Common perceptual and visual disturbances in HPPD include geometric forms; false, fleeting perceptions in the peripheral fields; flashes of color; intensified color; and halos around objects.[71] One finding described after LSD use is palinopsia, or â€œtrailing,â€• which refers to the continued visual perception of an object after it has left the field of vision. Interestingly, these visual perceptions are associated with normal ophthalmologic examinations and abnormal EEG evaluations, suggesting a cortical etiology for the visual symptoms.

Although many drugs have been tried to treat patients with HPPD, most have not proven beneficial. However, there have been no randomized trials to compare the efficacy of different pharmacologic interventions in HPPD. Clonazepam reportedly improved symptoms of LSD-induced HPPD in one study of 16 patients.[63] Haloperidol and risperidone are associated with an exacerbation of panic and visual symptoms.[3 , 7] Clonidine may also be a therapeutic option for HPPD. Patients being treated with tricyclic antidepressants or selective serotonin reuptake inhibitors have an inconsistent response to therapy.[16 , 17]

Summary

Hallucinogens are a diverse group of xenobiotics that alter and distort

perception, thought, and mood without clouding the sensorium. The lysergamide, phenylethylamine, and tryptamine hallucinogens share a serotonergic mechanism of action; however, other neurotransmitters may be responsible for the complex effects of these hallucinogens. Salvinorin A, a novel hallucinogen, exerts its effects via the Î´ opioid receptor. Acute adverse psychiatric effects of hallucinogens include panic reactions, true hallucinations, psychoses, and major depressive dysphoric reactions. Hallucinogens rarely produce life-threatening problems, but have been known to cause autonomic instability, seizures, and hyperthermia, particularly in overdose. Meticulous supportive care with attention to abnormal vital signs is often the only therapy required. Long-term consequences of LSD use may include prolonged psychotic reactions, severe depression, exacerbation of preexisting psychiatric illnesses, and hallucinogen-persisting perception disorder.

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Chapter 81
Cannabinoids

Michael McGuigan

A 25-year old man was arrested for erratic driving on a city street. He was not involved in a crash or injured. On initial questioning the man stated that he was not drinking or using any other mind-altering substances. The police noted inappropriate smiling and atypical answers to their battery of standard questions. Although the man claimed that he was not intoxicated he was asked by the police to take a breath alcohol test, which was negative. However, his behavior was of sufficient concern to the police that they brought him to the emergency department (ED).

In the ED the patient was alert, oriented, and compliant with all requests. He stated that he had no medical problems and took no medication. He mentioned that he had used marijuana infrequently in the past, but that it had been at least 6 months since his last use. He denied the use of other drugs.

The patient had normal vital signs, including temperature. His pupils were normal and reactive, extraocular movements were intact, there was no nystagmus, and his sclera were minimally injected. He had a

supple neck and clear lungs. His neurologic examination including his gait, was normal. A bedside rapid glucose was 95 mg/dL.

At the request of the police, the patient's urine was sent to the hospital laboratory for analysis for drugs of abuse. The analysis results were positive for cannabinoids and negative for all other drugs assayed. The patient was charged with driving under the influence of drugs.

In court, the man was convicted of the charges on the grounds that in his deposition testimony he reiterated his claim that he had not used drugs for 6 months, yet had a positive urine toxicology test. Even if he was a heavy marijuana user, this 6 months was too long for an assay to remain positive. The man sued the hospital. See Chapter 135 for further discussion.

Cannabis is a collective term referring to the bioactive substances from *Cannabis sativa.* The *C. sativa* plant contains a group of more than 60 chemicals (C21 group) called cannabinoids. In this chapter, the term *cannabis* encompasses all cannabis products. The major cannabinoids are cannabinol, cannabidiol, and tetrahydrocannabinol. The principal psychoactive cannabinoid is Î”^{9}-tetrahydrocannabinol (THC). Marijuana is the common name for a mixture of dried leaves and flowers of the plant. Hashish and hashish oil are the pressed resin and the oil expressed from the pressed resin, respectively. The concentration of THC varies from 1% in low-grade marijuana up to 50% in hash oil. Pure THC and a synthetic cannabinoid are available as prescription drugs with the generic names of dronabinol and nabilone, respectively.

History and Epidemiology

Cannabis has been used for more than 4000 years. The earliest documentation of the therapeutic use of marijuana is the 4th century B.C. in China.[74] Cannabis use spread from China to India to North Africa, reaching Europe around 500 A.D.[63] In colonial North America,

cannabis was cultivated as a source of fiber.

Marijuana was used as an intoxicant from the 1850s until the 1930s when the US Federal Bureau of Narcotics began to portray marijuana as a powerful, addicting substance. Despite this, marijuana was listed in the *United States Pharmacopoeia* from 1850 to 1942. In 1970, The Controlled Substances Act classified marijuana as a Schedule I drug.

Currently, marijuana is the most commonly used illicit drug in the United States. A recent study by the Substance Abuse and Mental Health Services Administration[107] reported that 95 million persons age 12 years and older (40% of that population) had tried marijuana at least once. Of these, 94.6% were age 18 years and older. Approximately 14.6 million persons used marijuana in the month prior to the survey, 4.8 million of whom used it on 20 or more days in the month prior to the survey. The number of first-time users was estimated to be 2.6 million in 2001. These incidence figures have remained essentially unchanged since 1995.

Medical Uses

Cannabinoids are proposed for use in the management of many clinical conditions (Table 81-1), but have only been approved for the control of chemotherapy-related nausea and vomiting that are resistant to conventional antiemetics, for breakthrough postoperative nausea and vomiting, and for appetite stimulation in HIV patients with anorexia-cachexia syndrome. The claims of benefit in the other medical conditions in Table 81-1 are not supported by robust evidence.[5,36,56,120]

Pharmacology and Pathophysiology

Î”^{9}-THC (sometimes referred to in the literature as Î”^{1}-THC) was isolated in 1964. In the early 1990s, two specific cannabinoid-binding receptors were identified: CB1 (or *Cnr1*) and CB2 (or *Cnr2*).

Subsequent research identified endogenous cannabinoid receptor ligands (anandamide, palmitoylethanolamide), as well as cannabinoid receptor agonists and antagonists.[27,42,108]

CB1 receptors are distributed throughout the brain with high densities in the basal ganglia, substantia nigra, globus pallidus, cerebellum, hippocampus, and cerebral cortex (particularly the frontal regions). CB2 receptors are located peripherally in immune system tissues (splenic macrophages), peripheral nerve terminals, and the vas deferens. Both receptors inhibit adenylyl cyclase and stimulate potassium channel conductance.[88] CB1 receptors are located on the presynaptic side of central nervous system synapses and their activation inhibits the release of acetylcholine, L-glutamate, Î³-aminobutyric acid, noradrenaline, dopamine, and 5-hydroxytryptamine.[52,57,99] CB2 receptors are believed to participate in the regulation of immune responses and inflammatory reactions.

TABLE 81-1. Medical Conditions Proposed for Cannabinoid Use

Anorexia-cachexia syndrome secondary to HIV infection[a]
Asthma
Glaucoma
Nausea and vomiting (resistant)[a]
Neurologic disorders
Anxiety
Depression
Epilepsy
Head injury
Insomnia
Migraine headaches
Multiple sclerosis

	Muscle spasticity and spasms Pain Parkinson disease Tourette syndrome
[a]	FDA approved use.

The neuropharmacologic mechanisms by which cannabinoids produce their psychoactive effects have not been fully elucidated.[43,52,88] Nevertheless, activity at the CB1 receptors is believed to be responsible for the clinical effects of cannabinoids,[10,27,52,108] including the regulation of cognition, memory, motor activities, nociception, and nausea and vomiting. Chronic administration of a cannabinoid agonist reduces CB1 receptor density in several regions of the rat brain.[11]

Pharmacokinetics and Toxicokinetics

The pharmacokinetics of cannabinoids have been extensively reviewed.[35]

Absorption

The rate and completeness of absorption of cannabinoids depend on the route of administration and the type of cannabis product.

Inhalation of smoke containing THC results in the onset of psychoactive effects within minutes. From 10â€“35% of available THC is absorbed during smoking and peak plasma concentrations of THC occur an average of 8 (range: 3â€“10) minutes after the onset of smoking marijuana. Peak plasma levels depend on the dose; a marijuana cigarette containing 1.75% THC produces a peak plasma THC concentration of approximately 85 ng/mL.[46]

Ingestion of cannabis results in an unpredictable onset of

psychoactive effects in 1â€“3 hours. Because of THC's instability in acidic gastric fluid and first-pass hepatic clearance,[85] 5â€“20% of available THC reaches the systemic circulation following ingestion. Peak plasma concentrations of THC usually occur 2â€“4 hours after ingestion but delays up to 6 hours are described.[31,64] The therapeutic serum concentration of THC for the treatment of nausea and vomiting is greater than 10 ng/mL.[17]

Dronabinol has an oral bioavailability of approximately 10% with high interindividual variability.[35,85] Peak plasma concentrations occur 2â€“3 hours after ingestion. Nabilone has an oral bioavailability estimated to be greater than 90% and reaches peak plasma concentrations 2 hours after ingestion.[98]

Distribution

THC has a steady-state volume of distribution of approximately 2.5â€“3.5 L/kg.[35] Previous estimates of up to 10 L/kg are considered erroneous because of inaccuracy of the quantitative method used. THC is 98% bound, primarily to plasma lipoproteins. Cannabinoids are lipid soluble and accumulate in fatty tissue in a biphasic pattern. Initially, THC is distributed to highly vascularized tissues (eg, liver, kidneys, heart, muscle). Following smoking or intravenous administration, the distribution half-life is less than 10 minutes.[46,85] After the initial distribution phase, THC accumulates more slowly in less vascularized tissues and body fat. Repeated administration of Î”^{8}-THC (an isomer of Î”^{9}-THC) to rats over 2 weeks resulted in steadily increasing concentrations of Î”^{8}-THC in body fat and liver, but not in brain tissue. Once administration of Î”^{8}-THC stopped, the cannabinoids were slowly released from fat stores as adipose tissue turned over.[84]

THC crosses the placenta and enters the breast milk. Concentrations in fetal serum are 10â€“30% of maternal concentrations. Daily marijuana smoking by a nursing mother resulted in concentrations of THC in breast milk that are 8-fold higher than concomitant maternal

serum concentrations; THC metabolites do not accumulate in breast milk.[90]

Metabolism

THC is nearly completely metabolized by hepatic microsomal hydroxylation and oxidation by the cytochrome P450 (CYP) system (primarily CYP2C).[35] The primary metabolite (11-hydroxy-Î”^{9}-THC or 11-OH-THC) is active and is subsequently oxidized to the inactive 11-nor-Î”^{9}-THC carboxylic acid metabolite (THC-COOH) and many other metabolites.[1,3,93]

The plasma concentrations of THC and its metabolites change over time. Smoking a marijuana cigarette results in peak plasma concentrations of THC before finishing the cigarette. In 6 volunteers, peak plasma concentrations of THC occurred at 8 (range: 6â€“10) minutes after onset of smoking, of 11-OH-THC at 13 (range: 9â€“23) minutes, and of THC-COOH at 120 (range: 48â€“240) minutes[46] (Fig. 81-1). Approximately 1 hour after beginning to smoke a marijuana cigarette, the THCâ€“toâ€“11-OH-THC ratio is 3:1 and the THCâ€“toâ€“THC-COOH ratio is 1:2; at approximately 2 hours the ratios are 2.5:1 and 1:8, respectively; at 3 hours the ratios are 2:1 and 1:16, respectively.[46]

Ingestion of cannabis results in much more variable concentrations and time courses of THC and metabolites (Fig. 81-1). Nonetheless, at 2â€“3 hours postingestion the ratios are similar to those after smoking: THCâ€“toâ€“11-OH-THC is 2:1 and THCâ€“toâ€“THC-COOH ranges from 1:7 to 1:14.[31,116]

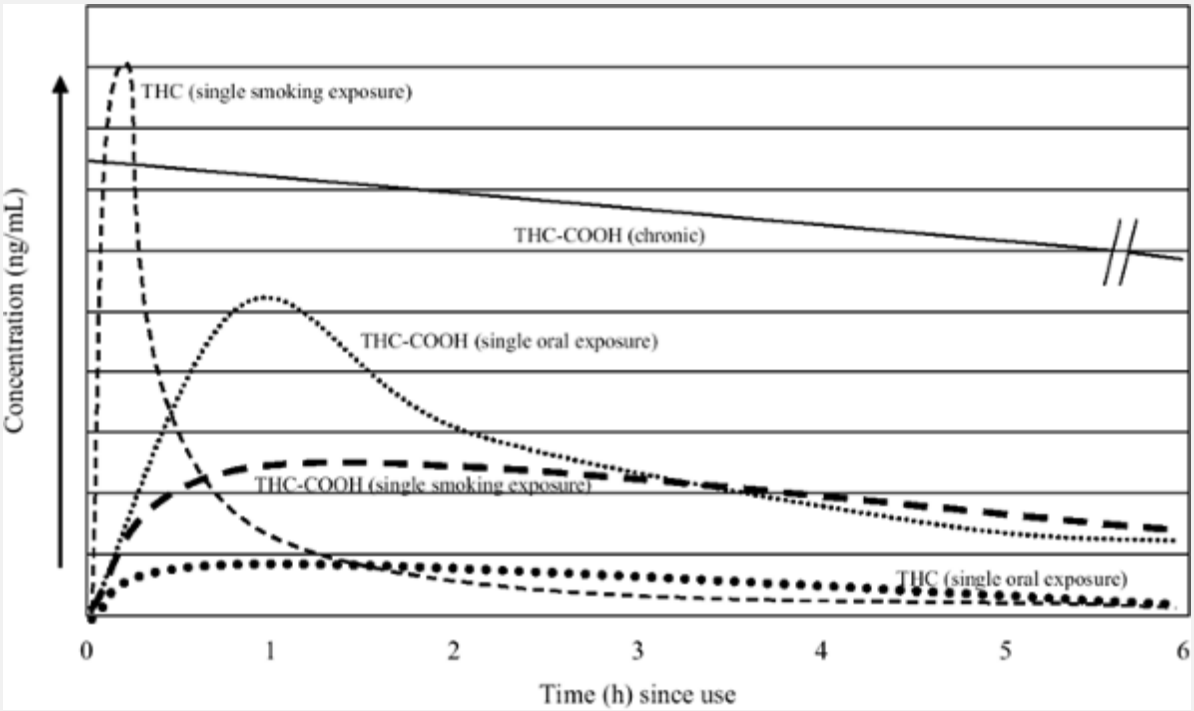

Figure 81-1. Estimated relative time course of THC and its major metabolite based on the route of exposure.

----------THC (single smoking exposure);----------THC-COOH (single smoking exposure);

----------THC (single oral exposure);----------THC-COOH (single oral exposure);

----------THC-COOH (chronic exposure).

Excretion

Reported elimination half-lives of THC and its major metabolites vary considerably. Following intravenous doses of THC, the mean elimination half-life ranges from 1.6â€“57 hours.[35] Elimination half-

lives are expected to be similar following inhalation.[35,46] The elimination half-life of 11-OH-THC is 12â€“36 hours and the elimination half-life of THC-COOH ranges from 1â€“6 days.[58,116]

THC and its metabolites are excreted in the urine and the feces. In the 72 hours following ingestion, approximately 15% of a THC dose is excreted in the urine and roughly 50% is excreted in the feces.[1,15,116] Following intravenous administration, approximately 15% of a THC dose is excreted in the urine and only 25â€“35% is excreted in the feces.[116] Inhalation is expected to produce results similar to intravenous administration.[35,46] In 5 days, 80â€“90% of a THC dose is excreted from the body.[40,50]

Cannabinoids were measured in the urine following smoking a marijuana cigarette containing 27 mg of THC[70] (Fig. 81-1). THC urine concentrations peaked at 2 hours (mean: 21.5 Âµg/L; range: 3.2â€“53.3 Âµg/L) after smoking and were undetectable (<1.5 ng/mL) in 5 of the 8 subjects by 6 hours after smoking. Urine concentrations of 11-OH-THC peaked at 3 hours (77.3Â± 29.7 Âµg/L). The primary urinary metabolite is the glucuronide conjugate of THC-COOH.[119] THC-COOH urine concentrations peak at 4 hours (179.4 Â± 146.9 Âµg/L)[70] and it has an average urinary excretion half-life of 2â€“3 days (range: 0.9â€“9.8 days).[35] Both 11-OH-THC and THC-COOH remained detectable in the urine of all 8 subjects for the 8 hours of the study.[70]

Following discontinuation of use, metabolites may be detected in the urine of chronic users for several weeks.[26,53] Factors such as age, weight, and use more than once a day only partially explained the long excretion period.[26]

Clinical Manifestations

The clinical effects of THC use, including time of onset and duration of effect, vary with the dose, the route of administration (ingestion is slower in onset than inhalation), the experience of the user, the

user's vulnerability to psychoactive effects, and the setting in which the drug is used. The concomitant use of central nervous system depressants such as ethanol, or stimulants such as cocaine, alters the psychological and physiologic effects of cannabis.

Psychological Effects

Use of cannabis produces variable psychological effects.[33] The variation, which occurs both between and within users, may be a result of drug tolerance, level or phase of intoxication, physical and social settings, or user expectations or cognitive set. The most commonly self-reported effect is relaxation. Other commonly reported effects are perceptual alterations (heightened sensory awareness, slowing of time), a feeling of well-being (including giddiness or laughter), and increased appetite.[33]

Physiologic Effects

Use of cannabis is associated with physiologic effects on cerebral blood flow, the heart, the lungs, and the eyes.

In a controlled double-blind positron emission tomography study,[71] intravenous THC increased cerebral blood flow, particularly in the frontal cortex, insula, cingulate gyrus, and subcortical regions. These increases in cerebral blood flow occurred 30â€“60 minutes after dosing and were still elevated at 120 minutes.[72] Similar blood flow changes result from smoking marijuana.[87]

Common acute cardiovascular effects of cannabis use include increases in heart rate and decreases in vascular resistance.[55,104] Cannabis produces dose-dependent increases in heart rate within 15 minutes of starting a marijuana cigarette (from a baseline mean of 66 beats/min to a mean of 89 beats/min) that reach a maximum (mean: 92 beats/min) 10â€“15 minutes after peak plasma THC concentrations. These changes last for 2â€“3 hours.[7] Increases in

blood pressure may occur with cannabis use. In a study of 6 subjects, an increase in blood pressure from a baseline mean of 119/74 mm Hg to a mean of 129/81 mm Hg occurred, but was not statistically significant.[7] In a double-blind, controlled study of ten men being investigated for angina pectoris, smoking a marijuana cigarette resulted in statistically significant changes in blood pressure from a baseline mean of 123/79 mm Hg to a peak mean of 132/84 mm Hg.[94] In contrast, repeated THC ingestions resulted in significant slowing of heart rate (from a mean of 68 beats/min to a low of 62 beats/min) and lowering of blood pressure (from a mean of 116/62 mm Hg to a low of 108/53 mm Hg).[8] Decreased vascular tone may cause postural hypotension accompanied by dizziness and syncope.

THC administered through inhalation or ingestion produces a dose-related short-term decrease in airway resistance and an increase in airway conductance in both normal and asthmatic individuals,[110] although the mechanism is not clear. Smoking marijuana results in an immediate increase in airway conductance, which peaks at 15 minutes and lasts 60 minutes; ingestion of cannabis produces a significant increase in airway conductance at 30 minutes, which peaks at 3 hours and lasts 4 to 6 hours.[111,112]

The principal ocular effects of cannabis are conjunctival injection and decreased intraocular pressure. Cannabinoids, applied topically to a rabbit eye, resulted in hyperemia of the conjunctival blood vessels 2 hours after application.[77] Inhaled, ingested, or intravenous cannabis causes a fall in intraocular pressure in 60% of users[34] by acting on CB1 receptors in the ciliary body.[92] The mean reduction in intraocular pressure is 25% and lasts 3â€“4 hours.

Acute Toxicity

In addition to the physiologic and psychological effects described above, acute toxicity may include decreases in coordination, muscle strength, and hand steadiness. Lethargy, sedation, postural

hypotension, inability to concentrate, slurred speech, and slow reaction time also may occur.[83,117]

In young children, the acute ingestion of cannabis is potentially life-threatening.[54,73] Ingestion of estimated amounts of 250â€“1000 mg of hashish resulted in obtundation in 30â€“75 minutes. Tachycardia (>150 beats/min) was found in one-third of the children. Less commonly reported findings include apnea, cyanosis, bradycardia, hypotonia, and opisthotonus.

Acute Adverse Reactions

Cannabis users occasionally may experience distrust, dysphoria, fear, or panic reactions. Transient psychotic episodes are associated with cannabis use. Commonly reported adverse reactions to the prescribed dose of dronabinol or nabilone include postural hypotension, dizziness, sedation, xerostomia, abdominal discomfort, nausea, and vomiting.

One case of acute pancreatitis (serum amylase up to 3200 IU/mL) following a period of heavy cannabis use is reported, but the causal relationship is unclear.[32]

Life-threatening ventricular tachycardia (200 beats/min) has been reported.[95] In 6 individuals with acute cardiovascular deaths, postmortem whole-blood THC concentrations ranged from 2â€“22 Âµg/L (mean: 7.2 Âµg/L; median: 5 Âµg/L).[4] While the temporal association is clear, causality is less clear because 3 of the 6 people had significant preexisting cardiac pathology. The risk of myocardial infarction is increased 5 times over baseline in the 60 minutes after marijuana use, but subsequently declines rapidly to baseline risk levels.[78] Atrial fibrillation with palpitations, nausea, and dizziness was temporally associated with smoking marijuana in 3 patients.[62,105]

Chronic Use Adverse Effects

Long-term use of cannabis is associated with a number of adverse effects.

Immune System

Cannabinoids affect host resistance to infection by modulating the secondary immune response (macrophages, T and B lymphocytes, acute phase and immune cytokines). However, an immune-mediated health risk from using cannabis has not been documented.[60]

Respiratory System

Smoking marijuana delivers more particulates to the lower respiratory tract than does smoking tobacco[122] and marijuana smoke contains carcinogens similar to tobacco smoke. Case reports and a hospital-based case-control study suggest that cancers of the respiratory tract (mouth, larynx, sinuses, lung) are associated with the regular smoking of marijuana, although exposure to tobacco smoke and ethanol may be confounding factors.[16,110,113] A recent cohort study with 8 years of followup demonstrated no association between marijuana smoking and smoking-related cancers,[38] and a recent population-based case-control study found that marijuana use was not associated with an increased risk of developing oral squamous cell carcinoma.[97]

Reproductive System

Reduced fertility in chronic users is a result of oligospermia, abnormal menstruation, and decreased ovulation.[13]

Cannabis is a Class C drug in pregnancy[12] and affects birthweight and length but does not cause fetal malformations. Statistically significant reductions in birthweight (mean: 79 g less than nonusers) and length (mean: 0.5 cm shorter than nonusers) are reported in women who had urine assays positive for cannabis during pregnancy.[123] The results of three other studies are difficult to

interpret because marijuana use in pregnancy was poorly documented.[39,42,121] Epidemiologic studies based on self-reporting of cannabis use do not support an association between the use of cannabis during pregnancy and teratogenesis.[61,67,121,123]

The effect of maternal use of cannabis during pregnancy on neurobehavioral development in the offspring has been studied. No detrimental effects are reported in children born to heavy marijuana users in rural Jamaica.[24] Tremors and increased startling are reported in infants younger than 1 week of age whose mothers used cannabis during pregnancy.[29] There were no abnormalities in the children of heavy users (>5 joints per week) in Ottawa, Canada

at 12, 24, and 36 months of age, but lower scores in verbal and memory domains at 48 months are reported.[28,40] The results of studies evaluating the effect of in utero exposure to cannabis on postnatal neurobehavioral development are equivocal because of methodologic concerns regarding exposure assessment and control of covariates,[23] including the continued parental use of cannabis during the postnatal and early childhood periods. The role of postnatal and early childhood secondhand exposure to cannabis in the development of neurobehavioral problems has not been evaluated.

Endocrine System

In experimental animals, cannabis exposure is associated with suppression of gonadal steroids, growth hormone, prolactin, and thyroid hormone; in addition, cannabis alters the activity of the hypothalamicâ€“pituitaryâ€“adrenal axis.[13] In human studies, the results are inconsistent, long-term effects have not been convincingly demonstrated, and clinical consequences are undefined.[13]

Neurobehavioral Effects

There is a concern that chronic cannabis use results in deficits in

cognition and learning that last well after cannabis use has stopped. Neuropsychological tests administered to 10 cannabis-dependent adolescents, 8 adolescent noncannabis drug abusers, and 9 nondrug users showed significant differences that persisted for the duration of the study (6 weeks of abstinence) between the cannabis group and the other groups in a visual retention test and a memory test.[102] In a study of 3 experienced marijuana smokers, cannabis impaired arithmetic and recall tasks up to 24 hours after smoking.[41] Adults who were heavy cannabis users (more than 7 uses/wk) had impairments in math skills, verbal expression, and memory retrieval processes; light and intermediate users showed no impairments.[9] After 1 day of abstinence, 65 heavy marijuana users (median: use on 29 of past 30 days) showed greater impairment than light marijuana users (median: use on 1 day of past 30 days) on neuropsychological tests of attention and executive functions.[91] The authors were uncertain whether this difference was caused by residual xenobiotic in the brain, a withdrawal effect from the drug, or a direct neurotoxic effect of cannabis.

An â€œamotivationalâ€• syndrome is attributed to cannabis use. The syndrome is a poorly defined complex of characteristics such as apathy, underachievement, and lack of energy.[19,101] The association of the syndrome with cannabis use is based primarily on anecdotal uncontrolled observations.[44] Anthropologic field studies, evaluations of US college students, and controlled laboratory experiments have failed to identify a causal relationship between cannabis use and the amotivational syndrome.[44] A study evaluating the role of depression in the amotivational syndrome found significantly lower scores on â€œNeed for Achievementâ€• scales in heavy users (median: daily use for 6 years) with depressive symptoms compared to heavy users without depressive symptoms and light users (median: several times per month for 4.5 years) with or without depressive symptoms.[82] These data suggest that symptoms attributed to an amotivational syndrome are caused by depression, not cannabis. Another study found that behavior that could be interpreted as amotivation was

inversely related to the perceived size of the reward.[19]

Abuse, Dependence, and Withdrawal

The *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*[2] defines marijuana abuse as repeated instances of use under hazardous conditions; repeated, clinically meaningful impairment in social/occupational/educational functioning; or legal problems related to marijuana use. Marijuana dependence is defined as tolerance, compulsive use, impaired control, and continued use despite physical and psychological problems caused or exacerbated by use. The prevalence of marijuana use disorders increased significantly between 1992 and 2002 among black men and women and among young Hispanic men.[21]

The amount, frequency, and duration of cannabis use required to develop dependence are not well established.[18,109] Much of the support for cannabis dependence is based on the existence of a withdrawal syndrome. In animals repeatedly given cannabis, the administration of a CB1 receptor antagonist produced signs of withdrawal.[66,106] In humans, chronic users experience unpleasant effects when abstaining from cannabis. The time of onset of withdrawal symptoms is not well characterized.[13,106] The most reliably reported effects are irritability-restlessness-nervousness and appetite and sleep disturbances.[106] Other reported acute withdrawal manifestations include tremor, diaphoresis, fever, and nausea. These symptoms and signs are reversed by the oral administration of THC.[37] The duration of withdrawal manifestations, without treatment, is not clearly established.[14,106]

Cannabis and Driving

The perceptual alterations caused by cannabis suggest that its recent use should be associated with automobile crashes. However, neither experimental nor epidemiologic studies have provided definitive answers about the effects cannabis use has on driving ability. The

published analytical studies of the relationship between cannabis and driving behavior/motor vehicle crashes have been reviewed.[6] In experimental driving studies, cannabis impairs driving ability but cannabis-using drivers recognize their impairment and compensate for it by driving at slower speeds and increasing following distance. However, the slower reaction time caused by cannabis results in impaired emergency response behavior.

The epidemiologic studies evaluating the association of cannabis use and traffic crashes provide no evidence that cannabis alone increases the risk of causing fatal crashes or serious injuries.[6,86] Studies of 2500 drivers injured in multiple vehicle crashes found that those with blood tests positive for THC had no higher culpability rate than xenobiotic-free drivers.[68,69] A recent study comparing past driving records of subjects entering a drug treatment center with controls found that a self-reported history of cannabis use was associated with a statistically significant increase in adjusted relative risk for all crashes (relative risk 1.49, 95% confidence interval 1.17â€“1.89) and for â€œat faultâ€• crashes (relative risk 1.68, 95% confidence interval 1.21â€“2.34).[20]

The results of studies evaluating the effect of a combination of cannabis and ethanol are contradictory.[6] One study supported potentiation of effects,[114] one could not evaluate the role of xenobiotics other than ethanol,[118] and one did not support potentiation.[51]

Diagnostic Testing

Cannabinoids can be detected in plasma or urine. Enzyme-multiplied immunoassay technique (EMIT) and radioimmunoassay (RIA) are routinely available; gas chromatography-mass spectrometry (GC/MS) is the most specific assay and is used as the reference method.

EMIT is a qualitative urine test that is often used for screening purposes. EMIT identifies the metabolites of THC. In these tests, the

concentrations of all metabolites present are additive. For the Emit II Cannabinoid 20-ng Assay, the cutoff level for distinguishing positive from negative samples is 20 ng/mL. A positive test means that the total concentration of all the metabolites present in

the urine was at least 20 ng/mL. A positive urine test for cannabis only indicates the presence of cannabinoids, it does not identify which metabolites are present or in what concentrations. Qualitative urine test results do not indicate or measure intoxication or degree of exposure. The National Institute on Drug Abuse guidelines for urine testing specify test cut-off concentrations of 50 ng/mL for screening and 15 ng/mL for confirmation.

Variables affecting the duration of detection of urinary metabolites include dose, duration of use, acute versus chronic use, route of exposure, and sensitivity of the method. In addition, factors affecting the quantitative values of urine THC and metabolites include urine volume, concentration, and pH. Using GC/MS, metabolites may be detected in the urine up to 7 days following a single marijuana cigarette.[48,49]

The length of time between stopping cannabis use and a negative EMIT urine test (<20 ng/mL) depends on the severity of use. Release of THC from adipose tissue is important in drug testing because chronic users may release cannabinoids in quantities sufficient to result in positive urine tests for several weeks. In addition, vigorous exercise may stimulate the release of cannabinoids from fat depots. In light users being tested daily under observed abstinence, the mean time to the first negative urine test is 8.5 days (range: 3â€“18 days) and the mean time to the last positive urine is 18.2 days (range: 7â€“34 days).[26] In heavy users (mean: 9 years of using at least once a day) being tested under the same conditions, the mean time to the first negative urine test result (EMIT assay <20 ng/mL) was 19.1 days (range: 3â€“46 days) and the mean time to the last positive urine sample was 31.5 days (range: 4â€“77 days).[26]

Standard laboratory analyses identify THC and its metabolites but cannot identify the source of the THC (eg, marijuana, hashish, dronabinol). EMIT will not identify nabilone because it is not THC; however, nabilone can be specifically identified using high-performance liquid chromatography-tandem mass spectrometry.[96]

Immunoassays may give false-negative and false-positive test results (Table 81-2). To help identify evidence tampering, negative urine immunoassays should be accompanied by examining the urine for clarity and measuring urinary specific gravity, pH, temperature, and creatinine.[103,115]

TABLE 81-2. Xenobiotics or Conditions Purported to Produce Inaccurate Screening Test Results

False Negative[a]	False Positive
Bleach (NaOCl)	Dronabinol
Citric acid	Efavirenz
Detergent additives	Ethacrynic acid
Dettol[b]	Hemp seed oil
Dilution	NSAIDs
Glutaraldehyde	Promethazine
Lemon juice	Riboflavin

Potassium nitrite (KNO_3)	
Salt (NaCl)	
Tetrahydrozoline	
Vinegar (acetic acid)	
Water	

[a] Xenobiotics producing false-negative urine tests are usually added to a urine sample, not ingested.
[b] Dettol is an antiseptic containing isopropyl alcohol (8â€“11%), pine oil (8.4%), and chloroxylenol (4.8%).

Passive Inhalation

Studies of passive exposure to marijuana smoke and the urinary excretion of cannabinoids have used enclosed spaces with nonsmokers present during and after active smoking.[22,65,80,81,89]

In an unventilated 6.9 Ã— 8.2 Ã— 7.9-foot room (12,225.8 L of air), 5 adult volunteers were exposed to the sidestream smoke of 4 or 16 marijuana cigarettes (THC 25 mg/cigarette) smoked simultaneously over 1 hour on each of 6 consecutive days.[22] After being exposed to 4 marijuana cigarettes, 4 of the volunteers had at least 1 positive urine by EMIT assay (cut-off: 20 ng/mL) at some unspecified time during the 6 study days; exposure to 16 marijuana cigarettes resulted in positive EMIT assays only after the second day's exposure.

In a car (1650 L of air), 3 adult volunteers were exposed to the

smoke from 12 marijuana cigarettes smoked by 2 people over 30 minutes.[80] EMIT analyses of urine samples from 1 passive inhaler were positive at time 0â€“4 hours and on days 2 and 3; a second passive inhaler had 1 positive urine test at time 4â€“24 hours after exposure.

Three adult volunteers in a 10 Ã— 10 Ã— 8-foot unventilated room (21,600 L of air) were exposed to the sidestream smoke of 4 marijuana cigarettes (THC 27 mg/cigarette) smoked simultaneously over 1 hour.[81] The concentrations of cannabinoids in urine samples taken 20â€“24 hours after exposure were less than 6 ng/mL when analyzed using RIA methodology.

Another study used an unventilated room (total volume of 27,950 L) containing 3 desks and a filing cabinet.[65] Over 10â€“34 minutes, each of 6 volunteers smoked a marijuana cigarette (THC 17.1 mg/cigarette) and left the room. Four nonsmoking adult males were in the study room for 3 hours from the start of smoking. The door was opened and closed 18 times during the study. The maximum urine cannabinoid concentration (measured by RIA) in the nonsmokers was 6.8 ng/mL at 6 hours after the start of smoking.

Another study used a closed 8 Ã— 8 Ã— 10-foot room (15,500 L of air) with each of 4 subjects smoking 2 marijuana cigarettes containing 2.5% THC on one occasion and 2.8% THC on a second occasion.[89] On each occasion, 2 nonsmoking subjects were in the room for 1 hour from the onset of smoking. None of the nonsmokers' urine samples (from 0â€“24 hours) from either exposure period tested positive on an EMIT assay with a cut-off of 20 ng/mL. An identical experiment in a closed car (approximately 3500 L of air) resulted in 1 of 23 urine specimens testing positive at 6 hours.

Saliva

Saliva samples may be used to establish the presence of cannabinoids and time of cannabis consumption. Cannabinoids (THC,

THC-COOH, 11-OH-THC) in saliva may be from the smoke of the marijuana or hashish or from a preliminary metabolism in the mouth.[100] Saliva THC concentrations above 10 ng/mL are consistent with recent use and correlate with subjective intoxication and heart rate changes.[75]

Hair

Hair sample analysis is not useful in identifying THC or its metabolites. Only small quantities of nonâ€“nitrogen-containing substances, such as cannabinoids, are found in hair pigments.[25,59,76]

Sweat

The analysis of perspiration to test for cannabinoids is a recent development. Perspiration deposits drug metabolites on the skin and

these are renewed even after the skin is washed. Detection threshold is reported to be 10 ng/mL but forensic confirmation by alternative means is required.[59]

Estimating Time of Exposure

A measurable serum concentration of THC is consistent with recent exposure and intoxication but there is poor correlation between serum THC concentrations and degree of intoxication.[45]

The ratio of THC to THC-COOH has been used to estimate time of smoking marijuana. Similar concentrations of each indicate cannabis use within 20â€“40 minutes and imply intoxication. In naive users, a concentration of THC-COOH that is greater than THC indicates that use probably occurred more than 30 minutes ago. Serum THC-COOH concentrations >40 ng/mL suggest chronic cannabis use.[79] The high background concentrations of THC-COOH in habitual users make estimations of time of exposure unreliable in this population.

Serum concentrations of THC and THC-COOH were used in a logarithmic equation to predict the time since smoking a marijuana cigarette.[70] The ratio provided acceptable results up to 3 hours after smoking (predicted time of exposure averaged 27 minutes longer than actual exposure time) but more than 3 hours after smoking the predicted exposure time was overestimated by 3 hours. Mean overestimations of predicted exposure time of 2.5â€“4.2 hours for smoking and of 1.6 hours for ingestions are reported when serum samples are taken more than 4 hours after exposure.[47]

Chronic use or oral administration of cannabis increases the concentration of 11-OH-THC relative to the concentrations of THC or THC-COOH. In these cases, estimating time of exposure based on relative concentrations is problematic. In 4 subjects, ingestion of cannabis produced total metabolite plasma concentrations less than 20 times the plasma concentration of THC for 3 hours after ingestion, suggesting that a ratio of this magnitude is consistent with recent oral consumption.[64]

Management

Gastrointestinal decontamination is not recommended for patients who ingest cannabis products, nabilone, or dronabinol because clinical toxicity is rarely serious and responds to supportive care. In addition, a patient with a significantly altered mental status, such as somnolence, agitation, or anxiety, has risks associated with gastrointestinal decontamination that outweigh the potential benefits of the intervention.

Agitation, anxiety, or transient psychotic episodes should be treated with quiet reassurance and benzodiazepines (lorazepam 1â€“2 mg IM or diazepam 5â€“10 mg IV) or antipsychotics (haloperidol, ziprasidone) as needed. There are no specific antidotes for cannabis. Coingestants, such as cocaine or ethanol, should be identified and their effects anticipated and treated as indicated.

Summary

Cannabis is a commonly used and widely available xenobiotic. Common manifestations of acute cannabis toxicity include relaxation, perceptual alterations, sedation, tachycardia, postural hypotension, inability to concentrate, slurred speech, and slow reaction times. Feelings of distrust, fear, or panic may occur. Obtundation, apnea, bradycardia, hypotonia, and opisthotonus are reported in young children following ingestion of cannabis. THC or its metabolites can be identified in blood or urine, but treatment is not guided by drug concentrations. Treatment of an overdose, a high degree of toxicity, or an acute adverse reaction is symptomatic and supportive.

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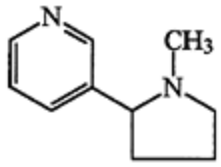
Chapter 82
Nicotine and Tobacco Preparations

Morton E. Salomon



MW = 162 daltons

Nicotine

At 8:15 A.M. an 11-month-old boy was found eating cigarette butts out of an ashtray. The parents cleaned his lips and mouth with cold water. Twenty minutes later the child vomited 3 times. The parents contacted their regional poison center, which advised them to bring the child immediately to an emergency department (ED). En route, via ambulance, the child vomited again. On presentation to the ED at 9:00 A.M., the child was noted to be tremulous and diaphoretic with excessive salivation. He had a glassy-eyed look and did not interact with his parents. His vital signs were: blood pressure, 128/78 mm Hg; pulse, 150 beats/min; respiratory rate, 28 breaths/min; and temperature, 99.7Â°F (37.6Â°C). Pulse oximetry measured 96% saturation on room air.

Pupils were 3 mm and reactive to light. The skin was pale without rashes or bruises. The anterior fontanel was appropriately open (1 cm) and flat. The mouth was clear of particulate matter. Examination of the chest, heart, and abdomen were normal, as were his pulses. The neurologic examination was nonfocal; however, at 9:10 A.M., approximately 1 hour after the ingestion, the child had a generalized seizure lasting less than 15 seconds. There was no incontinence, eye rolling, or focal neurologic findings. The ED staff placed a 28-French orogastric tube into the child's stomach and lavaged with 100-mL aliquots of 0.9% sodium chloride. Lavaging produced a scant amount of brown particulate material along with other stomach contents. After the stomach contents were cleared, 10 g of activated charcoal with sorbitol were delivered through the orogastric tube, which was then replaced by a nasogastric tube. Over the next 30 minutes, the child became increasingly lethargic. Neurologic examination demonstrated progressively more hypotonia, and his deep tendon reflexes became undetectable. The blood pressure decreased to 76/50 mm Hg, the pulse decreased to 84 beats/min and his respiratory rate decreased to 18 breaths/min. His skin was mottled and cool. The pulse oximeter registered 88â€“89% on room air. An arterial blood gas analysis done prior to placing the child on oxygen showed: pH 7.44; PCO_2 , 46 mm Hg; and PO_2 , 57 mm Hg. By 9:45 A.M. the child was intubated and placed on a ventilator. Copious clear secretions were noted from both the mouth and endotracheal tube and the child was given 0.2 mg of atropine intravenously. The complete blood count (CBC), electrolytes, glucose, calcium, magnesium, and renal function tests done at the time of admission were all within normal limits.

Four hours after presentation, the child was more alert and breathing more effectively and began fighting the ventilator. He was sedated with a continuous midazolam infusion, and was gradually weaned from the respirator and extubated 11 hours after the ingestion. He was discharged home 48 hours after ingestion in stable condition and his parents were counseled regarding poison prevention. Followup examination 15 days later revealed no apparent sequelae.

Fifty million Americansâ€”25% of the adult populationâ€”smoke cigarettes despite antismoking public education campaigns, widespread knowledge of its health consequences, and decreasing social acceptance.[6 , 78] In the United States, 350,000 deaths annually are attributable to cigarette smoking, making it the single most important cause of preventable premature mortality.[57] It is now widely accepted that tobacco use is addictive and that nicotine is the component primarily responsible for dependency.[72]

Nicotine is a tertiary amine, that is a colorless, bitter-tasting, and a highly water-soluble volatile liquid that is weakly alkaline (pK_a = 8.0â€“8.5).[6] The principal source of nicotine is the tobacco plant, *Nicotiana tabacum* , from which nicotine was first isolated in 1826.[13] Nicotine also can be isolated from multiple plant species in the Solanaceae family. *N. tabacum* is not the only tobacco plant in this family. The first tobacco to be brought back from the New World to

Europe was *N. rustica* , which contains a much higher concentration of nicotine (approximately 18%) and which is still found in â€œTurkish tobacco.â€• [39] Nicotine is also found in small concentrations in plants outside the *Nicotiana* genus, and even in plants outside the Solanaceae family. In addition, there are a number of alkaloids with chemical structures and physiologic activity similar to that of nicotine in tobacco plants and botanical species related to tobacco.[39]

Nornicotine, anabasine, and anabatine are structurally similar alkaloids also found in tobacco. Anabasine is the principal alkaloid found in *N. glauca* .[65] Lobeline, derived from *Lobelia inflata* , or â€œIndian tobacco,â€• is frequently used as a nicotine substitute.[32] Cystisine, found in mescal beans, is used for its mind-altering properties. Coniine, the lethal alkaloid in â€œpoison hemlock,â€• is also chemically related to nicotine.

History and Epidemiology

The principal sources of nicotine exposure and poisoning are tobacco

products: cigarettes, cigars, pipe tobacco, chewing tobacco, and snuff. Nicotine is also the essential component of smoking-cessation products such as nicotine gum, nicotine patches, nicotine nasal and oral sprays, and nicotine lozenges. Nicotine had a brief application as an animal tranquilizer and was used extensively as an agricultural insecticide in the 1920s and 1930s; formulations of this product are still used by â€œorganicâ€• gardeners.

Sources and Uses of Nicotine

Cigarettes

Cigarettes are the most widely used tobacco products in Western culture and the most likely to be implicated in nicotine poisoning. When a cigarette is burned, the smoker inhales both gaseous and particulate matter. Nicotine is found in the particulate phase of cigarette smoke, along with tar. The total nicotine content of a â€œregularâ€• American cigarette varies between 13 and 20 mg. â€œLow nicotineâ€• cigarettes contain half this amount, and many European cigarettes contain up to 30 mg of nicotine.[8 , 20 , 70] When a cigarette is smoked, more than half the nicotine escapes in the sidestream smoke and a large fraction remains in the butt and filter.[2] As a result, a typical cigarette delivers 0.5â€“2.0 mg of nicotine (average: 1.0 mg) to the smoker.[32] This amount depends on the total nicotine content of the cigarette as well as the individual's smoking technique. The nicotine content written on a cigarette package is determined by burning cigarettes on mechanical smoking machines in a standardized manner.[45] A smoker, on the other hand, extracts variable amounts of nicotine from a cigarette to maintain a steady blood nicotine concentration. Smokers vary the degree of nicotine extraction by altering the rate of puffing, the puff volume, the depth and duration of inhalation, and the size of the residual butt.[6 , 45] African Americans extract, on average, 30% more nicotine per cigarette smoked than whites.[58] When smokers switch from â€œregularâ€• to â€œlow-tarâ€• cigarettes, they often maintain a similar nicotine intake by increasing

the number of cigarettes they smoke and by puffing in a more vigorous manner (Table 82-1).[45]

Not all cigarettes are made from pure tobacco. It is common, especially in Asia, to create cigarettes out of a mixture of tobacco and other products. â€œKreteksâ€• are cigarettes composed of 60% tobacco and 40% ground clove. In the United States, they are especially popular with adolescents because of their pleasant odor and euphorigenic effect. Unfortunately, kreteks are more addicting than tobacco alone.[39] Moreover, eugenol, the major active ingredient in cloves, is believed to be the probable cause of the severe lower respiratory complications of acute lung injury and hemorrhage that occur in some users.[39]

1 whole cigarette
13â€“30
0.5â€“2.0
1 low-yield cigarette
3â€“8
0.1â€“1.0
1 cigarette butt
5â€“7
â€”
1 cigar
15â€“40
0.2â€“1.0
1 g of snuff (wet)
12â€“16
2.0â€“3.5
1 g of chewing tobacco
6â€“8
2.0â€“4.0
1 piece of nicotine gum
2 or 4
1.0â€“2.0
1 nicotine patch

8.3â€“114
5.0â€“22/24 h
1 nicotine nasal spray
0.5
0.2â€“0.4
[a] Delivered through intended use of standard dose.

Source	Content (mg)	Delivered (mg)[a]

TABLE 82-1. Sources of Nicotine

Smokeless Tobacco

Smokeless tobacco, especially snuff, has regained popularity in the United States. Because smoking is not involved, and with the present laws in many states making it illegal to smoke in public places, the public generally believes that smokeless tobacco is more socially acceptable and less of a health risk.[23,39] In fact, in comparison to nonsmokers, there is as much as 48 times the risk of oropharyngeal cancers among longtime users of smokeless tobacco, in addition to other oral and nonoral health hazards.[12,13,39]

Smokeless tobacco comes in two varieties: chewing tobacco and snuff. Snuff is a finely cut tobacco powder packaged dry or moist. In Europe, especially Great Britain, small pinches of dry snuff are inhaled through the nostrils. In the United States, dry and wet snuff are usually â€œdipped.â€• This involves placing a bite-size amount of tobacco (a â€œquidâ€•) between the mucous membranes and the gums. Chewing tobacco is generally packaged as â€œtwistsâ€•â€”leaf tobacco twisted into ropelike portionsâ€”or â€œplugsâ€•â€”shredded tobacco pressed into cakes. These forms are chewed or simply placed in the gingival recess. Generally, the nicotine from smokeless tobacco dissolves in the saliva and is absorbed through the mucous membranes of the mouth. However, approximately one-third of smokeless tobacco users swallow their saliva, absorbing additional nicotine in the intestinal tract.[12,13,

[69] Snuff contains approximately 14 mg of nicotine per gram of tobacco. A typical quid contains 1.5â€“2.5 g of tobacco, which the user â€œdipsâ€• for 20â€“30 minutes. Ten percent of the available nicotine crosses the oral mucosa, producing a total nicotine dose of 2.0â€“3.5 mg/dip. Tobacco chewers use approximately 7 g of tobacco at a time. The nicotine content of a typical â€œchawâ€• is 7.8 mg/g of tobacco. Only 8% of this nicotine is absorbed through the oral mucosa, because the pH of chewing tobacco is only 6.5. Ultimately, the tobacco chewer gets approximately the same dose of nicotine or slightly more than the tobacco snuffer.[11] The smokeless tobacco user who takes 8â€“10 dips or chaws per day gets a nicotine dose equivalent to 30â€“40 cigarettes per day, and cotinine (nicotine metabolite) concentrations found in their urine are similar to those found in the urine of smokers.[5 , 11]

Less Common Sources

Although poisoning from smokeless tobacco usually occurs by ingestion in children, 1 case report of nicotine poisoning occurred when a child licked the contents of a spittoon.[21] Another unusual source of nicotine poisoning is tobacco enemas, where tobacco is soaked in water and the juice of this extract is added to enemas for the treatment of pinworm. This practice has produced at least 1 reported case of severe nicotine poisoning.[20]

Green-leaf tobacco sickness occurs when a tobacco harvester handles dew-laden tobacco leaves. The nicotine dissolves in the water and is absorbed through the worker's skin, if cutaneous precautions are not taken.[6 , 39] Transcutaneous nicotine poisoning is also reported in smugglers who hide tobacco leaves under their clothing.[39]

Nicotine salts, such as nicotine sulfate, were popular pesticides in the 1920s and 1930s. These compounds generally contain 40% nicotine; when they come in contact with moist skin, significant doses of nicotine are absorbed. Several cases of severe nicotine poisoning from skin exposure or ingestion, including deaths, have occurred.[9 , 39 , 55]

Although industrial scale manufacture of nicotine insecticides was discontinued by 1950, these products are available through catalogues and web sites catering to the organic gardener.

Gum

Nicotine is prepared in the form of gum to assist abstinent smokers with withdrawal symptoms. Nicotine resin gum is packaged in 2 strengths: 2 mg and 4 mg per stick. It is designed to be chewed slowly and intermittently. When used correctly, blood concentrations of nicotine are less than those achieved through cigarette smoking, even when 4-mg gum is chewed. Because of alkaline buffers, approximately 53â€“72% of the nicotine in the gum is absorbed through the buccal mucosa. Additional amounts can be absorbed through swallowed saliva.[6] However, when the gum is chewed rapidly and vigorously, nicotine concentrations in the blood can rise rapidly, producing adverse effects, especially in children.[70] Severe nicotine poisoning in a 20-month-old child occurred from the use of nicotine gum.[68] Moreover, adverse effects are reported in adults who have used the gum while continuing to smoke.[50 , 70] If the gum is swallowed, it is less likely to be toxic because the nicotine is released in an acidic milieu resulting in an ionized state and absorbed slowly during GI transit, producing low blood concentrations.[6]

Patches

There are currently four nicotine-releasing adhesive patches available to aid in the treatment of smoking cessation. These patches, designed for 16â€“24 hours of use, vary in size and nicotine release rates, and contain 8.3â€“114 mg of nicotine per patch. Only a portion of the total nicotine load of the patch is actually absorbed during the cutaneous application.

Nasal Spray and Inhaler

In 1996, a nicotine nasal spray was released in the United States as

another treatment modality for withdrawal symptoms during smoking cessation. The metered-dose inhaler contains 100 mg of nicotine in a concentration of 10 mg/mL, and is designed to deliver 200 equivalent puffs. Each puff contains 0.5 mg of nicotine of which slightly more than half will pass into the circulation through the nasal mucosa.[49] Absorption is diminished slightly by rhinitis and delayed by the use of Î±-adrenergic decongestants.[40] The recommended dose is 2 sprays (1 mg)â€”1 in each nostrilâ€”every 30â€“60 minutes. The user titrates the dosing frequency to withdrawal symptoms, using a maximum of 40 doses (80 puffs) per day and creating a steady-state serum nicotine concentration of 6â€“18 ng/mL.

A nicotine metered-dose oral inhaler for smoking cessation is now available. The device is designed to mimic smoking by providing airway stimulation as well as nicotine replacement. Absorption of nicotine occurs primarily through the buccal and pharyngeal mucosa, but slow, deep inhalation can redirect some nicotine into the pulmonary tree and achieve absorption there. Typical use achieves an average steady-state serum nicotine concentration of 7 ng/mL.[41]

Absorption
Lungs, oral mucosa, skin, intestinal tract, gastric acidity inhibits absorption
Volume of distribution
1 L/kg
Protein binding
5â€“20%
Metabolism
80â€“90% hepatic, remainder in lung and kidney; principle metabolites are cotinine, nicotine-â€²-*N* -oxide
Half-life
1â€“4 h, shorter in smokers (average, 2h); half-life of cotinine is 19 h
Elimination
2â€“35% excreted unchanged in urine

TABLE 82-2. Pharmacologic Characteristics of Nicotine

Pharmacology and Pharmacokinetics

Table 82-2 summarizes the pharmacologic characteristics of nicotine.

Absorption

The typical cigarette smoker will adjust his or her use of cigarettes and pattern of smoking to maintain an average nicotine concentration of 30 ng/mL.[6] Nicotine is readily absorbed from the buccal mucosa, respiratory tract, intestinal tract, and skin. The usual site of absorption is the lungs. Inhaled nicotine from cigarette smoke reaches the brain in approximately 8 seconds, with central nervous system (CNS) concentrations of nicotine rising rapidly and then declining rapidly as the drug is redistributed to other tissues.[6 , 32] The cigarette smoker achieves a serum nicotine concentration of 5â€“30 ng/mL after a single cigarette.[6]

Nicotine from cigar and pipe tobacco, as well as from chewing tobacco, snuff, and nicotine resin chewing gum, is generally absorbed through the buccal mucosa. Pipe and cigar tobacco are air-cured to achieve an alkaline pH of 8.5. Smokeless tobaccos and nicotine gum are buffered. The alkaline pH of all of these products enhances buccal absorption.[6] Smokeless tobacco users generally achieve nicotine concentrations comparable to those of cigarette smokers. Pipe and cigar smokers usually average lower nicotine concentrations, unless they inhale the smoke from these products.[6]

Nicotine generally achieves a volume of distribution of 1 L/kg. It readily crosses the placenta and is also transmitted in small concentrations in breast milk.[6]

Metabolism and Elimination

Habitual tobacco users generally metabolize 80â€“90% of their nicotine intake, excreting 10â€“20% in urine unchanged. Metabolism takes place primarily in the P450 system of the liver, but also, to a lesser extent, in the kidney and lung.[9,32] The two major oxidative metabolites of nicotine are cotinine and nicotine-1-*N*-oxide. Both of these compounds are pharmacologically inactive and are excreted primarily by the kidney.[6,32] The half-life of nicotine is 1â€“4 hours but generally averages 2 hours in chronic users.[6,32] Because nicotine metabolism in the liver is an inducible transformation, smokers metabolize the drug more rapidly than nonsmokers. The elimination half-life of cotinine is approximately 19 hours, making cotinine levels in the urine a better marker of recent tobacco use and total tobacco exposure.[6,32] Clearance of cotinine is slower in African Americans than in whites.[58]

Î²-Adrenergic antagonists
Nicotine
Benzodiazepines
Opioids
Caffeine
Phenacetin
Cyclic antidepressants
Theophylline
H_2-histamine antagonists

TABLE 82-3. Xenobiotics with Enhanced Metabolism in Smokers

Renal excretion of unchanged nicotine can vary from 2â€“35% of the total dose,[6] depending on urine flow and urine pH. Experimentally, acidification of the urine traps nicotine ions and enhances direct elimination.[6,20] Nonsmokers eliminate a larger proportion of nicotine unchanged in the urine because of their slower hepatic metabolism.[35]

Drug Interactions

A number of studies demonstrate that smokers have altered metabolism of many commonly used xenobiotics. Smokers metabolize via autoinduction the xenobiotics listed in Table 82-3 more quickly than do nonsmokers.[32, 35] Nicotine itself is metabolized more rapidly in smokers. The therapeutic effectiveness of opioids, benzodiazepines, nifedipine, and Î²-adrenergic antagonists is diminished in smokers.[32] Smokers with peptic ulcer disease are also more likely to fail treatment with H_2 antagonists and antacids.[6] The presumed mechanism for this change in drug metabolism is induction of microsomal enzyme systems. However, because there are 3000 components to tobacco smoke, it is difficult to know exactly which components affect metabolism. In all likelihood, nicotine is not responsible for the induction. For example, IV nicotine does not affect theophylline metabolism in humans.[6] It is more likely that polycyclic aromatic hydrocarbons (PAH), released by the combustion of tobacco, are responsible for the induction of P448 microsomal enzymes in the liver.[35] Xenobiotics whose metabolism is affected by smoking are in part metabolized by this system. In contrast, xenobiotics using the P450 system exclusively are not affected by chronic smoking.[35] This conclusion would be further supported by demonstrating the absence of xenobiotic interactions in users of smokeless tobacco, nicotine gum, and transdermal nicotine patch users. Nicotine and ethanol are frequently used concurrently, and animal studies demonstrate that pretreatment with ethanol exaggerates cardiovascular responses to IV nicotine. Heart rate and blood pressure increase in an additive way. Smokers are more apt to suffer from dysrhythmias and sudden death during alcohol use. It is likely that this is the result of increased oxygen demand triggered by additive cardiovascular stimulation.[7] Because ethanol does not influence the rate of nicotine metabolism, the etiology of this additive response is unclear.

Pathophysiology

Nicotine binds stereospecifically to select acetylcholine receptors, generally referred to as nicotine receptors (Chap. 14).[6, 32] There are nicotine receptors throughout the body, particularly in the autonomic

ganglia, adrenal medulla, central nervous system, spinal cord, neuromuscular junctions, and chemoreceptors of the carotid and aortic bodies.[6 , 32] In the CNS, the highest density of nicotine receptors can be found in the limbic system, midbrain, and brainstem.[6] The physiologic effects on the CNS are multiple, complex, and dose-dependent. At doses commonly encountered with tobacco use there is stimulation of the reticular activating system and an alerting pattern on electroencephalogram (EEG).[32 , 68] There is a facilitation of memory and attention, with a decrease in aggression and irritability.[32] Although nicotine might reduce skeletal muscular tone and decrease deep-tendon reflexes, its central and neuromuscular stimulatory effects can also produce tremor.[32 , 65] At very high doses, nicotine induces seizures. Studies in mice suggest that nicotine-induced seizures can be controlled by the neuroinhibitory agent 5-Î±-pregnan-3Î±-ol-20-one. It is therefore postulated that nicotine produces seizures at high doses by a CNS disinhibition mechanism at CNS nicotine receptor synapses.[42]

Gastrointestinal effects are probably mediated by nicotine stimulation of vagal centers in the medulla oblongata. Even at low doses, nicotine exposure produces nausea and vomiting in the naive tobacco user. Nicotine also increases gastroesophageal reflux, probably by either lowering sphincter pressure or increasing acid secretion.[62] Diarrhea can be stimulated by larger doses of nicotine, which is probably mediated by both central and parasympathetic excitation.[20 , 32]

Nicotine exerts a number of endocrinologic effects either by acting directly on nicotine receptors in the endocrine gland or by stimulating neurohumoral pathways in the CNS. It enhances the release of catecholamines, and stimulates the production of vasopressin (antidiuretic hormone), growth hormone, adrenocorticotropin, cortisol, prolactin, serotonin, and Î²-endorphins. It also affects pancreatic exocrine functions in rats. In rats pretreated with nicotine doses comparable to exposures that moderate smokers receive there is an increase in amylase, trypsin, and chymotrypsin activity.[15] With repeated exposure, tolerance develops to many of these effects.[6]

Nicotine is an anorexiant, especially to sweet foods, while increasing basal energy expenditures. It also causes moderate increases in serum glucose by reducing insulin sensitivity.[51] These effects explain why nicotine promotes weight loss. Smokers weigh, on average, 6â€“10 lbs less than nonsmokers. With repeated exposure, tolerance develops to many of these effects.[6, 32] Habitual use of nicotine also decreases estrogen levels in female smokers, probably by promoting hydroxylation of estradiol. As a result, women who smoke are at increased risk for osteoporosis.

Clinical Manifestations

More than 60% of reported nicotine exposures produce no toxicity and only 1% produced moderate to major toxicity. This low proportion of serious poisoning is not surprising, because 98% of these exposures are unintentional and more than 90% occur in children younger than 6 years of age (Chap. 130).[8] Nonetheless, serious exposures do occur, even in young children, and seem to be dose related. In one report, 23 (45%) of 51 childhood exposures to nicotine resulted in some degree of symptomatology. Only 8 (16%) of these 51 children required evaluation by a physician and only 4 children (8%) developed significant symptoms of lethargy, unresponsiveness, and limb jerking.[70] Similarly, another study reported that only 1 (5%) of 20 children who ingested nicotine became moderately ill and required 24 hours of hospitalization.[8] Most unintentional exposures in small children result from the ingestion of tobacco products. The tobacco itself usually induces spontaneous vomiting, which limits its own absorption.

Early (15â€“60 min)
Abdominal pain
Bronchorrhea
Hypertension
Agitation/anxiety
Headache
Nausea

Hyperpnea
Tachycardia
Ataxia/dizziness
Hyperactivity
Salivation
Pallor
Blurred vision
Muscle fasciculations
Vomiting

Confusion
Distorted hearing
Seizures
Tremors
Delayed (0.5â€“4 h)
Diarrhea
Apnea
Bradycardia
Coma
Lethargy
Hypoventilation
Dysrhythmias
Hypotension
Shock
Hyporeflexia
Hypotonia
Weakness
Muscle paralysis

Gastrointestinal Respiratory Cardiovascular Neurologic

TABLE 82-4. Signs and Symptoms of Acute Nicotine Poisoning

A child who ingests 1 or more cigarettes or 3 or more cigarette butts has a 90% chance of becoming symptomatic. Conversely, ingestion of smaller amounts will produce symptoms only half the time.[78] In a retrospective review of cigarette ingestions by 10 children, each of the 4 children who became severely poisoned had ingested at least 2 whole cigarettes.[44] One-half piece or more of 2-mg nicotine chewing gum usually produces symptoms in a child.[70]

Table 82-4 outlines the symptoms associated with acute nicotine exposure. Clinical signs of low concentrations of nicotine, such as those occurring routinely in smokers, include tremor and increased heart rate, respiratory rate, blood pressure, and alertness.

In marked contrast to these relatively mild effects associated with cigarette smoking, when nicotine is taken in â€œtoxicâ€• quantities, as in an insecticide exposure, for example, the effects are more severe. The symptoms may follow a biphasic pattern in which there is initial stimulation followed quickly by inhibition.[65] Early symptoms of toxicity often include nausea, vomiting, diaphoresis, and increased salivation. Cardiovascular signs include tachycardia, hypertension, and pallor secondary to vasoconstriction. Early neurologic manifestations include headache, dizziness, ataxia, and, in moderately severe cases, confusion as well as visual and auditory distortions.[8,65]

In the most severe exposures, these generally mild symptoms can be quickly overshadowed by signs of more extreme stimulation, such as seizures, muscle fasciculations, and atrial fibrillation.[8,65,68] Although seizures do occur, there are no reports of nicotine-induced status epilepticus in nonexperimental conditions. These symptoms are often succeeded by signs of multisystem depression, such as bradycardia and hypotension, and a curarelike neuromuscular blockade that leads to muscle paralysis, particularly respiratory paralysis.[55,65,68] Death is generally attributable to respiratory depression or paralysis of the intercostal muscles complicated by increased bronchial secretions or to cardiovascular collapse.[9,55,65] Timely and adequate respiratory and

cardiovascular support generally leads to full recovery without sequelae.[9 , 55]

Vomiting is the most common symptom of nicotine poisoning, occurring in more than 50% of symptomatic patients. However, it is not a reliable sign of toxicity.[70] Patients can present with lethargy and respiratory depression without prior vomiting or any other signs of CNS stimulation.[9] Moreover, nicotine chewing gum ingestions in children produce vomiting less frequently (20% incidence) than do cigarette ingestions.[70]

Following the ingestion of tobacco products, children usually manifest symptoms within 30â€“90 minutes. When children chew nicotine gum, symptoms are usually apparent within 15â€“30 minutes, a result of more rapid absorption through the buccal mucosa.[68 , 70] When death occurs, it usually occurs within 1 hour of exposure, however with mild poisonings, symptoms generally last only 1â€“2 hours after exposure. With severe toxicity, however, full recovery might take 48â€“72 hours.[68]

As little as 1 mg of nicotine can produce symptoms in a young child. Four to 8 mg of nicotine might produce symptoms in an adult, especially a nonhabituated victim.[20] Nicotine doses of 0.8â€“1.0 mg/kg are considered to be lethal dose in adults.[20 , 21 , 44] In a prospective study of nicotine ingestions in children, the 3 most severely poisoned infants ingested a minimum of 1.4 mg/kg. The 25 asymptomatic children ingested a mean of 0.5 mg/kg, and all asymptomatic children ingested less than 1 mg/kg.[70] These numbers indicate a very narrow range between nontoxic and significantly toxic doses.

Green-leaf tobacco sickness generally produces a mild to moderate illness consisting of nausea, vomiting, headaches, dizziness, pallor, and diaphoresis.[6 , 39] However, in two recent outbreaks of green-leaf tobacco sickness in Kentucky, nearly 25% of the affected tobacco workers required hospitalization. A significant portion of these poisoned workers were younger than age 18 years.[3 , 48]

One study exposed dogs transdermally and orally to 3 different

commercially available nicotine patch systems. The topical administration provided 1â€“2 mg/kg over 24 hours, producing serum concentrations as high as 43 ng/mL. Two of 12 topical applications elicited salivation and vomiting. Oral exposure up to 13 mg/kg produced maximal serum concentrations of 73 ng/mL, with only vomiting in 2 of 12 oral challenges.[47]

Published reports from a 2-year postmarketing surveillance study by 34 poison centers describe toxicity from misuse or from unintentional exposure to transdermal nicotine patches. Transdermal application of 2â€“20 transdermal nicotine patches in 9 adults resulted in very serious toxicity. Eight patients were admitted to intensive care; 4 had refractory seizures; and 4 required assisted ventilation. However, 7 of the 9 patients ingested cointoxicants in suicide attempts, and the maximum nicotine level recorded was only 27 ng/mL.[81] Thirty-six exposures in children were less severe. Half the children had topical exposures and half had bitten, chewed, or swallowed the patches. Nearly 40% developed symptoms, but only 27% required medical evaluation and only 5% were hospitalized for 24 hours or more.[80] It seems, therefore, that unintentional exposure to nicotine patches has not yet produced serious toxicity.

Diagnostic Testing

Toxicologic assay for nicotine or its metabolites is of limited value in the management of a patient with an acute poisoning. The presence

of nicotine or cotinine in the urine might reflect coincidental active or passive smoke exposure and therefore does not confirm nicotine as the cause of poisoning.[68] Serum nicotine levels must be determined shortly after exposure and are difficult to interpret. A serum nicotine level greater than 50 ng/mL generally predicts serious toxicity, but lower levels can also be significant in the nontolerant patient.[65]

Management

Unintentional ingestions of nicotine in small children almost invariably involve small amounts, with spontaneous vomiting providing adequate decontamination. Thus many patients do not need medical evaluation. Individuals who ingest 1 or more whole cigarettes or 3 or more cigarette butts, who acquire their exposures from a more toxic source (a nicotine insecticide or a tobacco enema), who develop symptoms other than vomiting, or who are potentially suicidal should be referred to an ED without delay. Patients with mild symptoms and no complicating circumstances can generally be observed for 4 hours in the ED and released if symptoms have resolved.[65]

Initial Management

The patient with a significant recent oral exposure, who has not vomited prior to presentation, should be decontaminated by orogastric lavage. Emesis induced by syrup of ipecac should be avoided because nicotine poisoning may cause unexpected seizures or respiratory depression.[9, 70] Activated charcoal effectively binds nicotine and should be used to reduce absorption in gastrointestinal (GI) exposures. Pharmacokinetic studies indicate that nicotine appears in the GI tract, even when administered intravenously.[70] Because this suggests that nicotine undergoes enteroenteric or enterohepatic circulation, multiple-dose activated charcoal should be considered in patients with serious exposures.

In cases of skin exposure to wet tobacco leaves, concentrated nicotine liquid, or nicotine pesticide powder, the patient's clothing should be promptly removed, bagged, and not returned to the patient and the skin thoroughly washed with soap and water. The medical staff must wear impervious gloves and gowns during these procedures to avoid secondary exposure.

Symptom-Directed Treatment

Because of the variety of stimulatory and depressant effects in the

neuromuscular, sympathetic, parasympathetic, and central nervous systems, treatment of nicotine toxicity is a complex therapeutic problem. Treatment is based on a symptom analysis with primary emphasis on respiratory support. Seizures are usually treated with a benzodiazepine. Loading the patient with longer-acting anticonvulsants is generally unnecessary.[9 , 44 , 65] Cardiovascular compromise is treated with atropine for symptomatic bradycardia and fluids for hypotension.[65] If hypotension does not respond to fluids, a vasopressor such as dopamine or norepinephrine is recommended.[68] By reversing bradycardia with atropine, there is some risk of further exacerbating the vasoconstrictive effects. For this reason, some authors also suggest using concomitant phentolamine, an Î±-adrenergic antagonist, in the treatment of nicotine overdose.[20 , 65] Such combined therapy is unnecessary, however, as adrenergic stimulation is rarely life-threatening in nicotine poisoning, and adrenergic antagonism can exacerbate hypotension in the delayed phase. Respiratory compromise, caused by respiratory depression is generally treated with oxygen, intubation, and positive pressure ventilation as indicated.

Enhancing Elimination

Although nicotine is a weak base (pK_a = 8.0â€“8.5) and excretion can theoretically be enhanced by acidification of the urine, this approach is to be condemned,[9 , 65] because the potential risks of acidification in a patient with seizures and possible rhabdomyolysis outweigh any of the theoretical benefits.[65] Furthermore, because the symptoms in nicotine poisoning are generally short-lived, acidification is unnecessary. Fluid diuresis may also enhance elimination and is safer but also is unnecessary because of the limited urinary elimination.[9]

Antidotes

There is no specific antidote for nicotine poisoning. Pempidine and mecamylamine demonstrate both competitive and noncompetitive antagonism to the central effects of nicotine,[46] and hexamethonium, a

ganglionic blocker, prevents nicotine-induced seizures in animals.[65] None of these blockers has been reported as used, either experimentally or clinically, to treat overdoses in humans. Although their application is theoretically of interest, new approaches with these blockers are unlikely to be developed because severe nicotine poisoning is rare and nonspecific supportive measures are almost always adequate when initiated in a timely manner.

Nicotine Withdrawal and Treatment

Tobacco use meets all of the World Health Organization (WHO) definitions of addiction. There is an overpowering compulsion to continue taking the drug. There is a tendency to develop tolerance to its effects and therefore to keep increasing the dosage. Psychological and physical dependency develops, and the absence of tobacco produces discomfort in the smoker. Finally, tobacco has detrimental consequences for both the individual user and society at large.[52]

Tobacco addiction occurs with other forms of tobacco besides cigarettes, especially with smokeless tobacco. Of course, many smokeless tobacco users switch to this product to wean themselves from cigarettes.[52 , 59]

Individuals dependent on tobacco, like any other substance-dependent individuals, go through multiple cycles of quitting and relapsing. While spontaneous quitting without any special treatment program is the most common route to abstinence, the achievement rate by this method is only 1% of users per year.[6 , 36] Women cigarette smokers have a lower rate of quitting success than men.[56]

Smokers are much more likely than nonsmokers to have other substance dependencies.[36] Conversely, 80â€“95% of alcohol and drug abusers also smoke cigarettes. It has been suggested that nicotine use promotes the release of endogenous endorphins. Therefore, withdrawal from nicotine might have a strong biochemical resemblance to withdrawal from opioids.[16] In fact one study was able to precipitate withdrawal symptoms in nicotine-dependent rats with subcutaneous naloxone and then reverse

the abstinence symptoms with morphine sulfate.[43] On the other hand, nicotine's neurochemical effects on the brain, and on other neurotransmitters

such as dopamine, closely resemble that of other psychostimulants. (For an in-depth discussion of the physiology of withdrawal see Chap. 15 .)

With so many substances involved in cigarette smoking, it is quite likely that tobacco dependency is a complex addiction, involving both psychological components, such as oral gratification, and physical dependency. It is now widely accepted that the primary addictive component of tobacco is nicotine,[53 , 59 , 78] but this is the subject of some controversy and is supported primarily by indirect evidence.

Clinical Manifestations of Nicotine Withdrawal

Manifestations of nicotine withdrawal can occur within 2â€“8 hours of the last cigarette. In fact, most moderate to heavy smokers experience some withdrawal symptoms as they wake up each morning. Withdrawal reaches maximum intensity at 24â€“48 hours, and then diminishes over a 2-week period of abstinence. After 1 month, symptoms are gone, except for the cravings for cigarettes and an increase in appetite.[6 , 66] Approximately 80% of smokers experience withdrawal symptoms when quitting, and withdrawal is nearly universal among smokers using 20 or more cigarettes per day.[6] Nicotine withdrawal is not confined to cigarette smokers alone. The same syndrome is reported in smokeless tobacco users and chronic users of nicotine chewing gum.[6 , 52]

Most of the symptoms associated with tobacco withdrawal are subjective, leading to an overall feeling of dysphoria. These manifestations, widely described in the literature, are summarized in Table 82-5 .[14 , 27 , 32 , 38 , 52] The most dramatic and intense symptom of tobacco abstinence is a craving for cigarettes, which can continue for months to years.[6] Cravings for cigarettes are less intense and diminish

more quickly in people who are totally abstinent, as compared to those who are only partially abstinent.[66]

One study evaluated 7 smokers in a battery of computerized performance tasks over a 24-hour period of abstinence. With increasing abstinence, the smoker's responses showed increased latencies and decreased accuracy.[71] Moreover, EEG studies evaluating smokers in withdrawal show a decrease in high-frequency activity and an increase in low-frequency activity, consistent with diminished arousal.[32]

Anger/aggression/hostility
Decreased arousal pattern on EEG
Anxiety
Decreased blood pressure
Blurred vision
Decreased heart rate
Confusion
Diminished psychomotor performance
Constipation
Impaired short-term memory
Craving for cigarettes
Reduced plasma catecholamines
Drowsiness
Weight gain
Gastrointestinal upset
Headache
Hunger
Impaired concentration
Irritability/impatience
Moodiness
Restlessness
Sleep disturbance

Subjective Objective

TABLE 82-5. Clinical Manifestations of Nicotine Withdrawal

The most common objective physical manifestation of nicotine abstinence is a decrease in heart rate by a mean of 9 beats/min within the first day of abstinence; it is a unique feature of nicotine withdrawal syndrome.[27] This decrease remains constant when measured over the next 5 weeks of abstinence, suggesting that heart rate reduction in tobacco abstinence reflects the absence of stimulation from nicotine, rather than withdrawal symptomatology.[79] Concentrations of epinephrine and norepinephrine also decrease in abstinent smokers. This is probably another manifestation of the absence of nicotine effect and undoubtedly contributes to the reduction in mean heart rate.[17]

Management of Acute Nicotine Withdrawal

In clinical practice, nicotine withdrawal syndrome is encountered when tobacco users attempt to quit in the interest of their long-term health or when acute illness forces abstinence. The discomfort is a primary obstacle to smoking cessation and contributes significantly, but not solely, to the low success rate of attempts to quit smoking. Therefore, any treatment approach that lessens nicotine withdrawal symptoms, without reinitiating the use of tobacco products, is more likely to aid the effort to quit, which in turn will have many long-term health benefits. An in-depth discussion of smoking cessation management falls outside the purview of a textbook on toxicologic â€œemergencies.â€• Physician counseling, behavioral interventions, nicotine replacement therapies, and select antidepressants raise cessation rates. A brief overview is included because of the current medical and public health significance of this subject.

Nicotine Replacement Therapy

One approach to the treatment of nicotine abstinence syndrome is to provide nicotine without tobacco. This therapy offers nicotine in a safer,

more clinically controllable form that minimizes nicotine withdrawal symptoms. After the patient breaks the smoking habit, the nicotine replacement agent is gradually tapered.[63]

Nicotine gum is the oldest of the nicotine substitution therapies. It ameliorates many symptoms of nicotine withdrawal, especially feelings of irritability, aggression, and dysphoria. However, it seems less effective in eliminating cigarette craving and increased hunger.[10]

The effectiveness of nicotine chewing gum in promoting long-term smoking abstinence has been extensively studied.[33, 74, 75] A meta-analysis of all these studies, with special emphasis on double-blind, randomized, placebo-controlled trials with 1 or more years of followup study, indicates that nicotine chewing gum in conjunction with a formal program of behavioral therapy can produce 1-year abstinence rates of 29â€“49%.[1, 6, 77] On the other hand, when nicotine gum is used in general medical practice, without structured behavioral interventions, improvement in smoking abstinence is short-lived and smoking cessation rates at 6â€“12 months are similar to those of placebo-treated patients.[4, 6, 33]

Unfortunately, many smokers who use nicotine gum to quit develop dependency on the gum itself. As an adjuvant to smoking cessation, nicotine gum should be used for a *maximum* of 3 months. However, several studies have reported continued use of the gum at 1-year followup (6â€“38% of users).[6, 25, 26] Self-administration of the gum may reinforce some of the behavioral patterns that sustain smoking. It can be argued that the behavioral components of the

addictive process must be decisively interrupted for successful treatment of the addiction.[59]

Transdermal nicotine patches have supplanted chewing gum as the preferred nicotine-replacement therapy. Because nicotine patches are easier to use, requiring only once-a-day application, compliance is better. The dose of nicotine delivered to the patient is more predictable, nicotine steady-state concentrations are higher, and different dose

patches make tapering easier to control. Finally, because no specific behavioral action is required of the patient, other than putting the patch on in the morning, a transdermal nicotine patch does not require self-administration of nicotine by the user and therefore does not mimic oral smoking behavior.[59 , 63]

There are four patch systems currently available, each of which comes in several different doses of nicotine. Three of the patch systems are designed for 24-hour use, and the newest is made for 16-hour use to approximate more closely nicotine intake patterns of the smoker.[54] The patches generally deliver steady-state nicotine serum concentrations of 10â€“15 ng/mL, which are maintained throughout the application of the patch.[24]

Several double-blind, placebo controlled studies have demonstrated that, at 6â€“12-month follow-up, transdermal nicotine patch users achieve abstinence 2â€“4 times more frequently than placebo users.[14 , 19 , 22 , 77 , 78] Many studies have demonstrated that long-term efficacy is present even with little or no formal behavioral intervention accompanying the program.[1 , 14 , 77]

The most consistent adverse effect of the transdermal nicotine patch is skin irritation at the site of the patch. In one trial, approximately 5% of patients withdrew from the study because they could not tolerate the cutaneous irritation.[1]

Both nicotine nasal spray and nicotine oral inhaler reduce withdrawal symptoms and promote abstinence more effectively than placebo.[41 , 73 , 76] Both treatment modalities are based on the belief that airway stimulation will mimic smoking more closely and therefore be more effective in reducing cigarette cravings. Furthermore, the application of nicotine to mucous membranes provides a rapid transient rise in serum nicotine and thus reduces cigarette cravings more promptly than slower forms of nicotine delivery.[30] Although these characteristics are probably real, the replication of smoking's airway sensations might actually make long-term abstinence more difficult to achieve.

To date there have been no head-to-head comparisons of any of the nicotine-replacement therapies. Both transdermal nicotine patch and nicotine nasal spray seem to be more effective than nicotine gum in reducing cigarette craving and increased appetite.[30 , 63] A meta-analysis of 103 nicotine-replacement therapy trials, with data from more than 30,000 patients, concluded that all nicotine-replacement therapy modalities were better than placebo in promoting abstinence at 6 or more months. Abstinence odds ratios were highest for nicotine nasal spray and lowest for nicotine gum.[67]

Clearly, nicotine replacement therapies are moderately effective in promoting smoking cessation, especially in the short term. To be successful, the patient must eventually face the inevitableâ€"withdrawal from nicotine itself. Theoretically, if other treatment modalities promote tobacco abstinence effectively without the use of nicotine replacement, they would have a substantial advantage.

Antidepressant Therapy

Antidepressant medications such as bupropion offer an encouraging alternative to nicotine replacement in smoking cessation. The idea of using antidepressants for smoking cessation grows out of the observations that nicotine has antidepressive effects; that anxiety and depression are frequent comorbid conditions in nicotine-addicted patients; that dysphoria is a common symptom of nicotine withdrawal; and that women have a more difficult time with nicotine abstinence.[31]

In a randomized double-blinded placebo-controlled comparison study of sustained-release bupropion, smoking abstinence at 52 weeks was 12% in the placebo group and 23% in the 300-mg per day bupropion group.[31] A subsequent trial, compared bupropion SR and nicotine patch, and both together, for smoking cessation efficacy in 893 subjects. The 1-year cessation rate was 16% in the patch groupâ€"roughly equivalent to placeboâ€"but was 30% in the bupropion group and 35% in the bupropion-plus-patch group. The bupropion-plus-patch group also had the smallest weight gain.[34] Another study of 211 adolescent smokers

also showed modest benefit from the combination of bupropion plus patch compared with patch alone.[37]

The sustained-release bupropion dose currently recommended is 150 mg twice a day. Patients should be started on treatment at least 1 week prior to their smoking quit date and continued on treatment for 8 weeks. There is an increased seizure risk with bupropion, but generally not at the doses recommended for smoking cessation unless patients are otherwise prone to seizures.[34]

Other antidepressants, including monoamine oxidase inhibitors and selective serotonin reuptake inhibitors, have no proven long-term benefit in smoking cessation.[28]

Summary

Nicotine, a tertiary amine from *N. tobacum* and other tobacco plants, is found commercially in a number smoking products and smoking-cessation treatment pharmaceuticals. It is commonly absorbed through the buccal mucosa or respiratory epithelium of the lungs, but can also be absorbed from the skin and intestine. Up to 90% of a nicotine â€œdoseâ€• is metabolized by an inducible P450 hepatic biotransformation, producing 2 inactive metabolites that are slowly excreted by the kidneys. It exerts its physiologic effects on selective acetylcholine receptors, primarily in neural tissue. Although the vast majority of reported nicotine exposures are unintentional and occur in children and produce mild or no toxicity, severe poisoning and even death can result, and there is a narrow range between nontoxic and significantly toxic doses. Clinical manifestations of consequential poisoning are complex but can be characterized as biphasic, with initial excitation followed quickly by inhibition. Management is symptom directed with special emphasis on seizure control and respiratory support.

In terms of smoking cessation management, it should be noted that although several xenobiotics will reduce the severity of nicotine

withdrawal, long-term smoking cessation is more difficult to achieve. In many approaches to smoking treatment, the overall mean 6â€“12-month success rate seems to be approximately 25%.[59] This is, of course, much better than the spontaneous abstinence rate of 1%, but as many as 70% of patients who achieve initial abstinence will be smoking again after 1 year.[16] Whatever approach is taken to treat tobacco abstinence, it seems the patient must start with a strong desire to quit, avoid unusually stressful situations, and have a social support network that encourages the effort to stop smoking. The most successful programs are multimodality treatments that combine counseling or other behavioral therapies with one or more pharmacologic interventions.

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Chapter 83
Phencyclidine and Ketamine

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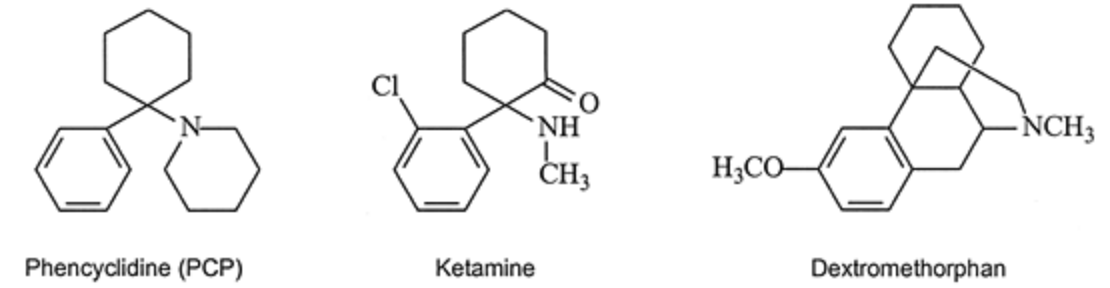

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A 17-year-old boy was brought to the emergency department (ED) by his school supervisor and 2 police officers. The boy was extremely agitated, but having transient periods of blank staring

and myoclonic movements of both arms. It took several members of the ED staff to keep him on a stretcher.

Initially, no history was obtainable from the patient, who responded to verbal stimuli with inappropriate physical gestures and a few nonsensical words. The school supervisor reported that the boy had become suddenly agitated and had created a disturbance in the lunchroom, throwing chairs about the room.

His vital signs were: blood pressure, 130/90 mm Hg; pulse, 110 beats/ min; respiratory rate, 18 breaths/min; and temperature, 99.9Â°F (37.2Â°C). He was well developed and well nourished, anicteric, and acyanotic. The head and neck examination were normal. His breath sounds were clear to auscultation. He had a normal heart exam. His abdomen was soft and nontender and his bowel sounds were normal. The skin was cool and diaphoretic. Conjunctivae were normal; extraocular movements were intact, but there was persistent vertical and horizontal nystagmus; pupils were equal at 4 mm and reactive to light; fundi were normal. The patient moved all extremities, had good strength and normal, symmetric deep-tendon reflexes; muscle tone seemed increased and there were periodic myoclonic jerks; plantar flexion was elicited; a sensory examination could not be performed because of the patient's lack of response and agitation.

Blood was drawn for initial laboratory tests and an intravenous infusion of 5% dextrose in 0.45% sodium chloride solution was started at 200 mL/h. Fifty milliliters of 50% dextrose and 100 mg of thiamine were given IV. He was placed on 6 L of oxygen via nasal cannula. Fifty grams of activated charcoal were given together with 50 g of sorbitol by mouth.

The initial laboratory data, including complete blood count, electrolytes, arterial blood gas analysis, and urinalysis, were all normal. An ECG revealed a sinus tachycardia at 110 beats/min and was otherwise normal.

By the time the physical examination and laboratory tests were completed, the patient had become calm and cooperative. He related that while at lunch, one of his friends had put mustard on his sandwich and that it tasted â€œterrific.â€• He recalled finishing the sandwich and then slowly â€œfreaking outâ€• and losing control of his mind and body.

By the time the patient's mother arrived in the ED, his clinical condition had significantly improved. Within 3 hours after the patient's arrival, he was cooperative and his neuropsychiatric examination was entirely normal. Because he had no prior history of drug abuse, he was discharged home and arrangements were made for a followup examination with his pediatrician.

History and Epidemiology

Phencyclidine (PCP) was discovered in 1926, but it was not developed as a general anesthetic until the 1950s. At the time, the Parke Davis drug company was searching for an ideal intravenous anesthetic that would rapidly achieve analgesia and anesthesia with minimal cardiovascular and respiratory depression.[36] It was marketed under the name Sernyl because it rendered an apparent state of serenity when administered to laboratory monkeys. Its surgical

use began in 1963, but PCP was rapidly discontinued when a 10â€“30% incidence of postoperative psychoses and dysphoria was documented over the subsequent 2-year period.[79] By 1967 the use of PCP was limited exclusively to veterinary medicine as a tranquilizer marketed under the name Sernylan.

Simultaneously, in the 1960s, PCP was developing as a San Francisco street drug called â€œthe PeaCe Pill.â€•[66] Numerous street names have been given to phencyclidine: on the West Coast it was called â€œAngel Dust, PCP, crystal, crystal joints (CJs)â€•; Chicago called it â€œTHCâ€• or â€œTACâ€•; the East Coast

opted for â€œthe sheets,â€• â€œHog,â€• or â€œelephant tranquilizer.â€•[120] Ironically, the drug was initially unpopular with drug users because of its dysphoric effects and unpredictable oral absorption.[154] With time, however, its use spread in a similar geographic pattern to that of marijuana and lysergic acid diethylamide (LSD), from the coastal United States to the Midwest region.[66]

Phencyclidine abuse became widespread during the 1970s.[25] The relatively easy and inexpensive synthesis coupled with the common masking of PCP as LSD, mescaline, psilocybin, cocaine, amphetamine, and/or â€œsynthetic THCâ€• (tetrahydrocannabinol) added to its allure and consumption.[120] By the late 1970s PCP abuse had reached epidemic proportions.[7] The Drug Abuse Warning Network (DAWN) reported that the number of PCP related emergencies and deaths more than doubled in the two years from 1975 to 1977. In 1978 the National Institute of Drug Abuse reported that of the young adults (18â€“25 years old), 13.9% had used PCP.[50] The manufacture of phencyclidine was ultimately prohibited in 1978 when the drug was added to the list of federally controlled substances. Classifying PCP as a Schedule II drug led to its decrease in availability and, consequently, a decrease in its use. Although the 1980s brought about a cocaine epidemic that eclipsed PCP, PCP has remained consistently available on the streets, primarily regionalized to large cities in the northeastern United States and in the Los Angeles area,[103] where PCP use continues to rise and fall with societal trends. Because many of the PCP congeners made during the manufacturing process were being abused in place of PCP, the Controlled Substance Act of 1986 made these derivatives illegal and established that the use of PCP's precursor, piperidine, necessitated mandatory reporting. With this new law in place, those possessing similar but not identical illegal substances could be prosecuted. This led to a further decline in the popularity of phencyclidine. Beginning in 1984, the overall use of PCP remained

flat, reaching a nadir in 1994.[182] Since 1994, however, there has been an increase of reported PCP abuse. DAWN reported that the number of PCP-related emergencies increased 28% in the years between 1995 and 2002. According to the 2002 the National Survey on Drug Use and Health (NSDUH), lifetime use of PCP was highest among those 26 years of age and older (3.5%) compared with people ages 18â€“25 years (2.7%) and those ages 12â€“17 years (0.9%).[182] In the 2003 NSDUH report, the number of PCP users remained at approximately 200,000.[183]

Laboratory investigation of phencyclidine derivatives led to the discovery of ketamine, a chloroketone analog. Ketamine was introduced for general clinical practice in 1970 and was marketed as Ketalar, Ketaject, and, for veterinary use, Ketavet. Because ketamine has approximately 5â€“10% of the potency of PCP and a much shorter duration of action, it provides greater control in clinical use. Thirty-five years of clinical experience have established that ketamine provides adequate surgical anesthesia, a rapid recovery, and less prominent emergence reactions than does PCP.[56,81,157,195] Because of the simplicity and efficacy of its use it is regularly employed in operating rooms, emergency departments, and throughout the developing world where little clinical monitoring is available during surgical and emergency procedures.[53,78,79,80,81,82,158,194]

Abuse of ketamine was first noted on the West Coast in 1971.[168] During the 1980s there were reports of its abuse internationally, as well as among physicians.[3,68] The nonmedical use of dissociative anesthetics has continued to increase throughout the 1990s, and into the 2000s in spite of the common complications associated with their use.[181] At present, ketamine, methylenedioxyamphetamine (MDA), and methylenedioxymethamphetamine (MDMA) have regained popularity with today's youth. The same pharmacologic qualities that made ketamine more popular than PCP clinically are also responsible for its nonmedical popularity. Ketamine is regularly

consumed at all-night â€œrave partiesâ€• and in nightclubs because of its â€œhallucinatoryâ€• and â€œout-of-bodyâ€• effects, relatively inexpensive price, and short duration of effect (a single snort lasting between 15 and 20 minutes).[11,44,92,96,196]

The use of ketamine is not limited to the inner city. In the past decade, the media reports police arrests in affluent suburban communities for possession and sale of ketamine, as well as more in-depth and frequent reporting of the effects of its toxicity among users.[44,92,155,196] In contrast to PCP, ketamine is not manufactured illegally, but rather, diverted illicitly from legitimate medical, dental, and veterinary sources. Additionally, with the advent of the Internet, its availability has dangerously grown nationwide; a sham â€œbiotechâ€• Internet company was seized by New York City police in the year 2000 for selling so-called date-rape drugs, including ketamine.[131]

Adverse reactions do occur, although, there are few reports of fatalities secondary to ketamine during this period of increased use.[72,111,136] Because of its abuse potential, ketamine was placed in Schedule III of the Controlled Substance Act in 1999.[157] In 2002, DAWN reported that there was a dramatic rise (more than 2000%) of ketamine-related ED visits between 1994 and 2001. Despite any clear reason, after a peak of 679 ketamine-related ED visits in 2001, there was a decline to 260 visits in 2002.[183]

Pharmacology

Chemistry

Phencyclidine's chemical name 1-(1-phenylcyclohexyl) piperidine provided the basis for its street acronym PCP. During its unlawful chemical synthesis, numerous analogs are made which have similar effects on the central nervous system (CNS) and which have been used as PCP substitutes. These â€œdesignerâ€•

arylcyclohexylamines are aliphatic- or aromatic-substituted amines, ketones, or halides, and appear similar to the parent compound. More than 60 psychoactive analogs are mentioned in the medical literature and the following salient points of the 5 most prevalent compounds are worth mentioning. TCP and PCC are piperidine derivatives. Piperidine, the synthetic precursor, was formerly easily purchased for manufacturing PCP and its derivatives. TCP, a thiophene analog (1-[1-(2-thienyl)cyclohexyl] piperidine), produces even more intense effects than PCP. An intermediate of PCP synthesis, PCC (1-piperidino-cyclohexanecarbonitrile) was a constituent of up to 22% of illicit drug preparations analyzed for phencyclidine. This most likely resulted from a poor manufacturing process.[14,167] PCC degrades to piperidine, which is recognizable by its strong fishy odor. The presence of its carbonitrile group adds to its toxicity by generating cyanide when smoked.[12,14,174,175] The pyrrolidine derivative, PHP (phencycloclohexylpyrrolidine), is comparable clinically to PCP and is not detected by many of the available drug-screening methods.[27,89] More potent than PCP, PCE (1-phenyl-cyclohexylethylamine) was commonly available on the street as a white powder indistinguishable from PCP.[167]

Ketamine and tiletamine, two legal congeners of PCP, are used clinically for sedation and anesthesia. In large quantities, both are also used in veterinary medicine for animal sedation. Ketamine (Ketaset and Ketalar) is the only dissociative anesthetic product manufactured for human use for the purpose of anesthesia, conscious sedation, and the treatment of bronchospasm. The development of a mechanistic approach to pain therapy in the last 15 years has brought a renewed interest in the use of ketamine as an adjuvant to multimodal pain treatment. Ketamine is used prophylactically and therapeutically in children and adults in the management of postoperative pain. For the treatment of pain ketamine is administered intravenously (median dose: 0.4 mg/kg;

range: 0.1â€“1.6), orally, intramuscularly, rectally, subcutaneously, intraarticularly, caudally, epidurally, transdermally, intranasally, or added to a patient-controlled analgesia device.[61,90,107,160]

The molecular structure of ketamine [2-(ortho-chlorophenyl)-2-methylaminocyclohexanone] contains a chiral center, producing a racemic mixture of 2 resolvable optical isomers or enantiomers, the D(+)-isomer and L(â€“)-isomer. Commercially available preparations of ketamine contain equal concentrations of the 2 enantiomers. These 2 molecules differ in their pharmacodynamic effects. In a randomized, double-blind evaluation of patients undergoing surgery, the D(+)-isomer of ketamine was a more effective anesthetic, but manifested a higher incidence of psychotic emergence reactions than the L(â€“)-isomer. In other studies, the D(+)-isomer causes a greater increase in both blood pressure and pulse than the D(â€“)-isomer, as well as more bronchodilating effects.[158,195]

Pharmacokinetics and Toxicokinetics

Phencyclidine is a white, stable solid that is readily soluble in both water and ethanol. It is a weak base with a pK_a between 8.6 and 9.4 with a high lipid-to-water-partition coefficient. It is rapidly absorbed from the respiratory and the gastrointestinal tracts; as such, it is typically self-administered by oral ingestion, nasal insufflation, smoking, or intravenous and subcutaneous injection.

The effects of PCP are dependent on routes of delivery and dose. Its onset of action is most rapid from the intravenous and inhalational routes (2â€“5 minutes) and slowest (30â€“60 minutes) following gastrointestinal absorption.[42,43] Sedation is commonly produced by doses of 0.25 mg intravenously, whereas oral ingestion typically requires 1â€“5 mg to produce similar sedation. Signs and symptoms of toxicity usually last 4â€“6 hours, and large overdoses generally resolve within 24â€–48 hours, but

effects may persist in a chronic user.[16,54,57,119,141,154] However, in the PCP-intoxicated patient, the relationships between dosage, clinical effects, and serum levels are not reliable or predictable.

There are several explanations for PCP's protracted CNS effects. It has a large volume of distribution of 6.2 L/kg.[42,200] Its high lipid solubility accounts for its entry and storage in adipose and brain tissue. Also on reaching the acidic CSF, PCP becomes ionized, producing CSF concentrations approximately 6â€“9 times greater than those of serum.[133]

PCP undergoes first-order elimination over a wide range of doses. It has an apparent terminal half-life of 21 Â± 3 hours under both control and overdose settings.[42,95] More prolonged toxicity has been reported in patients who â€œbody-packâ€• PCP in plastic bags.[95,203] Ninety percent of PCP is metabolized in the liver and 10% is excreted in the urine unchanged. Evidence indicates that PCP undergoes hepatic oxidative hydroxylation into 2 monohydroxylated and 1 dihydroxylated metabolites. All 3 compounds are conjugated to the more water-soluble glucuronide derivatives and then excreted in the urine.

Urine pH is an important determinant of renal elimination of PCP. In acidic urine, PCP becomes ionized and then cannot be reabsorbed. Acidification of the urine increased renal clearance of PCP from 1.98 Â± 0.48 L/h to 2.4 Â± 0.78 L/h.[42] Additional studies have found a much higher renal clearance (8.04 Â± 1.56 L/h) if the urine pH was decreased to <5.0.[10] Although this may account for a 23% increase in the renal clearance, it only represents a 1.1% increase of the total drug clearance.

Similarly, ketamine is water soluble but also has a high lipid solubility that enables it to distribute to the CNS readily. It has a pK_a of 7.5 and a volume of distribution of 1.8 Â± 0.7 L/kg. Ketamine has approximately 10% of the potency of PCP,[81,97] and human trials demonstrate that its clinical effects, similar to PCP, are both route and dose dependent.[46,49,56,176] Peak

concentrations occur within 1 minute of IV administration and within 5 minutes of a 5-mg/kg IM injection.[195,204] Ketamine distributes immediately into the CNS with the duration of its hypnotic and anesthetic effects being principally caused by its redistribution from the brain to other tissues.[195] Recovery time averages 15 minutes for IV administration, but it is prolonged to between 30 and 120 minutes for intramuscular administration. Oral or rectal doses are not well absorbed and undergo substantial first-pass metabolism.[158,195] In contrast to oral administration of ketamine where symptoms last 4â€“8 hours, symptoms after nasal administration last for 45â€“90 minutes.

Ketamine is extensively metabolized in the liver by the cytochrome P450 (CYP) isozyme CYP2B6 and to a lesser extent by CYP3A4 and CYP2C9.[202] Its biotransformation is complex with numerous metabolites described.[2,158,195] The major pathway involves its *N*-demethylation to norketamine, a metabolite with one-third the anesthetic potency of ketamine. Norketamine is hydroxylated at different sites within its hexanone ring, producing varying second chiral centers. The majority of these diastereoisomers are glucuronidated to more water-soluble derivatives that are then excreted in the urine.[81,158] Ketamine also undergoes ring hydroxylation prior to *N*-demethylation as a minor metabolic pathway. The elimination half-life, which reflects both metabolic and excretory phases, is 2.3 Â± 0.5 hours and is prolonged when xenobiotics requiring hepatic metabolism are coadministered.[117] Because of the enzymatic hepatic metabolism, both tolerance, and enzyme induction are reported following chronic administration.[81,158]

Available Forms

PCP is available on the street in a variety of forms, including powder, liquid, tablets, leaf mixtures, and rock crystal. Because of its uncontrolled illegal manufacture, the contents of PCP sold vary

considerably, with powder often the purest form, containing approximately 5 mg per dosage.[153] Leaf mixtures are made by sprinkling approximately 1â€“10 mg of phencyclidine onto parsley, oregano, mint, tobacco, or marijuana. A typical PCP joint (known as â€œcrystal joint,â€• â€œKJ,â€• or â€œsupergrassâ€•) is developed for smoking and contains about 1 mg per 150 mg of plant product.[7] Mentholated cigarettes dipped into liquid PCP are known as â€œsupercools.â€•

Since PCP's inclusion in the federal Controlled Substance Act of 1970, PCP has been infrequently incorporated into marijuana cigarettes. Currently, there are reports of marijuana cigarettes again being adulterated with PCP. These are being sold on the street under varying names like â€œIllyâ€• in Connecticut, â€œHydroâ€• in New York City, â€œDipâ€• in New Jersey, â€œWetâ€• in Philadelphia, and â€œFryâ€• in Texas.[91] The cigarettes are treated with â€œembalming fluid,â€• which

allegedly enhances the drug's euphoric effects. Embalming fluid, which contains formalin (formaldehyde in methanol), is used as a medium to allow a uniform distribution of PCP in these cigarettes.[91] It is difficult to discern whether this â€œenhancedâ€• mixture is purchased intentionally or is placed in these cigarettes surreptitiously.

On the street and on the Internet, ketamine is known as â€œvitamin K,â€• â€œSpecial K,â€• â€œSuper K,â€• â€œKet,â€• or simply â€œK.â€• It is available in a liquid form that is dried into a pure-white crystalline powder and is typically self-administered by ingestion or insufflation in a fashion similar to PCP. It is rarely injected intravenously or intramuscularly in liquid form.

When used by injection there is an observed demographic and behavioral difference among those who initiate drug injection use with ketamine and those who initiate injection use with another

drug and later transition into ketamine injection.[114]

Ketamine is primarily sold as tablets, capsules, or powder. These formulations are often adulterated with substances such as caffeine, MDMA, ephedrine, methamphetamine, heroin, and cocaine (a mixture known as CK or Calvin Klein).[59,161] In fact, other than alcohol, MDMA (39%), heroin (17%), and cocaine (14%) are the most frequently mentioned substances used with ketamine.[185] Exemplifying the commercial growth of ketamine, some of the tablets are even found to contain a â€œKâ€• logo.[59] Common sedating doses are 75â€“300 mg orally (30â€“75 mg for insufflation). Higher doses, ranging between 300 and 450 mg orally (100â€–250 mg for insufflation), result in substantial CNS toxicity. These manifestations are similar to the clinical emergence reactions that patients experience with ketamine anesthesia.

Pathophysiology

The arylcyclohexylamines, of which PCP and ketamine are prototypes, are a group of anesthetics that functionally and electrophysiologically â€œdissociateâ€• the somatosensory cortex from higher centers.[46,194] The precise mechanisms by which PCP and ketamine achieve these effects are complex and not fully understood; however, investigation of the nature of PCP-induced psychosis has led to a substantial identification of the various sites of PCP activity.

Most studies demonstrate that PCP and ketamine bind with high affinity to sites located in the cortex and limbic structures of the brain.[122] They block the *N*-methyl-D-aspartate (NMDA) receptors at serum concentrations encountered clinically.[190,205] Analogs of PCP (TCP, PCE, PHP, ketamine) and dizocilpine or MK-801 also interact with the NMDA receptor in a doseâ€“response manner that corresponds appropriately to their neurobehavioral effect.[26,164,197] These xenobiotics bind to the NMDA receptor at a site independent of glutamate.[97,102,122,199] As such they antagonize glutamate's

action on this channel noncompetitively and block Ca^{2+} influx (Fig. 14-14).

PCP and ketamine bind to the biogenic amine reuptake complex with 10â€“20% of the affinity to which they bind to the NMDA receptor. Binding occurs at physiologic concentrations that normally take place after subanesthetic doses.[4,149] This weak inhibition of the catecholamine and dopamine reuptake accounts for the respective sympathomimetic and psychomotor effects. An increase in blood pressure and heart rate is induced. Rapid intravenous infusion produces a more pronounced effect than by intramuscular injection, with the D(+)-isomer having a greater effect than the D(â€“)-isomer.[195]

In significant overdoses, PCP and ketamine also stimulate Ïƒ receptors at concentrations generally associated with coma, although with lower affinity than NMDA receptors.[177,198] Both D_2 and Ïƒ receptors have an inhibitory effect on the cholinergic receptor pathways.[198] At the higher concentrations typically associated with death, PCP and ketamine also bind to the nicotinic, opioid, and muscarinic cholinergic receptors.[189]

Data indicate that NMDA antagonists produce effects on behavior, sensation and cognition that resemble aspects of endogenous psychoses, particularly schizophrenia.[98,146] The behavioral abnormalities were first observed in studies in the late 1950s when PCP, administered to healthy volunteers, generated a form of organic psychosis that mimicked schizophrenia. When the drug was administered to schizophrenic patients it uniformly intensified their primary symptoms of profound disorganization, some of these symptoms lasted for weeks.[119] PCP psychosis is so similar to schizophrenia that many psychiatrists cannot distinguish them without a prior indication of drug abuse history.[173]

Current interest in the role of excitatory neurotransmitter systems in the pathophysiology of schizophrenia has led to similar observations in patients after ketamine administration.

Subanesthetic doses of ketamine administered to both healthy and schizophrenic volunteers induced a mild, dose-related, short-lasting increase in psychotic symptoms. Although the normal and schizophrenic volunteers had different levels of baseline psychosis, the magnitude, time course, and doseâ€“response changes in positive symptoms were similar across the two populations. Both groups experienced thought disorganization, such as concreteness and loose association, hallucinations and delusions along a gradient of intensity.[109,111,112,113]

There is a connection between PCP psychosis and sensory processing. PCP and ketamine inhibit sensory perception in a dose-dependent manner. This processing in sensory information corresponds to their relative affinities to the NMDA receptor and not to the Ïƒ receptor.[6,149] Clinically, the impairment of sensory input produced by PCP resembles that of patients who are deprived of sensory stimulation.[132] When external stimulation was reduced by environmental sensory deprivation, the psychotomimetic effects of PCP were diminished,[40] giving credence to the theory that it may not be anxiety that causes perceptual dysfunction in schizophrenia, but the converse.

Many of the NMDA antagonists, including PCP and ketamine, have a negative effect on cognition and memory. There is substantial animal evidence, including primates, that repeat administration of PCP and ketamine result in cognitive and memory impairement.[87,100] Both impair concentration, recall, learning, and retention of new information.[13,30,52,54,73,86,87,88,109,126,135,143] In humans, ketamine selectively impairs explicit,[72] episodic,[51,138,139] and procedural memory,[138] as well as disrupts frontal cortical function as measured by the Wisconsin Card Sorting Task and verbal fluency[109,126] in a doseâ€“dependent manner. In addition, the frequent use of ketamine produces long-lasting impairments in many aspects of memory.[52,139] Learning and memory impairments in volunteers who were administered subanesthetic doses of ketamine (0.65 mg/kg) are independent of the subject's attention

and related psychosis.[126] Accordingly, it is presumed that the NMDA receptor antagonists interfere with those functions that integrate interoceptive and exteroceptive input in which goal-directed action becomes possible, similar to the organic psychosis in schizophrenia.

It was discovered that hypofunction of the NMDA receptor causes neuroanatomical and neurobehavioral toxicologic effects.

Animals exposed to NMDA antagonists such as PCP and dizocilpine, transiently demonstrated neuronal vacuolar degeneration in the retrosplenial cortex and the posterior cingulate areas of the brain.[144,145] Single high doses or repeated exposure to NMDA receptor antagonists are associated with a higher incidence of cellular death.[45,62,63,144] This injury seems to be related to the induction of selective expression of individual heat shock proteins in this anatomical area.[166] The major function of cingulate cortical neurons is to mediate affective responses to pain.[191]

Excitatory amino acids are neurotransmitters responsible for mediating seizure activity in the brain. As NMDA inhibitors, the anticonvulsant properties of PCP and ketamine are inconclusive. Animals administered PCP or PCP analogs progress through dose-related clonic activity followed by tonicâ€“clonic convulsions, as is typical of classic convulsant compounds.[149] Animal research also demonstrates wide interspecies variability of the EEG effects of PCP.[57] In a murine seizure model, ketamine possessed selective anticonvulsant properties.[31] In addition, ketamine preserves learning proficiency in rats when administered shortly after onset of status epilepticus, an effect that may prove useful in the clinical setting when combined with conventional antiepileptic medications.[178]

In humans, although these dissociative xenobiotics induce excitatory activity in the thalamus and limbic areas, they do not affect cortical regions.[48,49,56,69] Excitation, muscle twitching,

posturing,[134] and tonicâ€“clonic motor activity with or without EEG changes are reported with these subcortical EEG alterations.[34,47,69,134] In the clinical setting, many report ketamine to possess anticonvulsant properties at clinical doses that may be explained by an NMDA inhibitory effect.[34,47]

The NMDA receptor is also responsible for the development of the neuronal organization of the central nervous system.[93,94,169,170] It is linked to hypoxicâ€“ischemic brain injury by mediating calcium influx, a final pathway in cell death. The uninhibited firing of NMDA afferent neurons secondary to brain injury causes their death, as well as the death of efferent neurons downstream. In neonatal rats, ketamine increases the rate of neuronal apoptosis.[163] NMDA antagonists such as PCP block hypoxic brain injury from stroke and trauma.[17,118] In a rat model of ischemic stroke, PCP had a protective effect on the brain, demonstrated by a decreased rate of seizure activity.[17] This effect is transient and has not been studied in human subjects.

PCP induces modest tolerance in rats and squirrel monkeys. The development of tolerance is mostly secondary to PCP's pharmacologic effect rather than to biodispositional changes. Dependence was also observed in monkeys who self-administered PCP (10 mg/kg/d to serum concentrations of 100â€“300 ng/mL) over 1 month by the appearance of dramatic withdrawal signs when access was denied. Signs included vocalizations, bruxism, oculomotor hyperactivity, diarrhea, piloerection, difficulty remaining awake, tremors, and, in 1 case, convulsions.[15] These signs appeared within 8 hours of abstinence and were most severe at about 24 hours. When either PCP or ketamine (2.5 mg/kg/h) was readministered to the animals, PCP withdrawal symptoms were reversed, indicating cross-dependence from PCP to ketamine.[20,172]

Physiologic dependence in humans has not been studied formally. It is implied to occur by the observation that 68 chronic PCP users

developed depression, anxiety, irritability, lack of energy, sleep disturbance, and disturbed thoughts after 1 day of abstinence from drug use.[156] Additionally, neonates whose mothers used PCP developed jitteriness, vomiting, and hypertonicity that lasted for at least 2 weeks.[180] These symptoms may represent PCP withdrawal or intrinsic teratogenic effects on neurologic development.[76,93] Although there are no controlled studies observing the physiologic symptoms of withdrawal in humans who chronically use PCP or ketamine, there is a definite psychological dependence on the sensations experienced during recreational use of the drugs.[168] There are few case reports of ketamine dependency in the medical literature where patients report a need to use an increased quantity of drug to get the same effect.[137,150] In addition, ketamine impairs response inhibition, which is found to be related to increases in subjective ratings of desire for the drug.[138]

Clinical Manifestations

The reported signs and symptoms of patients presenting to the emergency department with PCP toxicity are variable. The variations are a result of differences in dosage, the multiple routes of administration, concomitant drug use, and other associated medical conditions. In addition, individual differences in susceptibility to the drug's effects, the development of tolerance in chronic users, as well as contaminants in the drug manufacture, may account for erratic clinical findings.

Vital Signs

Body temperature is rarely affected directly by PCP and ketamine. In one large series, only 2.6% of patients demonstrated hyperthermia (temperature >101.8Â°F [38.8Â°C]).[129] In an experimental animal model, PCP failed to increase body temperature.[36,57] When hyperthermia does occur, all the known

complications, including encephalopathy, rhabdomyolysis, myoglobinuria, electrolyte abnormalities, and liver failure, occur (Chap 16).[8,19,39,151]

Most PCP- and ketamine-toxic patients demonstrate mild sympathomimetic effects. PCP consistently increases both the systolic blood pressure (SBP) and diastolic blood pressure (DBP) in a dose-dependent fashion.[36,57] (Doses of 0.06 mg/kg of PCP IV increased the SBP and DBP by 8 mm Hg, whereas 0.25 mg/kg produce a 26 and 19 mm Hg increase in SBP and DBP, respectively.) PCP also increases the heart rate, although inconsistently.[84] Likewise, ketamine produces mild increases in blood pressure, heart rate, and cardiac output via this same mechanism.[49,121,176,186,195]

Cardiopulmonary

Rarely are cardiovascular catastrophes encountered in PCP toxicity.[60,130] These complications may result from direct vasospasm of blood vessels,[5,35] causing severe systemic hypertension[61] and cerebral hemorrhage.[22] Hypertension, abnormal behavior, and miosis in children strongly suggest PCP poisoning.[105]

The effect of PCP and ketamine on cardiac rhythm is controversial. Dysrhythmias are only observed in animals poisoned with very large doses of PCP. Ketamine is observed to both enhance and diminish epinephrine-induced dysrhythmias in animals.[21,58,85,106] The considerable experience in the use of ketamine anesthesia on humans undergoing surgery or cardiac catheterization has not demonstrated prodysrhythmic effects.[65,142]

As these dissociative anesthetics were designed to retain normal ventilation, hypoventilation is uncommon. In clinical studies, PCP increased the minute ventilation, tidal volume, and respiratory rate of volunteers.[84] Clinically, in PCP-toxic patients, irregular

respiratory patterns occur with tachypnea much more often than

with bradypnea.[8,129] Hypoventilation, when present, is usually secondary to the use of particularly high doses of PCP. Pulmonary edema secondary to respiratory depression is also a rare occurrence. Large doses of PCP (20 mg/kg) administered to laboratory animals produced respiratory depression.[36] Although respiratory depression in humans is an extremely rare event, it has been reported with fast or high-dose infusions of ketamine.[77,195] In fact, ketamine has been used successfully to prevent intubation in patients with refractory asthma.[71,159,181,195]

Neuropsychiatric

The majority of patients with PCP and ketamine toxicity who are brought to medical attention manifest diverse psychomotor abnormalities.[12,18,28,68,100,188] As dissociative anesthetics, these drugs produce a lack of response to external stimuli by dissociating various elements of the mind. Consciousness, memory, perception, and motor activity appear dissociated from each other. This dissociation prevents the user from attaining cognition and properly assembling all this information to construct a reality. Clinically the person may appear inebriated, either calm or agitated, and sometimes violent. In large overdoses, the drug's anesthetic effect causes patients to develop stupor or coma. In recreational use, â€œdissociativesâ€• are not taken for these effects, but rather for so-called out-of-body experiences. In addition patients often have disordered thought processes (including disorientation as to time, place, and person) or amnesia, paranoia, and dysphoria.[67]

The manifestations of PCP and ketamine toxicity are better illustrated by the results of their effects in controlled human studies. Volunteers who took oral PCP doses of up to 7.5 mg/d, or ketamine 0.1 mg/kg, exhibited inebriation, but higher doses (PCP

>10 mg/d; ketamine 0.5 mg/kg) generally caused a more severe impairment of mental function.[57,109] Intravenous doses of 0.1 mg/kg of PCP[16,54,119,141,162] or 0.5 mg/kg of ketamine[109,149] causes diminution in all sensory modalities (pain, touch, proprioception, hearing, taste, and visual acuity) in a doseâ€“dependent fashion. Both drugs also cause feelings of apathy, depersonalization, hostility, isolation, and alterations in body image.[16,54,70,109,119,149] The deficits in sensory modalities are evident prior to the development of the psychological effects of PCP, with pain perception disappearing first. This alteration in analgesic perception is caused by a blocking action on the thalamus and midbrain (Fig. 83-1).[141]

Abnormal stereognosis and proprioception occur in a doseâ€“dependent manner. This disturbed perception results in body image distortions described as â€œnumbness,â€• â€œsheer nothingness,â€• and â€œdepersonalization.â€• The decrease of proprioceptive sensation to gravity probably gives the sensation of â€œtrippingâ€• or â€œflying.â€• Because all sensory modalities are affected, visual, auditory, and tactile illusions and delusions are common. Hallucinations are typically auditory rather than visual, which are more common with LSD use. Ketamine's hallucinogenic effects on healthy human volunteers are linearly related to steady-state concentrations between 50 and 200 ng/mL.[23] The majority of ketamine users report experiencing a â€œk-hole,â€• a slang term to the intense psychological and somatic state experienced while under the influence of ketamine. This experience varies with the individual, but can include buzzing, ringing or whistling sounds, traveling through a dark tunnel, intense visions and out-of-body or near-death sensations.[55]

The reaction to the misperceived or disconnected reality may result in unintentional actions and violent behavior. The hallmark of PCP toxicity is the recurring delusion of superhuman strength and invulnerability resulting from both the anesthetic and dissociative properties of the drug. There are case reports of

patients presenting with trauma either from jumping from high altitudes, fighting large crowds or the police, or self-mutilation. The true extent and incidence of violence is probably less than previously suggested.[24]

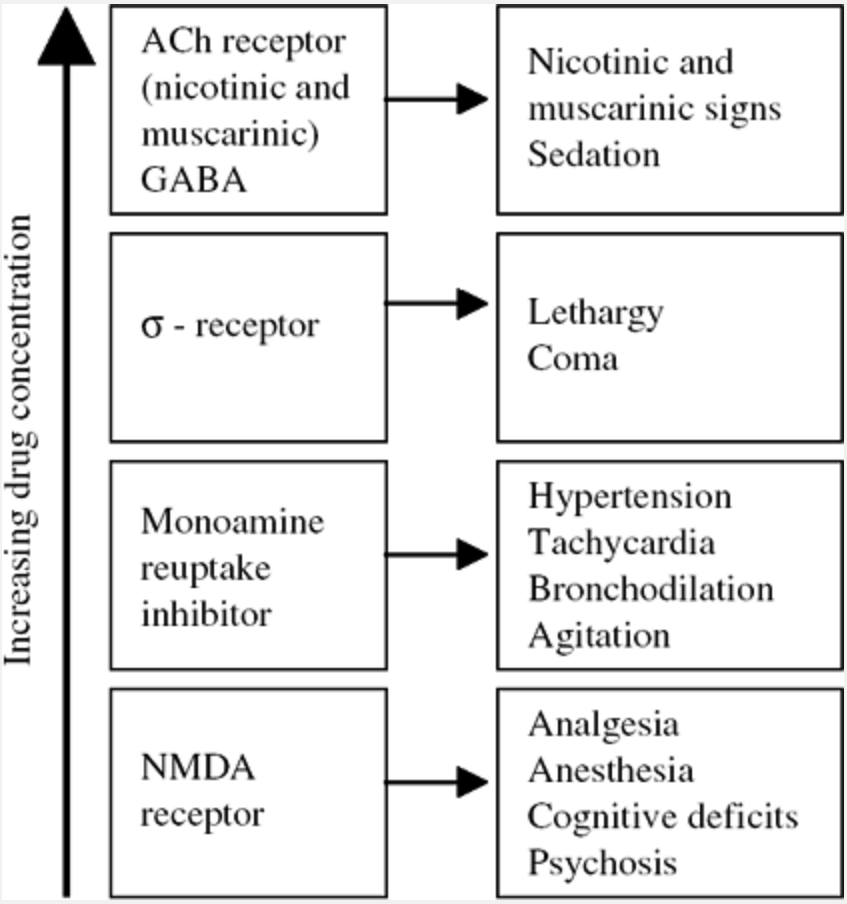

Figure 83-1. Clinical effects of phencyclidine and ketamine. Phencyclidine and ketamine bind to different receptors in the CNS with varying degrees of affinity; that is an increasing concentration is necessary to achieve the consequential clinical effects. ACh = acetylcholine.

Typically, neurologic signs include rotatory nystagmus, ataxia, and

altered gait. Initially, except for ataxia, motor movement is not impaired, until the patient becomes unconscious. On physical examination, use of dissociative agents typically produces relatively small pupils and (horizontal, vertical, and/or rotatory) nystagmus, and diplopia. In the largest case series reported to date, nystagmus and hypertension were noted in 57% of patients who had taken PCP.[129] Smaller and more limiting studies have found an incidence of nystagmus of 89% or higher.[18] Other cerebellar manifestations were also encountered, most notably dizziness, ataxia, dysarthria, and nausea. A pooled data compilation of 35 reports demonstrated that emesis occurred 8.5% of the time.[81] In fact, Internet chat groups devoted to substance abuse commonly direct users to â€œmix dissociatives with marijuanaâ€• for its antiemetic effect.

Larger doses of PCP produce loss of balance and confusion, the latter characterized by inability to repeat a set of objects, frequent loss of ideas, blocking, lack of concreteness, and disordered linguistic expression.[51,57,109,119,162] Similarly, ketamine users report a high incidence of incoordination, confusion, unusual thought content and an inability to speak.[55] In general, dissociative anesthetics stimulate the central nervous system but seizures rarely occur, except at high doses. The largest case series of PCP-toxic patients detected a 3.1% incidence of seizures.[129]

Although PCP- and ketamine-toxic patients also present with motor disturbances, it is not clear to what extent PCP and ketamine are actually responsible for these manifestations. The most common of the reported disturbances are dystonic reactions: opisthotonos, torticollis, tortipelvis, and risus sardonicus (facial

grimacing). Myoclonic movements, tremor, hyperactivity, athetosis, stereotypies, and catalepsy also occur.[12,29,68,129] A slight increase in muscle tone results from a dopaminergic effect.[119] Laryngospasm requiring intubation has been reported after the use of ketamine anesthesia. The incidence of this

complication is less than 0.017%.[81] In comparison, the incidence of laryngospasm following traditional general anesthesia is 2%.[147]

Emergence Reaction

The acute psychosis, observed during the recovery phase of PCP anesthesia, limits its clinical use. This bizarre behavior, characterized by a confused state, vivid dreaming, and hallucinations, is termed an â€œemergence reaction.â€• These reactions occur most frequently in middle-age males, with a reported incidence of 17â€“30%.[84,104] The most violent emergence reactions follow an intravenous dose of approximately 0.25 mg/kg (total: 20 mg) of phencyclidine.[57] The mildest degrees of agitation produced by phencyclidine resemble the effects of ethanol intoxication. These same postanesthetic reactions also limit the clinical use of ketamine. The incidence of emergence reactions following ketamine administration may approximate 50% in adults and 10% in children.[81] Patients older than age 10 years, females, and persons who normally dream frequently and/or have a prior personality disorder incur the greatest risk.[81] The incidence of the occurrence of emergence reactions appears to be exacerbated when the drugs are rapidly administered intravenously, and in those patients who are exposed to excessive stimuli during recovery. Although it has not been proved in a controlled study, reducing external stimuli during the recovery phase might reduce emergence reactions.

Both cholinergic and anticholinergic clinical manifestations occur in the PCP- or ketamine-toxic patient. Miosis, mydriasis, blurred vision, profuse diaphoresis, hypersalivation, bronchospasm, bronchorrhea, and urinary retention occur.[12,18,116,128,129] Clinically, ketamine stimulates salivary and tracheobronchial secretions; both of which are equally and effectively inhibited by atropine and glycopyrolate.[137] Furthermore, in a randomized, double-blind trial, after infusion of 1.5 mg/kg of ketamine in

healthy volunteers, physostigmine decreased nystagmus, blurred vision, and the time to recovery.[185]

Ironically, the very characteristics that were thought to make phencyclidine ideal for anesthesiaâ€”the preservation of muscle tone and cardiopulmonary functionâ€”magnify the difficulties in managing an individual who manifests dysphoria after an overdose. The course of delirium, stupor, and coma associated with PCP and ketamine is extremely variable, although the manifestations are much milder and shorter acting following ketamine use.

Diagnostic Testing

Most hospital laboratories do not perform quantitative analysis of PCP, but many can do a qualitative urine test for the presence of the drug. Qualitative testing is more important than a quantitative determination as serum concentrations do not correlate closely with the clinical effects. PCP may not be part of a routine toxicologic screening and it therefore may be necessary to request a specific analysis if confirmation is required.

When a routine toxicologic screen is reported as negative this result should not lead to the erroneous conclusion that PCP exposure has been excluded. If it is necessary to confirm the suspicion that PCP is the offending agent, urine is most commonly used for analysis, although serum, and possibly gastric contents, can be employed. Rarely is it essential to make this determination.

PCP is qualitatively detected by an enzyme immunoassay at a sensitivity of 10.00 ng/mL. High-affinity antibodies were once studied as specific PCP antagonists that may reverse PCP-induced toxicity.[148,187] The detection of PCP is thus dependant on the concentration of PCP in the body fluid tested and the affinity of the antibody for the PCP molecule. As such, the immunoassay antibody binding to a molecule similar to PCP can anticipate false-positive

reactions. Metabolites of PCP, such as PCE, PHP, TCP and its pyrrolizidine derivative TCPy, cross-react with the immunoassay at concentrations 30 times higher than those used to detect PCP. Because of its similar structure to PCP, dextromethorphan and its metabolite dextrorphan, also cross-react with Syva enzyme-multiplied immunoassay and fluorescence polarization PCP assays (Chap. 7).[92]

Although nonspecific, laboratory findings resulting from PCP use can include leukocytosis, hypoglycemia, and elevation of muscle enzymes, myoglobin, BUN, and creatinine.[129] The EEG reveals diffuse slowing with Î¸ and Î´ waves, which may return to normal before the patient improves clinically.

There is no commercially available immunoassay for ketamine. When necessary, ketamine is detected by gas chromatography and mass spectroscopy. The increase in popularity in ketamine use in certain parts of the world has led to the development of rapid-detection urine assays that are sensitive, specific, and accurate.[37,192] There is anecdotal evidence that ketamine also cross-reacts with the urine PCP immunoassay because of their structural similarity.[165] Other authors, including the manufacturer who tests the reactivity of the commercially available PCP immunoassay with ketamine, do not find such results.[32,188]

Management

Agitation

Conservative management is indicated for PCP and ketamine toxicity and includes maintaining adequate respiration, circulation, and thermoregulation. The psychobehavioral symptoms observed during acute dissociative reactions and during the emergence reaction are similar. To treat the symptoms of agitation and alteration of mental status of acutely toxic PCP patients, it is

helpful to recognize that both pharmacologic[1,33,38,41,64,81,82,123,127] and behavioral[40,41,81,110] modalities have been employed to diminish agitation and emergence phenomena during conscious sedation with ketamine. To prevent self-injury, a common form of PCP-induced morbidity and mortality, the patient must be safely restrained, initially physically, and then chemically. An intravenous line must be established and blood drawn for electrolytes, glucose, BUN, and creatinine determinations. The use of 0.5â€“1.0 g/kg of body weight of dextrose and 100 mg of thiamine HCl intravenously should be considered if indicated.

Psychomotor agitation from PCP toxicity may cause hyperthermia and should be identified early on. Treatment should be accomplished immediately with adequate sedation to control motor activity. Physical restraint should only be used temporarily, if necessary, until chemical sedation is achieved. Rapid immersion in an ice water bath may be necessary because body temperatures greater than 106Â°F (41.1Â°C) place the patient at a great risk for end-organ injury. These patients will need volume repletion and

electrolyte supplementation because hyperthermia increases fluid loss from sweat.

In the pharmacologic treatment of emergence reactions, butyrophenones and benzodiazepines have been employed with benzodiazepines demonstrating the most success. A benzodiazepine such as diazepam, administered in titrated doses of up to 10 mg intravenously every 5â€“10 minutes until agitation is controlled, is usually safe and effective. Numerous studies demonstrate the benefits of benzodiazepines, although under certain conditions,[38,81] they may prolong recovery time. Midazolam may be more effective than diazepam under certain circumstances.[33,127] In contrast, phenothiazines may lower the seizure threshold, and both phenothiazines and butyrophenones may cause acute dystonic reactions. Phenothiazines may also

cause significant hypotension, worsen hyperthermia, and exacerbate any anticholinergic effects from these drugs.

Some behavioral modalities have also been implemented in the treatment. Early studies demonstrated that the psychotomimetic effects of PCP were diminished when external stimulation was reduced by environmental sensory deprivation.[40] The practice of placing patients in a quiet room with minimal sensory stimulation is recommended by many, but has never been formally studied in a double-blind, controlled trial. Conversely, it is observed in patients undergoing ketamine anesthesia that emergence reactions are less violent when patients are talked to or when music is played.[110,171]

Although it is always important to ask the patient the names, quantities, times, and route of all drugs taken, the information obtained from such a patient is notoriously unreliable. Even when the patient is trying to cooperate and give an accurate history, many street psychoactive xenobiotics are drug mixtures whose contents are unknown to the patient. Consequently, pharmacologic management is complex and often sign- or symptom-dependent. Although some authors have attempted to define the appropriate therapy for specific PCP congeners and for ketamine-induced psychosis, no single approach has been consistently efficacious.[73,108,124]

Decontamination

Patients with a history of recent oral use of PCP are candidates for gastrointestinal decontamination, but they should be considered too unstable for induced emesis, as uncontrolled agitation or respiratory compromise can rapidly develop. Although there is rarely, if ever, an indication, if congestion is suspected, orogastric lavage may be initiated but the patient may need to be sedated. Activated charcoal, 1 g/kg, should be administered as soon as possible, and repeated every 4 hours for several doses. Activated

charcoal will effectively adsorb PCP and increase its nonrenal clearance; even without prior gastric evacuation this approach is usually adequate.[155] Unless there are specific contraindications, a single dose of a cathartic, such as sorbitol, can be given.

Theoretically, xenobiotics that are weak bases, such as PCP, can be eliminated more rapidly if the urine is acidified. Although urinary acidification with ammonium chloride was previously recommended,[9] we do not recommend this approach. The risks associated with acidifying the urineâ€”simultaneously inducing a systemic acidosis, thereby potentially increasing urinary myoglobin precipitationâ€”outweigh any perceived benefits (Chap. 10).

As opposed to the problems in applying ion-trapping to renal excretion, ion-trapping results in the active mobilization of PCP into gastric secretions. Phencyclidine is in a substantially ionized (and therefore nonâ€“lipid-soluble) form in the acid of the stomach and can be absorbed only when it reaches the more alkaline intestine. As a result, gastric suction can remove a significant amount of the drug, as well as interrupt the gastroenteric circulation (by which the drug is secreted into the acid environment of the stomach only to be reabsorbed again in the small intestine).[9] Continuous gastric suction, however, can also be dangerous and unnecessary. It should be considered only in comatose patients. Continuous suction may result in trauma to the patient as well as in fluid and electrolyte loss, which can further complicate management and possibly interfere with the efficacy of activated charcoal. For these reasons the administration of multiple-dose activated charcoal rather than continuous nasogastric suction appears to be the safest and most effective way of removing ion-trapped drug from the stomach.

Most patients rapidly regain normal CNS function anywhere from 45 minutes to several hours after using these drugs. However, those who have taken exceedingly high doses or who have an underlying psychiatric disorder may remain comatose or exhibit

bizarre behavior for days, or even weeks, before returning to normal. Those who regain normal function rapidly should be monitored for several hours and then, after a psychiatric consultation, should receive drug counseling and any additional social support available. Patients whose recovery is delayed should be treated supportively and monitored carefully in an intensive care unit.

Many patients become depressed and anxious during the â€œposthighâ€• period, and chronic users may manifest a variety of psychiatric disturbances.[201] These individuals typically present with repeated drug use, hospitalizations, and poor psychosocial functioning in the long term.

The major toxicity of PCP appears to be behaviorally related: self-inflicted injuries, injuries resulting from exceptional physical exertion, and injuries sustained as a result of resisting the application of physical restraints are frequent. Patients appear to be unaware of their surroundings and sometimes even oblivious to pain because of the dissociative anesthetic effects. In addition to major trauma, rhabdomyolysis and resultant myoglobinuric renal failure account in large measure for the high morbidity and mortality associated with PCP intoxication. If significant rhabdomyolysis[39,151] has occurred, myoglobinuria may be present. Early fluid therapy should be used to avoid deposition of pigment into the kidneys, leading to renal failure. Urinary alkalinization as part of the treatment regimen for rhabdomyolysis would potentially increase PCP reabsorption and deposition in fat stores, but this is only theoretical and is not recommended.

Although the clinical experience with recreational use of ketamine is limited, toxic manifestations appear to be similar, yet milder and shorter-lived, when compared to PCP. In a study of 20 patients who presented with acute ketamine toxicity, all were treated conservatively and successfully with intravenous hydration, and sedation with benzodiazepines.[188]

Summary

As â€œdissociativeâ€• anesthetics became clinically available, their abuse potential was also discovered. The popularity of PCP and ketamine results from their ability to produce an â€œout-of-body experienceâ€• with seemingly hallucinatory effects. The action of these drugs is largely mediated by the NMDA receptor. Their toxicity, in great part neuropsychiatric in nature, is managed by supportive

care. The popularity of ketamine may be related to its lesser toxicity and milder distortion of the personality.

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Chapter 84
Antimony

Asim F. Tarabar

Antimony (Sb)
Atomic number
=
51
Atomic weight
=
121.75
Normal concentrations
Serum
=
0.8â€“3 Âµg/L
Urine (24 hour)
=
0.5â€“6.2 Âµg/L
Urine (24 hour)
=
35 Âµg/g creatinine
A 19-year-old Hispanic man with a history of alcoholism presented to the

(ED) complaining of 1 day of repeated vomiting, diarrhea, and abdominal history was significant for multiple failed attempts to achieve alcohol abst help him attain sobriety, his parents sent him an aversive medication fro â€œSoluto Vital.â€• On the day prior to admission the patient ingested t of the bottle that was labeled to contain tartar emetic and small amounts *Strophanthus.* The normal dose was listed as 20â€“25 drops. His estimate was 500 mg. Approximately 30 minutes after ingestion he experienced ab vomited multiple times. Massive diarrhea rapidly ensued.

Physical examination revealed a young man in distress with the following pressure, 104/71 mm Hg; pulse, 96 beats/min; respirations, 18 breaths/ 96.6Â°F (35.9Â°C). The remainder of the examination was remarkable fo a clear chest, and a normal heart examination. His abdomen was tender but there was no rebound tenderness or guarding. Neurologic examination was no indication of suicidality. His stool tested negative for occult blood

An intravenous line was inserted, and the patient was resuscitated with (solution. Specimens were sent for a complete blood count, electrolytes, a enzymes. An electrocardiogram was interpreted as normal. In the ED, the episodes of vomiting despite antiemetic therapy. His diarrhea also contin studies were consistent with volume loss and possibly renal injury (blood creatinine, 2.4 mg/dL; hematocrit, 60%; urinalysis, 2+ protein) the patien hospital.

The vomiting gradually subsided and a single dose of 50 g of activated c without a cathartic. By 12 hours after admission, his creatinine had impro total urine output was only 500 mL for the first 24 hours. The following d was discharged. Subsequently, his 24-hour urine reported an antimony c or 682 Âµg/g creatinine. The patient never returned for followup care.

Chemistry

Antimony (Sb) is located in the same group on the periodic table as arsen shares many chemical, physical, and toxicologic properties. Because it can nonmetal, antimony is classified as metalloid (Chap 12).[77] Pure antimony white, brittle, hard metal that is easily pulverized.[61 , 89] However, becaus

rapidly converted to either antimony oxide or antimony trioxide, it is ext

rare to find isolated elemental antimony in nature. It has been suggested originates from *anti monon* (enmity to solitude) because antimony is almo other metal.[59] Thus, for the purposes of this chapter, the term *antimony* nature, antimony can be found in more than 100 different minerals,[59, 49] cervantite, valentine, and kermesite.[30] The sulfide ore (stibnite) is the m Bolivia and South Africa are among the leading producers.[89] Like arsenic, both organic and inorganic compounds with trivalent and pentavalent oxi inorganic trivalent antimony compounds include antimony trioxide (SbO_3 (SbS_3), antimony trichloride ($SbCl_3$), antimony potassium tartrate (C_8 H (SbH_3). Antimony pentasulfide (Sb_2 S_5) and pentoxide (Sb_2 O_5) are pe compounds that can act as oxidizing agents.[40] From an industrial perspec application of antimony is the use of antimony oxychloride (Sb_6 O_6 Cl_4)

Tartar emetic (antimony potassium tartrate) is an odorless trivalent antim potent emetic effect[40] and a sweet metallic taste.[41] Antimony potassium t one of the most toxic antimony compounds, with minimal lethal doses rep and 1200 mg.[59] There are large species variations of the LD_{50} (median le subjects) in experimental animals, with a reported range of 115 mg/kg in mg/kg in mice. In comparison, because of a low water solubility, antimor practically, to be nontoxic, with an LD_{50} >20,000 mg/kg.[32]

History

In spite of the fact that antimony and its compounds are regarded as am remedies in the practice of medicine, they remain unfamiliar to most peo discovered during exploration of old Mesopotamian civilization (3rd and 4 suggested that both the Sumerians and the Chaldeans were able to produ The reference to eye paint in the Old Testament suggested the use of an thousand years, Asian and Middle Eastern countries used antimony sulfide cosmetics, including rouge and black paint for eyebrows, also known as k Because of the scarcity of antimony sulfide, lead replaced antimony as a modern cosmetic preparations.

One of the first monographs on metals, written in the 16th century, inclu

antimony.[84] The medicinal use of antimony for the treatment of syphilis, dates to the medieval period. Paracelsus (1493â€“1541) was credited wi compounds as therapeutic agents and increasing their popularity. In spite potential, many of the disciples of Paracelsus enthusiastically continued th Various antimony compounds were used also as topical preparations for t leprosy, mania, and epilepsy.[89] Orally administered tartar emetic (antimo used for treatment of fever, pneumonia, and inflammatory conditions, bu of its significant toxicity.[11 , 27 , 39] Historically, the therapeutic dose rang tartrate was from 20 mg every 10 minutes (until vomiting occurred) to 4(

The use of antimony as a homicidal poison[80] was recognized, and this pra the 20th century (Chap 1).

The current medical use of antimony is limited to the treatment of leishm kala-azar, and schistosomiasis, and to sporadic use as aversive therapy f Pentavalent compounds are used because they are better tolerated. In sp in vitro,[27] there is no current oncologic use of antimony.

Some contemporary homeopathic[35] and anthroposophical[75] practices still antimonial compounds as home remedies; however, these practices are r

Because of its poor physical properties (eg, inflexible metal), the element very few industrial uses. In contrast, its alloys with copper, lead, and tin applications. Industrial and occupational exposure to antimony occurs mai dust or fumes during the processing or packaging of antimony compounds also be occupationally exposed to antimony.[34] Antimony concentrations in from 10â€“60 mg/kg.[34 , 63] This may be an additional factor contributing concentrations of antimony found in workers' lungs.[34]

In developed countries, antimony poisoning rarely occurs following intent preparations.[89]

Toxicokinetics

Absorption

Antimony may be absorbed by inhalation, ingestion, or transcutaneously.

gastrointestinal tract begins immediately on ingestion, and the oral bioav ranges from 15â€“50%.[33, 85] This poor gastrointestinal absorption in hum concomitant emesis, necessitates parenteral administration of many ant pharmaceuticals. Pulmonary absorption of many inorganic antimony compo limited by low solubility.[59] In contrast, animal data suggest that inhaled absorbed from the lung, distributed to various organs, and subsequently urine.[26]

Distribution

Distribution apparently depends on the oxidation state of antimony. In an trivalent antimony is incorporated into the red blood cells within 2 hours similar time frame, 90% of pentavalent antimony will still be found in the administered intravenously or orally, antimony is predominantly distribute organs, including liver, kidneys, thyroid, and adrenals.[66, 89] Uptake by t mechanisms of diffusion and saturable binding. Repeated exposures cause independent of the concentration in red cells.[74] In a hamster model, follo organic antimonials, the greatest concentration of antimony was found in inhalation, antimony accumulates predominantly in red blood cells, and to extent in liver and spleen.[26, 28] The fact that elevated urine and serum are measured more than 2 years after the treatment suggests that antimo for a prolonged period of time.[58]

Excretion

Although antimony and arsenic share many toxicokinetic properties, unlik trivalent antimony is not methylated in vivo.[3] Trivalent antimony is excret conjugation with glutathione. A significant proportion of excreted antimo recirculation.[3] The remainder is excreted in urine. The overall elimination 10% of a given dose cleared in the first 24 hours, 30% in the first week, antimony is still detected in the urine 100 days after administration.[57, 8 much more rapidly excreted by the kidneys than trivalent antimony (50â€ 24 hours).[89] In workers, urine concentrations of pentavalent antimony co intensity of exposure.[3]

Pathophysiology

Elemental antimony is considered to be more toxic than its salts, but bec elemental form is relatively uncommon, this fact is of limited clinical rele metals, antimony binds to sulfhydryl groups to inhibit a variety of metab Trivalent antimony compounds are more toxic than the pentavalent comp higher affinity for erythrocytes and sulfhydryl groups.[54] Tartar emetic and also considered local irritants of the gastrointestinal tract. One proposed activation of enterochromaffin cells that are located in the gastrointestinal secrete serotonin. Released serotonin acts on the 5-HT_3 receptors, stimul and activating the vomiting center.[38 , 87] In addition, there is apparent action, particularly after administration of higher doses of antimony.[89] Fr perspective, trivalent antimony compounds also inhibit phosphofructokinas energy for schistosomes.[14 , 89]

Clinical Manifestations

Data on human toxicity of antimony are very limited, and are largely ext occupationally exposed patients and from the reports of adverse effects leishmaniasis with antimony. There are very few case reports of intentio For didactic purposes, we recognize three distinct populations that may p toxicity.

Workers with occupational exposures usually present with subtle clinical toxicity develops slowly over time. It is important to recognize that antim concentration of arsenic as impurity, making it difficult to distinguish whe are caused by contaminants or by the antimony. Therapeutic side effects may have a somewhat subacute to acute clinical picture, as some patient require prolonged treatment with antimony to achieve cure,[82] exposing th large cumulative doses.

Patients with oral ingestions present with acute symptoms mimicking the other metal salts. Several cases were described after the use of old porc use of antimony compounds as home remedies.[1 , 53 , 62 , 79]

Local Irritation

The majority of antimony toxicity is based on local irritation. In sufficien acts as an irritant to the eyes, skin, and mucosa. Chronic exposure can [72] Irritation of the upper respiratory tract can lead to pharyngitis.

Systemic

Gastrointestinal in acute exposures, antimony can rapidly produce nausea pain, and diarrhea. Some patients may report a metallic taste in the mou gastrointestinal irritation can progress to hemorrhagic gastritis. Workers antimony dusts have a much higher incidence of gastrointestinal ulcers ir (63 per 1000 vs. 15 per 1000).[12] A large series of patients developed ch pancreatitis following treatment with pentavalent antimonial agents.[31] Be cases improved despite continuation of treatment, the authors presumed direct toxicity. In another series, several patients with HIV who were trea meglumine antimonate developed severe pancreatitis and died.[24]

Cardiovascular

In animals, antimony decreases myocardial contraction, decreases corona producing decreased systolic pressure,[89] and causes bradycardia.[23] The cardiac effects are related to changes on the electrocardiogram (ECG). Pr interval, inversion or flattening of T waves, and ST segment changes are during treatment of visceral leishmaniasis with pentavalent antimonial co stibogluconate and meglumine antimonate).[18 , 90] Torsades de pointes wa treated with pentavalent antimonial preparations.[65 , 81] In patients with disease (eg, cardiomyopathy), ECG changes can occur even with antimony considered to be therapeutic.[37] These changes are not necessarily associ cardiac function.[44] However, it is important to recognize that pentavalent the treatment of leishmaniasis are associated with sudden deaths, probably development of ventricular dysrhythmias.[16 , 78]

Thrombophlebitis is common after IV use of antimony, but has been repo occurs orally.[55]

Respiratory

Local irritation from antimony trioxide can produce laryngitis, tracheitis, lung injury was reported after acute exposure to antimony pentachloride.

Although antimony oxides are capable of causing metal fume fever,[29] this comparison to exposure to zinc oxide.[2 , 29] Antimony metal fume fever is concentrations below 5 mg/m^3 .[20]

Renal

Patients treated with sodium stibogluconate can develop varied manifesta ranging from renal cell casts, proteinuria, and increased blood urea nitro renal failure.[4 , 70] Some patients can also develop renal tubular acidosis[4] necrosis.[71]

Hematologic

Severe anemia was reported in HIV-positive patients during the treatmen stibogluconate, with documented transient severe bone marrow dyseryth complete recovery on discontinuation of the therapy.[46]

Patients treated with sodium stibogluconate for visceral leishmaniasis oc thrombocytopenia.[9 , 45 , 51] Rare cases of epistaxis are described during t unclear if they are associated with thrombocytopenia.[52] Visceral leishma

itself is known to be associated with pancytopenia, probably as a result o peripheral blood cells.[69] It may be difficult to determine whether this phe disease itself or is secondary to the treatment, although some authors su immune thrombocytopenia.[69]

Leukopenia is frequently observed in patients treated with antimonial co authors speculate that antimony-induced lymphopenia is associated with herpes zoster in HIV patients.[91]

Dermatologic

Antimony spots[76] are papules and pustules that develop around sweat an

may resemble varicella. A similar skin rash was described in the 18th cer application of antimony tartrate for medicinal use.[59] Interestingly, these interpreted as a sign of cure.[39]

Neurologic

A patient with cutaneous leishmaniasis who was treated with sodium sti antimony) developed a reversible, peripheral sensory neuropathy in temp treatment.[13] The authors suggested that neuropathy may be the result c antimony.

Reproductive

In animal studies, antimony exposure causes ovarian atrophy, uterine m conception.[7] Limited information from the Russian literature describes an spontaneous abortion and premature births in women who were occupatic salts. Antimony was found in the blood, urine, placenta, amniotic fluid, an women.[7]

Carcinogenicity

Initial studies in female rats reported lung tumors after inhalational expo trioxide.[36 , 86] Likewise, a survey among antimony smelter workers sugge cancer, with a latency of 20 years, in comparison to a nonexposed popul concomitant exposure to arsenic and its effects could not be excluded and inadequately controlled for workers' smoking habits.[50]

Patients with schistosomiasis have an increased incidence of bladder tum compounds are considered to be one potential cause.[89]

Stibine

Antimony compounds can react with nascent hydrogen forming an extrem (SbH_3), which resembles arsine (AsH_3) (Chap. 85). Stibine is probably compound. It is a colorless gas with a very unpleasant smell that rapidly temperatures above 302Â°F (150Â°C).[43 , 89] Historically, stibine release

charging of lead storage batteries.[89] In addition to GI symptoms that inc abdominal pain, stibine has strong oxidative properties capable of produc (Chap. 24). Similar to arsine,[73] severe stibine exposure may result in h and death. Maintenance workers are advised to avoid use of drain cleane capable of releasing hydrogen in situations where antimony may be prese

Diagnostic Testing

Standard laboratory testing to help identify volume depletion and renal in patients with acute antimony toxicity. A complete blood count, electrolyte and a urinalysis should be obtained. When there is a known or suspected additional studies should include tests for hemolysis, such as determinatio haptoglobin. Blood should also be obtained for a blood type and cross-ma likely to be required.

An ECG should be obtained to evaluate for QTc prolongation and other ch myocardial disease should have more frequent monitoring of cardiac funct

Antimony concentration in a 24-hour urine collection can be used for asse exposure to either trivalent or pentavalent antimony.[3] A normal urinary nonexposed patients is reported in the range of 0.5â€“6.2 Âµg/L.[58 , 88] T US population is 0.128 Âµg/L, with concentrations of the 95th percentile serum antimony concentration is impractical because it cannot be determi However, it is suggested that normal serum concentration of antimony is Âµg/L,[58] although some laboratories use higher values.[64]

Treatment

Decontamination

Following a significant acute ingestion, the majority of the patients devel emesis is unlikely to offer any additional benefit. In contrast, gastric lava especially if performed before the onset of spontaneous emesis. Although antimony is adsorbed to activated charcoal, based on experience with sal mercury, administration of activated charcoal seems reasonable. Additiona a documented enterohepatic circulation, multiple-dose activated charcoal r

patients exposed to stibine, decontamination involves removal from the e administration of high-flow oxygen. Theoretically, severe stibine exposure transfusion for removal of stibineâ€“hemoglobin complex.[73]

Supportive Care

The mainstay of treatment for antimony poisoning is good supportive car anticipate massive volume depletion and begin rehydration with isotonic Electrolytes and urine output should be followed closely. A central venous required in patients with cardiovascular instability. Antiemetics are indicat comfort and to facilitate the administration of activated charcoal. Followir hematocrit should be followed closely and blood should be transfused bas

Chelation

Human experience with regard to chelation of antimony is rather limited l serious toxicity and the rarity of instances when patients have received c available data are based on animal experimentation. Dimercaprol, succim dimercaptopropane-sulfonic acid (DMPS) all improve survival of experime One animal study that compared survival after treatment with multiple c

concluded that the most effective antidotes were DMPS and succimer.[6]

A single case series documented survival in 3 of 4 patients exposed to ta intramuscular dimercaprol at a dose of 200â€“600 mg/d. All 4 patients h excretion of antimony.[55] In another case report, a patient survived after but without evidence of enhanced antimony excretion in urine.[3] Although are difficult to make, it is reasonable to begin therapy with intramuscular certain that antimony is removed from the gastrointestinal tract, at which switched to oral succimer. Because chelation doses for antimony poisonin chelators should be administered in doses and regimens that are determin effective for other metals (see Antidotes in Depth: Dimercaprol [British A Antidotes in Depth: Succimer [2,3-Dimercaptosuccinic Acid]).

Summary

Antimony is an element whose physical, chemical, and toxicologic proper arsenic. Although uncommon, antimony toxicity does occur. The hallmarks gastrointestinal manifestations leading to profound volume depletion and Electrocardiographic findings may assist in the identification of this xenol supportive, although chelation may be indicated in life-threatening cases.

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Chapter 85
Arsenic

Marsha Ford

Arsenic (As)

Atomic number = 33

Atomic weight = 74.92

Normal concentrations

Whole blood = < 5Âµg/L(0.665 Âµmol/L)

Urine (24 hour) = <5Âµg/L (< 6.65 Âµmol/L)

Urine (24 hour) = <100 Âµg/g creatinine

A 55-year-old woman was hospitalized for diarrhea, nausea, vomiting, and weakness of unknown etiology. The patient had type II diabetes mellitus and had been in her usual state of health until 5 weeks earlier when, after eating noodle paste, she and her husband developed persistent nausea, vomiting, and diarrhea. Both were

admitted with dehydration and hypokalemia and treated for 1 week. On discharge the patient's weakness necessitated the use of a cane for walking. Approximately 3 weeks later, the patient's husband complained of weakness, then vomited and had a syncopal episode. He was resuscitated with intravenous (IV) fluids and admitted to the hospital. The following day he suddenly became hypotensive, had a cardiopulmonary arrest, and died. Four days later, the patient again developed nausea, vomiting, diarrhea, and weakness. She also noted numbness in her hands and feet, described as â€œpins and needles.â€• She distinguished this from the numbness in her toes, previously ascribed to diabetic neuropathy. The patient had also been bedridden for the past 10 days because of weakness and an inability to walk. There were no further neurologic complaints.

Her past medical history revealed type II diabetes mellitus for 3 years, hypertension, and an episode of an unknown cardiac dysrhythmia. Her medications included NPH insulin, digoxin, ranitidine, multivitamins, and thiamine. There was no history of alcohol abuse. Review of systems was pertinent for a 20-lb weight loss over the past month and diffuse tissue swelling. Physical examination revealed a weak woman lying in bed. Vital signs were: blood pressure, 120/75 mm Hg; pulse, 90 beats/min; respirations, 20 breaths/min; and temperature, 100.4Â°F (38Â°C). Examination of the head, ears, eyes, nose, and throat demonstrated periorbital edema and bilateral carotid bruits. Lungs were clear to auscultation, and the cardiac examination revealed normal rate with a 2/6 systolic ejection murmur radiating to the aortic region. Abdominal examination revealed mild distension with bowel sounds present, and no tenderness or organomegaly. Pulses were 1+ in all the extremities. Neurologic examination revealed orientation to time, place, and person; cranial nerves IIâ€“XII were intact; muscle strength was 4â€“5/5, except for quadriceps and iliopsoas strength of 3/5 bilaterally; deep-tendon reflexes were 1+ at the biceps and 0 at the brachioradialis, knees, and ankles. Plantar reflexes were normal. Sensory examination revealed abnormal position sense

decreased in the upper extremities and absent in the lower extremities, and vibration and position sense decreased in both upper and lower extremities.

During the next 3 days the patient's muscle strength diminished in a caudal-to-rostral pattern, and she was transferred to the ICU, with a presumptive diagnosis of Guillain-BarrÃ© syndrome. Review of the records from the first hospitalization revealed a prolonged QTc interval on routine ECG, and a finding of mild hypotension requiring 6 days of intravenous crystalloid infusions, an unusual requirement for the presumed diagnosis of gastroenteritis. In the ICU, laboratory examination revealed a hemoglobin (Hb) of 8.1 g/dL with a mean corpuscular volume (MCV) of 93.3 Âµm^3 and a white blood cell (WBC) count of 2400 cells/mm^3. Other laboratory tests were within normal limits, including serum iron, cortisol, vitamin B_{12}, folate, and thyroid function tests. Westergren sedimentation rate was normal at 19 mm/h. Her ECG demonstrated a normal sinus rhythm, QRS axis of 60Â°, and a prolonged QTc interval of 610 msec. Lumbar puncture measured a normal opening pressure of 135 mm H_2O, and the CSF contained 5 WBC/mm^3, 0 red blood cells (RBC)/mm^3, protein 42 mg/dL, and glucose 98 mg/dL. Radiopaque material was noted on a plain abdominal radiograph. The toxicologic consultant ordered a stat spot urine for arsenic, which measured 16,422 Âµg/L. The patient underwent chelation therapy until the urinary arsenic was less than 50 Âµg/L. During recovery the patient experienced extreme pain, even with light touch to the extremities. Ten months later the patient had gradually recovered from her peripheral neuropathy to the point that she could feed herself. An investigation was unsuccessfully pursued.

The therapeutic use of arsenic (arsenic trioxide) for acute promyelocytic leukemia (APL), as well as its emergence as a significant environmental toxin, has renewed interest in its pharmacology and toxicology.[167] The role of arsenic in our pharmacopeia may expand; its efficacy in treating various other

leukemias, lymphomas, and multiple myeloma is being studied.[115] This chapter discusses the properties and toxicity of inorganic arsenic, the most prevalent toxic form.

TABLE 85-1. Sources of Arsenic

Inorganic
Occupational/Manufacturing
Animal feed (additive)
Brass/bronze
Ceramics/glass
Computer chips
Dyes/paints
Electron microscopy
Fireworks (Chinese)
Fossil fuel combustionâ€”coal
Herbicides
Insecticides/pesticides
Metallurgy
Mining
Rodenticides
Semiconductors (gallium arsenide)
Smeltingâ€”copper, lead, zinc, sulfide minerals
Soldering
Wood preservatives
Medicines/Contaminated Drugs
Chemotherapy (acute promyelocytic leukemia)
Depilatory
Herbals/alternative medicines
Homeopathic remedies
Kelp
â€œMoonshineâ€• ethanol
Opium

Other
Contaminated well water
Contaminated foods/candies, eg, licorice
Organic
Melarsoprol (trypanocidal)
Parasitic therapy (veterinary)
Seafood (arsenobetaine)

TABLE 85-2. Arsenic

Enviromental	
MCL	50 ppb
Occupational standards	
ACGIH	
TLV-TWA (elemental, inorganic compounds, arsenous acid, arsenic acid)	0.01 mg/m^3
TLV-STEL	Not established
BEI (inorganic plus methylated metabolites in urine)	35 Âµg arsenic/L
OSHA	

PEL-TWA	
• Organic compounds • Inorganic compounds	0.5 mg/m^3 0.01 mg/m^3
PEL-STEL	Not established
NIOSH	
REL-TWA	Not established
REL-STEL (inorganic compounds)	0.02 mg/m^3 (15 min ceiling)

ACGIH = American Conference of Governmental Industrial Hygienists; BEI = biologic exposure index (urine sampling occurs at end of workweek); MCL = maximum contaminant level of drinking water, United States Environmental Protection Agency; MW = molecular weight; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limits, REL = recommended exposure limits; STEL = short-term exposure limit; TLV = threshold limit values; TWA = time-weighted average.

Arsenic is a metalloid that exists in multiple forms: elemental, gaseous (arsine), organic, and inorganic [(As^{3+} [trivalent, or arsenite] and As^{5+} [pentavalent, or arsenate])]. Tables 85-1 and 85-2 list sources of, and facts about arsenic. Additional trivalent arsenicals include tetra-arsenic tetrasulfide (realgar; As_4S_4) and diarsenic trisulfide (orpiment; As_2S_3). Realgar and orpiment have

been used by the Chinese to treat malignancies, diarrhea, and infections of the chest and liver.[99] Arsenic metal is considered nonpoisonous because of its insolubility in water and bodily fluids.[141] The toxicity of exogenous organic forms is low. The gaseous form, which is highly toxic, is discussed in Chap. 24.

History and Epidemiology

Arsenic poisoning can be unintentional, suicidal, homicidal, occupational, environmental, or iatrogenic.[74,75,101,120] Mass poisonings have occurred. Nearly 400 residents of Hong Kong fell ill after eating contaminated bread from the Esing Bakery in 1857; two bakery foremen were thought to have tampered with the recipe. The 1900 Staffordshire Beer Epidemic in England saw 6000 beer drinkers fall ill and 70 die from beer brewed with sugar made with arsenic-contaminated sulfuric acid. In Wakayama, Japan, 70 people were poisoned by eating intentionally contaminated curry at a festival in 1998. In 2003, the largest recent outbreak of arsenic poisoning in the United States occurred in New Sweden, Maine, when adulterated church coffee resulted in the death of one parishioner and the hospitalization of an additional 15 victims. Hydroarsenicism from contaminated groundwater has resulted in mass environmental poisonings for the past 4 decades. Arsenic trioxide reemerged as a treatment for promyelocytic leukemia in the 1990s after physicians in Harbin, China found a high remission rate in patients given Ailing-1, a crude arsenic trioxide infusion.[88,188] Adverse drug effects can occur but the majority of infusions are tolerated without discontinuing therapy.[116,138]

Contaminated soil, water, and food are the primary sources of arsenic for the general population. Pentavalent arsenic is the most common inorganic form in the environment.[38] The primary form of arsenic in fish and shellfish is arsenobetaine. Although arsenosugars can be found in crustaceans, seaweed, and algae,[94] less than 1% is inorganic arsenic.[44] Inorganic arsenic can be found in larger amounts

in other foodstuffs, such as rice and produce, along with smaller amounts of its methylated metabolites.[142,181]

In the past 2 decades, consumption of contaminated water has emerged as the primary cause of large-scale outbreaks of chronic arsenic toxicity. Arsenic leaches from various minerals and ores, as well as from industrial waste.[108] In Bangladesh, millions of people have been poisoned by drinking water from tube wells contaminated with arsenic leached from ground minerals.[21] Ironically, the wells were dug to obtain safer groundwater. Hydroarsenicism has also been reported in Chile, Taiwan, Thailand, India, Mexico, and Argentina. In 2001, the United States Environmental Protection Agency decreased the maximum contaminant level of arsenic in drinking water to 10 parts per billion (ppb, or 0.010 mg/L), after statistical modeling indicated an increased risk of lung and bladder cancer from water contaminated

with arsenic at the formerly acceptable level of 50 ppb.[25,46] The World Health Organization also recommends a level of 10 ppb.

Pharmacology

Arsenic trioxide (As_2O_3; Trisenox) is administered therapeutically in doses of 0.15â€“0.16 mg/kg/d by either the intravenous or oral route.[88,147] At this dose its beneficial effects in acute promyelocytic leukemia (APL) occur predominantly by initiating cellular apoptosis when arsenic concentrations reach 0.5â€“2.0 Âµmol/L. Apoptosis is triggered by several mechanisms. The trivalent arsenic ion binds to mitochondrial membrane sulfhydryl (SH) groups, damaging mitochondrial membranes and collapsing membrane potentials. Cytochrome c is released from the damaged mitochondria with subsequent activation of caspases 9, 3, and 8, and initiation of apoptosis. Cells may be more susceptible to arsenic-induced apoptosis if the intracellular levels of catalase and glutathione peroxidase (H_2O_2 scavenging enzymes) and glutathione-*S*-

transferase (responsible for conjugating glutathione to xenobiotics) are reduced.[28,54,76,136] Arsenic trioxide also facilitates apoptosis by downregulating gene expression of BCL2, a prosurvival protein that protects against apoptosis.[26] Finally, arsenic trioxide can arrest cells early in mitosis, leading subsequently to apoptosis.[64]

Low-dose arsenic trioxide treatment (0.08 mg/kg/d) beneficially promotes cell differentiation of APL cells when arsenic concentrations reach 0.1â€“2.0 Âµmol/L. This differentiation is impaired by the promyelocytic leukemia-retinoic acid receptor Î± (PML-RARÎ±) oncoprotein. This oncoprotein results from the APL-defining translocation of chromosomes 15 and 17. The PML portion of this oncoprotein plays a key role in leukemogenesis by interfering with RARÎ± activity that is essential for normal myeloid cellular development. Trivalent arsenic degrades this PML portion, freeing RARÎ± to facilitate cell differentiation.[28,111]

Melarsoprol (*Mel B;* ARSOBAL), the arsenoxide derivative of an organic arsenical, is used to treat the meningoencephalitic stage of West African (Gambian) and East African (Rhodesian) trypanosomiasis. The drug concentrates in trypanosomes via a purine transporter. Its target is trypanothione, the primary reducing agent in trypanosomes. Melarsoprol binds to trypanothione to produce *Mel T*, a competitive inhibitor of trypanothione reductase that is responsible for maintaining adequate levels of trypanothione. The resulting decrease in trypanothione leads to a loss of reducing capacity with subsequent lysis of the parasite.[158]

Pharmacokinetics and Toxicokinetics

Absorption

Inorganic arsenic is tasteless and odorless and is well absorbed by the gastrointestinal, respiratory, intravenous, and mucosal routes. *Gastrointestinal* absorption is facilitated by increased solubility and

smaller particle size, and occurs predominantly in the small intestine, followed by the colon. Poorly soluble trivalent compounds such as arsenic trioxide (As_2O_3) are less-well absorbed than more soluble trivalent and pentavalent compounds that, in aqueous solution, have an oral bioavailability greater than 90%. However, when placed in an aqueous solution, As_2O_3 is more toxic than an identical dose of undissolved As_2O_3 eaten in food.[164] A rodent experiment demonstrated approximately 70% GI absorption of dimethylarsinic acid (cacodylic acid). Systemic absorption via the *respiratory* tract depends on the particulate size, as well as the arsenic compound and its solubility. Large, nonrespirable particles are cleared from the airways by ciliary action and swallowed, allowing GI absorption to occur. Respirable particles lodging in the lungs can be absorbed over days to weeks or remain unabsorbed for years.[19,174] *Dermal* penetration of arsenic through intact skin does not pose a risk for acute toxicity but potentially may be problematic with chronic application. H_3AsO_4 applied to intact skin in Rhesus monkeys resulted in absorption of a mean of 2.0â€“6.4% of the applied dose.[175] Skin irritation and damage may increase systemic absorption.[53,135]

Pharmacokinetics

Intravenous administration of a single 10-mg dose of As_2O_3 to 8 patients, followed by data collection for 24 hours, showed mean pharmacokinetic values as follows: maximum plasma concentration (Cp_{max}) of 6.85 Âµmol/L, Î± elimination half-life ($t_{1/2}$ Î±) of 0.89 Â± 0.29 hours, and Î² elimination half-life ($t_{1/2}$ Î²) of 12.13 Â± 3.31 hours. Nail and hair levels increased during As_2O_3 administration. In 6 patients, 1â€“8% of the daily dose was eliminated in a 24-hour urine. Repeat pharmacokinetic studies on day 30 of treatment were not statistically different.[145] Another study of patients receiving a single dose of 5 mg of As_2O_3 intravenously demonstrated mean pharmacokinetic values as follows: Cp_{max} of 2.636 Âµmol/L, $t_{1/2}$ Î± of 1.413 hours, $t_{1/2}$ Î² of 9.411 hours, serum clearance of 1.987 L/h,

and area under the plasma drug concentration versus time curve (AUC) of 12.706 Âµmol/L/h. A single dose of 10 mg intravenously showed a Cp_{max} of 6.799 Â± 0.314 Âµmol/L.[144] Arsenic trioxide 10 mg given orally for APL demonstrated total plasma and blood AUC values that were 99% and 87%, respectively, of the corresponding values reported for a 10-mg intravenous dose administered in the same 9 patients.[87]

A study in humans receiving intravenous radioarsenic isotope (^{74}As) showed arsenic clearing from the blood in three phases:

- *Phase 1 (2â€“3 hours)*â€”Arsenic is rapidly cleared with a $t_{1/2}$ of 1â€“2 hours; more than 90% may be cleared during this phase.
- *Phase 2 (3 hours to 7 days)*â€”A more gradual decline occurs, with an estimated $t_{1/2}$ of 30 hours; by 10 hours postinfusion the arsenic is concentrated in red blood cells (RBCs) by a 3:1 ratio compared to plasma.
- *Phase 3 (10 or more days)*â€”Clearance continues slowly with an estimated $t_{1/2}$ of 300 hours.[110]

The rapid clearance in phases 1 and 2 explains why blood testing for arsenic is unreliable, except early in acute poisoning.

Initial distribution is predominantly to liver, kidney, muscle, and skin. The skin is rich in sulfhydryl groups; the skin's elimination $t_{1/2}$ of arsenic was estimated to be 1 month in a rabbit study.[42] Distribution to brain also occurs quickly. In the ^{74}As study, 0.30% of the administered dose was found in biopsy samples in the first hour postinfusion. This peak declined to 0.16% by day 7.[110] Ultimately, arsenic distributes to all tissues. Arsenic crosses the placenta and accumulates in the fetus,[100] but is not appreciably excreted in breast milk.[35]

Metabolism, by adding methyl groups, occurs primarily in the liver, but also occurs in the kidneys, testes, and lungs (Fig. 85-1). If the

arsenic is pentavalent, approximately 50â€“70% will first be reduced to trivalent arsenic.[151,165] This bioactivation step requires the oxidation of glutathione[39] and can begin within 15 minutes of

exposure.[165] *S*-adenosylmethionine (SAM) is the primary methyl donor. Nonenzymatic methylation has also been demonstrated in an in vitro study using human liver cytosol; here, methylcobalamin (methyl B_{12}) was the methyl donor.[185] Dietary and vitamin deficiencies, as well as high doses of inorganic arsenic, may diminish the ability to methylate arsenic.[169] Addition of one methyl group produces monomethylarsonic acid (MMA^V); adding a second methyl group produces dimethylarsinic acid (DMA^V). Production of a trivalent intermediate in this reaction, monomethylarsonous acid (MMA^{III}), is catalyzed by MMA^V reductase. In rabbits this is the rate-limiting enzyme in the biotransformation pathway; however, no data exist to confirm a similar role in human metabolism.[167,186] Conversion of MMA^V to DMA^V is catalyzed by a methyltransferase.

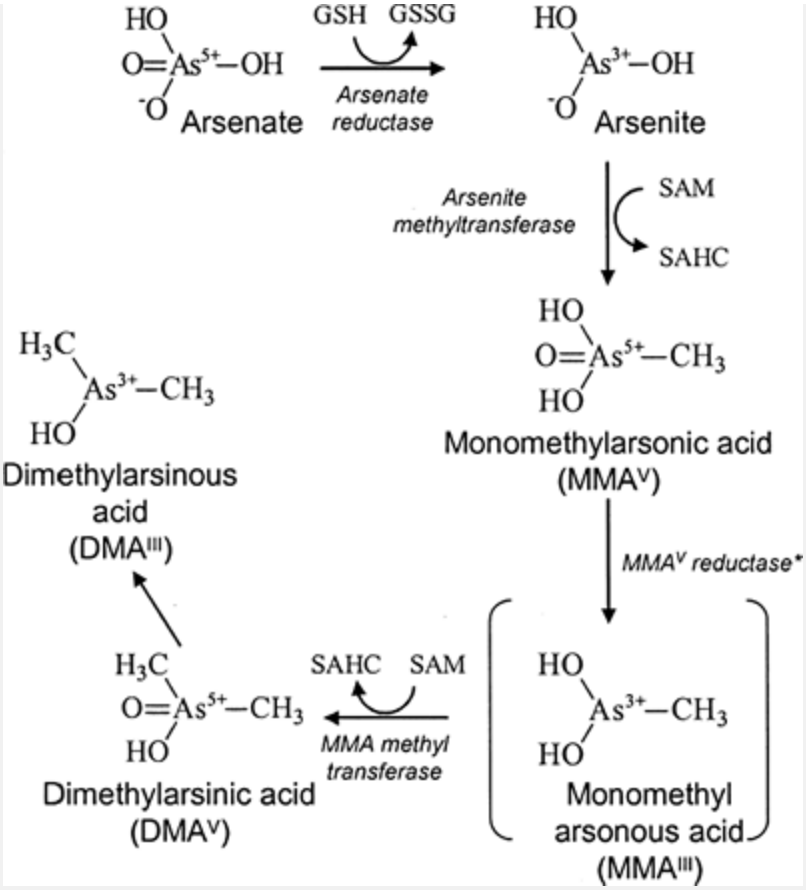

Figure 85-1. Metabolism of arsenate [As^{5+}] and arsenite [As^{3+}]. DMA = dimethylarsinic acid; GSH = glutathione; MMA = monomethylarsonic acid; SAHC = *S*-adenosylhomocysteine; SAM = *S*-adenosylmethionine. The asterisk (*) denotes MMA^V reductase, the rate-limiting enzyme in rabbit studies of arsenic metabolism; the analogy to humans is unknown.

These monomethylation and dimethylation steps were previously thought to detoxify As^{3+}. Estimated human LD_{50} (median lethal dose for 50% of test subjects) doses were reported to be arsenic trioxide, 1.43 mg/kg; MMA^V 50 mg/kg; and DMA^V 500 mg/kg. However, it is important to note that the doses cited for MMA and DMA apply to arsenic existing in the pentavalent form (As^{5+}). Studies in animals

and cell cultures indicate that MMA^{III} may be more toxic than As^{3+}.[104,124,125] Cytotoxicity studies in human hepatocytes revealed descending toxicity of arsenic and its metabolites as follows: MMA^{III} > arsenite > arsenate > MMA^{V} = DMA^{V}. Thus, toxicity increases with the formation of MMA^{III}.

Urinary elimination of unchanged arsenic and its methylated metabolites occurs via glomerular filtration and tubular secretion; active reabsorption does occur.[161] Human studies demonstrate renal arsenic elimination of 46â€“68.9% within the first 5 days postingestion.[20,77,126] Approximately 30% is eliminated with a half-life of greater than 1 week, while the remainder is slowly excreted with a half-life of greater than 1 month.[20,109] Fecal elimination is considerably less, with reported amounts ranging from 0.21â€“6.1% in humans.[110,154]

Arsenobetaine is also well absorbed and is excreted unchanged in the urine.[165] Elimination occurs more rapidly than with inorganic arsenic. In a study involving human volunteers, 25% was excreted within 2â€“4 hours, 50% by 20 hours, and 70â€“83.7% after 166 hours. A two-component exponential model shows nearly 50% of the arsenobetaine eliminated, with a first component $t_{1/2}$ of 6.9â€“11.0 hours and a second component $t_{1/2}$ of 75.7 hours.[77]

Pathophysiology

Investigations of the pathophysiologic effects induced by toxic doses of arsenic, in contradistinction to therapeutic doses, have elucidated the toxic mechanisms discussed below. The apoptotic mechanisms thought to be responsible for some therapeutic effects of arsenic trioxide have not been studied in toxicity models.

Trivalent Arsenic

The primary biochemical lesion of As^{3+} is inhibition of the pyruvate dehydrogenase (PDH) complex (Fig. 85-2). Normally,

dihydrolipoamide is recycled to lipoamide, a necessary cofactor in the conversion of pyruvate to acetyl-coenzyme A (CoA). As^{3+} binds the sulfhydryl groups of dihydrolipoamide, blocking lipoamide regeneration.[131] Acetyl-CoA is a central molecule in metabolism, and the resulting decrease leads to several deleterious effects:

- Decreased citric acid cycle activity and thus decreased adenosine triphosphate (ATP) production. Disruption of oxidative phosphorylation leads to production of hydrogen peroxide and oxygen radicals.
- Decreased gluconeogenesis that can worsen hypoglycemia. Pyruvate carboxylase catalyzes the conversion of pyruvate to oxaloacetate (initial step in gluconeogenesis), and this reaction requires the carboxylation of biotin, a CO_2 carrier attached to pyruvate carboxylase. Biotin cannot be carboxylated unless acetyl-CoA is attached to the enzyme.[132,152]

In the citric acid cycle, oxidation of Î±-ketoglutarate to succinyl-CoA uses an Î±-ketoglutarate dehydrogenase complex that contains the same cofactors as the PDH complex, including lipoamide. Arsenic also blocks the dihydrolipoamideâ€“lipoamide recycling in this complex, thus interfering with citric acid cycle activity at a second point. Succinyl-CoA is necessary for production of porphyrins and amino acids, and deficiency may contribute to the anemia and wasting seen with chronic arsenic poisoning. Arsenic inhibition of thiolase, the catalyst for the final step in fatty acid oxidation, also impairs ATP production. Diminished fatty acid oxidation results in decreased acetyl-CoA, in the loss of the reduced form of nicotinamide adenine dinucleotide (NADH) and the reduced form of flavin adenine dinucleotide ($FADH_2$) (electron carriers reduced during fatty acid breakdown whose subsequent oxidation yields ATP). Trivalent arsenic also inhibits glutathione synthetase, glucose 6-phosphate dehydrogenase (required to produce nicotinamide adenine dinucleotide phosphate [NADPH]), and glutathione reductase.[5] These

inhibitions result in decreased levels of reduced glutathione, which is required to facilitate arsenic metabolism, protect RBCs from oxidative damage, maintain

hemoglobin in the ferrous state, and scavenge hydrogen peroxide and other organic peroxides.

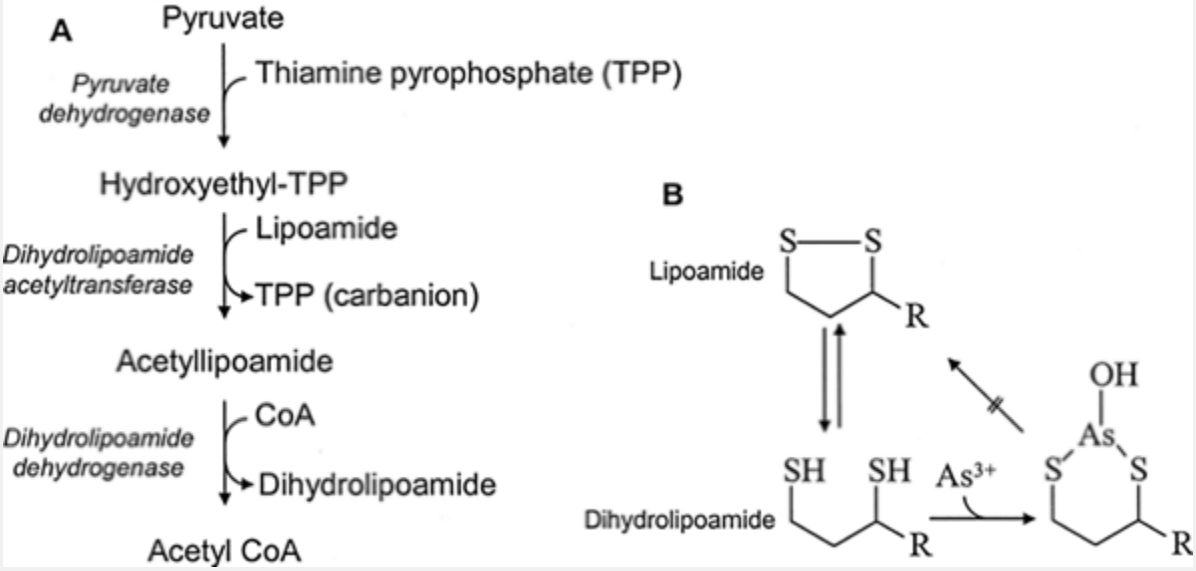

Figure 85-2. Effect of trivalent arsenicals (As^{3+}) on pyruvate dehydrogenase (PDH) complex. A. The PDH complex is composed of the three enzymes, which use thiamine pyrophosphate (TPP) and lipoamide as cofactors to decarboxylate pyruvate and form acetyl CoA. B. Arsenic interferes with the regeneration of lipoamide from dihydrolipoamide, thereby altering the function of the PDH complex.

Arsenic affects cardiac repolarization currents. When toxicity occurs, the result is ventricular dysrhythmias, including torsades de pointes. An in vitro study of cells exposed to As^{3+} demonstrated blockade of the delayed rectifier channels I_{Ks} and I_{Kr}. Interestingly, activation of

$I_{K\text{-}ATP}$, a weak inward rectifier channel, also occurred; this activation could potentially counteract some of the effects of As^{3+} on the I_{Ks} and I_{Kr} channels.[41]

Animal experiments with phenylarsine oxide, a trivalent arsenical, demonstrate inhibition of insulin-induced glucose transport involving vicinal sulfhydryl groups, as well as Î²-cell damage in pancreatic islets attributed to inhibition of the Î±-ketoglutarate dehydrogenase complex.[17] These findings support a link between exposure to arsenic and the development of diabetes mellitus.[91,128] The impaired glucose transport, plus the inhibited gluconeogenesis (discussed above), can lead to glycogen depletion and hypoglycemia.[133] Several animal experiments indicate improved central nervous system (CNS) glucose content[132] and an increase in survival time with glucose treatment.[34,166]

Pentavalent Arsenic

Several mechanisms can cause toxicity from As^{5+}; pentavalent arsenic can be transformed to As^{3+}.[73,168] Pentavalent arsenic also resembles phosphate chemically and structurally, may share a common transport system for cellular uptake with phosphate,[73] and can uncouple oxidative phosphorylation by substituting for inorganic phosphate (P_i) in the glycolysis reaction catalyzed by glyceraldehyde 3-phosphate dehydrogenase (Fig. 85-3). The resulting unstable product, 1-arseno-3-phosphoglycerate, spontaneously hydrolyzes to 3-phosphoglycerate, so glycolysis continues, but the ATP normally produced during conversion of 1,3-bisphosphoglycerate to 3-phosphoglycerate is lost. Uncoupling may also occur if adenosine diphosphate (ADP) forms ADP-arsenate, instead of ATP, in the presence of As^{5+}. The ADP-arsenate rapidly hydrolyzes, thus uncoupling oxidative phosphorylation.

Effects on RBCs include decreased membrane fluidity and ATP depletion.[177] Chronic arsenic exposure is associated with vascular disease; in vitro studies demonstrate inhibition of endothelial cell

proliferation and glycoprotein synthesis in addition to lipid peroxidation.[27] A study or rodent and human platelets demonstrates increased platelet aggregation and arterial thrombosis.[95] Noncirrhotic hepatic portal fibrosis can develop. In a controlled study where mice chronically ingested water containing equal parts As^{3+} and As^{5+} for up to 15 months, the development of portal fibrosis was preceded by decreased hepatic glutathione (GSH), increased lipid peroxidation, and diminished levels or activities of numerous enzymes involved in regenerating GSH or scavenging free radicals.[139] Proposed mechanisms by which arsenic induces cancer include DNA damage induced by a dimethyl sulfide (DMS)-derived peroxyl radical, gene amplification, replacing phosphate in DNA during replication, and increased cell proliferation.[80,180] Experimental evidence and human studies support a number of etiologic or contributing factors for skin keratosis and cancer,[1] including chronic stimulation of keratinocyte-derived growth factors such as transforming growth factor-Î± (TGF-Î±); impaired methylation; mutation in the p53 tumor-suppressor gene; inhibition of poly(ADP-ribose) polymerase vital for DNA repair; and interference with mitotic spindle and microtubular function.[56,72,179]

Pigmentary changes also occur, and hyperpigmentation is attributed to increased melanin.

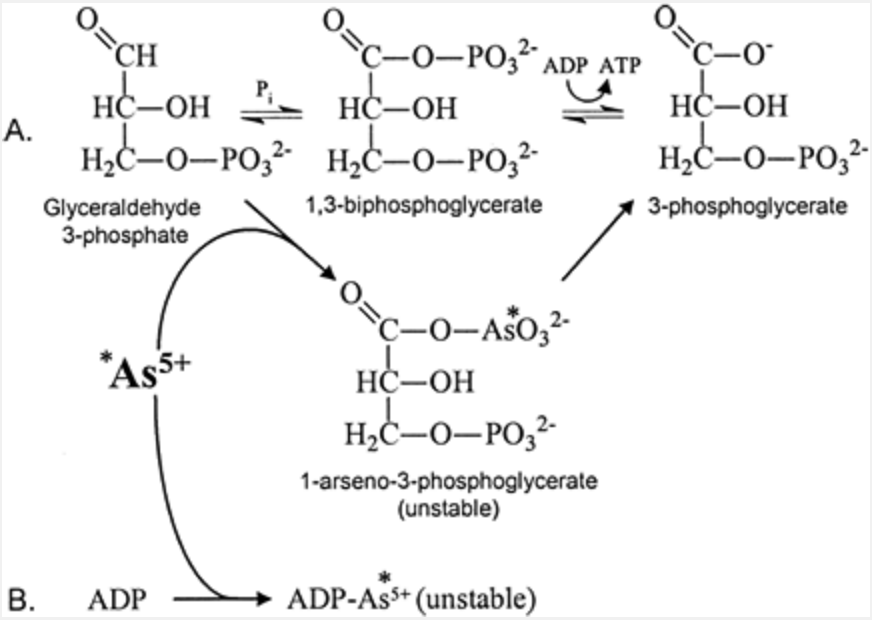

Figure 85-3. Pathophysiologic effects of pentavalent arsenic (As^{5+}). A. As^{5+} substitutes for inorganic phosphate (*), bypassing the formation of 1,3-bisphosphoglycerate (1,3-BPG), and thus losing the ATP formation that occurs when 1,3-BPG is metabolized to 3-phosphoglycerate. B. Energy loss also occurs if As^{5+} substitutes for P_i and blocks the formation of ATP + AMP from two ADPs. ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate.

Clinical Manifestations

Toxic Effects: Inorganic Arsenicals

Toxic manifestations vary, depending on the amount and form of arsenic ingested, as well as the chronicity of ingestion. Other influencing factors include individual variations in methylation and excretion. Larger doses of a potent compound, such as arsenic

trioxide, will rapidly produce manifestations of acute toxicity, whereas chronic ingestion of substantially lower amounts of pentavalent arsenic in groundwater will slowly result in a different clinical picture. Manifestations of subacute toxicity can develop in patients who survive acute poisoning, as well as in patients who are slowly poisoned environmentally. To avoid misdiagnosis, the physician must be aware of these differences.

Acute Toxicity

Gastrointestinal signs and symptoms of nausea, vomiting, abdominal pain, and diarrhea, which occur 10 minutes to several hours following ingestion, are the earliest manifestations of acute poisoning by the oral route. The diarrhea has been compared to that seen with cholera and may resemble â€œrice water.â€• Severe multisystem illness can ensue in the extensive exposure. Cardiovascular signs, ranging from sinus tachycardia and orthostatic hypotension to shock, can develop. Reported cases have mimicked myocardial infarction or systemic inflammatory response syndrome, with intravascular volume depletion, capillary leak, myocardial dysfunction, and diminished systemic vascular resistance.[10,14,16,60,78,143] Acute encephalopathy can develop and progress over several days, with delirium, coma, and seizures attributed to cerebral edema and microhemorrhages.[22,50,143] Seizures may be secondary to dysrhythmias, and the underlying cardiac rhythm should be assessed. In 3 cases, seizures secondary to torsades de pointes associated with a prolonged QTc interval developed 4 days to 5 weeks after acute arsenic ingestion.[14,58,149] Acute lung injury, acute respiratory distress syndrome and respiratory failure, hepatitis, hemolytic anemia, acute renal failure, rhabdomyolysis, other ventricular dysrhythmias, and death can occur.[16,48,63,112,153] Three people died after suddenly developing bradycardia, followed by asystole.[16,78,101] Fever may develop, misleading the practitioner to diagnose sepsis.[43,78] Hepatitis can occur and may be a result of altered intrahepatic heme metabolism causing an increased synthesis of

bilirubin or a result of altered protein transport between hepatocytes.[3] Acute renal failure may be secondary to ischemia caused by hypotension, tubular deposition of myoglobin or hemoglobin, renal cortical necrosis, and direct renal tubular toxicity.[18,55,140,162] Glutathione depletion may be contributory.[70] Unusual complications include phrenic nerve paralysis, unilateral facial nerve palsy, pancreatitis, pericarditis, and pleuritis.[11,187] Fetal demise has been reported, with toxic arsenic levels found in the fetal organs.[16,100]

Acutely poisoned patients with less severe illness may experience gastroenteritis and mild hypotension that persist despite antiemetic and intravenous crystalloid therapies. Hospitalization and continued intravenous fluids may be required for several days.[93] The prolonged character of the gastrointestinal symptoms is atypical for most viral and bacterial enteric illnesses and should alert the physician to consider arsenic poisoning, especially if there is a history of repetitive gastrointestinal illnesses. A metallic taste or oropharyngeal irritation can occur; the latter can mimic pharyngitis.[16,67] The garlicky breath odor attributed to inorganic arsenicals has also been reported with exposure to arsine gas. Gastrointestinal ulcerative lesions and hemorrhage have been reported.[50,60] Toxic erythroderma and exfoliative dermatitis result from a hypersensitivity reaction to arsenic.[155]

Subacute Toxicity

In the days and weeks following an acute exposure, prolonged or additional signs and symptoms in the nervous, gastrointestinal, hematologic, dermatologic, pulmonary, and cardiovascular systems can occur. Encephalopathic symptoms of headache, confusion, decreased memory, personality change, irritability, hallucinations, delirium, and seizures may develop and persist.[43,52] Sixth cranial nerve palsy and bilateral sensorineural hearing loss are reported.[33,58] Peripheral neuropathy typically develops 1â€“3 weeks

after acute poisoning, although in one series 9 patients developed maximal neuropathy within 24 hours of exposure.[33,67,93] Sensory symptoms develop first, and diminished to absent vibratory sense may be present. Progressive signs and symptoms include numbness, tingling, and formication with physical findings of diminished to absent pain, touch, temperature, and deep-tendon reflexes in a stocking-glove distribution. Superficial touch of the extremities may elicit severe or deep, aching pains, a finding that also occurs with thallium poisoning. Motor weakness may then develop. The most severely affected patients manifest an ascending flaccid paralysis that mimics Guillain-BarrÃ© syndrome.[33,67,93] Respiratory problems can include dry cough, rales, hemoptysis, chest pain, and patchy interstitial infiltrates.[67,123] These findings may be misinterpreted as viral or bronchitic disease. Leukopenia, and less commonly anemia and thrombocytopenia, occur from days to 3 weeks after an acute exposure, but resolve as bone marrow function returns.[74,97]

Dermatologic lesions can include patchy alopecia, oral herpetiform lesions, a diffuse pruritic macular rash, and a brawny nonpruritic desquamation. Diaphoresis and edema of the face and extremities can develop. Mees lines (transverse striate leuconychia of the nails) are 1â€“2-mm-wide horizontal nail bands that represent disturbed nail matrix keratinization. (See ILMEESUNES in the Image Library at http://www.goldfrankstoxicology.com) They are uncommon in arsenic poisoning. In one series of 74 patients with acute and chronic toxicity, Mees lines were found in only 5% of the patients. Mees lines are also reported with thallium poisoning, chemotherapy, Hodgkin disease, helminthic infections, renal failure, and systemic lupus erythematosus.[1,179] A minimum of 30 days after exposure is required for the lines to extend visibly beyond the nail lunulae. Contact dermatitis has been reported from topical exposure in an occupational setting. Other possible toxic manifestations of subacute inorganic arsenic toxicity include nephropathy, fatigue, anorexia with weight loss, torsades de pointes, and persistence of gastrointestinal symptoms.[10,105]

Chronic Toxicity

Chronic low-level exposure to inorganic arsenicals typically occurs from occupational or environmental sources. Malignant and nonmalignant skin changes, hypertension, diabetes mellitus, peripheral vascular disease, and several internal malignancies are associated with drinking water containing arsenic that is consumed by study populations.[121,183] The skin is very susceptible to the toxic effects of arsenic; multiple dermatologic lesions have been reported in populations suffering from hydroarsenicism.[108,183] Alterations in pigmentation occur first, with hyperpigmentation being the most common. Hypopigmentation (â€œraindropâ€• pattern) can also occur. (See ILARSENIC1 in the Image Library.) Hyperkeratoses typically develop on the palms and soles, but can be diffuse. (See ILARSENIC2 in the Image Library.) Squamous and basal cell

carcinomas and Bowen disease may occur. Bowen disease usually proliferates in multiple sites, especially on the trunk, and is noted for developing on sun-protected areas. Latency periods for developing keratoses, Bowen disease, and squamous cell carcinoma were 28, 39, and 41 years, respectively, in 17 patients chronically exposed to environmental or medicinal arsenic.[178] Gastrointestinal symptoms of nausea, vomiting, and diarrhea are less likely but can occur. Hepatomegaly was present in 190 of 248 patients with hydroarsenicism; liver biopsy in 69 cases revealed a noncirrhotic portal fibrosis in 91.3%.[139] Portal hypertension and hypersplenism have occurred. Hepatic angiosarcomas have been linked to arsenic exposure.[32,79,92] Population studies in areas of Bangladesh and Taiwan with arsenic contaminated water show an increased prevalence of diabetes mellitus.[128,160] Restrictive lung disease was reported in 9 of 17 patients, and a restrictive plus obstructive pattern occurred in another 7 cases.[108] Aplastic anemia and agranulocytosis are documented in patients exposed to arsenic.[43] A doseâ€“response relationship between arsenic exposure and vascular

disease is reported in several populations. After adjusting for age, sex, hypertension, diabetes mellitus, cigarette smoking, and alcohol consumption, a significant relationship was observed with cerebrovascular disease in a region of Taiwan.[31] Blackfoot disease, an obliterative arterial disease of the lower extremities, occurring in Taiwan, is linked to chronic arsenic exposure,[159] as is ischemic heart disease.[23] Incidence of Raynaud phenomenon and vasospasm was reported to be increased in smelter workers exposed to arsenic compared to a control group.[90] Encephalopathy and peripheral neuropathy are the neurologic manifestations most commonly reported.[13,66] Electromyographic studies of 33 patients with chronic ingestion of arsenic-contaminated water revealed 10 patients with findings consistent with sensory neuropathy. The minimum time for exposure was 2 years. Interestingly, 3 patients consumed water with an arsenic concentration that slightly exceeded the contaminant level of 50 ppb that was previously permissible in the United States.[69] Arsenic is classified as a definite carcinogen by the International Agency for Research on Cancer (IARC, Group 1) and the National Toxicology Program (NTP). Cancers known to develop include lung (adenocarcinomas and oat cell carcinomas) and skin. Bladder carcinoma is strongly associated; transitional cell carcinoma was the most common type in one large epidemiologic study.[30] Suprisingly perhaps, a critical literature review of animal and human studies found that exposure to environmental arsenic was unlikely to cause reproductive or developmental toxicity.[40]

Melarsoprol

The therapeutic use of melarsoprol can produce many of the toxic effects that occur with inorganic arsenic, including fever, encephalopathy, and acute cerebral edema with seizures and coma. Whether these effects are caused by drug toxicity or by an immune reaction elicited by trypanosomal antigens is unknown.[122,158] Other adverse effects include vomiting, abdominal pain, peripheral neuropathy with hypersensitivity reactions, hypertension, myocardial

damage, and albuminuria. Hemolysis can occur in patients with glucose-6-phosphate dehydrogenase deficiency, and erythema nodosum in patients with leprosy. In a study of the usefulness of melarsoprol as a treatment for refractory or advanced leukemia, reported adverse effects included fatigue, vomiting, diarrhea, vertigo, fever, seizures, headache, back pain, and injection site pain.[148]

Adverse Drug Effects: Arsenic Trioxide

The most common adverse effects are *dermatologic* (skin dryness, pigmentary changes, maculopapular eruptions with or without pruritus), *gastrointestinal* (nausea, vomiting, anorexia, diarrhea and dyspepsia), *hematologic* (leukemoid reactions), *hepatic* (elevation of aminotransferase concentrations typically â‰¤10 times the upper limit of normal values; with a reported incidence of 20% with low-dose and 31.9% with conventional-dose therapy[144]), *cardiac* (prolonged QTc interval in 40â€“63% of patients, first-degree atrioventricular block, ventricular ectopy, monomorphic nonsustained ventricular tachycardia, torsades de pointes, sudden asystole, and death),[138,144,147,163,176] *facial edema*, and *neurologic* (paresthesias, peripheral neuropathy, and headache). All of these effects occurred more commonly in one case series with conventional-dose therapy (0.16 mg/kg/d) when compared to low dose therapy. They are usually treated symptomatically without discontinuing As_2O_3 treatment. Leukemoid reactions, defined as white blood cell counts greater than 10 Ã— 10^9/L, develop in approximately 50% of patients between 14 and 42 days of beginning treatment. Such patients are at risk for intracerebral hemorrhage or infarction and for the APL syndrome. This syndrome is similar to the retinoic acid syndrome; the remission induction treatment phase is the period of greatest risk.[145] Approximately 20â€“25% of patients will develop one or more signs or symptoms of this syndrome, including pulmonary interstitial infiltrates and/or pleural effusions, dyspnea, tachypnea, fluid retention, myalgias, arthralgias, fever, and weight

gain.[106,116,138,144,145]

Diagnostic Testing

Timing of testing for arsenic must be correlated with the clinical course of the patient and whether the poisoning is acute, subacute, chronic, or remote with residual clinical effects. To properly interpret laboratory measurements, confounding factors, such as food-derived organic arsenicals or accumulated arsenic (DMA and arsenobetaine) in patients with chronic renal failure, must be considered.[37,189,190] Failure to understand potential confounders, as well as the time course of arsenic metabolism, clearance, and effect on laboratory parameters, can complicate the assessment of possible arsenic poisoning.

Urine and Blood

Diagnosis ultimately depends on finding an elevated urinary arsenic concentration. In an emergency, a spot urine may be sent prior to beginning chelation therapy. A markedly elevated arsenic concentration verifies the diagnosis in a patient with characteristic history and clinical findings, whereas a low level does not exclude arsenic toxicity.[171] In 9 acutely symptomatic patients, initial spot urine arsenic levels ranged from 192 to 198,450 Âµg/L.[81] Because urinary excretion of arsenic is intermittent, definitive diagnosis hinges on finding a 24-hour urinary concentration equal to or greater than 50 Âµg/L, 100 Âµg/g creatinine, or 100 Âµg total arsenic. All urine should be collected in metal-free polyethylene containers; acid-rinsed containers are no longer necessary. If testing is performed by an outside reference laboratory, specimens from acutely ill patients should be sent via express transportation with a request for a rapid result.

When interpreting slightly elevated urinary arsenic levels, laboratory findings must also be correlated with the history and clinical findings,

because seafood ingestion is reported to transiently elevate urinary arsenic excretion up to 1700 Âµg/L.[9] When seafood arsenic is a consideration, speciation of arsenic can be accomplished

by high-performance liquid chromatography (HPLC) separation, followed by inductively coupled plasma-mass spectrometry (ICPMS), HPLC via ion-pair chromatography coupled with hydride-generation atomic-fluorescence spectrometry (HGAFS), or by hydride generation coupled with cold-trap gas chromatography-atomic absorption spectrometry. These techniques separate arsenobetaine (AsB), As^{3+}, As^{5+}, MMA, and DMA.[47] Arsenobetaine can also be directly measured by silica-based cation-exchange separation, followed by atomic absorption spectrometry.[117] Two other methods, selective hydride-generation atomic-absorption spectrometry (HGAAS) and resin-based ion-exchange chromatography, do not directly measure AsB; instead, they indirectly derive this value by subtracting the sum of all measured arsenic species from the total arsenic concentration.[117] If arsenic speciation cannot be done, the patient can be retested after a 1-week abstinence from fish, shellfish, and algae food products.

Conditions under which urine is stored can affect total arsenic recovery, as well as proportionality of the species. The various arsenic speciesâ€”arsenate (As^{5+}), arsenite (As^{3+}), MMA, DMA, and AsBâ€”remain stable for 2 months in urine stored without preservatives at either â€“4Â°F (â€“20Â°C; freezer) or 39.2Â°F (4Â°C; refrigerator); AsB is stable for 8 months under these conditions. Storage for longer than 2 months can alter the recovery of various species. Addition of 0.1% hydrochloric acid (HCl) facilitates reduction of arsenate to arsenite and also decreases MMA and DMA levels. Acid-washed collection containers should not be used if measurement of the various arsenic species is planned. Total arsenic recovery can be diminished by any of the following: specimen storage for greater than 2 months, acidification, or testing using the HPLC-ICPMS and HPLC-HGAFS methods, in which samples are filtered prior to undergoing HPLC separation.[47]

Diagnostic evaluation of chronic toxicity should include laboratory parameters that may become abnormal within days to weeks following an acute exposure. Tests should include a complete blood count, renal and liver function tests, urinalysis, and 24-hour urinary arsenic determinations. Complete blood count findings can include a normocytic, normochromic, or megaloblastic anemia; an initial leukocytosis followed by development of leukopenia, with neutrophils depressed more than lymphocytes, and a relative eosinophilia; thrombocytopenia; and a rapidly declining hemoglobin, indicative of hemolysis or a gastrointestinal hemorrhage.[89] Basophilic stippling of RBCs can be seen; this can occur in other toxic and clinical disorders. Karyorrhexis, a rupture of the RBC cell nucleus with chromatin disintegration into granules that are extruded from the cell, and dyserythropoiesis are reported in both lead- and arsenic-toxic patients. Both findings are caused by arsenic-induced inhibition of DNA synthesis and damage to the nuclear envelope.[45] The karyorrhexis can occur within 4 days and resolve by 2 weeks after poisoning, and may be an early indication of arsenic toxicity.[89] Elevated serum creatinine, aminotransferases, and bilirubin, as well as depressed haptoglobin concentrations, may develop. Urinalysis may reveal proteinuria, hematuria, and pyuria. Cerebrospinal fluid examination in patients with CNS findings can be normal or exhibit mild protein concentration elevation, measured at 26.5 mg/dL in one case.[67] Urinary arsenic excretion in subacute and chronic cases varies inversely with the postexposure time period, but low-level excretion can continue for months after exposure. In a study of 41 cases of arsenic-induced peripheral neuropathy, most patients with a neuropathy of 4â€“8 weeks duration had total 24-hour urinary arsenic measurements of 100â€“400 Âµg.[67]

Hair and Nail Testing

In cases of suspected arsenic toxicity, in which the urinary arsenic measurements fall below accepted toxic levels, analysis of hair and nails may yield the diagnosis. Arsenic can be detected in the

proximal portions of hair within 30 hours of ingestion.[184] Inorganic arsenic is the form best absorbed by these tissues and the form most commonly found in human poisoning cases; small amounts of methylated metabolites may also be detected.[127] Arsenobetaine has not been found in hair and tissues in human and animal studies.[181,182] Hair grows at rates varying from 0.7â€“3.6 cm per month, with a mean rate of 1 cm per month.[173] The Society of Hair Testing has made the following recommendations for collection of hair specimens, in the context of testing for drugs of abuse: (a) collect approximately 200 mg of hair from the posterior vertex region of the scalp using scissors to cut as close to the scalp as possible, and (b) tie the hairs together, wrap in aluminum foil to protect from environmental contamination, and store at room temperature.[173] Nails grow approximately 0.1 mm per day. Total replacement of a fingernail requires 3â€“4 months, whereas toenails require 6â€“9 months of growth. These facts, plus the frequency of hair cutting, should be considered when estimating the usefulness of measuring arsenic levels in these tissues. The normal values of the testing laboratory should be used to determine whether arsenic levels are elevated. In cases of remote toxicity, hair and nail arsenic measurements may or may not be elevated, depending on the time elapsed since exposure. Sequential hair analysis to assess the time(s) of exposure can be performed by solid sampling graphite furnace atomic absorption spectrophotometry, or by x-ray fluorescence spectrometry.[82,156,157]

Challenge Testing

The role of challenge testing is unclear. In a study of people chronically exposed to elevated levels of arsenic in groundwater, a baseline urine was collected at â€“2 to zero hours in an exposed group (whose groundwater contained arsenic 510â€“660 Âµg/L), and in a control population (whose groundwater contained arsenic 0â€“21 Âµg/L). Sodium 2,3-dimercapto-1-propane sulfonate (DMPS) 300 mg was then administered, and urines were collected in 2-hour aliquots

for the next 6 hours. Total concentrations of inorganic arsenic, MMA, and DMA were elevated in the post-DMPS aliquots in both groups, more so in the exposed group. On a percentage basis, MMA levels were elevated the most.[8] It is unknown whether a DMPS challenge could assist in diagnosing an acute or a remote exposure with non-diagnostic urine, hair, and nail measurements.

Other Tests

Abdominal radiographs might demonstrate radiopaque material in the gastrointestinal tract soon after an ingestion;[2,29,60,61,68] however, even after an acute ingestion the absence of radiopaque materials on abdominal radiographs is reported.[36] The incidence of positive radiographs after an ingestion is unknown, and a negative radiograph should not eliminate arsenic as a diagnostic consideration. Electrocardiographic changes reported include QRS widening, QTc prolongation, ST segment depression, T-wave flattening, ventricular premature contractions, nonsustained monomorphic ventricular tachycardia, and torsades de pointes.[12,119,147,163] Nerve conduction studies (NCS) can confirm or diagnose clinical or subclinical axonopathy. Both the sensory nerve action potential

(SNAP) and the motor compound muscle action potential (CMAP) measure the number of axons that can conduct impulses. However, the sensory studies are more sensitive than motor studies in detecting axonal degeneration and demyelination; decreased SNAP measurements can indicate subclinical neuropathy. In motor nerve studies, the amplitude (height of the CMAP) is a more sensitive measure of the number of axons that can conduct impulses than is the conduction velocity; this can be explained by the pattern of axonal destruction. Nerve biopsies have confirmed disintegration of both axons and myelin in patients with arsenic-induced peripheral neuropathy; the axonal loss begins distally in the lower extremities and is initially scattered. Thus, conduction along the remaining functional axons can be sufficient to produce normal or only slightly

decreased conduction measurements on NCS.[57,67,83,93,114,118]

Management

General

Acute arsenical toxicity is life-threatening and mandates aggressive treatment. Advanced life support monitoring and therapies should be initiated when necessary, but with a few caveats. Careful attention to fluid balance is important because cerebral and pulmonary edema may be present. Xenobiotics that prolong the QTc, such as the class IA, class IC, and class III antidysrhythmics, should be avoided. Potassium, magnesium, and calcium concentrations should be maintained within normal range to avoid exacerbating a prolonged QTc. Glucose concentrations and glycogen stores should be maintained parenterally with dextrose and hyperalimentation solutions, or with enteral feedings, in view of their beneficial effects, in experimental models of arsenic poisoning.[98,132,133,152] Arsenic poorly adsorbs to activated charcoal, cholestyramine, and bentonite. Activated charcoal should be administered in the presence of significant ingestions. If radiopaque material is visualized in the gastrointestinal tract, whole-bowel irrigation can be administered until the radiopaque material is no longer seen on repeat abdominal radiograph. Continuing nasogastric suction may be important in removing arsenic resecreted in the gastric or biliary tract. Arsenite was still detectable in the gastric aspirate in 3 patients 5â€“7 days following an ingestion.[103] There is no clinical experience with the use of *N*-acetylcysteine to increase glutathione levels; an animal experiment suggested a protective effect.[129]

In cases of chronic toxicity, patients should be removed from the arsenic source and gastric decontamination should be performed if there is evidence of arsenic in the gastrointestinal tract. Arsenic can be readily removed from skin with soap, water, and vigorous scrubbing. In all cases, when homicidal intent is suspected, patients

should be advised against accepting food or drink from anyone who might be responsible. Also, the hospital visitors should be closely monitored and outside nutritional products should be forbidden.

Chelation Therapy

The decision to initiate chelation therapy should depend on the clinical condition of the patient as well as the laboratory results for arsenic in urine, hair, or nails. A severely ill patient with known or suspected acute arsenic poisoning should be chelated immediately, prior to laboratory confirmation. In a series of 33 patients who had coma, seizures, or both, 24 patients were treated with British anti-Lewisite (BAL) within 6 hours (mean: 1 hour) and 75% survived, compared with a survival rate of 45% of 9 patients who were treated later (range: 9â€“72 hours; mean: 30 hours).[43] Cases of subacute and chronic toxicity can await rapid laboratory confirmation prior to beginning chelation, unless the clinical condition deteriorates.

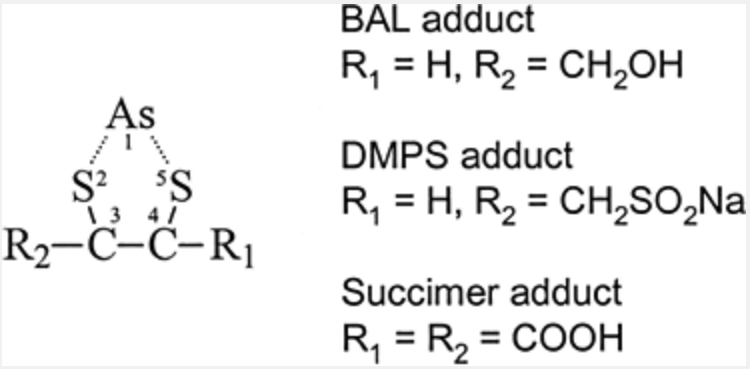

Figure 85-4. 1,2,5-Arsadithiolane adducts with BAL, DMPS, and DMSA.

Specific

Chelators

Dimercaprol (BAL) and 2,3-dimercaptosuccinic acid (succimer) are the 2 chelators available in the United States. A third drug, DMPS, is distributed by Heyl, a German pharmaceutical company, as Dimaval, but it is not approved or marketed in the United States (see Antidotes in Depth: Succimer [2,3-Dimercaptosuccinic Acid]). All contain vicinal dithiol moieties that bind arsenic to form stable 1,2,5-arsadithiolanes (Fig. 85-4), and all are most effective when administered in doses equimolar to the arsenic burden.[113] Dosing regimens and adverse effects are listed in Table 85-3.

TABLE 85-3. Chelators

Dosage	Adverse Effects
BAL 3â€“5 mg/kg every 4â€“6 h	Hypertension; febrile reaction; diaphoresis; nausea; vomiting; salivation; lacrimation; rhinorrhea; headache; painful injection; injection site sterile abscess; hemolysis in G6PD-deficient patients; chelation of essential metals (prolonged course)
SUCCIMER 10 mg/kg/dose every 8 h for 5 d, then 10 mg/kg/dose every 12 h	Nausea; vomiting; diarrhea; abdominal gas and pain; transient elevations of hepatic aminotrans-ferases and alkaline phosphatase; rash; pruritus; sore throat; rhinorrhea; drowsiness; paresthe-sias; thrombocytosis; eosinophilia

DMPS Dose: 5 mg/kg/dose IM, administered as a 5% solution Day 1: q6â€“8h Day 2: q8â€“12h Day 3 and thereafter: q12â€“24h	Allergic reactions; increased copper and zinc excretion; nausea; pruritus; vertigo; weakness, toxic epidermal necrolysis
End point: for chelation is a 24 hour urinary arsenic of < 50 Âµg/L	

In the United States, BAL remains the initial chelating drug for acute arsenical toxicity.[113] It is the only intracellular and extracellular chelator available in the United States. BAL is administered parenterally and thus is not affected by the patient's gastrointestinal motility. Its therapeutic-to-toxic ratio is narrow, with adverse effects likely to occur in patients receiving doses of 4 mg/kg or greater. It is administered intramuscularly in peanut oil; the injections are painful and can lead to sterile skin abscesses. In a cellular study of glucose uptake impaired by a lipophilic arsenical, BAL was superior to succimer and DMPS in restoring cellular equilibrium.[113] A human case series found increased survival with early use of BAL and improvement in encephalopathy within 24 hours of initiating therapy.[43] However, other acute cases treated promptly with BAL developed peripheral neuropathy.[93] In a study of subacute cases with peripheral neuropathy, BAL accelerated neurologic recovery but did not affect the overall recovery rate.[33] Despite starting BAL therapy 8 hours postexposure, a man who had ingested 2.15 g of arsenic

developed severe toxicity and neurologic deficits.[49] Most concerning are the animal experiments indicating that BAL shifts arsenic into the brain and testes, two organs that have bloodâ€“organ barriers susceptible to this lipophilic drug.[7,71,85] It is clear that BAL has limitations, and that we need a safer, more effective intracellular/extracellular parenteral chelator.

Succimer is an oral hydrophilic analog of BAL and is the chelator of choice for subacute and chronic toxicity. It has proven effective in animal studies and in reported human cases.[7,84,96,102,146] In mice exposed to sodium arsenite, succimer was more effective than either DMPS or BAL in decreasing lethality, and more potent than BAL in restoring activity in the pyruvate dehydrogenase complex.[7] It is equal or superior to BAL in speeding arsenic elimination.[113] Liver function tests and essential metal levels should be monitored in patients requiring prolonged therapy.[51,62]

DMPS is also a water-soluble analog of BAL. Although not approved for use in the United States, it has been used on an investigational basis in a few cases (Karen Simone, PharmD, and Anthony Tomassoni, MD, personal communication). It can be administered by the oral, intravenous, and intramuscular routes. It is eliminated from the body more slowly than succimer and has the advantage of intracellular as well as extracellular distribution.[4] It predominantly binds MMA^{3+} and possibly removes the MMA^{3+} from endogenous ligands. The DMPSâ€“MMA^{3+} complex is eliminated in the urine.[6,8,59] It may also work by synergistically increasing the nonenzymatic methylation of As^{3+}.[185] Two brothers ingested nearly pure arsenic trioxide (1 and 4 g each) and were treated with intravenous and oral DMPS. The brother who ingested 4 g developed hypotension, renal failure, respiratory insufficiency, and asystolic cardiac arrest. DMPS was started 32 hours postingestion, and the patient survived with normal renal function and no neurologic dysfunction. His sibling had a milder course; DMPS was started 48 hours postingestion, and there were no neurologic sequelae on followup examination.[112] DMPS significantly increased biliary excretion of arsenic in a guinea pig

model, but did not increase fecal excretion. The latter is most likely a result of enterohepatic recirculation of the DMPSâ€“As complex.[130] D-Penicillamine has not demonstrated efficacy in chelating or reversing the biochemical lesions of arsenic and should not be used. Its previous advantage of oral administration is no longer relevant with the availability of succimer.

Hemodialysis

Hemodialysis removes negligible amounts of arsenic, with or without concomitant BAL therapy, and is not indicated in patients with normal renal function.[15,65] In patients with renal failure, hemodialysis clearance rates have ranged from 76â€“87.5 mL/min, with or without concomitant BAL therapy.[107,170] In 2 acutely toxic patients with renal failure, total arsenic removed during a 4-hour dialysis measured 4.68 mg in one and 3.36 mg in the other. Concomitant 24-hour urinary arsenic excretions were 3.12 mg and 2.03 mg, respectively. When renal function returned, however, the 24-hour urinary excretion of arsenic far exceeded that recovered with dialysis, with reported levels of 18.99 mg in the first patient and 75 mg in the second patient.[170] There are no published rigorous data regarding hemodialysis removal of a water-soluble complex such as DMPSâ€“As.[86]

Summary

Arsenicals produce multisystem toxicity by a variety of pathophysiologic mechanisms. A thorough understanding of inorganic arsenic metabolism and excretion as well as the different clinical manifestations of acute, subacute, and chronic toxicity are necessary to avoid misdiagnosis. Chelation therapy with BAL in the United States, or with DMPS elsewhere, if available, should be started immediately in the severely ill patient. Treatment can await laboratory results for patients with subacute or chronic toxicity, unless clinical deterioration intervenes. Environmental contamination

of water sources has become a major health problem in many countries, including the United States.

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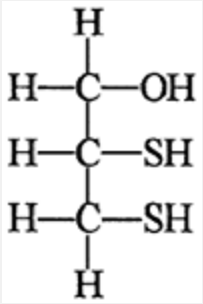
Antidotes in Depth

Dimercaprol (British Anti-Lewisite or BAL)

Mary Ann Howland

Principles of Chelation



2,3-Dimercaptopropanol (BAL)

Prior to a discussion of chelators, it is critical to understand the principles of chelation. Soft metal ions, such as Hg^{2+}, Au^{+}, Cu^{+}, and Ag^{+} have large ionic radii with a large number of electrons in their outer shell. Accordingly, they form the most stable complexes with sulfur donors and are referred to as sulfur seekers (Chap. 12).[1,5,28] The chelator or ligand, in this case, a sulfur-containing compound such as British anti-Lewisite (BAL), forms a coordinate bond with the metal by donating a pair of free electrons. Hard metals such as Na^{+}, K^{+}, Mg^{2+}, Ca^{2+}, and Al^{3+} are referred to as oxygen seekers and form the best complexes with hard ligands containing a carboxyl (COO^{-}) group, such as edetate calcium disodium ($CaNa_2EDTA$). Borderline metal ions, such as Pb^{2+}, Cd^{2+}, Cu^{2+}, As^{3+}, and Zn^{2+}, prefer nitrogen-donating ligands but will also react with both hard and soft ligands. Antidotes for metal poisoning often contain more than one type of donating group, making them effective for more than one type of metal. BAL has two adjacent sulfur groups, thus the term *dithiol;* the presence of these two sulfur groups permits the formation of a ring structure with the metal, thereby enhancing chelator stability.[1,5,28]

The most useful chelators have relatively low intrinsic toxicity, form stable complexes with the chelated metals, have tissue distribution characteristics similar to the metal to be chelated, and effect a favorable clinical outcome when administered.[1,5,28] Other desirable aspects of the metalâ€“chelator complex are elimination from the body without breaking and no redistribution to the brain or other critical organs. Unfortunately, there is no currently available chelator with all of these attributes. In addition, there are no published double-blind, randomized, placebo-controlled trials comparing outcomes with the use of metal chelators such as dimercaprol, $CaNa_2EDTA$, or succimer on lead, arsenic, or mercury poisoning in humans. The majority of efficacy data to date are derived from animal studies, several case series compared to historical controls, and several case reports. The most rigorous

human data usually describe a reduction in metal concentrations rather than improvements in clinical parameters. Redistribution characteristics of metalâ€“chelator complexes are being rigorously investigated in animal models, because redistribution to vital tissues such as the brain is of great concern. Although BAL has been in use since the late 1940s,[20] much of our current practice relies on opinion and historical precedence, and many pharmacokinetic and toxicokinetic questions remain unanswered.

History

Investigation into the use of sulfur donors as antidotes was precipitated by the World War II threat of chemical warfare with lewisite (dichloro(2-chlorovinyl)arsine) and mustard gas (dichlorodiethyl sulfide). Both are vesicant gases that cause tissue damage when combined with protein sulfhydryl (SH) groups[31] (Chap. 126). These investigations led to the discovery of the dithiol 2,3-dimercaptopropanol, called British anti-Lewisite, which combines with Lewisite to form a stable 5-membered ring.

Chemistry

BAL has a molecular weight of 124.2 Daltons and a specific gravity of 1.21.[32] BAL is an oily liquid with only 6% weight/volume water solubility, 5% weight/volume peanut oil solubility, and a disagreeable odor. Aqueous solutions are easily oxidized and therefore unstable. Peanut oil stabilizes BAL and benzyl benzoate (in the ratio of 1 part BAL to 2 parts of benzyl benzoate) renders the BAL miscible with peanut oil.[32]

Pharmacokinetics

There are no recent pharmacokinetic studies with BAL. The limited amount of information available dates back to the late 1940s. Plasma concentrations of BAL peak about 30 minutes after IM

administration and distribution occurs quickly.[32,35] Within 2 hours after IM administration to rabbits, plasma concentrations drop quickly. Urinary excretion of BAL metabolites, perhaps partially as glucuronic acid conjugates, accounted for nearly 45% of the dose within 6 hours and 81% of the dose within 24 hours.[32,34] Very little is excreted unchanged in the urine.[32] BAL is concentrated in the kidney, liver, and small intestine.[30] BAL can also be found in the feces, strongly implying that enterohepatic circulation exists. Hemodialysis may be useful in removing the BALâ€“metal chelate in cases of renal failure.[19,25,37]

Use of BAL for Arsenic Poisoning

Animal Studies

The fear that Lewisite might be sprayed over the land and its population, causing skin lesions, led researchers to investigate the potential for cutaneous application of BAL.[36] This was based on its limited water solubility and high lipid solubility. In a rodent model, low concentrations of topical BAL were very effective both in preventing lewisite-induced toxicity and in reversing toxicity when administered within 1 hour of skin exposure.[29,31] In rabbits, ocular application of BAL proved effective in preventing eye destruction

if applied within 20 minutes of exposure.[19] Additionally, urinary arsenic concentrations were significantly increased after the application of BAL.[31]

The effectiveness of both parenteral single-dose and multiple-dose BAL against lewisite and other arsenicals was studied in rabbits. When begun within 2 hours of lewisite exposure, BAL injections of 4 mg/kg every 4 hours led to a 50% survival of exposed rabbits. This dose regimen was demonstrated to be one-seventh of the maximum tolerated dose of BAL.[13]

The most recent animal studies demonstrate that although studies with BAL increase the LD_{50} (median lethal dose for 50% of test subjects) of sodium arsenite, the therapeutic index of BAL is low and arsenic redistribution to the brain occurs.[2,3,4,16,33] In these same animal models, succimer and the investigational agent 2,3-dimercaptopropane sulfonate (DMPS) also increased the LD_{50}, but with a better therapeutic index and without causing redistribution to the brain.

Human Studies

Experiments in human volunteers who were given minute amounts of arsenic demonstrated that BAL increased urinary arsenic concentration by approximately 40%, with maximum excretion occurring 2â€“4 hours after BAL administration.[38] BAL was subsequently used in the treatment of arsenical dermatitis resulting from syphilis therapy with organic arsenicals. When applied to affected skin, topical BAL produced erythema, pruritus, and dysesthesias, but had no adverse effects on unaffected skin. Intramuscular BAL produced both subjective and objective improvement, limited the duration of the arsenical dermatitis, and increased urinary arsenic elimination.[9,23,24]

In a study of 227 patients with inorganic arsenic poisoning, maximal efficacy and minimal toxicity were achieved when 3 mg/kg of BAL was administered intramuscularly every 4 hours for 48 hours and then twice daily for 7â€“10 days. This regimen resulted in complete recovery in 6 of 7 patients with severe arsenic-induced encephalopathy and demonstrated the importance of administering BAL as soon as possible after the exposure. Of 33 patients with severe arsenic-induced encephalopathy, 18 of 24 (75%) treated within 6 hours survived, versus only 4 of 9 (44%) treated after a delay of at least 72 hours.[12] Furthermore, the effectiveness of BAL was also demonstrated in 3 patients who were treated successfully after mistakenly receiving 10â€“20 times the

therapeutic dose of Mapharsen (oxophenarsine hydrochloride). A fourth patient, treated with inadequate doses of BAL, died.[12] These cases also support the effectiveness of BAL in treating arsenic-induced agranulocytosis, encephalopathy, dermatitis, and probably arsenical fever.[12]

When BAL first became more widely available, 42 children who were treated following arsenic ingestions were compared to a historical group of 111 other children who had ingested arsenic.[39] The percentage of children exhibiting symptoms on presentation were similar between groups (46%), but in the group of treated children there were fewer deaths (0 vs. 3), a shorter average hospital stay (1.6 vs. 4.2 days), and fewer cases of persistent symptoms at 12 hours (0% vs. 29.3%).

Ocular damage caused by lewisite is partly a result of the liberation of hydrochloric acid, which results in an acid injury causing localized superficial opacity of the cornea and deep penetration of lewisite into the cornea and aqueous humor with resultant rapid necrosis. In an experimental model, a 5% BAL ointment or solution applied within 2 minutes of exposure prevented the development of a significant reaction; application at 30 minutes lessened the reaction, but did not prevent permanent damage.[17]

Mercury

Because mercury also reacts with sulfhydryl groups, animal studies were performed to assess the affinity and ability of thiols to competitively chelate inorganic mercury and prevent toxicity. As in the case of arsenic, the dithiols BAL and BAL glucoside were more effective than the monothiol 1-thiosorbitol in preventing mercury-induced death and uremia.[15] The clinical efficacy of BAL in treating inorganic mercury poisoning was substantiated in patients who ingested mercuric chloride.[22,21] Thirty-eight patients ingesting more than 1 g of mercuric chloride who were treated with BAL

within 4 hours of exposure were compared to historical controls.[21] There were no deaths in the 38 patients treated with BAL as compared to 27 deaths in the 86 untreated patients. Death typically resulted from hemorrhagic gastritis and renal failure.[21] BAL is particularly useful for patients who have ingested a mercuric salt, as the associated gastrointestinal toxicity of the mercuric salt limits the potential of an orally administered antidote such as succimer.

Animal models demonstrate that when BAL is administered to chelate mercury following poisoning from elemental mercury vapor or exposure to short-chain organic mercury compounds, brain levels of mercury may increase.[6,8] However, in a rat model, the initiation of BAL therapy within 1 day of exposure to short-chain organic mercury compounds prevented neurologic toxicity.[40] When treatment was delayed for 12 days, no effect on established neurotoxicity could be demonstrated. As a result of these limited and somewhat contradictory data, BAL therapy is not recommended when patients are exposed to short-chain organic mercury compounds because it may increase brain concentrations of methyl mercury.[5,19] Other therapies may have greater usefulness (Chap. 92).

Lead

BAL may be used in combination with $CaNa_2EDTA$ to treat patients with severe lead poisoning. In all other cases, succimer has become the chelator of choice. When administering BAL in patients with lead encephalopathy, it is essential to administer the BAL first, followed 4 hours later by $CaNa_2EDTA$, concomitantly with the second dose of BAL. This regimen prevents the $CaNa_2EDTA$ from redistributing lead into the brain (the converse with regard to arsenic).[10,11] Providing two different chelators also reduces the blood lead level significantly faster than either one alone, and maintains a better molar ratio of chelator to lead.[10] Once the

mobilization of lead has begun, it is important to provide uninterrupted therapy to prevent redistribution of lead to the brain.[10]

Adverse Effects and Safety Issues

The toxicity of BAL is dose dependent and affected by urinary pH. An acidic urine allows dissociation of the BALâ€“metal chelate. Less than 1% of 700 intramuscular injections resulted in minor reactions, such as pain at the injection site, among patients

who received 2.5 mg/kg of BAL every 4â€“6 hours for 4 doses.[12] When doses of 4 mg/kg and 5 mg/kg were given, the incidence of adverse effects rose to 14% and 65%, respectively.[12] At these higher doses, the following symptoms were reported in decreasing order of frequency: nausea; vomiting; headache; burning sensation of lips, mouth, throat, and eyes; lacrimation; rhinorrhea; salivation; muscle aches; burning and tingling of extremities; tooth pain; diaphoresis; chest pain; anxiety; and agitation.[23] These effects were maximal within 10â€“30 minutes of exposure, and usually subsided within 30â€“50 minutes.[12] Elevations in systolic and diastolic blood pressure and tachycardia commonly occurred and correlated with increasing doses.[19,26] Thirty percent of children given BAL may develop a fever that can persist throughout the therapeutic period.[19] A transient reduction in the percentage of polymorphonuclear leukocytes may also occur.[19] Doses above 5 mg/kg should not be administered because of the high risk of adverse reactions. Doses above 25 mg/kg can be expected to produce a hypertensive encephalopathy with convulsions and coma.[39]

BAL is not very effective in the presence of arsenic-induced hepatotoxicity.[24] Moreover, in rats, preexistent hepatotoxicity was exacerbated when BAL was used for treatment of arsenic poisoning. Therefore, unless the hepatotoxicity is considered

arsenic-induced, hepatic dysfunction is a contraindication to BAL use.[31] BAL should not be used for patients poisoned by methylmercury because animal studies demonstrate a redistribution of mercury to the brain.[5,19]

Because dissociation of the BALâ€“metal chelate will occur in an acid urine, the urine of patients receiving BAL should be alkalinized with hypertonic $NaHCO_3$ to a pH of 7.5â€“8.0 to prevent renal liberation of the metal.[19] BAL should be used with caution in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as it may cause hemolysis.[18] In these cases, a risk-to-benefit analysis must be made because G6PD-deficiency syndromes are variably expressed in young cells. In addition, chelators are relatively nonspecific and may bind metals other than those desired, thus causing deficiency of an essential metal. For example, BAL given to mice increased copper elimination to 3 times normal.[7] BAL is formulated in peanut oil; therefore, the patient should be questioned regarding any known peanut allergy. Limited evidence suggests that iron supplements should not be given to patients who are receiving BAL because the BALâ€“iron complex appears to cause severe vomiting and decreases metal chelation.[10,11,14]

Unintentional IV infusion of BAL could theoretically produce fat embolism, lipoid pneumonia, chylothorax, and associated hypoxia.[34]

Dosing

Commercially available BAL is a yellow, viscous liquid with a sulfur odor. It is available in 3-mL ampules containing 100 mg/mL of BAL, 200 mg/mL of benzyl benzoate, and 700 mg/mL of peanut oil. This drug should only be administered by deep IM injection.

The dose of BAL for lead encephalopathy is 75 mg/m^2 IM every 4 hours for 5 days.[10,11] As noted earlier, the first dose of

dimercaprol should precede the first dose of $CaNa_2EDTA$ by 4 hours. Thereafter, intravenous $CaNa_2EDTA$, in a dose of 1500 $mg/m^2/d$ (up to a maximum of 2â€“3 g) as a continuous infusion, or divided into 2â€“4 doses, should be administered. These daily doses are equimolar.

The dose of BAL for severe inorganic arsenic poisoning has not been established. One regimen suggests the use of 3 mg/kg IM every 4 hours for 48 hours and then twice daily for 7â€“10 days.[12] Another regimen uses 3â€“5 mg/kg IM every 4â€“6 hours on the first day and then tapers the dose and frequency, depending on the patient's symptomatology. A third regimen reduces the number of injections by day 2 and terminates therapy within 5â€“7 days.[39]

The dose of BAL for patients exposed to inorganic mercury salts is 5 mg/kg IM initially, followed by 2.5 mg/kg every 8â€“12 hours for 1 day, followed by 2.5 mg/kg every 12â€“24 hours until the patient appears clinically improved, up to a total of 10 days.

Summary

BAL (dimercaprol) is an effective metal chelator used clinically in the treatment of inorganic mercury and arsenic toxicity, and in conjunction with edetate calcium disodium for lead encephalopathy and severe lead toxicity. [19,26]

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Chapter 86
Bismuth

Rama B. Rao

Bismuth (Bi)

Atomic number = 83

Atomic weight = 208.98

Normal concentrations

Serum = 2â€“11 mg/L(9.52 nmol/L)

Urine = <4Âµg/L (< 20 nmol/L)

A 65-year-old man with a history of colon cancer requiring a colectomy with an ileostomy presented to his primary care physician for confusion and memory loss. He was admitted to the hospital for evaluation. His vital signs were blood pressure, 130/75 mm Hg; pulse, 72 beats/min; respirations, 18 breaths/min; oral temperature, 98.9Â°F (37.1Â°C); oxygen saturation, 99%. He was awake and alert, but could no longer remember his wife's name or

their telephone number. His head and neck examination were remarkable for darkened gums. His lung and heart examinations were unremarkable. The abdominal examination was notable for a functioning ileostomy, with dark stool in the ostomy bag, negative for occult blood. His neurologic examination revealed normal cranial nerve function, preserved reflexes, and mild tremor. A rapid reagent blood glucose was 110 mg/dL. His serum chemistries, liver function, magnetic resonance imaging of his brain, and spinal fluid analysis were all normal. Despite this, he became progressively more confused and developed myoclonus. He eventually became comatose and neurologically unresponsive with periodic twitching of lower extremities. He required nasogastric tube feeding and intubation. The diagnosis of Creutzfeldt-Jacob disease was entertained, and brain death protocols ensued. It was subsequently revealed that he was taking 12 oz of bismuth subgallate daily to diminish stool odor, and that this therapy was continued while hospitalized. The bismuth was stopped and the patient slowly started to awaken. Within 2 weeks he recovered his mental status completely. He was discharged to a rehabilitation center and subsequently made a complete recovery.

Bismuth is a metal that is either elemental or compounded as a salt. Elemental bismuth is nontoxic. Bismuth salts are employed for therapeutic uses and are responsible for the toxicities described in this chapter. Thus, in this chapter, *bismuth* refers to *bismuth salts*.

Bismuth is one of many xenobiotics commonly used for treatment of traveler's diarrhea, nausea, and vomiting, as well as for treatment of the flatus and odor associated with ileostomies and colostomies.[13] It is an active ingredient in both prescription and nonprescription oral preparations, as well as in bismuth-impregnated surgical packing paste.[8,56]

In the gastrointestinal tract, bismuth binds to sulfhydryl groups and decreases fecal odor through formation of bismuth sulfide.[49]

Sulfhydryl binding is also the proposed mechanism of the antimicrobial effect of bismuth, causing lysis of *Helicobacter pylori*, the causative bacteria in peptic ulcer formation. Bismuth may also inhibit bacterial enzyme function, as well as prevent adhesion of *H. pylori* to the gastric mucosa.[55]

History and Epidemiology

Nearly 300 years ago, bismuth was recognized as medicinally valuable. It was included in topical salves and oral preparations for various gastrointestinal disorders. Renal toxicity was described as early as 1802. In the early 20th century, cases of renal failure were reported in pediatric patients administered intramuscular bismuth salts for the treatment of gingivostomatitis.[6,24,47] Administration of bismuth thioglycollate and its related water-soluble compounds, triglycollamate and trithioglycollamate, was responsible for the renal failure.[7,11,28,54] Children with renal toxicity would typically present with abdominal pain, oliguria, anuria, malaise, and vomiting. Renal failure occurred with as little as one or two treatments. Alterations in consciousness usually abated with treatment or resolution of the uremia. As the use of intramuscular injections was abandoned, this form of bismuth-induced renal failure became uncommon.

Syphilis was previously treated with intramuscular bismuth. A rash known as â€œerythema of the 9th dayâ€• occasionally occurred. This consisted of a diffuse macular rash of the trunk and extremities that resolved without intervention.[15]

After administration of â€œAnalbisâ€• antipyretic rectal suppositories, patients developed hepatic failure, described histopathologically as

yellow atrophy with vacuolization.[2,21] An investigation of the suppositories suggested that diallylacetic acid, and not bismuth, was the hepatotoxin. This preparation is no longer marketed.

More recently, epidemics of bismuth-induced encephalopathy, particularly among patients with ileostomies or colostomies, were reported in France, Britain, and Australia. As a result, some countries banned or restricted bismuth preparations to prescription only. Bismuth subsalicylate, which is currently available in the United States as a nonprescription drug, is still periodically responsible for cases of encephalopathy.[14] Other reported causes of bismuth-induced encephalopathy include systemic absorption from bismuth-impregnated surgical packing paste, and transdermal absorption from chronic application of a bismuth-containing skin cream.

Toxicokinetics

Bismuth is present in nature in both the trivalent and pentavalent forms. The trivalent form of bismuth is employed for all medicinal uses ionic, as the bismuthyl (BiO) moiety, generated by hydrolysis of trivalent bismuth compounds yields a low-solubility alkaline salt. Most of orally administered bismuth remains in the gastrointestinal (GI) tract, being excreted in the feces; only 0.2% is systemically absorbed. Absorption of some bismuth preparations, such as colloidal bismuth subcitrate may increase as gastric pH increases.[35] The peak absorption ranges between 15 and 60 minutes, with high intra- and interindividual variation.[22,24] The plasma-to-blood ratio of bismuth is 1.55.[3] The distribution and elimination of orally administered bismuth follows a complex, multicompartmental model. The volume of distribution in humans is unknown.

Once in the circulation, bismuth binds to Î±$_2$-macroglobulin, IgM, Î²-lipoprotein, and haptoglobin. Bismuth rapidly enters liver, kidney, lungs, and bone. Bismuth can cross the placenta and enter the amniotic fluid and fetal circulation. It also readily crosses the bloodâ€“brain barrier. Evidence in a rat model suggests that, when administered intramuscularly, bismuth can access the central

nervous system via retrograde axonal transport.[48] In other animal models, bismuth is identified in the fenestrated membranes of synaptosomes,[37,40] localizing in the thalamus and cerebellum. This entry is similar to human reports, which also describe diffuse cortical uptake in toxic exposures.[24] Ninety percent of absorbed bismuth is eliminated through the kidneys, where it induces the production of its own metal-binding protein.

Some authors propose three different half-lives to describe the pharmacokinetics of orally administered therapeutic doses of bismuth. The first, a distribution half-life, is approximately 1â€“4 hours. The second, the plasma half-life, lasts 5â€“11 days. The third is the half-life of urinary excretion, lasting between 21 and 72 days,[3] with urinary bismuth detected as late as 5 months after the last oral dose.[22]

Pathophysiology

Similar to other metals, bismuth toxicity involves multiple organ systems. The effect of different bismuth salts can be categorized into 4 groups, based on the solubility and gastrointestinal absorption of the agent (Table 86-1).[42]

The mechanism of bismuth encephalopathy is thought to be related to neuronal sulfhydryl binding. In patients who die of bismuth encephalopathy, the gray matter concentration of bismuth is nearly twice that of the white matter.[24] In an encephalopathic patient dying from concomitant sepsis, the autopsy revealed loss of cerebellar Purkinje cells, which was not expected from sepsis alone.[25] The factors predisposing some individuals to encephalopathy from group II bismuth salts, however, are not well defined. Age, gender, and duration of therapeutic use do not predict the likelihood of developing encephalopathy.

TABLE 86-1. The Absorptive Characteristics of Bismuth Salts

Group	Chemistry	Toxicity	Examples
I	Insoluble in water Inorganic	Minimal	Bismuth subnitrate
II	Lipid soluble Organic	Neurologic	Bismuth subsalicylate Bismuth subgallate
III	Water soluble Organic	Renal	Bismuth triglycollamate
IV	Hydrolyzable Water soluble Organic	Minimal	Bicitropeptide

Clinical Manifestations

Acute

Acutely massive overdoses of bismuth ions can result in abdominal pain and oliguria or anuria. Acute renal failure can occur and is not limited to exposure to the water-soluble bismuth salts (group III). In reported cases, overdoses of colloidal bismuth subsalicylate or tripotassium dicitratobismuthate (TDC) caused acute tubular necrosis.[1,17,19,47,51] Histopathologically, bismuth causes

degeneration of the proximal tubule, similar to the effects of other heavy metals. While these xenobiotics are potentially neurotoxic, signs of encephalopathy are generally absent. In one case, a patient with bismuth-induced renal failure was described as having diminished deep-tendon reflexes, muscle weakness, and myoclonus, without an alteration in consciousness.[17]

Chronic

The most common toxicologic finding associated with repeated therapeutic doses of oral bismuth compounds is a diffuse, progressive myoclonic encephalopathy. Affected patients exhibit neurobehavioral changes, such as apathy and irritability. With continued exposure, these patients may develop difficulty concentrating, diminished short-term memory, and, occasionally, visual hallucinations.[26,27] A movement disorder characterized by muscle twitching, myoclonus, ataxia, and tremors may ensue. Weakness and, rarely, seizures may advance to immobility.[29,31] With continued bismuth administration, these patients can develop coma and die.

Rarely, patients recovering from severe encephalopathy may complain of scapular, humeral, or vertebral pain because of fractures caused by severe neuromuscular manifestations such as myoclonus.[12]

Like several other metals, bismuth can cause a generalized pigmentation of skin. Deposition of bismuth sulfide into the mucosa causes a blue-black discoloration of gums.[57] (See ILBISMUTH in the Image Library at http://www.goldfrankstoxicology.com) This can occur in the absence of toxic effects. Formation of the same compound in the gastrointestinal tract causes blackening of the stool. Liver failure is rarely reported, except in patients with multisystem organ failure from fatal neurotoxicity.

Diagnosis

The clinician must have an index of suspicion based on the acute or chronic nature of the exposure. Patients with acute massive overdoses should be observed and evaluated for possible renal failure. The earliest findings suggestive of renal compromise may be hematuria and proteinuria on urinalysis. Formation of nuclear inclusion bodies can be identified on renal biopsy or on postmortem examination of the kidney.[11,39]

The diagnosis of bismuth encephalopathy is based on a history of exposure coupled with diffuse neuropsychiatric and motor findings.[27] Other causes of encephalopathy should be entertained and excluded (Table 86-2). An abdominal radiograph will likely demonstrate radiopacities of bismuth in the intestines. Stool will be black, but will test negative for occult blood.

The presence of bismuth in the blood is confirmatory of exposure, but absolute concentrations correlate poorly with morbidity. In a review of 310 patients with bismuth encephalopathy, 288 patients (93%) had a blood concentration >100 Âµg/L, with the majority of these blood concentrations between 100 Âµg/L and 1000 Âµg/L.[26] Twenty-two patients suffered encephalopathy at blood concentrations below 100 Âµg/L.[26] In another report, 2 patients with encephalopathy had blood concentrations of 900 Âµg/L and 2500 Âµg/L, both of whom recovered when the concentration fell below 500 Âµg/L.[5] Just as blood concentrations do not reflect severity of illness, tissue concentrations may also poorly correlate with severity of illness. An example was noted in a patient who recovered from a severe encephalopathy. On discharge, he had low blood bismuth concentrations and died 3 months later of unrelated trauma. At autopsy he was found to have an elevated central nervous system (CNS) bismuth burden, but no reported symptoms at the time of the trauma.[9]

The electroencephalographic (EEG) findings of patients with bismuth encephalopathy generally demonstrate nonspecific slow wave changes.[14,17] In one study, the EEG findings were described in association with blood concentrations. At less than 50 Âµg/L, the EEG was normal or demonstrated diffuse slowing. In patients with blood concentrations of less than 1500 Âµg/L, the findings of sharp wave abnormalities were noted. At higher concentrations (>2000 Âµg/L), some patients with neurologic events, such as myoclonic jerks, did not have corresponding EEG changes. The authors proposed that an elevated body burden might have an inhibitory effect on the cerebral cortex.[9]

In encephalopathic patients with blood concentrations >2000 Âµg/L, diagnostic imaging, such as computed tomography, may demonstrate a diffuse cortical hyperdensity of the gray matter. These findings tend to resolve with recovery. Magnetic resonance imaging was normal in another encephalopathic patient.[14]

TABLE 86-2. Differential Diagnosis of Bismuth Encephalopathy

Creutzfeld-Jacob disease
Ethanol withdrawal
Lithium toxicity
Neurodegenerative leukoencephalopathies
Nonketotic hyperosmolar coma
Postanoxic and posthypoglycemic encephalopathies
Progressive multifocal ataxia
Viral encephalopathies

Treatment

Typically, supportive care results in a complete recovery. Some authors suggest GI decontamination with activated charcoal and polyethylene glycol solution.[44] Although evidence for this approach is lacking, it appears to be a reasonable initial intervention, especially in patients with severe encephalopathy.

In patients with renal toxicity, resolution is generally observed with supportive care. The use of chelating agents in acute overdose without neurotoxicity is probably not indicated. Withdrawal of the source of bismuth often results in complete reversal of symptoms within days to weeks, even in severely ill patients.

In general, the data regarding chelation are limited, and in vitro and animal models do not clearly predict in vivo human models. Chelation therapy with British anti-Lewisite (BAL) is beneficial in experimental models,[44,47] reportedly beneficial in humans,[30] and often recommended, although clear evidence of efficacy is lacking. BAL undergoes biliary elimination, offering a major advantage over other chelators in patients who may develop renal insufficiency. One study advocated the addition of dimercaptopropane sulfonate (DMPS), as BAL with hemodialysis did not affect clearance, whereas the addition of DMPS to patients needing hemodialysis was effective in enhancing elimination.[47] It is uncertain whether the clinical course of the patients was improved. In human volunteers using colloidal bismuth subcitrate, succimer and DMPS, both at a dose of 30 mg/kg, increased urinary elimination of bismuth by 50-fold.[45]

In an animal model, D-penicillamine was most efficacious in enhancing elimination of bismuth. In a human volunteer model using therapeutic doses of TDC, however, a single dose of D-penicillamine did not enhance urinary excretion.[32]

The precise timing, dosage, indications, and choice of chelator are unknown; however, chelation with succimer has few side effects and might limit the potentially fatal complications associated with

prolonged immobilization. BAL, which has more side effects, can be considered in encephalopathic patients with renal failure in whom no neurologic improvement is noted within 48 hours of bismuth withdrawal and whole-bowel irrigation.

Prevention is the most effective means of avoiding neurotoxicity. Patients and their families should be taught to recognize the subtle manifestations of bismuth-induced neurotoxicity. Blood concentrations of bismuth are not routinely performed, but a bismuth concentration >100 Âµg/L, or symptoms at lower levels, warrant withdrawal of bismuth therapy.

Bismuth Drug Interactions and Reactions

The coadministration of proton pump inhibitors (PPIs) may affect the absorption of some bismuth preparations. In a prospective evaluation of patients receiving different treatment regimens for *Helicobacter pylori*-induced dyspepsia or peptic ulcer disease, individuals taking PPIs had a statistically significant elevation in their blood bismuth concentrations. The authors suggest that the bismuth preparation usedâ€”colloidal bismuth subcitrateâ€”is more soluble and absorbable at the higher gastric pH of patients on PPIs. All of these patients received short courses of therapy (2 weeks). Although the investigators did not attempt to follow neurobehavioral

or neuropsychiatric changes, none of the patients had clinically evident bismuth toxicity.[35]

Based on this investigation, coadministration of PPIs with longer courses of colloidal bismuth subcitrate should be avoided or only offered with extreme caution. Ranitidine, which is frequently prescribed with a bismuth compound for dyspepsia or ulcer disease, does not affect the pharmacokinetics of bismuth

absorption.[22]

In the United States, where bismuth subsalicylate is the most common oral bismuth-containing compound, up to 90% of the salicylate is absorbed.[36] Salicylate toxicity has been reported and salicylate concentrations should be performed in both acute and chronic exposures. Methemoglobinemia from subnitrate salt of bismuth is uncommonly described.[20]

Summary

The most likely manifestations of bismuth toxicity are either neuropsychiatric or renal, depending on the type of compound and whether the etiology is related to chronic therapy or acute overdose. The factors predisposing some individuals to neurotoxicity from therapeutic use of oral bismuth compounds are poorly understood. Thus patients using therapeutic bismuth with new movement disorders or alterations in mental status should be assessed for possible bismuth-induced encephalopathy.

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Chapter 87
Cadmium

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Cadmium (Cd)

Atomic number = 48

Atomic weight = 112.40

Normal concentrations

Whole blood = < 5Âµg/L(4 nmol/L)

Urine = <3Âµg/g creatinine(2.6 nmol/L creatinine)

A 53-year-old man who performed metalwork as a hobby became ill approximately 6 hours after welding in his shop. He developed a violent cough, and sought care from a local physician. The physician, who elicited the history of metalwork, diagnosed metal fume fever, reassured the patient that his symptoms would pass, and discharged him home.

The next morning the patient's condition worsened, and he presented to a local emergency department complaining of severe shortness of breath. His vital signs were blood pressure, 105/64 mm Hg; pulse, 117 beats/min; respiratory rate, 22 breaths/min and labored; and temperature, 101.3Â°F (38.5Â°C). Pulmonary examination revealed diffuse crackles. Pulse oxygenation was 87% on room air. Supplemental oxygen of 4 L/min via nasal cannula was administered, and the patient's oxygen saturation improved to 94%. Arterial blood gas analysis and cooximetry confirmed the patient's hypoxia and excluded methemoglobinemia and carboxyhemoglobinemia. A chest radiograph demonstrated diffuse infiltrates suggestive of bronchoalveolar fluid. Further history revealed that the patient had been welding with a cadmium-containing solder, without appropriate respiratory precautions. A working diagnosis of cadmium pneumonitis was established.

The patient's respiratory status slowly declined over the course of the next 24 hours, necessitating endotracheal intubation. He was treated with intravenous corticosteroids (dexamethasone 10 mg IV every 6 hours) and a broad-spectrum antibiotic (ceftriaxone, 1 g IV every 12 hours), but continued to deteriorate despite aggressive and appropriate supportive care and expired on hospital day 4.

History and Epidemiology

Cadmium, atomic number 48, is a transition metal in group IIB of the periodic table. In its pure atomic form, it is a bluish solid at room temperature. It is readily oxidized to a divalent ion, Cd^{2+}. Naturally occurring cadmium commonly exists as cadmium sulfide (CdS), a trace contaminant of zinc-containing ores.[37]

Cadmium sulfide, cadmium oxide, and other cadmium-containing compounds are refined to produce elemental cadmium, which is used for industrial purposes. When combined with other metals, cadmium forms alloys of relatively low melting points, which accounts for its extensive use in solders and brazing rods. Today, cadmium is

principally used as a reagent in electroplating and in the production of nickel-cadmium batteries. Other current and historical uses of cadmium include as a pigment, as part of the phosphorescent system in black-and-white televisions, and as a neutron absorber in nuclear reactors. Cadmium salts have also been used as veterinary antihelminthics.[12]

As cadmium processing has increased, so has the incidence of cadmium toxicity. Cadmium exposure with resultant toxicity usually occurs in 1 of 3 settings: environmental, occupational, or hobby work.

Environmental Exposure

Environmental exposure to cadmium generally occurs through the consumption of foods grown in cadmium-contaminated areas. Because cadmium is fairly common as an impurity in ores, areas where mining or refining of ores takes place are at highest risk for contamination. Many countries, including Sweden[44] and Belgium,[11] have reported on environmental cadmium exposure, but the most remarkable historical example of environmental cadmium pollution occurred in Japan.

In the 1950s, a mine near the Jinzu River basin discharged large amounts of cadmium into the environment, contaminating the rice that was a staple of the local food supply. An epidemic of painful osteomalacia followed, affecting hundreds of people, with postmenopausal multiparous women being most affected.[63] The afflicted were prone to develop pathologic fractures, and were reported to call out â€œitai-itaiâ€• (translated literally as â€œouch-ouchâ€•) as they walked, because of the severity of their pain.[29] These symptoms were ultimately linked to the cadmium.

Environmental exposure also occurs in smokers, who have higher blood cadmium concentrations than do nonsmokers,[84] probably as a result of cadmium contamination of the soil in which the tobacco is grown. This is noteworthy, in that cadmium and tobacco may be

synergistic causes of chronic pulmonary disease.[58]

Occupational and Hobby Exposure

Welders, solderers, and jewelry workers who use cadmium-containing alloys are at risk for developing acute cadmium toxicity through inhalation of cadmium oxide fumes. Other workers who do not work with metals per se may develop significant chronic cadmium toxicity through exposure to cadmium-containing dust.

Hobbyists who work with cadmium solders have exposures similar to occupational metalworkers. Significant cadmium toxicity in this population invariably results from metalworking in a closed space with inadequate ventilation and/or improper respiratory precautions.

Toxicokinetics

There is no known biologic role for cadmium. The bioavailability of elemental cadmium is unknown. Orally ingested cadmium salts are poorly (5â€“20%) bioavailable. However, inhaled cadmium fumes (cadmium oxide) are readily bioavailable (up to 90%).[91] Because the only data on cadmium toxicokinetics come from work with cadmium salts and oxides, â€œcadmiumâ€• in the following discussion refers to these species, unless otherwise noted.

After exposure, cadmium is taken up into the bloodstream, where it is bound to $\hat{I}\pm_2$-macroglobulin and albumin.[92] It is then quickly and preferentially redistributed to the liver and kidney. Although other organs, such as the pancreas, spleen, heart, lung, and testes, can take up part of an acute cadmium load, they do so much less avidly.[26] Cadmium enters target organs by 3 mechanisms: zinc and calcium transporters; uptake of cadmiumâ€“glutathione or cadmiumâ€“cysteine complexes by transport proteins; and endocytosis of cadmium-protein complexes.[96]

After it is incorporated in the liver and kidney, cadmium is complexed with metallothionein, an endogenous thiol-rich protein that is

produced in both organs. Metallothionein binds and sequesters cadmium. Slowly, hepatic stores of the cadmiumâ€“metallothionein complex (Cd-MT) are released. Circulating Cd-MT is then filtered by the glomerulus. A significant amount is reabsorbed and concentrated in proximal tubular cells.[79,80] This, in part, explains why the kidney is the principal target organ in cadmium toxicity.

There is no evidence that cadmium ions are oxidized, reduced, methylated, or otherwise biotransformed in vivo. The volume of distribution (Vd) of cadmium is unknown, but is presumably quite large as a consequence of significant hepatic sequestration. Cadmium distribution and elimination are complex, and an 8-compartment kinetic model is proposed.[51] The slow release of cadmium from metallothionein-complexed hepatic stores accounts for its very long biologic half-life of 10 or more years.

Pathophysiology

Cellular Pathophysiology

Cadmium is very quickly and efficiently complexed to metallothionein in vivo, which raises the question of whether free cadmium or the cadmium-metallothionein complex is the ultimate toxicant. It appears, however, that unbound cadmium mediates cellular damage.[26,36,56,61,80] The metallothionein complex is protective[23,56] and functions as a natural chelating agent with a strong affinity for cadmium.[19,52] Although metallothionein may play a role in proximal tubular concentration of cadmium, renal damage is actually attenuated by metallothionein, as metallothionein-deficient mice demonstrate more toxicity after cadmium exposure than controls.[56]

There are several mechanisms by which cadmium interferes with cellular function. Cadmium binds to sulfhydryl groups, denaturing proteins and/or inactivating enzymes. The mitochondria are severely effected by this process,[1] which may result in an increased

susceptibility to oxidative stress.[45] Cadmium also interferes with E-cadherin, N-cadherin and Î²-cateninâ€“mediated cellâ€“cell adhesion.[67,68,69] Finally, the demonstrated interference of cadmium with calcium transport mechanisms[88,89] might lead to intracellular hypercalcemia and, ultimately, apoptosis.

Specific Organ System Injury

Kidney

The renal damage caused by cadmium develops over years. Proteinuria is the most common clinical finding, and correlates with proximal tubular dysfunction, which manifests as urinary loss of low-molecular-weight proteins such as $Î²_2$-microglobulin and retinol-binding protein. Cadmium also produces hypercalcuria,[76] possibly also via damage to the proximal tubule.

Bone

Cadmium-induced osteomalacia is a result of abnormalities in calcium and phosphate homeostasis, which, in turn, result from renal proximal tubular dysfunction. In one autopsy study, the severity of osteomalacia in cadmium-exposed subjects correlated with a decline in the serum calcium-phosphate product.[83]

Lung

Acute cadmium pneumonitis is characterized by infiltrates on the chest radiograph and hypoxia. Human autopsy studies[33,66,77,93] generally show degeneration and/or loss of bronchial and bronchiolar epithelial cells.

Gastrointestinal Tract

Based on case reports,[8,94] ingested cadmium salts appear to be caustic substances with the potential to induce significant nausea,

vomiting, and abdominal pain, and result in GI hemorrhage, necrosis, and perforation. With respect to their effect on the GI mucosa, cadmium salts appear to be similar to mercuric salts (Chap. 92).

Clinical Manifestations

Acute Poisoning

Pulmonary/Cadmium Fumes

Cadmium pneumonitis results from inhalation of cadmium oxide fumes. The acute phase of cadmium pneumonitis may mimic metal fume fever (Chap. 119), but in fact, the two entities are distinctly different, both in mechanism and in clinical consequences. Whereas metal fume fever is benign and self-limited, acute cadmium pneumonitis can progress to hypoxia, respiratory insufficiency, and death.

Published case reports of patients who develop acute cadmium pneumonitis[4,5,33,66,77,85,93,95] are strikingly similar in the presentation described. Within 6â€“12 hours of soldering or brazing with cadmium alloy in a closed space, patients typically develop constitutional

symptoms, such as fever and chills, as well as a cough and respiratory distress.

On initial presentation, these patients may not appear significantly ill and instead may have a normal physical examination, oxygenation status, and chest radiograph. This relatively benign presentation may lead both to the misdiagnosis of metal fume fever and the underestimation of the severity of the patient's illness. As the pneumonitis progresses to acute lung injury (ALI) (Chap. 119), crackles and rhonchi develop, oxygenation becomes impaired, and the chest radiograph develops a pattern consistent with alveolar filling.

Despite aggressive supportive care, death may occur, usually within 3â€“5 days.[33,66,77,93]

Patients who survive an episode of acute cadmium pneumonitis may develop chronic pulmonary ailments, including restrictive lung disease,[4,5] diffusion abnormalities,[4] and pulmonary fibrosis.[85] Recovery without sequelae is also reported after exposure.[95]

Oral/Cadmium Salts

Although most acute cadmium exposures are inhalational, acute oral exposures also occur. In one case,[8] a 17-year-old woman ingested approximately 150 g of cadmium chloride and presented to the emergency department with hypotension and edema of the face, pharynx, and neck. Her condition quickly deteriorated, and she suffered a respiratory arrest. She was intubated, underwent orogastric lavage, chelation with an unspecified agent, and charcoal hemoperfusion. Multisystem organ failure ensued, and she died within 30 hours of presentation. At autopsy, the most significant finding was hemorrhagic necrosis of the upper GI tract. Her blood cadmium concentration was more than 2000 times normal.

In a second case,[94] a 23-year-old man ingested approximately 5 g of cadmium iodide in a suicide attempt and presented with acute hemorrhagic gastroenteritis. His condition deteriorated, and despite treatment with ethylenediaminetetraacetic acid (EDTA) and supportive measures, he died on hospital day 7. Autopsy did not reveal a specific cause of death.

Chronic Poisoning

Chronic cadmium poisoning generally occurs through occupational exposures, although instances of mass environmental exposure, such as occurred in Japan,[29,62] are reported. All studies of chronic cadmium poisoning in humans are retrospective, and thus neither randomized nor controlled. In addition, and especially in the industrial

setting, cadmium exposure may serve simply as a marker for other exposures, such as toxic vapors, other metals, or solvents. These other toxins may contribute to, or cause, the pathologic condition described.

Nephrotoxicity

The most common finding in chronic cadmium poisoning is proteinuria. Low-molecular-weight proteinuria is usually more significant than, and generally precedes, glomerular dysfunction, although some cadmium-exposed workers manifest predominantly glomerular proteinuria.[7] There is a doseâ€“response relationship between total-body cadmium burden and renal dysfunction,[11,43,44,63,87] although this relationship may not be as strong at low doses.[39] In most patients, proteinuria is generally considered to be irreversible even after removal from exposure,[38,49,72] but improvement is sometimes reported.[86] Less clear is the question of whether renal dysfunction progresses after removal from exposure, with studies showing both stable[38] and deteriorating[41,71,72] renal function in cadmium-exposed workers following cessation of exposure. The routes and duration of exposure, as well as blood and urine cadmium concentrations, differ markedly between these studies, limiting the importance and breadth of wider applicability of any analysis.

Occupational cadmium exposure is also associated with nephrolithiasis,[42,75] likely as a result of hypercalciuria.[76]

Pulmonary Toxicity

Large studies of workers chronically exposed to cadmium fail to demonstrate consistent effects on chronic lung disease. In one study of 57 workers with sufficient exposure to cadmium oxide to produce renal dysfunction, there was no evidence of pulmonary dysfunction, even in those with the greatest cumulative cadmium exposure.[28] In contrast, other studies demonstrate both restrictive[18] and

obstructive[22,74] changes on pulmonary function tests. Interestingly, a followup study of the group with restrictive lung disease showed improvements after cadmium exposure was reduced.[17] The discrepancies in these results may be partly a result of markedly different degrees of exposure among the various groups.

Cadmium is associated with pulmonary neoplasia; the carcinogenicity of cadmium is discussed separately (see Cancer below).

Musculoskeletal Toxicity

Osteomalacia, which was one of the most prominent features of the Itai-Itai epidemic, is a condition in which inadequate mineralization of mature bone predisposes to pathologic fractures. Although mentioned in case reports,[9,49] osteomalacia is generally not a prominent feature of most people occupationally exposed to cadmium. Victims of the original Itai-Itai epidemic were mostly women, whereas occupational cadmium exposures typically occur in men. In addition, differences in cumulative dosing and in route of exposure (oral vs. pulmonary) may account for some of the unique prominence of osteomalacia in the Itai-Itai epidemic.

Hepatotoxicity

Although the liver stores as much cadmium as any other organ, hepatotoxicity is not a prominent feature in humans with cadmium exposure, probably because hepatic cadmium is usually complexed to metallothionein.[40] The liver can potentially be a target organ, however, and hepatotoxicity is easily inducible in animals.[1,26,27,70]

Neurologic Toxicity

Cadmium exposure is linked to olfactory disturbances,[59,73,82] impaired higher cortical function,[90] and Parkinson syndrome.[64,90]

Other Organ Systems

Cadmium induces hypertension in rats,[55] but human studies have not shown a convincing link.[32,65] Although there is evidence that cadmium may cause immunosuppression affecting both humoral and cell-mediated immunity in animals,[25] a single human study showed no overt immunopathology in an occupationally exposed cohort.[48] The testes are clearly a target organ in animal exposures,[54] but the testes are not considered a major target organ in humans.

Cancer

Cadmium induces tumors in multiple animal organs, an effect that is exacerbated by zinc deficiency.[91]

In humans, cadmium exposure is associated with lung cancer. The strength of this association has been questioned because most studies have methodologic problems, such as coexposure to arsenic, a known pulmonary carcinogen.[10,50] Despite this, cadmium is designated as a human carcinogen by the International Agency for Research on Cancer.[13]

Diagnostic Testing

Other than to confirm exposure, cadmium concentrations have limited usefulness in the management of the acutely exposed patient. Diagnosis and treatment are based on the patient's history, physical examination, and symptoms. In a patient exposed to cadmium oxide fumes, ancillary tests, such as arterial blood-gas analysis and chest radiography, are more useful than actual cadmium concentrations.

In the patient chronically exposed to cadmium, both cadmium concentrations and ancillary testing may prove helpful. Urinary cadmium concentrations, which reflect the slow, steady-state turnover and release of metallothionein-bound cadmium from the liver, are a better reflection of the total-body cadmium burden than are whole blood concentrations. Workers at high risk for cadmium toxicity

should undergo a regular urinalysis for proteinuria, and the development of proteinuria should prompt immediate reassignment to exposure-free areas. For asymptomatic workers without proteinuria, 15 Âµg Cd/g urinary creatinine is considered acceptable, although renal dysfunction has occurred at concentrations as low as 5 Âµg Cd/g urinary creatinine.[21,43] This concentration is significantly higher than that of the general US population, 95% of whom have concentrations that are less than 2 Âµg Cd/g urinary creatinine.[16]

Management

Acute Exposure

Oral Exposure/Cadmium Salts

After the status of the patient's airway, breathing, and circulation are addressed, attention can be given to gastrointestinal decontamination. Although large oral exposures to soluble cadmium salts are rare, they frequently prove fatal.[8,94] The lowest reported human lethal dose is 5 g. In light of this, if a significant exposure occurs but emesis has not occurred, gastric lavage is appropriate. In this situation, a small nasogastric tube should suffice, as inorganic cadmium salts are powders, not pills. There are no specific data regarding the use of activated charcoal for acute oral cadmium toxicity; however, activated charcoal is a relatively benign intervention and is indicated in the treatment of some metal salts, such as thallium and mercury (Chaps. 92 and 96). Activated charcoal should thus be given in the absence of any contraindications (such as known perforation or pending endoscopy).

Given the relative lack of experience with acute oral cadmium poisoning, all patients with known exposures and/or abnormal findings consistent with cadmium toxicity or exposure should be admitted to the hospital for supportive care, monitoring of renal and hepatic function, and possibly evaluation of the gastrointestinal tract for

injury.

Although it seems logical to use chelation therapy in any patient with an acute life-threatening ingestion of a metal compound, the benefit of chelation in acute cadmium exposure is unproven. Multiple chelating agents have been tried, all in animal models, with inconsistent results.

The ideal chelating agent for treatment of oral cadmium toxicity would be well tolerated, decrease gastrointestinal absorption of cadmium, decrease the concentration of cadmium in organs such as the kidney and liver, and not increase cadmium concentrations in other critical organs such as the brain. Of the chelating agents studied for cadmium toxicity thus far, succimer comes closest to fulfilling these criteria. In models of acute oral cadmium toxicity, succimer decreases the gastrointestinal absorption of cadmium[3,6] and improves survival[6,47] without increasing cadmium burdens in target organs.[2,6]

In a patient thought to have ingested potentially lethal amounts of cadmium, treatment with succimer is reasonable. The succimer should be given as soon as possible after the ingestion, as the effectiveness of chelating agents decreases dramatically over time in experimental models of cadmium poisoning.[15]

It must be stressed, however, that supporting data for chelation are promising but not definitive, and are only derived from animal models. Furthermore, succimer dosing in human cadmium poisoning is unstudied. Doses that are well tolerated (10 mg/kg/dose TID) are appropriate.

Other chelating agents that may be beneficial, but for which further investigation is needed, include diethylenetriaminepentaacetic acid (DTPA)[6,14] and 2,3-dimercaptopropane sulfonate (DMPS),[14,47] both of which reduce tissue burdens and increase survival.

Most other chelating agents have been found to be either ineffective or detrimental, including 2,3-dimercaptopropanol (British anti-Lewisite, BAL),[14,19,46] penicillamine,[14,57] cyclic tetramines (such as

cyclam and tACPD),[81] detergent formula chelating agents such as sodium tripolyphosphate (STPP) and nitrilotriacetic acid (NTA),[30,31] EDTA,[60] and dithiocarbamates.[3,34]

Pulmonary/Cadmium Fumes

The patient who is ill after exposure to cadmium fumes (generally cadmium oxide) invariably presents with respiratory complaints and possibly with constitutional symptoms. The airway should be assessed and appropriate oxygenation assured, although hypoxia may not be a problem acutely. Steroids are used in most reported cases, but there are no studies to support their efficacy. Because cadmium inhalation injuries are neither benign nor self-limited, all patients with acute inhalational exposures to cadmium should be admitted to the hospital for observation and supportive care until respiratory symptoms have resolved. All such patients should have long-term followup arranged with a pulmonologist to assess the possibility of chronic lung injury, even in instances of single exposures.

Chelation should not be entertained as an option for patients with single acute exposures to cadmium fumes, as these patients do not appear to develop extrapulmonary injury.[4,5,85,95]

Chronic Exposure

Patients chronically exposed to cadmium frequently come to attention during routine screening, as those who work with cadmium are under close medical surveillance. These patients may have developed proteinuria or, less commonly, chronic pulmonary complaints.

Management is challenging. Cessation of cadmium exposure is the first intervention. However, as mentioned earlier, chronic cadmium-induced renal and pulmonary changes are largely irreversible.

Chelation for chronic cadmium toxicity is not currently recommended. There is no evidence that chelation of chronically poisoned animals improves long-term outcomes. Furthermore, in a chronically exposed

patient, the majority of cadmium is bound to intracellular metallothionein, which greatly reduces its toxicity. Any attempt to remove cadmium from these deposits risks redistributing cadmium to other organs, possibly exacerbating toxicity, as is known to occur with BAL therapy.[24]

Of all the chelating agents tested thus far in animal models of chronic cadmium toxicity, the dithiocarbamates have shown the

most success in reducing total-body cadmium burdens. Unfortunately, the most effective agents, which are highly lipophilic, also tend to cause redistribution of cadmium to the brain; their lipophilicity not only allows them to cross cell membranes into hepatocytes, but also promotes their uptake into the lipid-rich central nervous system.[35] Numerous dithiocarbamates have been synthesized and studied with regard to cadmium decorporation, however, and several species effectively reduce whole-body, renal, and hepatic cadmium concentrations without an increase in CNS cadmium.[53,78] At this time, there are no FDA-approved dithiocarbamate preparations.

Further research into the subject of chelation for chronic cadmium poisoning is ongoing, and may produce an agent that is both safe and effective without exacerbating end-organ toxicity. At present, there is insufficient evidence to justify the use of any chelating agent in the treatment of chronic cadmium toxicity.

Summary

Cadmium is a toxic element with different effects dependent on the chronicity and route of exposure. After acute oral exposure, gastrointestinal injury predominates. After acute inhalation, a severe chemical pneumonitis may ensue. With chronic environmental or occupational exposure, nephrotoxicity (usually manifested by proteinuria) is the most significant finding, although other organ systems, such as the lungs, can be affected. Treatment for all patients with suspected cadmium poisoning consists of removal from

the source, decontamination if possible, and supportive care. In the rare instance of exposure from acute cadmium salt ingestion, treatment with succimer may be warranted. At this time there is insufficient evidence to recommend chelation in the chronically cadmium poisoned patient.

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Chapter 88
Chromium

Steven B. Bird

Chromium (Cr)

Atomic number	=	24
Atomic weight	=	51.99 daltons

Normal concentrations

Whole blood	=	20â€“30 Âµg/L (380â€“580 nmol/L)
Serum	=	0.05â€“2.86 Âµg/L (1â€–56 nmol/L)
Urine	=	<1 Âµg/g creatinine (<0.2 nmol/mmol creatinine)

Colleagues brought a 26-year-old chemistry graduate student to the emergency department after he admitted to drinking an

unspecified amount of a 70% potassium dichromate ($K_2Cr_2O_7$) solution. Immediately after arrival the student complained of abdominal pain and vomiting blood, followed soon after by hematochezia. His past medical history was significant only for depression, and the patient denied other ingestions or illicit drug use. His mental status was depressed to the point where the patient could offer no further history.

The patient was noted to be cyanotic, lethargic, and ill appearing. His vital signs were systolic blood pressure, 80 mm Hg; pulse, 140 beats/min; respiratory rate, 32 breaths/min; temperature, 98.6Â°F (37Â°C); and oxygen saturation, 85% on 100% oxygen via non-rebreather mask. His oropharynx contained fresh blood without obvious burns. Lungs were clear to auscultation. The abdomen was rigid without any detectable bowel sounds. Extremities were cool with cyanotic digits.

Large-volume crystalloid resuscitation was begun immediately through 2 large-bore IV lines, followed by both norepinephrine and vasopressin drips. General surgery and gastroenterology consultants were called. Several units of packed red blood cells were rapidly transfused to treat persistent hypotension accompanied by continued massive blood loss, suctioned from a nasogastric tube.

An initial arterial blood-gas concentration was pH, 7.09; PCO_2, 24 mm Hg; PO_2, 395 mm Hg; and bicarbonate, 10 mEq/L. Cooximetry demonstrated a methemoglobin concentration of 18%. A complete blood count revealed 18,000/mm^3 leukocytes; hematocrit, 34%; and platelets 210,000/mm^3. Blood chemistries were sodium, 137 mEq/L; potassium, 6.5 mEq/L; chloride, 110 mEq/L; carbon dioxide, 12 mEq/L; blood urea nitrogen, 19 mg/dL; creatinine, 1.7 mg/dL; and glucose, 96 mg/dL. The partial thromboplastin time and prothrombin time were 36 seconds and 15 seconds, respectively.

Bedside esophagogastroduodenoscopy demonstrated

circumferential burns involving the lower esophagus with apparent full-thickness burns involving the stomach and proximal duodenum. The patient was taken to the operating room where he died during attempted gastrectomy and bowel resection.

History and Epidemiology

Chromium (from the Greek word for color, *chroma*) is a naturally occurring element that may be found in oxidation states of â€“2 to +6, but primarily in the trivalent (Cr^{3+}) and hexavalent (Cr^{6+}) forms. It was first discovered in 1797 in the form of Siberian red lead (crocoite: $PbCrO_4$), and occurs only in combination with other elements, primarily as halides, oxides, or sulfides (Table 88-1). Chromium is found most abundantly in chromite ore ($FeCr_2O_4$).[8] Elemental chromium (Cr^0) does not naturally occur.

Elemental chromium is a blue-white metal that is hard and brittle. It can be polished to a fine, shiny surface, affords significant protection against corrosion, and can be added to steel to form stainless steel (which is primarily an alloy of chromium, nickel, and iron). One of the most important uses of chrome plating is to apply a hard, smooth, surface to machine parts such as crankshafts, printing rollers, ball bearings, and cutting tools. This is known as â€œhardâ€• chrome plating. Elemental chromium is also used in armor plating and safes, and as a catalyst for forming brick molds because of its high melting point and moderate thermal expansion.

The carcinogenic potential of hexavalent chromium was first recognized as a cause of nasal tumors in Scottish chrome pigment workers in the late 1800s. In the 1930s, the pulmonary carcinogenicity of chromium was described in German chromate workers.[13]

Chemical Principles

Chromium is an essential element involved in glucose metabolism. This may be through facilitation of insulin binding to insulin receptors or by amplification of the effects of insulin on carbohydrate and lipid metabolism. Chromium deficiency may play a role in the development of diabetes mellitus and arteriosclerosis.

TABLE 88-1. Common Forms of Chromium

Name	Chemical Formula	Oxidation State	Uses
Barium chromate	$BaCrO_4$	6+	Safety matches, anticorrosive, paint pigment
Calcium chromate	$CaCrO_4$	6+	Batteries, metallurgy
Chromic acid	H_2CrO_4	6+	Electroplating, oxidizer
Chromic chloride	$CrCl_3$	3+	Supplement in total parenteral nutrition
Chromic fluoride	CrF_3	3+	Mordant in dye industry, mothproofing

			agent for wool
Chromic oxide	Cr_2O_3	3+	Metal plating, wood treatment
Chromite ore	$FeCr_2O_4$	3+	Water tower treatment, held in National Defense Stockpile
Chromium picolinate	$C_{18}H_{12}CrN_3O_6$	3+	Nutritional supplement
Lead chromate	$PbCrO_4$	6+	Yellow pigment for paints and dye
Potassium dichromate	$K_2Cr_2O_7$	6+	Oxidizer of organic compounds, leather tanning, porcelain painting

The chemical properties and health risks of chromium depend mostly on its oxidative state and on the solubility of the chromium compound. Chromium is found naturally in the hexavalent (Cr^{6+}) or in the trivalent (Cr^{3+}) valence states, and these are the species

to which most human exposures occur. However, the Cr^{6+} and Cr^{3+} oxidation states have very different properties. The relationship between these oxidative states is described by the following equation:

$Cr_2O_7^{-2}$ + 14 H^+ + 6 electrons â†' 2 Cr^{3+} + 7 H_2O + 1.33 eV[15]

This difference of 1.33 eV in electric potential between the Cr^{6+} and Cr^{3+} states reflects the significant oxidizing potential of Cr^{6+} and the high energy required for the oxidation of Cr^{3+} to Cr^{6+}. Reduction of Cr^{6+} to Cr^{3+} only occurs in vivo by abstraction of electrons from cellular constituents such as proteins, lipids, DNA, and RNA, and plasma transferrin.[37]

The rapidity and completeness of the reduction of Cr^{6+} has been the subject of considerable scientific debate. Hexavalent chromium is reduced to Cr^{3+} in saliva, the gastrointestinal tract, respiratory tract epithelium and pulmonary macrophages, and in blood.[2,34] During this reduction of Cr^{6+} to Cr^{3+}, several other oxidative states transiently occur (namely, Cr^{4+} and Cr^{5+}) that contribute to the cytotoxicity, genotoxicity, and carcinogenicity of Cr^{6+} chromium compound.[47]

Although most Cr^{6+} is rapidly reduced on entering the stomach and GI tract, ingestion of Cr^{6+} in drinking water leads to measurable chromium concentrations in plasma, red blood cells, and urine. However, there is no increase in leukocyte DNAâ€“protein cross-linking, a marker of cytotoxicity and genotoxicity.[25] Hexavalent chromium can accumulate in most body tissues, raising concerns that chromium-induced toxicity and carcinogenesis may be more widespread than is currently understood.[13]

Environmental Exposure

The processing of chromium ores releases primarily Cr^{3+} into the environment. However, some quantity of hexavalent chromium is

released from chromate manufacturing and coal-based power plants.[6] The most significant environmental sources of Cr^{6+} are chromate production, ferrochrome pigment manufacturing, chrome plating, and some types of welding.[46]

The general population may be exposed to chromium via drinking water, food and food supplements (eg, chromium picolinate), joint arthroplasty, and cigarettes. Chromium has been used extensively in industrial cooling towers and air conditioning to prevent equipment and piping corrosion. Dermal exposure may occur from use of tanned leather products or wood treated with CCA (copper, chromate, and arsenate). CCA-treated lumber was voluntarily removed from the consumer market in December 2003, because of possible health concerns as a result of exposure to the arsenic and chromium. No specific adverse health effects related to CCA-treated lumber were reported by the Environmental Protection Agency prior to the voluntary withdrawal. Significant exposure from more than 160 chromate production waste sites within Hudson County, New Jersey was discovered in the late 1980s.[20] Surveillance of these residential areas continues today.

Occupational Exposure

Workers in industries that use chromium may be exposed to 100 times greater concentrations of chromium than the general population.[47] Chromium pigment production and leather tanning use significantly more trivalent chromium compounds, whereas metal finishing, wood preservation, and cooling towers use hexavalent chromium compounds (Table 88-2).

Several studies have focused on the risk of chromium exposure in welders.[41,42] Stainless steel welding liberates significantly more hexavalent chromium than do other types of welding. Other specifics,

such as the type of welding rod used and air contaminants, also

impact the occupational risk.

TABLE 88-2. Occupations At Risk for Chromium Exposure

Cement workers
Chromite ore workers
Electroplaters
Foundry workers
Galvanized steel workers
Glass polishers and glazers
Lithographers
Machinists
Painters
Photograph developers
Tanners
Textile dyers
Welders
Wood preservers

Pharmacology and Physiology

Because they possess significantly different properties, trivalent and hexavalent chromium must be evaluated separately.

Absorption

Trivalent Chromium Compounds

After oral administration, absorption of Cr^{3+} salts is limited. Approximately 98% of the compound is recovered in the feces, 0.1% is excreted in the bile, and 0.5â€“2.0% is excreted in the urine.[17,31,33] Human case reports and animal studies also

corroborate the generally poor absorption of Cr^{3+} salts by the oral, inhalational, and dermal routes, except through burns and other disrupted mucosal or epithelial surfaces.[28]

Hexavalent Chromium Compounds

Partly as a result of the structural similarity between hexavalent chromium compounds and phosphate and sulfate, Cr^{6+} is modestly absorbed after ingestion.[14] In human volunteers, approximately 10% of an orally ingested dose of sodium chromate was absorbed; duodenal administration increased absorption to roughly 50%.[17] This difference likely relates to the reduction of the hexavalent chromium to trivalent chromium in the acidic environment of the stomach. Similarly, 3 hours after a lethal ingestion of potassium dichromate (hexavalent), greater than 80% of the chromium was reduced to the trivalent state.[21] Hexavalent chromium compounds are generally not well absorbed after dermal exposure.

Inhalation of Cr^{6+} is the most consequential route of exposure. The exact rate of absorption is unknown, but is dependent on the solubility of the specific Cr^{6+} compound, the size of the particles, the phagocytic activity of the pulmonary macrophages, and general health of the lungs. Animal studies suggest that roughly 50â€“85% of small (<5 Âµm) Cr^{6+} potassium dichromate particles are absorbed.[46]

Distribution

Because most of the Cr^{6+} is rapidly reduced on absorption, Cr^{3+} accounts for virtually the entire body burden of chromium. Trivalent chromium accumulates to the greatest extent in the kidneys, bone marrow, lungs, lymph nodes, liver, spleen, and testes. The kidneys and liver account for approximately 50% of the total body burden.[14]

Elimination

Urinary excretion of trivalent chromium occurs rapidly. Roughly 80% of parenterally administered Cr^{6+} is excreted as Cr^{3+} in the urine and 2â€“20% in the feces.[33] The urinary excretion half-life of Cr^{6+} ranges from 15â€“41 hours.[23] Because Cr^{6+} undergoes reduction to Cr^{3+} following uptake by red blood cells, an apparent slow compartment is created, with the elimination half-life dependent on the life span of erythroctyes.[27] Small amounts of chromium are detectable in sweat, breast milk, nails, and hair.

Pathophysiology

Trivalent Chromium

Cr^{3+} is an essential trace metal required for the metabolism of glucose and fats.[22] Dietary chromium deficiency leads to elevated insulin concentrations, hypercholesterolemia, hyperglycemia, increased body fat, and the attendant risks of these metabolic derangements.

Chromium picolinate is a popular Cr^{3+} dietary supplement that is ingested in large daily doses.[11] There is a dearth of rigorous scientific investigation concerning the efficacy or safety of chromium picolinate. However, it appears that organ deposition of Cr^{3+} does occur.[39]

There is little or no rigorous evidence that exposure to Cr^{3+} compounds increases cancer risk. Animal work and epidemiologic studies of workers exposed to Cr^{3+} compounds have failed to demonstrate a statistically significant increased incidence of cancer.[3] There is no strong evidence of any significant end-organ toxicity as a consequence of exposure to Cr^{3+}, perhaps because Cr^{3+} is so poorly absorbed.

Hexavalent Chromium

Cr^{6+} is a powerful oxidizing agent that has corrosive and irritant effects. However, the greatest toxicity from Cr^{6+} lies in its ability to produce oxidative DNA damage. DNA strand breaks, DNAâ€“DNA and DNAâ€“protein cross-links, and nucleotide modifications all occur.[15] Modulation of the apoptosis regulatory gene p53 and activation of protein kinase C also occur.[4] Although the exact mechanisms of how Cr^{6+} effects this genotoxicity are unknown, transient toxic chromium intermediates such as Cr^{4+} and Cr^{5+}, formed during the intracellular reduction of Cr^{6+} to Cr^{3+}, are probably responsible.[40]

Inconsistent basic science data suggest that both immunostimulation and immunosuppression are mediated by chronic chromium exposure. At least one study suggests that chromium-induced immunosuppression may be responsible for implant-associated infections in patients after hip or knee arthroplasty.[49] Although human data are missing, adverse developmental effects, including cleft palate, hydrocephalus, and neural tube defects, are demonstrated in animals.[16]

Clinical Manifestations

The clinical manifestations of chromium poisoning depend on the valence of the element, the source and route of exposure, and the duration of exposure. The clinical manifestations of chromium exposure are best divided into acute and chronic (low-level exposure) effects.

Acute

Manifestations of acute, massive Cr^{6+} ingestions are similar to other corrosive metal ingestions. Gastrointestinal hemorrhage, with or without bowel perforation, may occur acutely and may lead to hepatic and pancreatic necrosis.[52] Because of the strong

oxidative properties of Cr^{6+}, intravascular hemolysis with disseminated intravascular coagulation may also develop. Renal effects include acute tubular necrosis leading to renal failure.[51] Metabolic abnormalities that occur after acute, massive, exposure include lactic acidosis, hyperkalemia, and uremia. Acute lung injury may develop acutely for up to 3 days after exposure. Although Cr^{6+} is generally not well absorbed after dermal exposure, it is a corrosive that causes inflammation and ulceration. Dermal chromic acid (H_2CrO_4) burns may lead to severe systemic toxicity with as little as 10% body surface area involvement.

Chronic

The respiratory tract is the organ most affected after chromium exposure. When inhaled, Cr^{6+} is a respiratory tract irritant that causes inflammation and, with continued exposure, ulceration (including nasal septal perforation).[24] Furthermore, the sensitizing effects of Cr^{6+} may lead to chronic cough, shortness of breath, occupational asthma, bronchospasm, and anaphylactoidlike reactions. Chronic deposition of Cr^{6+} particles may also lead to pulmonary fibrosis and pneumoconiosis.[38]

Epidemiologic studies of chromate workers in the 1980s indicated a significantly increased risk of lung cancer in those individuals exposed to Cr^{6+} compounds.[26,36] Small-cell and poorly differentiated lung carcinomas are the most common types, although nearly all pathologic types of lung cancer are associated with inhalational Cr^{6+} exposure.[1] The latency between exposure and development of lung cancer ranges from 13â€“30 years, although cases after as few as 2 years have been reported.[7]

Although conclusive evidence is missing, it appears that chronic exposure to Cr^{6+} may cause mild to moderate elevations in hepatic aminotransferases and abnormal liver architecture, as

seen on histologic specimens.[52] Unlike acute exposures, low-dose chronic chromium exposure occasionally causes only transiently elevated urinary $Î^2_2$-microglobulin levels, with no obvious lasting effects.[51]

Type IV (delayed-type) hypersensitivity reactions may occur 2 weeks after sensitization. Although uncommon in the general population, Cr^{6+} sensitivity has occurred in up to 24% of automobile part handlers and in cement workers.[29]

Because Cr^{3+} is a sensitizing agent,[19] occupational exposure to Cr^{3+} may lead to contact dermatitis (dermatitis toxicosis) in 10â€“20% of chromium workers,[12] although it is unclear to what degree exposure to Cr^{3+} itself, rather than reduced intracellular Cr^{6+}, is responsible for the dermatitis. Similarly, chromium-containing gaming table felt has led to hand dermatitis, referred to as â€œblackjack disease,â€• and painless, scarring, skin ulcerations (â€œchrome holesâ€•).

Diagnostic Testing

Chromium may be detected in blood, urine, and hair of exposed individuals. Because of the great difficulty in speciation, differentiation between Cr^{3+} and Cr^{6+} is generally not performed; instead, the total chromium concentration is generally reported. Needles used for phlebotomy and plastic containers used for sample storage may all contain significant amounts of chromium. Modern, highly sensitive assay equipment such as graphite furnace atomic absorption spectrometry, neutron activation analysis, and graphite spark atomic emission spectrometry, requires diligence in sample handling to ensure that biologic samples are not contaminated.

Because of the inherent difficulties in quantifying trace elements such as chromium, and the lack of standard chromium reference materials, the reported normal serum and urine chromium

concentrations in unexposed people have varied by more than 5000-fold over the last 50 years.[46] Consequently, older reference ranges should be interpreted with caution.[18] Similarly, there is no single reference range for either serum, blood, or urine chromium concentrations in normal subjects.

Blood or Serum

Chromium is distributed evenly between the serum and erythrocytes. Serum chromium concentrations reflect recent exposure to both Cr^{3+} and Cr^{6+}. Blood chromium concentrations, however, are indicative only of recent Cr^{6+} exposure, because of the inability of Cr^{3+} to cross the red blood cell membrane. Serum concentrations in people without occupational exposure to chromium have been reported to be from 0.05 Âµg/L (1 nmol/L)[10] to more than 2.8 Âµg/L (56 nmol/L).[46] It is not certain whether concentrations above these values should be considered potentially toxic, as no clear correlation has been found between serum or blood concentrations and physiologic effects.

Urine

Although urine chromium concentrations reflect the acute absorption of chromium over the previous 1â€“2 days, wide individual variations in metabolism and total-body burden limit the value of urinary chromium monitoring. Urine should be collected over a 24-hour period because of diurnal variation in excretion. Although not firmly established, urinary chromium concentrations in persons without occupational exposure to chromium are typically less than 1 Âµg/g creatinine.[30]

Hair and Nails

Hair and nail samples are unreliable indicators of exposure to chromium because of the difficulty distinguishing chromium

contamination of the hair sample from chromium incorporated into the hair during protein synthesis. Chromium concentrations in hair may be up to 1000 times higher than those found in serum.

Ancillary Tests

After confirmed or suspected chromium exposure, complete blood count, serum electrolytes, blood urea nitrogen, creatinine, urinalysis, and liver enzymes should be performed. If signs of systemic toxicity are evident, serial determinations of coagulation function and disseminated intravascular coagulation may be useful to guide therapy.

Management

Acute chromium ingestions are infrequent, but often severe, with significant morbidity and mortality. Consequently, after adequate airway, breathing, and circulatory support are addressed, attention should be given to decontamination.

Decontamination

As a consequence of its serious but very limited toxicity, Cr^{3+} compounds should require limited decontamination measures. However, as coingestants could be present, standard gut decontamination with activated charcoal should be considered.

Hexavalent chromium is corrosive, and profuse vomiting and hematemesis usually follow acute ingestions. Nasogastric lavage may be beneficial after Cr^{6+} ingestions if the patient presents to the emergency department within 1â€“2 hours of exposure. There are no data regarding the use of activated charcoal in acute chromium ingestions. However, as activated charcoal is a relatively benign therapy and other coingestants may be adsorbed by activated charcoal, a single dose of activated charcoal should be considered. Endoscopic visualization may be difficult after

administration of activated charcoal and the relative benefits of these two modalities need to be considered. Known or suspected perforation is an absolute contraindication to activated charcoal.

Oral *N*-acetylcysteine increases the excretion of chromium in rats,[5] but there are no human data to support use of this therapy. Years of clinical experience using *N*-acetylcysteine for other indications and the very low incidence of adverse effects, however, favor the administration of oral *N*-acetylcysteine for acute chromium toxicity.

Although ascorbic acid facilitates reduction of Cr^{6+} to Cr^{3+} in vitro, there are no data to substantiate decreased absorption.[44] There is some evidence that topical ascorbic acid may reduce dermal Cr^{6+} exposure, but this has not been demonstrated in controlled trials.[9] Thus, the routine use of ascorbic acid cannot be advocated at this time.

Chelation Therapy

The currently available chelating agents do not appear efficacious at either lowering serum or blood chromium concentrations or ameliorating chromium toxicity in experimental models. Specifically, ethylenediaminetetraacetic acid (EDTA) was found to have no effect on urinary chromium excretion in human subjects,[50] and dimercaprol (British anti-Lewisite, BAL) was not beneficial in an animal model of chromium poisoning.[32]

In a single study, DMPS (dimercaptopropane sulfonate) had no effect on urinary chromium excretion in humans.[45] D-Penicillamine also failed to increase urinary excretion of chromium.[32] There are no studies of chromium chelation with 2,3-dimercaptosuccinic acid (succimer), although there are no data to suggest that succimer would be harmful.

Extracorporeal Elimination

Hemodialysis, hemofiltration, and peritoneal dialysis are ineffective at removing chromium. Studies in animals and human case reports indicate that as little as 1% of chromium is removed by hemodialysis or hemofiltration after acute dichromate (a hexavalent compound) exposure.[21,35,43] Exchange transfusions may rapidly reduce blood chromium concentrations, but there are no data suggesting that clinical outcomes are positively affected.[48]

Summary

Chromium remains an uncommon, but serious, cause of acute metal poisoning. The acute exposure to chromium by ingestion causes gastrointestinal hemorrhage, hepatic necrosis, and renal failure. Toxicity after chronic chromium exposure includes ulcerations of the skin and nasopharynx, and more significantly, lung cancer. Definitive data regarding other types of cancer resulting from chronic Cr^{6+} exposure are unavailable. Regardless of the time course of the poisoning, treatment for chromium exposure includes removal of the patient from the source of exposure, gastrointestinal decontamination if indicated, and supportive care. There is insufficient evidence to support the use of chelating agents in either acute or chronic chromium poisoning.

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Chapter 89
Cobalt

Gar Ming Chan

Cobalt (Co)

Atomic number = 27

Atomic weight = 58.9

Normal concentrations

Serum	=	0.1â€“1.2 Âµg/L
Urine	=	0.1â€“2.2 Âµg/L

A 13-month-old, 10-kg girl was brought to the emergency department (ED) for evaluation of lethargy and vomiting of 1 week's duration and decreased oral intake and urine output for 8 hours. She had a normal birth history, no significant past medical history, and was fully immunized. On presentation to the ED, her

vital signs were blood pressure, 98/53 mm Hg; pulse, 180 beats/min; respiratory rate, 60 breaths/min; temperature, 96.5Â°F (35.8Â°C); and oxygen saturation 98% on room air. Physical examination revealed dry mucous membranes, normal reactive pupils, a clear chest with intercostal retractions, decreased bowel sounds, mottled skin, an increased capillary refill time, and a depressed mental status with minimal withdrawal to pain.

The patient was endotracheally intubated, resuscitated with 0.9% NaCl, and given ceftriaxone and ampicillin intravenously. Complete blood count revealed a white cell count of 12,000/mm^3, hemoglobin of 18.6 g/dL, an anion gap of 22 mEq/L, and a lactate concentration of 4 mmol/L. Analysis of the cerebral spinal fluid, including cell count and chemistry, was normal. The ED obtained cultures of the blood, urine, and cerebral spinal fluid (CSF) for testing. An electrocardiograph (ECG) showed a narrow complex tachycardia with low-voltage QRS complexes. Her chest radiograph revealed cardiomegaly and no infiltrates. An echocardiogram revealed a dilated cardiomyopathy with a moderate-size pericardial effusion. The patient was admitted to the pediatric intensive care unit.

Over the next 24 hours, the parents were questioned regarding genetic counseling, malnutrition, and neglect. Eventually, the patient's 4-year-old brother admitted to feeding her, about 20 refrigerator magnets 1 week prior to presentation. An abdominal radiograph revealed 20 radiopaque densities scattered throughout the gastrointestinal (GI) tract, which on reevaluation were visible on the original chest radiograph. Whole-bowel irrigation (WBI) was initiated via a nasogastric tube with polyethylene glycol electrolyte solution at 150 mL/h and titrated up to 250 mL/h. WBI was tolerated well. After 6 hours of WBI, all 20 magnets [samarium cobalt (SmCo)] were retrieved from the effluent, and a repeat abdominal radiograph revealed no further magnets in the GI tract.

The child's clinical condition did not improve. While undergoing a 24-hour urine collection for cobalt, 1000 mg/m^2/d of $CaNa_2EDTA$ (edetate calcium disodium) was administered by continuous intravenous infusion. Intravenous chelation with *N*-acetylcysteine (NAC) was also administered, using the standard 20-hour acetaminophen protocol (see Antidotes in Depth: *N*-Acetylcysteine). Intravenous thiamine (25 mg/d) was also initiated.

After 2 days of therapy, the patient's lethargy improved. Her leukocytosis, anion gap, and serum lactate concentration normalized. All of her cultures were sterile, and antibiotic therapy was discontinued. Additional laboratory results revealed hypothyroidism, evidenced by an elevated thyroid-stimulating hormone (TSH) concentration of 12 mIU/mL (normal: 1.7â€“9.1 mIU/L); a decreased total T_4 of 4.7 Âµg/dL (normal: 7.8â€“16.5 Âµg/dL); increased erythropoiesis, evidenced by an increased reticulocytosis of 8.3% (normal: â‰¤7%); and an increased erythropoietin (EPO) concentration of 30 mIU/mL (normal: 1.0â€“21.0 mIU/mL).

The patient was extubated on hospital day 3. Chelation therapy with $CaNa_2EDTA$ and NAC were stopped on day 5, and initial urine cobalt level was reported as 1237 Âµg/L. Her repeat echocardiogram prior to discharge showed substantial resolution of both the cardiomegaly and the effusion. The patient was discharged on hospital day 7 after her family received thorough counseling on poison prevention. The patient's thyroid and hematologic abnormalities had resolved completely at 2-week followup.

History and Epidemiology

The name cobalt (Co) originates from â€œkobold,â€• the German word for â€œgoblin,â€• and was given to the cobalt-containing ore, cobaltite (CoAsS), because it made exposed miners ill. Their

most likely related to arsenic toxicity from the ore, rather than from the cobalt. Georg Brandt discovered cobalt in 1753, during an attempt to prove that an element other than bismuth gave glass a blue hue.

The main industrial use of cobalt is the formation of hard, high-speed, high-temperature cutting tools. With an atomic number of 27 and a molecular weight of 58.93 daltons, Co is a light metal that has a melting point of 2723.1Â°F; (1495.1Â°C) and a boiling point of 5611.7Â°F (3099.9Â°C). These attributes make elemental cobalt a very useful industrial metal. When aluminum and nickel are blended with cobalt, an alloy (alnico) with magnetic properties is formed. Other uses for cobalt include electroplating, because of its resistance to oxidation, and as an artist's pigment because of its bright blue color.

A Co^{3+} ion is at the center of cyanocobalamin (vitamin B_{12}), which is synthesized only by microorganisms and is not found in plants. Common dietary sources include fish, eggs, chicken, pork and seafood; a diet deficient in cyanocobalamin results in pernicious anemia. Hydroxocobalamin, a Co^{3+}-containing precursor to cyanocobalamin, is a therapy for cyanide poisoning (see Antidotes in Depth: Hydroxocobalamin).

Medicinally, cobalt chloride was combined with iron salts and marketed in the 1950s as â€œRoncovite,â€• for the treatment of anemia. As recently as 1976, physicians still used cobalt in the treatment of anemias, thereby reducing transfusion requirements in spite of concomitant adverse effects.[34] The other common medical use of cobalt is as a radioactive isotope, cobalt-60 (^{60}Co), in the radiotherapy of head and neck cancers, breast cancer, and some tissue sarcomas of the extremities. This form of radiotherapy has been largely replaced by linear accelerators in the Western world.

Historically, epidemics of cardiomyopathy and goiter termed â€œbeer drinker's cardiomyopathyâ€• [10] and â€œcobalt-induced goiterâ€• [58] occurred between the 1960s and the 1970s. During this period, cobalt sulfate was added to beer as a foam stabilizer. In the 1970s, these epidemics were halted when the use of cobalt for this purely aesthetic purpose was discontinued. [91]

Sources of cobalt include chemistry kits, [63] weather indicators, [63] antiquated anemia therapies, [63] cement, [70] fly ash, [70] mineral wool, [70] asbestos, [70] molds for ceramic tiles, [40] the production of Widia-steel (used in the wood industry), [125] mining, [64] porcelain paint, [109] orthopedic implants, [62] and dental hardware. [5]

The most clinically important source, however, arises through the formation of cemented tungsten carbide, a â€œhard metal.â€• In tungsten carbide factories, powdered cobalt and tungsten are combined by an intense sintering process that exposes the metals to hydrogen, heated to 1832Â°F (1000Â°C). The first published investigation of these factories reported a 10-fold increase in workspace cobalt concentrations, compared to atmospheric concentrations. [37] These respiratory exposures have resulted in pulmonary toxicity, known as â€œhard-metal disease.â€• As a result of this report, occupational studies and preventive respiratory measures have greatly reduced the acceptable cobalt exposure level in the workplace.

Chemistry

Like other metals, cobalt is available in elemental, inorganic, and organic forms. The clinical effects of each form are less-well defined than the effects of mercury or arsenic. Elemental cobalt (Co^0) toxicity is reported by both inhalational [138] and oral exposures. [57,58] Inorganic cobalt salts most commonly occur in 1 of 2 oxidation states: cobaltous (Co^{2+}) or cobaltic (Co^{3+}). Inorganic cobalt salts, such as cobaltous chloride ($CoCl_2$) and cobaltous sulfate ($CoSO_4$), were historically used for the treatment of

anemias,[11,47,53,108,147] and were associated with the â€œbeer drinker's cardiomyopathy.â€•[1,87,93]

Organic cobalt exposure results from cyanocobalamin (vitamin B_{12}) ingestion, but because of its limited oral absorption and its rapid renal elimination, it is considered to be of low toxicity.[105] Other organic forms of cobalt (eg. stearate) are toxic, following oral exposures in rodents.[13] In comparison, the inorganic chloride, sulfate, and nitrate cobalt salts appear to have more acute toxicity in animal models, when compared to the organic forms, such as cobalt stearate.[13]

Toxicokinetics

Based on animal studies, oral absorption of cobalt oxides, salts, and metals via the gastrointestinal tract is highly variable, with a reported bioavailability of 5â€“45%.[71,81] In human studies, both iron deficiency and iron overload (hemochromatosis) enhance radiolabeled $^{57}CoCl_2$ absorption in the small bowel.[99] Inhaled cobalt oxide is approximately 30% bioavailable,[81] but the volume of distribution and elimination half-life are not defined.

Most (50â€“88%) absorbed cobalt (organic and inorganic) is eliminated renally, and the remainder is eliminated in the feces.[123] Acutely, an increase in the inorganic cobalt burden will result in increased renal elimination.[68] However, this initial increased elimination rapidly diminishes to a steady state, despite a large body burden.[2,99] Thus, a significant percentage of elimination of a large cobalt exposure will be delayed.

The characteristic elimination of cobalt correlates with the patterns of occupational exposure.[138] For example, a worker with a standard workweek will have much higher urine cobalt levels on Friday morning when compared to Monday morning.[138] However, Monday afternoon urine cobalt levels may be higher than Friday morning levels because of the rapid elimination that occurs

following an initial exposure.[2,138] Based on these findings, the exposure over time must be considered when interpreting urinary cobalt concentrations.[7]

Pathophysiology

Like most other metals, cobalt is a multiorgan toxin. $CoSO_4$ inhibits several key enzyme systems and interferes with initiation of protein synthesis.[8] Polynucleotide phosphorylase, an essential enzyme in RNA synthesis, requires Mg^{2+} to function normally. The enzyme functions at 50% that of normal in the presence of $CoSO_4$.[8] It is hypothesized that Co^{2+} is capable of displacing Mg^{2+}, the normally required cofactor, from the enzyme cofactor site.[8]

$CoCl_2$ increases the rate of glycolysis and at the same time decreases oxygen consumption,[20] suggesting that cobalt may inhibit aerobic metabolism. In vitro studies demonstrate that divalent cations, Zn^{2+}, Cd^{2+}, Cu^{2+}, and Ni^{2+}, inhibit Î±-ketoglutarate dehydrogenase, a mitochondrial Krebs cycle enzyme (Chap. 13).[143] When compared to these divalent cations, Co^{2+}, is not as potent an inhibitor of this same enzyme.[143] However, when NADH (the reduced form of nicotinamide adenine dinucleotide) is added to this in vitro model, Co^{2+} is capable of inhibiting up to 95â€“100% of the reaction.[143] This model suggests that NADH abundance, such as in chronic ethanol use, may potentiate the inhibition of

Î±-ketoglutarate dehydrogenase.[144] Cobalt may also complex with the reduced form of Î±-lipoic acid, thereby interfering with the Krebs cycle.[145] Moreover, cobalt salts are capable of inhibiting dihydrolipoic acid by complexing with its sulfhydryl groups.[23,143] These reactions result in the inability to convert both pyruvate into acetylcoenzyme A (acetyl-CoA) and Î±-ketoglutarate into succinylcoenzyme A (succinyl-CoA). These two enzymes are

integral in the efficient transition from anaerobic glycolysis to the Krebs cycle and for the Krebs cycle to produce reducing equivalents (Chap. 13 and Antidotes in Depth: Thiamine Hydrochloride). These toxic effects may help explain why the combination of chronic ethanol use and cobalt exposure results in cardiomyopathy (see â€œBeer Drinker's Cardiomyopathy below).[143]

In addition to enzyme inhibition, oxidant-mediated toxicity is supported by in vivo and in vitro studies of $CoCl_2$-induced pulmonary toxicity (see Chronic Exposure, Pulmonary below).[97] Xenobiotics implicated in free radical-mediated pulmonary injury are capable of accepting an electron from a reductant and subsequently transferring the electron to oxygen, forming a superoxide free radical (Chap. 12). Cobalt is then capable of accepting another electron, which starts the cycle over again, a process known as redox cycling. This will result in an accumulation of free radicals in the lung as a result of the abundance of oxygen ready to receive electrons and result in injury (Chap. 12).

Cobalt chloride inhibits tyrosine iodinase (Chap. 49).[74] This enzyme is responsible for combining iodine (I_2) with tyrosine to form monoiodotyrosine and serves as the first step in the synthesis of thyroid hormone. Inhibition of tyrosine iodinase results in a decrease in T_3 and T_4, which may result in clinical hypothyroidism and goiter (see Clinical Effects, Endocrine below).

Multiple animal models demonstrate that $CoCl_2$ administration results in reticulocytosis, polycythemia, and erythropoesis.[43,72,90,100,101,147] These events occur in both the bone marrow and extramedullary locations.[11,45] Although the pathogenesis of these events remains largely unknown,[23] one theory is that cobalt binds to iron-binding sites such as transferrin,[65] resulting in impaired oxygen transport to renal cells, which, in turn, induces erythropoietin production. In an animal model of anemia, a greater degree of gastrointestinal iron uptake

occurs in cobalt-treated rats compared to rats with either hypoxia or nephrectomy.[45] A similar study in mice suggested that the rise in iron uptake exceeded that following exogenous erythropoietin.[3]

Cobalt chloride inhibits neuromuscular transmission by competing with Ca^{2+}, another divalent ion. Cobalt ion is 20 times more potent than magnesium with regard to its ability to compete with calcium for a site on the motor nerve terminal.[142] This may be the manner by which some of the neurological symptoms occur.

Clinical Effects and Toxicity

The single, acute, minimal toxic dose of cobalt compounds is not well defined. In fact, varying effects have occurred at variable doses in different patients. Patients with â€œbeer drinker's cardiomyopathyâ€• received an average daily dose of 6â€“8 mg of $CoSO_4$ (over weeks to months) and developed life-threatening illness,[69,93] whereas infants being treated for anemia who received much higher daily cobalt doses of an iron-cobalt preparation (40 mg of $CoCl_2$ and 75 mg of $FeSO_4$) for 3 months did not develop similar toxic effects of acidemia, cardiomyopathy, or shock.[114] The inconsistency of these findings suggests that multiple factors are responsible for the development of the clinical manifestations; in this case, the role of ethanol metabolism may be an important variable. Death also has been reported after acute cobalt exposure.[63]

Organ systems affected by acute cobalt poisoning are endocrine,[57] gastrointestinal,[34,47] hematologic,[43,72,90,147] cardiovascular,[58] metabolic,[58] and the central[47,122] and peripheral nervous systems.[122] Chronic inhalational exposures affect the pulmonary[16,21,37,76,77,111,130] and dermatologic systems.[41,117,146] Radioactive ^{60}Co used for radiation therapy is associated with radiation burns (Chap. 128). Unlike acute toxicity, chronic cobalt exposure is not associated with an increased mortality rate; a cohort study evaluating more than 1100 persons with pulmonary

exposures to cobalt salts and oxides over a 30-year period was unable to show an increased mortality rate.[95]

Clinical Manifestations

Acute Exposure

Cardiovascular

â€œBeer Drinker's Cardiomyopathy.â€•

In 1966, a Veterans Affairs (VA) Hospital in Nebraska cared for 28 males with a history of beer drinking who presented with tachycardia, dyspnea, and lactic acidosis but without any finding of congestive heart failure.[87] The mortality rate for these cases was 38% and occurred rapidly, within 72 hours of presentation, as a consequence of severe acute metabolic acidosis and cardiac failure.[87] The survivors were successfully treated with supportive care and thiamine therapy.[87] Of the survivors, most responded immediately to therapy and a lack of response was found to be secondary to complications; most commonly, symptomatic pericardial effusions or embolic events.[87] Epidemiologic evaluation revealed that these men commonly drank large quantities of beer.

Ultimately, 64 cases and 30 fatalities were reported from Nebraska.[137] Autopsies were performed in 26 of the decedents. Common postmortem cardiac findings were dilated cardiomyopathy and cellular degeneration with vacuolization and edema and a lack of inflammation and fibrosis.[87] When cobalt was later implicated in the pathogenesis of these deaths, preserved cardiac tissue of 8 decedents revealed cobalt concentrations 10 times greater than that of controls.[137]

Within a year of the Nebraska cases, similar reports began to emerge from Quebec.[93] Forty-eight beer drinkers (only 2 of whom

were women) developed unexplained cardiomyopathy with a mortality rate of 46%.[93] The only common association among all of these patients was the consumption of brand â€œXXXâ€• beer.[93] The producers of this beer had factories in Quebec City and Montreal. The only difference between the two breweries was that the one in Quebec added 10 times the amount of $CoSO_4$ to the beer as a foam stabilizer.[91] Clinical findings in these cases included tachycardia, tachypnea, polycythemia, and low-voltage ECGs.[92] Reports began to appear 1 month after the Quebec City produced beer with the excessive cobalt was released on the market and no new patients were reported in Quebec after its beer with the excessive cobalt concentration was removed from the market.[91]

In 1972, 20 additional cases occurred in Minneapolis with similar findings of tachycardia, dyspnea, pericardial effusion, polycythemia, and lactic acidosis, and a mortality rate of 18% acutely, and 43% over a 3-year period.[1] Thus, several outbreaks have been recorded in beer drinkers with cardiomyopathy, metabolic acidosis, and a high mortality, all of which have been associated with the addition of $CoSO_4$ to the beer.

Because the clinical findings resemble the cardiomyopathy associated with chronic alcoholism[39] and infantile malnutrition,[106] a debate persists as to whether cobalt is the sole cause of this syndrome. The chronic alcoholism and infantile malnutrition cardiomyopathies are caused by poor protein intake and vitamin deficiency and both have histologic findings similar to those of cobalt cardiomyopathy. For example, myocardial biopsy of dogs with cobalt-induced cardiac failure revealed diffuse cytosolic vacuolization, loss of cross-striations, and interstitial edema,[120] all of which are similar to findings of malnutrition.[39,106] However, some other findings may be specific to cobalt-associated cardiomyopathy. For example, a small retrospective analysis revealed myocyte atrophy and myofibril loss to be present in

people with cobalt-associated cardiomyopathy significantly more often than in those with idiopathic dilated cardiomyopathy.[14]

Some animal models of cobalt cardiomyopathy were only able to reproduce pathologic and ECG findings if cobalt was combined with ethanol,[139] while others required protein deficiency.[115] Contrary to these studies, several rodent and canine models of cobalt poisoning and nutritional supplementation have demonstrated cardiac lesions,[51,119,120] cardiac failure,[54,119,120] and ECG abnormalities.[52,119]

Despite the implication that cobalt-induced cardiomyopathy requires malnutrition or alcoholism, a case of cardiac toxicity following acute cobalt poisoning has been reported.[57,58] However, it is difficult to identify other cases reported outside of the aforementioned small epidemics in beer drinkers. In a controlled study of occupationally exposed subjects evaluated with echocardiograms, significantly more cobalt-exposed workers had diastolic dysfunction when compared to controls.[79] However, none of these subjects under study developed congestive heart failure.[79] There are rare reports of cardiomyopathy in chronically exposed workers,[9,19,67] which suggests that the cardiomyopathy reported in the â€œbeer drinkersâ€• cohort is multifactorial and not solely caused by cobalt.

Another source of doubt regarding of the role of cobalt in the development of cardiomyopathy is the relatively low dose of cobalt needed to induce heart failure in these patients.[69] In patients receiving 20â€“75 mg/d of $CoCl_2$ for various red cell dysplasias, there were no reports of heart failure,[69] whereas the â€œbeer drinker's cardiomyopathyâ€• group reportedly consumed only 6â€“8 mg of $CoSO_4$ from drinking 24 pints of cobalt-containing beer.[69,91] All patients who developed cardiomyopathies were malnourished, which supports the theory that a multifactorial nutritional deficiency in the presence of excessive cobalt may be necessary for the development of cardiomyopathy.[69]

Endocrine

Both acute and chronic cobalt exposures are associated with thyroid hyperplasia and goiter. A series of patients with severe sickle cell anemia treated with cobalt therapy also developed goiter with varying degrees of thyroid dysfunction,[53,73] including clinical hypothyroidism.[74] In one patient, the goiter was so severe that airway obstruction developed.[73]

More recent occupational data suggest that inhalational exposure to cobalt metals, salts, and oxides may result in abnormalities in thyroid function studies.[138] When 82 workers in a cobalt refinery were compared to sex- and age-matched controls, exposed workers had significantly lower T_3 levels.[138]

Within the previously mentioned beer drinker's cardiomyopathy cohort, 11 of 14 decedents had abnormal thyroid histology.[116] Among them, the most common findings were follicular cell abnormalities and colloid depletion, which were not present on thyroid analysis from 11 randomly selected autopsies that served as controls.[116]

Hematologic

Anemias of the newborn,[17,66,108] erythrocyte hypoplasia,[124] red cell aplasia,[141] renal failure,[47] and chronic infection[113] have all been successfully treated with cobalt salts. Patients undergoing $CoCl_2$ therapy for these diseases had increased hemoglobin,[47,108] hematocrit,[47,108] and red cells,[47] but the benefits did not persist after cessation of therapy.[47,108]

In a published series, Peruvian cobalt miners working in an open pit at 4300 m (2.7 miles) elevation developed clinical effects, including headache, dizziness, weakness, mental fatigue, dyspnea, insomnia, tinnitus, anorexia, cyanosis, polycythemia, and conjunctival hyperemia, consistent with acute mountain sickness.[64] When the study group was compared to age-, height-,

and weight-matched high-altitude controls, the study group was noted to have higher chronic mountain sickness scores.[64] The only difference detected was elevated serum cobalt levels in the study group.[64]

In addition to effects on red cells, recent work demonstrates transient hemolysis, methemoglobinemia, and methemoglobinuria from subcutaneous $CoCl_2$ exposure in mice.[59] These findings may explain reports of dark urine following cobalt exposure in other animal models.[49,132] Human cases have not been reported.

Other

Gastrointestinal distress following the ingestion of â€œtherapeuticâ€• doses of cobalt salts,[122] as well as of elemental cobalt, has been reported.[63] Decreased proprioception, impaired cranial nerve VIII function, and nonspecific peripheral nerve findings are reported with acute oral $CoCl_2$ exposures.[122]

Chronic Exposure

Pulmonary

Two pulmonary diseases are associated with cobalt exposure: asthma and â€œhard-metal disease.â€• Occupational asthma is reported in hard-metal workers with a prevalence of 2â€“5%[16,76,77] at exposure levels as low as 50 Âµg/m^3.[77] As is the case with most causes of occupational asthma, cobalt-hypersensitivity-induced asthma is most likely immune-mediated rather than toxicologic.[18,76,130] Most hard-metal workers are exposed to other metals, such as tungsten (W) and nickel (Ni), in addition to Co, and these other metals may account for some cases of occupational asthma that are attributed to cobalt.[128,129] However, in a small but well-performed study of patients with cobalt-associated asthma, intradermal $CoCl_2$ resulted in a positive

wheal response in all subjects, and 50% of patients had a positive radioallergosorbent test (RAST) score, which correlated to the wheal size.[127]

Cobalt-associated pulmonary toxicity was first noted in tungsten-carbide workers,[37,55] and was subsequently referred to as â€œhard-metal disease.â€• Exposures result from the process by which tungsten-carbide is sintered with cobalt. Signs and symptoms of hard-metal disease include upper respiratory tract irritation, exertional dyspnea, severe dry cough, wheezing, and interstitial lung disease ranging from alveolitis to progressive fibrosis. The prevalence of hard-metal disease is largely unknown. In one study, 11 of 290 (3.8%) exposed workers were diagnosed with interstitial infiltrates on chest radiographs, but only 2 (0.7%) had a decreased predicted total lung capacity.[133]

Certain individuals who are exposed to large doses of hard-metal for prolonged periods never develop disease, which suggests that a susceptible population exists. A glutamate substitution for lysine in position 69 of the Î² unit HLA-DP has a strong association with hard-metal disease, similar to the situation with chronic beryllium disease.[107] Clinically, hard-metal disease is difficult to distinguish from berylliosis, although an occupational history should be helpful.

Common findings of hard-metal disease on histopathology are multinucleated giant cells and interstitial pneumonitis with bronchiolitis.[6] Elevated levels of cobalt in lung tissue can be detected,[112,131] even as long as 4 years after exposure.[112] Bronchoalveolar lavage commonly reveals multinucleated giant cells, type II alveolar cells, and alveolar macrophages in patients with interstitial lung disease.[21] The finding of multinucleated giant cells from bronchoalveolar lavage washing is characteristic of hard-metal disease.[18,24,25,88,140]

A cross-sectional study of more than 1000 tungsten-

carbideâ€“exposed workers found an increased odds ratio [OR] of 2:1 for having a work-related wheeze when exposed to greater than 50 Âµg/m^3 of Co.[134] In the same study, workers with exposures recorded at greater than 100 Âµg/m^3 had higher OR (5.0) of having a chest radiograph profusion score of â‰¥1/0.[134] This profusion score, established by The International Labor Organization (ILO) and most recently updated in 2000, is a grading system for pneumoconioses. When used to grade radiographs of asbestosis, this score correlates strongly with mortality risk,[86] reduced diffusing capacity, and decreased ventilatory capacity.[56,96] A score of 0/1 is suggestive but not diagnostic (â€œnegativeâ€•), and a score of 1/0 is presumptively diagnostic but not unequivocal (â€œpositiveâ€•).[26] Additional studies have similarly concluded that pulmonary disease occurs when individuals are exposed to doses of cobalt that approach 100 Âµg/m^3.[75] Thus, the current threshold limit value (TLV) is <50 Âµg/m^3.

Until 1984, all reported cases of hard-metal disease were associated with the combination of cobalt and other metals, such as nickel, cadmium, and tungsten.[6,55,77,134] Diamond polishers started using high-speed grinding disks coated with abrasive microdiamonds embedded in a matrix of cobalt powder.[78] Several case reports illustrate that cobalt-exposed diamond polishers develop clinical[48] and pathologic findings similar to hard-metal disease, strengthening the link to cobalt.[18,24,98] Some authors still contend that the presence of other metals[6,55,77,134] and diamond dust[24,48,98] are confounding factors.[138] As in cases of hard-metal disease, most reported cases show resolution of symptoms on removal from the exposure,[24] although this is not always sufficient.[98]

There are very few reports of isolated cobalt exposures. In an age- and sex-matched study of 82 workers with respiratory exposures to cobalt oxides, cobalt salts, cobalt metal, and no other metal, researchers were unable to detect a difference between exposed

(mean: 8 years; time-weighted average [TWA]: 125 Âµg/m^3, 25% >500Âµg/m^3) and unexposed workers with any objectively measured pulmonary tests.[138] Neither group had any abnormality in chest radiography that would suggest pulmonary fibrosis.[138] The only significant pulmonary differences detected were a higher reported rate of dyspnea, both on exertion and at rest, and the presence of wheezing in the exposed group.[138] These authors concluded that cobalt contributes to the development of pulmonary disease but is not independently responsible for the development of pulmonary fibrosis.[138]

Despite the progressive and debilitating nature of hard-metal disease, most signs and symptoms improve with cessation of exposure.[85,89,148] Moreover, the length and dose of exposure do not appear to correlate with the presence or severity of illness, suggesting that individual susceptibility is the most important risk factor for illness.[85,118]

Renal

A single report associates reversible renal tubular necrosis with the chronic administration of $CoCl_2$ as treatment for anemia.[122] Some animal models of cobalt cardiomyopathy demonstrate cellular changes in renal tissue.[50] However, when 26 cobalt-exposed hard-metal workers were evaluated for urinary albumin, retinol-binding protein (RBP), Î²$_2$-microglobulin, and tubular brush border antigens, no detectable difference could be found between the study group and controls.[44] Based on these few reports, it appears that acute and chronic exposure to cobalt has little effect on the kidneys.

Dermatologic

In a study of 1782 construction workers, 23.6% developed dermatitis and 11.2% developed oil acne while using cobalt-containing cement, fly ash, or asbestos.[70] As in hard-metal

disease, it is difficult to isolate cobalt as the sole contributor to the development of dermatitis. Nickel, the classic toxicant causing dermatitis, is commonly found in some of these preparations and may be implicated in the development of cutaneous sensitivity.[41,117]

Reproductive

A pregnant woman with hard-metal disease was able to bring her fetus to term and deliver without complication.[110] In pregnant rats, $CoCl_2$ exposure results neither in teratogenicity nor fetotoxicity.[103] Only doses that are toxic to the mother result in fetal toxicity.[33]

In mice, chronic exposure to cobalt results in impaired spermatogenesis and decreased fertility, without affecting follicular-stimulating hormone (FSH) or leuteinizing hormone (LH), whereas acute exposures did not demonstrate similar reproductive effects.[104] Additional murine studies discuss the possible interactions between cobalt with iron and zinc, which are both essential elements for spermatogenesis.[4] Despite these findings, there are no reported human cases that associate cobalt exposure with teratogenicity or impaired fertility.

Carcinogenesis

Based solely on animal experiments leading to the development of soft-tissue sarcomas following the injection of $CoCl_2$ into soft tissue, the International Agency for Research on Cancer (IARC) considers cobalt and cobalt-containing compounds possibly carcinogenic to humans.[12,22,35,135] There are case reports and cohort studies that suggest that pulmonary exposure to Co^{2+} increases the risk for lung cancer. However, these studies were unable to control for other known carcinogens such as arsenic.[22] The largest cohort study to date followed more than 1100 workers for more than 38 years and found no increase in the prevalence of

lung cancer.[94]

Diagnostic Testing

Body fluid cobalt concentrations are not readily available and therefore cannot be used to direct emergent clinical care. Some adjunctive testing that might support a clinical diagnosis of cobalt toxicity includes complete blood count (CBC), reticulocyte count, EPO concentration, and TSH concentration. The results of these tests might reflect the level of exposure or potential toxicity discussed above.

Cardiac Studies

Electrocardiogram, echocardiogram, and radionuclide angiocardiography with ^{99}Tc are useful screening tests for detecting abnormalities associated with cobalt cardiomyopathy and/or pulmonary hypertension caused by hard-metal disease.[19] It is important to remember that these cardiac tests are neither specific for, nor diagnostic of, cobalt-induced cardiomyopathy. Biopsy of myocardial

tissue may show multinucleated giant cells, but testing of this nature may be impractical.

Pulmonary Testing

Patients with hard-metal lung disease may demonstrate bilateral upper lobe interstitial lung disease on chest radiograph. However, patients may have signs and symptoms of disease without specific radiographic findings.[110] Pulmonary function testing in occupationally exposed workers may show decreased vital capacity[110] and a decrease in transfer factor for carbon monoxide (TLCO), both of which might be useful in identifying patients at risk for developing pulmonary fibrosis.[136] Some authors suggest

an inversion of the CD4/CD8 ratio in bronchoalveolar lavage washings as a useful tool for diagnosis and evaluation of progression of illness and that normalization is a marker for improvement.[111] Despite these available tests, a definitive diagnosis of hard-metal disease requires a tissue sample with findings of multinucleated giant cells in the setting of interstitial pulmonary fibrosis.

Cobalt Testing

Cobalt is primarily eliminated in the urine, and to a lesser extent in the feces, making urine cobalt evaluation most appropriate.[81] The difficulty lies in the interpretation of the result. Cobalt is detectable in the urine after inhalational exposure and reflects elimination kinetics that are rapid during an initial exposure, but which slow after prolonged exposure.[81,121] Because of this variable elimination pattern, it is difficult to interpret both urine and blood concentrations unless the dose and length of exposure are precisely known. Furthermore, the defined patterns may be applicable only to shift workers using soluble forms of cobalt.[81]

Further complicating the interpretation of urinary cobalt levels is the abundance of organic cobalt in the form of vitamin B_{12}. A detailed vitamin supplementation history is required prior to the interpretation of a urine or blood cobalt level, as a diet regimen high in vitamin B_{12} might increase urine cobalt concentrations. For this reason, speciation of cobalt has been investigated. The ratio of inorganic to organic cobalt is higher in occupationally exposed workers (2.3) when compared to controls (1.01), independent of the wide variations of urinary cobalt concentrations.[46] This is a promising area of study for the evaluation of a cobalt-exposed worker.

Toxic concentrations of cobalt in serum and urine are poorly defined. Published literature on â€œnormal concentrationsâ€• is fraught with variability that may reflect differences in the

population under study and the techniques used for measurement. Normal serum concentrations of cobalt are frequently reported as 0.1â€“1.2 Âµg/L.[2,10,57,58,61,126] In comparison, a single, acutely poisoned patient had a reported serum concentration of 41 Âµg/L.[57] Normal reference urine cobalt concentrations are between 0.1 and 2.2 Âµg/L.[2,10,57,58,61,102,126] In contrast, patient with an acute elemental cobalt ingestion had a concentration of 1700 Âµg/L on a spot urinalysis several days after the exposure.[58]

Patients with chronic exposures should be evaluated differently as discussed above (see Toxicokinetics). Exposed workers, without clinical disease, have reported spot urine concentrations that range from 10 Âµg/L to several hundred Âµg/L.[60]

Treatment

Acute Management

Patients with acute cobalt poisoning require aggressive therapy. It is reasonable to conclude that the same decontamination principles used for other metals apply to cobalt. There have been no studies to date examining the benefit of gastric emptying, activated charcoal, or whole-bowel irrigation (WBI). An attempt at WBI for radiopaque solid forms of cobalt should be made prior to endoscopic or surgical removal. Regardless of the decontamination procedure used, chelation therapy should not be initiated until the gastrointestinal cobalt source has been removed. If there is a large stomach burden in a solid form, endoscopic or surgical removal may be beneficial,[58] keeping in mind that the administration of activated charcoal, prior to surgical removal, can obscure visualization of the surgical field (Chap. 8). After decontamination, the next crucial steps are reduction of tissue burden and prevention of end-organ toxicity.

The data on chelation therapy are, unfortunately, limited to animal

models[27,28,29,30,31,32,33,82,83,84] and a single human case report.[58] The basis of chelation therapy originates from the mid-20th century when oral protein intake was found to result in a reduction of cobalt toxicity in calves[36] and rats.[51] Certain sulfur-containing proteins serve as good chelators for some metals.

In a series of animal models of acute cobalt toxicity, several agentsâ€”*N*-acetylcysteine (NAC), succimer, ethylenediaminetetraacetic acid (EDTA), glutathione, and diethylenetriaminepentaacetic acid (DTPA)â€”were evaluated for their ability to enhance urinary and fecal elimination of cobalt.[84] Succimer and EDTA enhanced fecal elimination;[84] glutathione and DTPA enhanced urinary elimination; and NAC enhanced elimination by both elimination routes.[84]

In two separate animal studies, NAC reduced tissue burden and injury caused by cobalt in the liver and spleen.[32,84] Glutathione, another sulfur-containing protein, also reduced tissue concentrations of cobalt, but only in the spleen.[84]

The sulfur-containing amino acids NAC,[28,32] L-cysteine,[27,28] L-methionine,[28] and L-histidine[31] were studied for their ability to reduce mortality in rats that were given an LD_{50} (median lethal dose for 50% of test subjects) of $CoCl_2$ orally and intraperitoneally. NAC, L-cysteine,[28] and L-histidine[31] therapy were more effective than L-methionine in protecting against mortality. In a similar fashion, Na_2EDTA was effective in reducing mortality.[30] In all of these therapies, the successful reduction in mortality from these therapies is predicated on early administration.[27,28,30,31,32]

In a murine model, L-cysteine, NAC, glutathione, L-histidine, sodium salicylate, D,L-penicillamine, succimer, *N*-acetylpenicillamine (NAPA), diethyldithiocarbamate (DDC), BAL, 4,5-dihydroxy-1,3-benzene disulfonic acid, DTPA, $CaNa_2EDTA$, and deferoxamine mesylate were each evaluated for exposures to an LD_{50} and an LD_{99} of $CoCl_2$.[83] Agents that were ineffective at

improving survival following an LD_{50} were sodium salicylate, NAPA, BAL, 4,5-dihydroxy-1,3-benzene disulfonic acid, and deferoxamine mesylate.[83] Chelators that were seemingly effective at LD_{50}, but not at LD_{99}, were L-histidine and D,L-penicillamine.[82] NAC, L-cysteine, and succimer were able to improve survival by 40â€“50%.[83] The most effective chelators at LD_{99} were EDTA and DTPA.[82,83] An expanded analysis of this data revealed that EDTA and DTPA had a better therapeutic index when compared to succimer.[83] In this study, BAL was ineffective,[83] as is suggested in an in vitro study where BAL was unable to chelate Co^{2+} that was already bound to Î±-ketoglutarate.[143]

Human chelation data are available from a single pediatric case report of the ingestion of multiple elemental cobalt-containing magnets, yielding a serum cobalt level of 4.1 Âµg/dL.[58] $CaNa_2EDTA$ 50 mg/kg/d IV for 5 days enhanced renal elimination of cobalt, and the metabolic acidosis and the cardiac dysfunction also resolved simultaneously.[58]

In conclusion, based on a single case report, several animal studies, and safety profiles, $CaNa_2EDTA$ and NAC can be considered as antidotal therapy. Indications for treatment include patients who demonstrate end-organ manifestations of toxicity, which includes acidemia, cardiac failure, pericardial effusion, clinically significant goiter, and hyperviscosity syndrome. Based on years of experience with lead, $CaNa_2EDTA$ should be administered in doses of 1000 mg/m^2/d by continuous infusion for 5 days. If the diagnosis is confirmed and signs of cardiac failure and metabolic acidosis persist after 5 days, an alternate chelator (succimer) can be started. Similarly, NAC dosing should be based on the acetaminophen experience. The 20-hour intravenous NAC protocol should be initiated, and continued as in the case of fulminant hepatic failure (see Antidotes in Depth: *N*-Acetylcysteine), for as long as the patient can tolerate therapy, or continued if cardiac failure or acidemia persist. If there are contraindications to

intravenous NAC, oral NAC can be administered using one of the acetaminophen treatment regimens. Thiamine hydrochloride should be administered to all patients presenting with or without overt cardiomyopathy, regardless of whether or not the patient is an alcoholic or malnourished. The dose of thiamine is not well defined but should be based on its safety and clinical experience with its use in the treatment of Wernicke encephalopathy. The daily administration of 100 mg of parenteral thiamine can be increased to 100 mg every hour for life-threatening manifestations (cardiac failure and metabolic acidosis) (see Antidotes in Depth: Thiamine Hydrochloride).

Occupational and Chronic Exposure

As is the case for occupational poisonings, prevention is of paramount importance. The use of skin protection and improvement of personal hygiene has reduced exposure and the amount of urinary cobalt in occupationally exposed workers.[80] Barrier and emollient creams cannot prevent the dermatitis associated with cobalt metal exposures.[42]

Large, statistically significant reductions in urinary cobalt were demonstrated after the implementation of aspirator systems over machines in the production of Widia steel.[15] These aspirators reduced ambient cobalt levels by as much as a factor of 6.[38]

Summary

Acute cobalt exposure results in multiorgan system toxicity, including the cardiac, endocrine, hematopoietic, gastrointestinal, and neurologic systems. In contrast, chronic toxicity, dependent primarily on the route of exposure, mainly involves the pulmonary and dermal areas. The evaluation of the patient is determined by the cobalt source and type (elemental, inorganic, or organic), route of poisoning, and time and duration of exposure. Cobalt

measurements in blood and urine are possible, but toxic concentrations are poorly defined. Treatment of a chronic-exposure patient is mainly symptomatic and is often dependent on improved industrial hygiene. Acute poisoning with end-organ manifestations may require aggressive GI decontamination and chelation therapy using $CaNa_2EDTA$ and NAC, and sometimes succimer.

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Chapter 90
Copper

Lewis S. Nelson

Copper (Cu)
Atomic number
=
29
Atomic weight
=
63.5
Normal concentrations
Whole Blood
=
70â€“140 Âµg/dL (11â€“22 Âµmol/L) for males, slightly for females
Total Serum
=
120â€“145 Âµg/dL
Free Serum
=
4â€“7 Âµg/dL

Ceruloplasmin
=
25â€“50 Âµg/dL (higher in women than men)
Urine
=
30â€“50 Âµg/L

A 16-year-old boy presented to the hospital 3 days after reportedly ingesting 1 tablespoon of K77 Root Killer crystals in an attempt to gain attention from his aunt. The patient denied suicidality and stated that he did not know that the granules, used to halt the growth of tree roots into the home septic system, were toxic. Immediately after ingesting the product, the boy was given milk by his aunt. According to the patient, this prompted 4 episodes of blue-colored emesis containing the ingested substance. Although he had abdominal pain for the next 72 hours, the patient did not seek medical care because he assumed that these symptoms would be transient. There was no suggestion that this was, indeed, a serious suicide attempt.

Ultimately, the patient presented to the hospital because he developed dark-brown discoloration of his urine, yellowing of his eyes, and worsening abdominal pain. He denied throat discomfort, hematemesis, or melena. His presenting vital signs were blood pressure, 102/52 mm Hg; pulse, 86 beats/min; and respirations, 18 breaths/min. Additionally, he was afebrile. His physical examination was significant for the presence of scleral and sublingual icterus, although dermal jaundice was not appreciated. His oropharynx was normal and his chest was clear. On abdominal examination there was moderate tenderness over the left upper quadrant and left costovertebral angle. There was no rebound or involuntary guarding. Stool obtained by rectal examination was negative for occult blood. The patient's neurologic examination was normal.

A chest radiograph was normal. His initial laboratory assessment was remarkable for a hematocrit of 20%, normal chemistries

(anion gap, 5) and renal function (BUN, 15 mg/dL; creatinine, 0.8 mg/dL). Hepatic studies revealed an aspartate aminotransferase (AST) of 54 IU/L, alkaline phosphatase of 77 IU/L, and a total bilirubin of 5.2 mg/dL with a direct bilirubin of 0.2 mg/dL.

The patient was started on oral D-penicillamine, 500 mg every 6 hours, all these findings were consistent with copper sulfate poisoning, and was hydrated aggressively with intravenous 0.9% sodium chloride at 500 mL/h. His clinical status improved over the next 72 hours, and no blood transfusion was required; his hematocrit fell to 15%.

Copper is among the more frequently reported metals to which patients are exposed. It routinely ranks third, behind lead and arsenic, in nonmedicinal metal exposures (medicinals include as iron or lithium), reported to US Poison Control Centers (Chap. 130). Still, acute symptomatic poisoning remains relatively rare in this country. In India, copper sulfate ingestion is a leading cause of suicide.[102] In that country, copper sulfate poisoning is reportedly responsible for nearly a third of all poisonings requiring hemodialysis and is the most common nephrotoxic indication for dialysis.[6 , 28 , 30] The dramatic clinical presentations and potential for poor outcome without appropriate treatment highlight the toxicologic significance of copper.

Copper, in its various forms, is still used extensively in our society. As the metal, it is used in both wiring and plumbing. Its use in coinage, at least in the United States, fell dramatically when it was replaced by zinc in the penny. Copper salts are widely used in fungicides, algicides, and plant growth regulators.[19] They are also important as catalysts, particularly in the petroleum industry. Among the most widespread uses of copper was in chromated-copper arsenate (CCA) in pressure-treated wood products. CCA, added to the wood to prevent rot, gained notoriety because of concerns about the leaching of arsenic into the environment, particularly around children's playgrounds (Table 90-1).[68]

History and Epidemiology

Copper is available naturally, either as native copper (elemental copper) or as one of its sulfide or oxide ores. Important ores include malachite ($CuCO_3$ Â·$(OH)_2$), chalcocite (Cu_2 S), cuprite (Cu_2 O), and chalcopyrite ($CuFeS_2$ or Cu_2 SÂ·Fe_2 S_3). Chalcopyrite, a yellow sulfide ore, is the source of 80% of the world's copper production. The smelting, or separation, of copper ores began about 7000 years ago; copper gradually assumed its current level of importance at the start of the Bronze Age, around 3000 B.C. Smelting begins with roasting to dry the ore concentrate, which, in more modern times, is further purified by electrolysis to a 99.5% level of purity. The sulfide ores have a naturally high arsenic content, which is released during the extraction process, posing a risk for those who perform copper smelting.

Chalcopyrite
$CuFeS_2$
Copper iron sulfide
Copper ore; source of 80% of world's copper
Chromated cupric arsenate
35% CuO
20% CrO_3
45% As_2 O_5
CCA
Wood preservative
Copper octanoate
$Cu[CH_3$ $(CH_2$ $)_6$ $COO]_2$
Copper soap
Fungicide in home garden products, paint, rot-proof rope and roofing
Copper triethanolamine complex

$Cu((HOCH_2CH_2)_3N)_2$
Chelated copper
Algicide
Cupric acetoarsenite
$Cu(C_2H_3O_2)_2 .3Cu(AsO_2)_2$
Paris or Vienna green
Insecticide, wood preservative, pigment[a]
Cupric arsenite
$CuHAsO_3$
Swedish or Scheele's green
Wood preservative, insecticide[a]
Cupric hydroxide
$Cu(OH)_2$

Fungicide
Cupric chloride
$CuCl_2$

Catalyst in petrochemical industry
Cupric chloride, basic
$CuCl_2 + CuO$
Basic copper chloride; copper oxychloride
Fungicide
Cupric oxide
CuO
Black copper oxide; tenorite
Glass pigment, flux, polishing agent
Cupric sulfate
$CuSO_4$
Roman vitriol, blue vitriol, bluestone, hydrocyanite
Fungicide, plant growth regulator, white wash, homegrown crystals
Cupric sulfate, basic
$CuSO_4 + CuO$
Bordeaux solution

		Fungicide	
Cuprous cyanide			
CuCN			
		Cupricin	
Electroplating solutions			
Cuprous oxide			
Cu_2O			
		Red copper oxide, cuprite	
Antifouling paint			

[a] No longer used in the United States.

Chemical Name	Chemical Structure	Common Name	Notes

TABLE 90-1. Important Copper Products

Although, as noted, acute copper poisoning is uncommon in the United States, the historical role of copper as a therapeutic agent remains noteworthy. Copper sulfate was used in burn wound debridement until cases of systemic copper poisoning were reported.[53] Interestingly, in one report, each wound debridement procedure was associated with a fall of 8â€“10% in the child's hematocrit. In the 1960s, copper sulfate (250-mg dose, containing 100 mg copper ion) ironically was a recommended emetic agent, typically for use in children following potentially toxic exposures.[60] It was recognized for its rapid onset and effectiveness, and it compared favorably with syrup of ipecac. However, copper-induced emesis was rapidly identified to be a highly dangerous practice, and use was generally discontinued,[53,70,106] although fatal cases still occur.[70] Copper salts are administered in religious rituals as a green-colored â€œspiritual water,â€• containing 100â€“150 g/L of copper sulfate as an emetic to â€œexpel one's sins.â€•[7,105]

There is a growing body of knowledge linking copper to the

promotion of both physiologic and malignant angiogenesis.[50] In this latter case, copper may enable tumor expansion, invasion, and metastasis. Additionally, copper binding to amyloid fibers in the brain of patients with Alzheimer disease may lead to local oxidative damage and cause the characteristic neurodegeneration.[24, 35] Copper is also similarly implicated in the pathogenesis of both Parkinson disease and autism.[27, 120]

Acute or chronic copper poisoning occurs when the metal is leached from copper pipes or copper containers. This occurs frequently when carbon dioxide gas, used for postmix soft drink carbonation, backflows into the tubing transporting water to the soda dispensers. This creates an acidic solution of carbonic acid that leaches copper from the equipment pipes.[116] Similarly, storage of acidic potable substances, such as orange or lemon juice, in copper vessels may cause copper poisoning. A particularly dangerous situation occurs when acidic water is inadvertently used for hemodialysis.[36, 73] In this circumstance, the leached copper avoids the normal gastrointestinal barrier and is delivered parenterally to the patient's circulation. In one reported series, the copper concentration in the dialysis water was 650 Âµg/L, causing several poisonings and the death of a patient with a whole-blood copper concentration of 2095 Âµg/L.[36] Similarly, stagnant water or hot water,[94] even if not highly acidic,[98] can accumulate copper ions from pipes and cause poisoning.[9, 37]

Although most natural water contains a small quantity of copper (4â€“10 Âµg/L), it is tightly bound to organic matter and therefore not orally bioavailable. Copper pipes typically add about 1 mg of copper to the daily intake of an adult. The Environmental Protection Agency guidelines permit up to 1.3 mg/L of copper in drinking water, although in some areas concentrations intermittently may be as high as 60 mg/L. Copper in water may be tasted at concentrations of 1â€“5 mg/L, and a blue-green discoloration is imparted when the levels are greater than 5

mg/L.[34] Acute gastrointestinal symptoms occurs when water contains more than 25 mg/L,[55] although levels as low as 3 mg/L are often considered toxic. In one blinded, randomized study comparing copper-adulterated water to pure water, women appeared more sensitive than men to copper, but both groups were symptomatic when the copper concentration was 6 mg/L.[8]

Metallic copper is ideal for electrical wiring because it is highly malleable and can be drawn into fine wire. Its electrical conductivity is only exceeded by silver. Similarly, its excellent heat conductivity accounts for its widespread use in cookware. Although the metal is reactive with air, it forms a resistant layer of insoluble copper carbonate on its surface. It is this water- and air-resistant compound that accounts for the green coloration of ornamental roofing and statues. Because copper is a soft metal, it must be strengthened prior to use in structural applications or as a coinage metal. This is most commonly done by the creation of copper alloys. Brass is an alloy of copper compounded with as much as 35% zinc. Similarly, bronze contains copper combined with up to 14% zinc. Gun metal is an alloy that contains 88% copper, 10% tin, and 2% zinc. Sterling silver and white gold also contain copper.

Chemical Principles

Metallic copper (Cu^0) has an oxidation state of zero and, although not in itself poisonous, may react in acidic environments to release copper ions. The metallic copper contraceptive intrauterine device (IUD) derives its efficacy from the local release of copper ions.[14] Metallic copper bracelets, worn by patients with rheumatoid arthritis and other ailments, purportedly derive their far-reaching antiinflammatory effect through dermal copper ion absorption and distribution to affected tissues.[114] Local copper ion release is responsible for the occasional case of dermatitis that occurs following skin exposure to copper metal.[54] Ingestion of large

amounts of metallic copper, for example as coins, may rarely produce acute copper poisoning.[119] Poisoning in this situation is a result of the release of large amounts of copper ion from copper alloy by the acidic gastric content. Also, finely divided metallic copper dust or bronze powder used in industry and for gilding, when inhaled, although not systemically bioavailable, may produce life-threatening bronchopulmonary irritation, presumably as a consequence of the local release of ions.[47]

The majority of patients suffering from acute copper poisoning are exposed to ionic copper. In copper sulfate, also known as cupric sulfate, the copper atom is in the +2 oxidation state. Copper sulfate is used as a fungicide and algicide, and to eradicate tree roots that invade septic, sewage, and drinking-water systems.[89] Copper sulfate is the most readily available form and is the form involved in the majority of nonindustrial copper salt exposures. Copper sulfate was a favorite ingredient in many home chemistry sets because of its brilliant blue color when dissolved in water. Although serious poisoning, particularly in children,[115] led regulatory agencies in the United States to restrict its use, it still accounts for the most consequential chemistry set-related toxic exposures reported in other countries.[79] Similarly, homegrown copper sulfate crystals from kits are occasionally responsible for fatal poisonings.[46]

Cuprous salts, containing copper in the +1 oxidation state, are unstable in water and readily oxidize to the cupric form. Regardless of oxidation state, there are numerous copper salts used in industry and agriculture (Table 90-1), many of which are not poisonous. Because those salts that are water soluble are more likely to be toxic, it is important to determine the nature of the copper product implicated in an exposure. Analogously, when examining the medical literature, it is critical to discern which form of copper is involved in the scientific experiment or case report before applying the results to clinical practice.

Pharmacology and Physiology

Copper is 1 of 8 essential metals that our body stores in milligram amounts (100â€“150 mg). Daily requirements of copper are approximately 50 Âµg/kg in infants and 30 Âµg/kg in adults. The average daily intake of copper in the United States is about 1 mg.[111]

The daily requirement is satisfied by nuts, fish, and green vegetables such as legumes, although our largest source is generally from drinking water. Copper deficiency is exceedingly rare even in the poorest communities, and is most frequently caused by excessive zinc intake[64] or by a genetic aberration such as Menkes â€œkinky-hairâ€• syndrome, in which intestinal copper uptake is impaired. Menkes syndrome is characterized by mental retardation, thermoregulatory dysfunction, hypopigmentation, connective tissue abnormalities, and pili torti (kinky hair). Interestingly, with the increased focus on the role of copper in neurodegenerative disorders and cancer, some authors suggest intentionally depleting patients of their copper stores with tetrathiomolybdate, an experimental copper chelator.[43]

Copper is absorbed by an active process involving a Cu-ATPase (adenosine triphosphatase) in the small intestinal mucosal cell membrane, also known as the Menkes ATPase (see below). The gastrointestinal absorption varies with the copper intake and the food source[51] and is as low as 12% in patients with high copper intake. In the presence of damaged mucosa, such as following acute overdose, the fractional absorption is likely to be significantly higher.[71] Once absorbed, copper is rapidly bound to carriers such as albumin, ceruloplasmin, and amino acids, such as histidine, for transport to the liver and other tissues. Its half-life in the plasma is approximately 15 minutes. After being released locally in the reduced form from its carrier, copper uptake by the hepatic cells occurs via a specific uptake pump.[91] This process, which is facilitated by the reducing agent ascorbic acid, provides a

potential window, however brief, for detoxification of the ion by chelating agents.

In the hepatocyte, complex trafficking systems exist (involving ceruloplasmin, metallothionein, and other metallochaperones within the cytoplasm) to prevent copper toxicity and to aid delivery to the appropriate enzymes.[40 , 90] A distinct Cu-ATPase, located on certain subcellular organelles such as the *trans* -Golgi network or pericanalicular lysosomes, assists in the appropriate localization and elimination, respectively, of the metal.[25] By this mechanism, copper is either incorporated into enzymes or released, as a metallothioneinâ€“copper complex, directly into the biliary system for fecal elimination.

Some copper is released from the liver, bound primarily to ceruloplasmin, an $\hat{I}\pm_2$ -sialoglycoprotein with a molecular weight of 132,000 daltons. Ceruloplasmin-bound copper accounts for approximately 90â€“95% of serum copper. Ceruloplasmin is a multifunctional protein that binds 6 atoms of copper per molecule. Copper bound to this carrier has a plasma half-life of approximately 24 hours. Ceruloplasmin is also involved in the mobilization of iron from its storage sites, and it serves an analogous role as a ferroxidase during the ferrousâ€“ferric conversion. Copper (I) is oxidized directly by ceruloplasmin, thereby avoiding the generation of reactive oxygen species. Approximately 5â€“10% of serum copper is bound to albumin under normal conditions, but following acute poisoning, the majority of the excess copper binds to albumin. The albumin-copper complex represents the â€œfreeâ€• or toxicologically active copper. The amount of unbound copper in the blood under normal circumstances is well below 1%.

Alcohol dehydrogenase
Metabolism of alcohols
Catalase

Detoxifies peroxide
Ceruloplasmin enzymes
Copper transport, ferroxidase
Cytochrome C oxidase
Electron transport chain
Dopamine Î²-hydroxylase
Converts dopamine to norepinephrine
Factor V enzymes
Coagulation cascade
Lysyl oxidase
Cross-links collagen and elastin
Monoamine oxidase
Deamination of primary amines
Superoxide dismutase
Detoxifies free radicals
Tyrosinase
Melanin production

Enzyme Function

TABLE 90-2. Important Copper-Containing Enzymes and Proteins and Their Functions

There are several important copper-containing enzymes in humans (Table 90-2). The common link among these enzymes is their participation in redox (reduction-oxidation) reactions in which a molecule, typically oxygen, donates or shares its electrons with another compound. In this respect, the physiology, chemistry, and toxicology of copper are most similar to that of iron. In fact, â€œblue-bloodedâ€• animals, such as octopi and spiders, use copper in hemocyanin, a blue pigment, in an analogous manner that â€œred-bloodedâ€• animals use iron in hemoglobin.

The volume of distribution of copper is 2.0 L/kg and the $t_{1/2}$ of erythrocyte copper is 26 days. The elimination of copper occurs

predominantly through biliary excretion following complexation with ceruloplasmin. Biliary excretion approximates gastrointestinal absorption, and averages 2000 Âµg/24 h.[5 , 90 , 112] Renal elimination under normal conditions is trivial, accounting for approximately 5â€“25 Âµg/24 h.[5]

Toxicology and Pathophysiology

Redox Chemistry

In acute overdose, a high fraction of the serum copper remains bound to low-affinity proteins, such as albumin, and thus is biologically active. Because copper, as a transition metal, is capable of assuming one of several different oxidation, or valence, states, it is an active participant in redox reactions. In particular, participation in the Fenton reaction and Haber-Weiss cycle explains the toxicologic effects of copper as a generator of oxidative stress and inhibitor of several key metabolic enzymes (see Fig. 12-2).[38] In particular, the mitochondrial electron transport chain and lipid membranes serve as ready sources of electrons for copper reduction, establishing a chain of events that ultimately leads to mitochondrial or membrane dysfunction, respectively.[81]

Erythrocytes

Cupric ion inhibits sulfhydryl groups on enzymes in important antioxidant systems, including glucose-6-phosphate dehydrogenase and glutathione reductase.[95] However, while support for these effects is only indirect, intraerythrocyte concentrations of reduced glutathione fall demonstrably following copper exposure.[77] This effect is presumably part of the protective role that glutathione, a nucleophile or reducing agent, normally has on oxidants, such as either cupric ions or the reactive oxygen species they generate.[75 , 76] Thus in the setting of copper poisoning, in which excessive quantities of oxidants are produced,

the depletion of glutathione presumably augments peroxidative membrane damage.

In the presence of sulfhydryl-rich cell membranes, such as those on erythrocytes, cupric ions are reduced to cuprous ions, which are capable of generating superoxide radicals in the presence of oxygen.[65] This one-electron reduction of oxygen regenerates the cupric ion, allowing redox cycling and continuous generation of reactive oxygen species (Fig. 90-1). The importance of hemoglobin-derived reactive oxygen species is demonstrated by the lack of hemolysis in the presence of anaerobic conditions or in an environment saturated with carbon monoxide.[12] The in vitro hemolytic activity of copper sulfate is reduced by albumin and several sulfhydryl-containing compounds, including D-penicillamine and succimer.[3] Interestingly, dimercaptopropane sulfonate (DMPS), another sulfhydryl-containing compound often used as a chelator, exacerbates copper-induced hemolysis. This paradoxical effect is variably ascribed to concomitant inhibition of superoxide dismutase, an important antioxidant enzyme, or to the ability of DMPS to efficiently reduce either membrane dithiols or cupric ions, in either case increasing the generation of superoxide.[2]

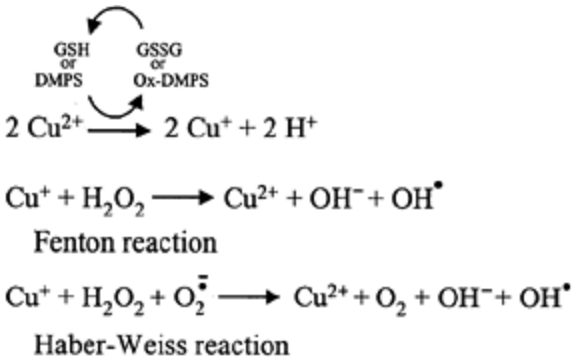

Figure 90-1. In the cupric or Cu^{2+} state, copper is reduced by sulfhydryl-containing compounds such as glutathione (GSH) or dimercaptopropane sulfonate (DMPS) to its cuprous form (Cu^{+}), forming disulfide links in the process. Oxidized glutathione (GSSG) is subsequently enzymatically reduced by glutathione reductase to

regenerate GSH. Superoxide anions (O_2^-), formed when molecular oxygen (O_2) acquires an additional electron, are continually generated by mitochondria. Both the Fenton and the Haber-Weiss reaction use the cuprous form of copper as a catalyst to convert hydrogen peroxide or superoxide radical into the more biologically consequential hydroxyl radical ($OH^{Â·}$).[14, 73]

Hemolysis frequently occurs within the first 24 hours in patients with acute copper poisoning.[30, 105, 118] This time of onset differs markedly from hemolysis that follows most other oxidant stressors and is likely a result of the differing nature of the erythrocyte insult; that is, the hemolysis following most oxidant exposures is caused by precipitation of hemoglobin as Heinz bodies and subsequent erythrocyte destruction by the reticuloendothelial system. This may also occur in the setting of acute copper poisoning, particularly following less substantial exposure. Additionally, and accounting for the early hemolysis, copper also directly oxidizes the erythrocyte membrane, thereby initiating red cell lysis independently of the reticuloendothelial system.[4, 93] Oxidant-induced disulfide cross-links in the erythrocyte membrane reduce its stability and flexibility, thereby predisposing to early cell rupture.[4]

Copper-induced oxidation of the heme iron within the erythrocyte produces methemoglobinemia.[80] Given the high incidence of hemolysis, the methemoglobin is commonly released within the plasma. In this situation, methylene blue should not be expected to reliably reduce the ferric iron because this reaction generally requires an intact erythrocyte.

Liver

Although most of the accumulated copper in hepatocytes is rapidly complexed with metallothionein or otherwise used, failure to

completely sequester copper ions allows their participation in redox reactions. Hepatic cells are protected from copper toxicity in vitro by prior induction of metallothionein with zinc or cadmium salts or by the infusion of metallothionein. These hepatic protective effects support the toxicologic significance of free intracellular copper. These findings also explain the therapeutic use of zinc acetate in patients suffering from Wilson disease,[21] because copper itself is not a good inducer of metallothionein in humans.

Copper ions also generate hydroxyl radicals, which are potent inducers of both lipid peroxidation, and other reactive oxygen species. Lipid peroxidation is confirmed in hepatocytes by the measurement of increased production of oxidation products. The peroxidative effect on biologic membranes is worse in animals deficient in vitamin E and is prevented by vitamin E replacement, presumably because of the role of vitamin E as a free radical scavenger.[59 , 103] These effects are most pronounced in mitochondria, perhaps as a consequence of the reduction of cupric to cuprous ion in these organelles.[45 , 104] Copper also accumulates in the cellular nuclei, where localized production of hydroxyl radicals may form DNA adducts and cause apoptosis.[92] Histologically, liver damage follows a centrilobular pattern of necrosis.

The sequelae of the potent hepatotoxic effects of copper are not isolated to the liver. Once liver necrosis occurs, typically at liver concentrations greater than 50 mg/g dry weight, massive release of copper into the blood occurs, which may be of sufficient magnitude to cause hemolysis. This sequence of events is common during the crises of Wilson disease, and may allow for an understanding of the delayed secondary episode of hemolysis that occurs in some copper-poisoned patients.

Kidney

The kidneys bioaccumulate copper. Although primarily bound to metallothionein when available, copper is otherwise free to participate in oxidant-generating reactions in a manner analogous to that of iron. Thus, reactive oxygen species are probably also responsible for the nephrotoxic effects of copper. Pathologic analyses of the kidneys of oliguric or anuric patients typically reveal acute tubular necrosis, and some analyses demonstrate hemoglobin casts. These findings suggests that renal failure may result indirectly from the hemoglobinuria induced by the massive release of free extracellular hemoglobin. The urinary hemoglobin, like myoglobin, may undergo conversion to ferriheme or release its iron, either of which results in oxidative stress on the renal tubular epithelial cell. Additionally, free intravascular hemoglobin may cause renal vasoconstriction through the local scavenging of nitric oxide within the renal arterioles.

Central Nervous System

Although charged entities such as copper ions do not readily cross the bloodâ€“brain barrier, elevated cerebrospinal fluid copper concentrations are characteristic of chronic copper overload conditions such as Wilson disease.[107] This accumulation is accomplished through carrier-mediated transport of albumin-bound, not ceruloplasmin-bound, copper into the central nervous system.

Clinical Manifestations

Acute Copper Salt Poisoning

Gastrointestinal irritation is the most common initial manifestation of copper salt poisoning. This syndrome includes the rapid onset of emesis and abdominal pain, possibly followed by gastroduodenal hemorrhage, ulceration, or perforation.[8 , 31] Blue coloration of the vomitus may occur following the ingestion of certain copper salts,

particularly copper sulfate.[46, 99, 115] Blue vomitus is not, however, pathognomonic for copper poisoning and also occurs in patients who ingest boric acid, methylene blue, or food dyes. Other common symptoms include retrosternal chest pain and a metallic taste. The lethal dose of ingested copper sulfate is suggested to be 0.15â€“0.3 g/kg, but this is unverified.

Given its location within the gastrointestinal tract, the liver receives the initial and most substantial exposure to any ingested copper. Consequently, hepatotoxicity is a frequent, although rarely an isolated,[56] manifestation of acute copper sulfate poisoning, typically occurring in the patients with more severe poisoning. Jaundice, while among the most common clinical and biochemical findings following overdose, can be hepatocellular or hemolytic.[10]

Hemolysis is more common than hepatotoxicity, and is invariably in those with liver damage.[77, 101] As noted, copper-induced hemolysis often occurs rapidly following exposure and may be severe (see Pathophysiology above and Chap. 24). In most reported cases, the discovery of significant methemoglobinemia occurs early in the patient's clinical course and is rapidly followed by hemolysis.[29] Because free methemoglobin is filterable, methemoglobinuria may occur, although it cannot be differentiated from other heme forms in the urine without specialized testing.

Renal and pulmonary toxicity occur occasionally and represent extraerythrocytic manifestations of the oxidative effects of the copper ions. In spite of massive intravascular hemolysis, hemoglobinuric renal failure is uncommon in patients who receive adequate volume-replacement therapy.[30]

Hypotension and cardiovascular collapse occur in patients with the most severe poisoning and is likely multifactorial in origin.[99] Undoubtedly, intravascular volume depletion from vomiting and

diarrhea is involved. However, the severity and poor patient outcome despite appropriate volume loading suggests that the

direct effects of copper on vascular and cardiac cells are also involved. Sepsis, as a result of transmucosal invasion, may also be partially responsible.[71]

Depressed mental status, ranging from lethargy to coma, or seizures following acute poisoning are likely epiphenomena related to damage to other organ systems. These findings are particularly common in patients with hepatic failure, and are comparable to those of hepatic encephalopathy from other causes. In patients with chronic copper poisoning, such as Wilson disease, neurologic manifestations are prominent (see Chronic Copper Poisoning below), and typically involve movement disorders.

Intravenous injection of copper sulfate reportedly produces a clinical syndrome identical to that which occurs following ingestion.[17 , 84] Inadvertent subcutaneous administration of a veterinary copper glycinate solution produced skin necrosis in the area of the injection.[11]

Although not strictly a form of copper poisoning, inhalation of copper oxide fumes, generated during welding or other industrial processes, may produce metal fume fever, a syndrome historically called â€œbrass chillsâ€• or â€œfoundry workers' ague.â€• Patients with this syndrome present with cough, chills, chest pain or fever that are most likely immunologic, and not toxicologic, in origin (Chap. 119). However, copper oxide formation, unlike zinc oxide, only occurs at extremely high temperatures, accounting for the relative infrequency of the copper-induced metal fume fever.

Chronic Copper Poisoning

Although hepatolenticular degeneration, known as Wilson disease, is a condition of chronic copper overload, there are qualitative similarities to acute copper poisoning. Wilson disease is an inherited, autosomal recessive disorder of copper metabolism affecting approximately 1 in 40,000 persons. The gene implicated

in this disease (ATP7B) codes for a hepatocyte membrane-bound copper-binding protein that is required for the maturation of ceruloplasmin and the biliary excretion of copper. Transgenic replacement models, in which human ATP7B is expressed in deficient animals, demonstrate normalization of copper excretion.[74] The resultant increase in hepatic copper concentrations produces continuing oxidative stress on the hepatocyte and cellular necrosis with the inevitable development of cirrhosis. Patients undergo periodic fluctuations in the extent of their copper-induced hepatotoxicity, and episodes of severe hepatotoxicity are frequently associated with hemolysis as stored copper is released from dying hepatocytes. The adverse effects of copper on the lenticular nucleus in the basal ganglia cause movement disorders such as ataxia, tremor, parkinsonism, dysphagia, and dystonia.[82] None of the other forms of copper poisoning are associated with substantial or direct neurotoxicity. Psychiatric manifestations, such as behavioral changes or mood disorders, may also occur.[21] Accumulation of copper within the cornea accounts for the characteristic green-brown Kayser-Fleischer rings. Although the patient's serum copper levels are decreased, they typically have a reduced ceruloplasmin concentration, caused by the failure of copper incorporation into ceruloplasmin and release from the liver, and an elevated urinary copper concentration. Treatment involves lifelong therapy with D-penicillamine, trientine (triethylene tetramine), or molybdenum salts if the patient is D-penicillamine sensitive. Zinc acetate, FDA approved as a maintenance therapy, induces the formation of intestinal metallothionein and thereby blocks copper absorption by enhancing intestinal mucosal cell sequestration.[22] Orthotopic liver transplantation results in improvement in nearly all aspects of the disease, including the central nervous system and ocular manifestations.[41]

Chronic exogenous copper poisoning is uncommon in adults, but is reported following the use of copper-containing dietary

supplements.[83] However, subacute or chronic exposure is common in children in some parts of the world. This condition, commonly called childhood cirrhosis in India or idiopathic copper toxicosis elsewhere, generally occurs in the setting of excessive dietary intake of copper because of copper-contaminated water from brass vessels used to store milk. These children may have a genetic predisposition to copper accumulation, as signs of chronic liver disease develop by several months of age and progress rapidly.[97, 100] Both serum copper and ceruloplasmin levels are markedly elevated, which differentiates this disease from Wilson disease. The incidence of the disease has fallen dramatically, probably as a result of improved nutrition and replacement of copper utensils and storage containers with those made of steel.

â€œVineyard sprayer's lung,â€• first described in 1969, refers to the occupational pulmonary disease that occurred among Portuguese vineyard workers applying Bordeaux solution, a 1â€“2% copper sulfate solution neutralized with hydrated lime ($Ca(OH)_2$).[86] The patients developed interstitial pulmonary fibrosis and histiocytic granulomas containing copper. Many of these workers also developed lung adenocarcinoma, hepatic angiosarcoma, and micronodular cirrhosis, raising the possibility of a carcinogenic effect of chronic copper exposure.[87] There is also a suggestion of an increased incidence of pulmonary adenocarcinoma among smelters, who are, however, exposed to many other xenobiotics, including arsenic, a known carcinogen.[72] Copper is not on the list of suspected carcinogens compiled by the International Agency of Research on Cancer (IARC).

Ophthalmic effects of copper salts, primarily following occupational exposure, include irritation of the corneal, conjunctival, or adnexal structures. Chronic ophthalmic exposure to particulate elemental copper or one of its alloys may result in chalcosis lentis, from the Greek word *chalkos*, or copper. This chronic exposure manifests as a green-brown discoloration of the lens or cornea, similar to Kayser-Fleischer rings.

Diagnostic Testing

Real-time testing for copper is impractical and almost all management decisions must be based on clinical criteria. Copper levels are often obtained for confirmatory or investigative purposes. Although never adequately studied, whole-blood copper concentrations may correlate better with clinical findings than do serum copper concentrations.[31] The rapid movement of copper from serum into the erythrocyte presumably explains this finding. However, although there is a statistical relationship between the whole-blood copper levels and the severity of poisoning,[31 , 113] there is little correlation between clinical findings at any given copper concentration, regardless of which biologic tissue is measured. Similarly, other than at extremely high or low values, there is no defined value at which the prognosis may be established with certainty. Reported serum copper concentrations in patients with hemolysis range from 96â€“747 Âµg/dL, and those following severe poisoning have values of 6600 Âµg/dL[46] and 8267 Âµg/dL.[29] Serum copper concentrations in 11 patients with copper-induced acute renal failure

ranged from 115â€“390 Âµg/dL.[28] The normal urinary copper excretion per 24 hours is approximately 25 Âµg, and is reportedly as high as 628 Âµg/24 h in patients with copper poisoning.[39]

Occasionally serum copper concentrations reveal a secondary rise, likely as a consequence of release during hepatocellular necrosis. This secondary rise typically occurs only in patients with life-threatening poisoning, and clinical evaluation is far more important and relevant than serial copper levels.[101]

Elevated copper levels are also noted in patients with inflammatory conditions, biliary cirrhosis, and pregnancy. These conditions are associated with an elevated ceruloplasmin, and the fraction of bound copper in the serum remains normal. Patients

with Wilson disease have elevated hepatocyte copper content, but their serum copper levels are generally below normal unless hepatic necrosis is occurring.

Although serum ceruloplasmin levels rise in patients with acute copper poisoning,[113] presumably reflecting increased hepatic synthesis, the ceruloplasmin concentration cannot be used to define the patient's prognosis. Tissue metallothionein levels may also rise after copper poisoning, but the implication of this finding, which is limited by the inability to rapidly obtain tissue samples, is unknown.[67]

Routine laboratory testing following acute copper salt poisoning should include an assessment for both hemolysis and hepatotoxicity. Differentiation of these etiologies as a cause for jaundice is made by standard methodology, such as comparison of the bilirubin fractions and an assessment of the hepatic enzymes and hemoglobin; that is, indirect bilirubin is proportionally elevated in patients with hemolysis, whereas the direct fraction rises in patients with hepatocellular necrosis. An assessment of the patient's electrolyte and hydration status is warranted. The prothrombin time may be prolonged in the absence of liver injury or disseminated intravascular coagulopathy and may be the result of a direct effect of free copper ions on the coagulation cascade.[80] In addition, many reports document an abnormal glucose 6-phosphate dehydrogenase (G6PD) activity, suggesting causation for hemolysis. However, interpretation of this test result is difficult, as copper poisoning interferes with the measurement of G6PD.

Although copper metal embedded in the skin is clearly visible, topically applied copper salts are not visualized.[15] The clinical usefulness of radiographs to identify ingested copper solutions is unstudied. Still, obtaining an abdominal radiograph, while probably of low clinical yield, may be justified, if it occasionally alters management.

Management

Optimal and aggressive supportive care is the cornerstone to the effective management of patients with acute copper poisoning. Attention to antiemetic therapy, fluid and electrolyte correction, and normalization of vital signs are the critical steps before consideration of chelation therapy. Gastrointestinal decontamination is of limited concern because the onset of emesis generally occurs within minutes of ingestion and is often protracted. Although oral activated charcoal is unlikely to be harmful, it is of unproved benefit, and it may hinder the ability to perform gastrointestinal endoscopy to evaluate the corrosive effects of a copper salt on the mucosal surface.[18] For this reason, even though activated charcoal may be able to adsorb the remaining copper in the proximal gastrointestinal tract, it is relatively contraindicated in most situations. Advanced therapy for patients with renal failure may include hemodialysis, and liver transplantation may be needed for patients with life-threatening hepatic failure.

Chelation Therapy

Chelation therapy should be initiated when hepatic or hematologic complications are present or the patient is severely poisoned. Studies on the efficacy of chelation therapy following acute copper salt poisoning are limited. Even when administered early and appropriately, organ damage and death still occur. Application of the data from the existing literature is complex because of the lack of controlled therapeutic studies of human copper poisoning. Although experimental animal models and uncontrolled human data exist, the results are frequently contradictory. Three drugs are clinically available, and most dosing and efficacy data derive either from their use in the treatment of patients with Wilson disease or from their effects on copper elimination during chelation of patients manifesting toxicity from other metals.

Most patients with copper poisoning are initially treated with intramuscular British anti-Lewisite (BAL).[108 , 115] Although BAL may be less effective, its use is appropriate in patients in whom vomiting or gastrointestinal injury prevents oral D-penicillamine administration. Furthermore, because the BALâ€“copper complex primarily undergoes biliary elimination, whereas D-penicillamine undergoes renal elimination, BAL proves useful in patients with renal failure. When tolerated, D-penicillamine therapy should be started simultaneously or shortly after the initiation of therapy with BAL.

Calcium disodium ethylenediaminetetraacetate ($CaNa_2$ EDTA) reduces the oxidative damage induced by copper ions in experimental models.[117] However, it does not greatly enhance the elimination of copper when used for the chelation of other metals.[96 , 109] In addition, short-term use of $CaNa_2$ EDTA inactivates dopamine Î²-hydroxylase in humans, presumably by chelating its copper moiety.[33] However, because the in vivo activity of this enzyme is restored on the addition of exogenous copper, the potential for inhibition of the formation of neuronal norepinephrine during the treatment of acute poisoning is unknown. Interestingly, CuCaEDTA is used as a copper supplement in animals, and overdose of this formulation results in copper poisoning.[42]

D-Penicillamine (Cuprimine), a structurally distinct metabolite of penicillin, is an orally bioavailable monothiol chelator. It is used in the treatment of lead, mercury, and copper toxicity, as well as in the management of rheumatoid arthritis and scleroderma. D-Penicillamine is effective in preventing copper-induced hemolysis in patients with Wilson disease. Its protective mechanism is primarily mediated through chelation of unbound copper ions, rendering them unable to participate in redox reactions.[62] The D-penicillamineâ€“copper complex undergoes rapid renal clearance in patients with competent kidneys. The use of D-penicillamine is not

formally studied in the patients with acute copper salt poisoning, but case studies and animal models suggest that copper elimination is enhanced.[20, 44, 53] The recommended dose is 1â€“1.5 g/d given orally in 4 divided doses. D-Penicillamine is also indicated for the treatment of chronic exogenous copper poisoning, such as Indian childhood cirrhosis. Initiation early in the course of disease, along with discontinuation of the exposure, is associated with hepatic recovery and dramatically improved survival rates.[13]

Although D-penicillamine appears effective, it is associated with several significant complications. For example, D-penicillamine is associated with a worsening of neurologic findings in nearly 50%

of patients treated for Wilson disease.[23] Subacute toxicities of D-penicillamine include aplastic anemia, agranulocytosis, and renal and pulmonary disease. Long-term use of D-penicillamine is also associated with the development of cutaneous lesions and immune system dysfunction. However, in the brief treatment necessary for acutely poisoned patients, the major risk is the potential for hypersensitivity reactions that occur in 25% of patients who are penicillin allergic. This hypersensitivity reaction is likely related to contamination of the pharmaceutical preparation with penicillin, rather than immunologic cross-reactivity.[52, 58] The use of D-penicillamine during pregnancy is associated with congenital abnormalities, although all of the data are derived from women with Wilson disease who had long-term therapy.[88]

Succimer is sometimes described as an ineffective copper chelator, although it is able to triple the baseline copper elimination in a murine model.[26] Given its ease of use, relative safety, and benefit in experimental models,[1] succimer may be used in lieu of D-penicillamine in patients with mild or moderate poisoning. Under these circumstances, the use of standard lead poisoning dosing regimens is warranted (Chap. 91 and Antidote in Depth: Succimer [2,3-Dimercaptosuccinic Acid]) DMPS, an experimental chelating agent which is gaining popularity for the treatment of arsenic

poisoning, prevents acute tubular necrosis in copper-poisoned mice.[78] DMPS also proved to be the most effective of a panel of chelators in a murine model of copper sulfate poisoning,[57] and it substantially increased urinary copper elimination in nonpoisoned individuals.[110] However, DMPS, unlike D-penicillamine, forms intramolecular disulfide bridges, which, in so doing, liberates an electron. This property, which accounts for its potency as a reducing agent, also probably explains its propensity to worsen copper-induced hemolysis in vitro.[2,3] Because an adequate analysis of risk versus benefit is unavailable, DMPS should not be used to chelate copper-poisoned patients at this time.

Trientine, an orally bioavailable agent, is the second-line agent for patients with Wilson disease, but its use in patients with acute copper poisoning is unreported. This, too, is the case with zinc therapy, which is also of proven efficacy in Wilson disease, but has no known role in the treatment of acute copper poisoning. The need for several weeks of zinc therapy prior to realizing full efficacy makes its therapeutic use in acutely poisoned patients questionable. Although large oral doses of zinc salts may limit the absorption of copper ion, the concomitant gastrointestinal irritant effects of zinc ion make this therapy impractical.[49]

Tetrathiomolybdate is an FDA-recognized chelating agent with orphan drug status that, although not marketed, may be available through compounding pharmacies, typically as ammonium tetrathiomolybdate. Tetrathiomolybdate is suggested to benefit copper-poisoned animals in uncontrolled studies,[85] but its use in acute copper poisoning in humans is unstudied. Tetrathiomolybdate depleted the copper stores in a patient with cancer who purchased the compound over the Internet as an â€œalternativeâ€• antiangiogenesis therapy.[69]

Extracorporeal Elimination

Limited data exist regarding the extent to which copper ion is

eliminated by various extracorporeal means. Exchange transfusion is of undefined, but probably limited, benefit in acute copper sulfate poisoning.[32] Hemodialysis membranes undoubtedly allow copper ions to cross, based on the epidemics in which hemodialysis actually resulted in copper poisoning.[36] Although copper should be similarly cleared by hemodialysis, its relatively large volume of distribution limits the potential clinical usefulness of this technique. Furthermore, copper ions are highly protein bound, and the dialyzable concentration is typically less than 1 pmol/L, suggesting that hemodialysis would have little clinical usefulness. This fact is supported by case reports in which serum or dialysate concentrations of copper are assessed.[84] Furthermore, given the propensity of hemodialysis to lyse erythrocytes, which may release stored copper and worsen toxicity, hemodialysis is not recommended.[48] Peritoneal dialysis is not useful in patients with fulminant Wilson disease.[66] Peritoneal dialysis removed less than 700 Âµg in a copper sulfate-poisoned child whose copper concentration was 207 Âµg/dL.[48] However, in the same patient, the addition of albumin to the dialysate removed 9 mg of copper at a time when the child's serum copper concentration had fallen to a lower level. One patient was treated with albumin dialysis using a 44 g/L albumin-containing dialysate and a slow dialysate flow rate (1â€“2 L/h) in a manner similar to routine continuous venovenous hemodiafiltration.[16 , 63] The patient's clinical condition improved, the serum copper concentrations normalized, and 105 mg of copper was removed. Plasma exchange enhanced the elimination of copper in patients with fulminant Wilson disease.[61 , 63] Copper removal ranged from 3â€“12 mg per treatment, but it is unclear if either of these removal techniques would be beneficial following an ingestion of gram quantities of copper sulfate.

Management of the hepatic toxicity requires little more than standard supportive care. The potential benefit of *N* -acetylcysteine is unstudied, although it is useful in many forms of fulminant hepatic failure. Liver transplantation should be

considered, but specific criteria for transfer to a specialized liver unit or for transplant, other than those that are applicable for Wilson disease or other more common, noncopper etiologies, are undefined.

There are no controlled data on the treatment of acute copper poisoning in pregnancy. The available data on pregnant women with Wilson disease document that D-penicillamine is teratogenic and that zinc may be the preferred therapeutic agent.

Summary

Acute copper poisoning is rare in the United States but is associated with dramatic toxicologic effects, primarily hemolysis and hepatotoxicity. The toxicologic effects of copper are primarily mediated by oxidative stress on the erythrocyte and hepatocyte, and this similarity to iron salt poisoning adds a framework for the conceptual understanding of the disease. The infrequency of acute copper poisoning severely limits our ability to perform controlled studies on its management. Chelation is most commonly performed with BAL and D-penicillamine, but succimer is likely to be beneficial. Succimer is more familiar to most clinicians and has fewer associated adverse effects, so it may be acceptable. Extracorporeal elimination is unlikely to be of benefit. Fortunately, exhaustive research into diseases of copper metabolism, particularly Wilson disease, which has periodic exacerbations similar to acute copper poisoning, provides insight into managing patients with acute copper salt poisoning.

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Chapter 91
Lead

Fred M. Henretig

Lead (Pb)

Atomic number = 82

Atomic weight = 207

Normal concentrations

Whole blood = < 10 Âµg/dL (<0.48 mmol/L)

A 3-year-old boy was rushed to the emergency department (ED) by the rescue squad after having a 20-minute seizure at home. He initially appeared postictal, with flaccid muscle tone and minimal response to painful stimulation. Soon after arrival, he had another seizure, was treated with intravenous diazepam, which, in turn, was complicated by respiratory failure necessitating endotracheal intubation. The electrocardiogram (ECG) monitor revealed a normal sinus rhythm. A rapid bedside test for blood glucose was 194 mg/dL. Arterial blood-gas determination after intubation revealed normal

ventilation and oxygenation, with metabolic acidosis. Another generalized seizure occurred 5 minutes later, but it resolved immediately with a second dose of diazepam 0.2 mg/kg.

Further history revealed that this child was in his usual state of health until 3 days prior to admission, when he developed symptoms of an upper respiratory infection. Two days later he developed tactile fever, vomited once, and appeared less active. On the day of admission, he seemed drowsy, vomited several times, and in the evening developed twitching and abnormal eye movements, prompting a call to the rescue squad.

His past medical history was notable for developmental delay, primarily in the speech and personal-social spheres. He spoke only single words, was not toilet trained, and was unable to dress himself. His mother denied any history of head trauma or recent ingestion, but did comment that 3 weeks previously she had to remove paint chips from the child's mouth.

Physical examination revealed an intubated child with a blood pressure of 84/50 mm Hg, a heart rate of 120 beats/min, a manually ventilated respiratory rate of 25 breaths/min, and a temperature of 100.9Â°F (38.3Â°C). There were no signs of external trauma. Cardiac, pulmonary, and abdominal examinations were normal. The neurologic examination revealed an obtunded child with intermittent withdrawal to pain. At times, tonic extensor posturing was noted. Pupils were 3 mm and sluggishly reactive, with normal fundi. Deep tendon reflexes were 3+ to 4+ on the left leg and 2+ to 3+ on the right leg. There was bilateral sustained ankle clonus. Plantar extension was present on the left, and the response was equivocal on the right.

The patient went immediately to CT scan, which revealed diffuse cerebral edema and loss of gray-white matter differentiation (Fig. 91-1). Recurrent seizure activity necessitated additional therapy with phenobarbital and was followed by midazolam infusion. The child was also treated with hyperventilation and dexamethasone for increased

intracranial pressure, and empirically with ceftriaxone and acyclovir for possible viral and/or bacterial central nervous system (CNS) infection. A lumbar puncture was performed, revealing opening pressure of 46 cm H_2O (Nl = 10â€“28 cm H_2O) clear, colorless fluid, and closing pressure of 15 cm H_2O. The cell count was 3 white blood cells (WBC)/mm^3 and 0 red blood cells (RBC)/mm^3, with cerebrospinal fluid (CSF) protein of 96 mg/dL and glucose of 108 mg/dL. One dose of mannitol was given after the lumbar puncture confirmed elevated intracranial pressure. Additional pertinent positive laboratory tests included hemoglobin, 6.6 g/dL; mean corpuscular volume (MCV), 50 Âµm^3; and peripheral blood smear positive for RBC basophilic stippling. Urinalysis showed 4+ glucose, 5â€“10 WBCs, 0â€“5 RBCs, and 1+ protein. Radiographic studies were negative for radiopaque foreign bodies of the abdomen, but positive for dense metaphyseal bands at the wrist (Fig. 91-2). Blood lead concentration was 220 Âµg/dL, and erythrocyte protoporphyrin was 649 Âµg/dL.

Despite anticonvulsant therapy with phenytoin, phenobarbital, and midazolam infusion, a continuous reading electroencephalogram demonstrated periodic epileptiform activity. Pentobarbital was added to the therapeutic regimen, resulting in intermittent burst suppression of up to 40 seconds' duration. The child underwent a

5-day course of parenteral chelation therapy with dimercaprol (British anti-Lewisite, BAL) and edetate calcium disodium ($CaNa_2$ EDTA). After a 2-day interval, the child received a second 5-day course of chelation, resulting in a blood lead concentration of 33 Âµg/dL.

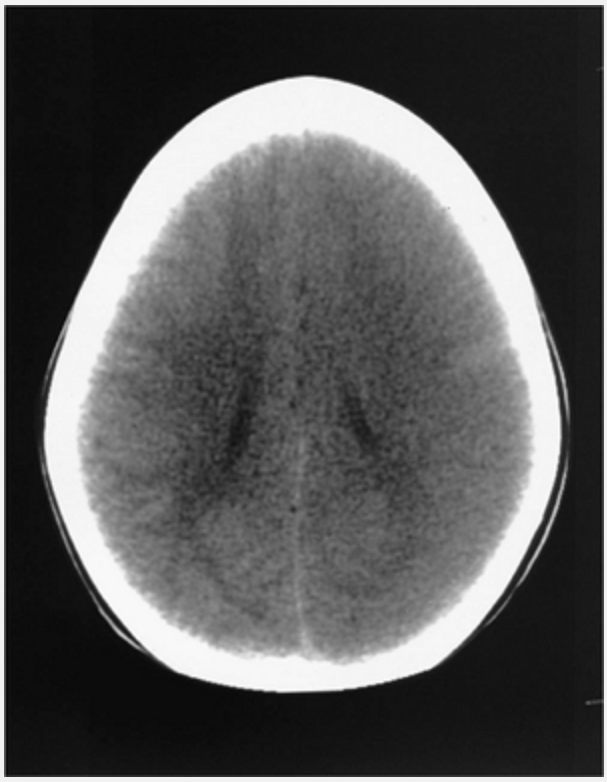

Figure 91-1. Computerized tomography scan of the brain reveals diffuse cerebral edema and loss of gray-white matter differentiation. *(Courtesy of Department of Radiology, St. Christopher's Hospital for Children, Philadelphia, PA.)*

The patient required high-dose pentobarbital for 6 days and continuous midazolam infusion for 14 days to suppress seizure activity. He was hospitalized for 23 days prior to transfer to a chronic care rehabilitative facility. His neurologic examination prior to transfer was notable for choreoathetoid movements and generalized hypotonia, inability to localize visual or auditory stimuli, and nonpurposeful movements of the extremities. An MRI on day 22 revealed cerebral and cerebellar cortical atrophy with multiple areas of infarction involving the frontal and parietal lobes (Fig. 91-3).

Physical Properties

Lead is a silvery-gray, soft metal, with an atomic weight of 207.21 and an atomic number of 82. It has a low melting point, 621.3Â°F (327.4Â°C), and boils at 2948Â°F (1620Â°C) at atmospheric pressure.[122] It is widely distributed geologically, and occurs principally as two isotopes, ^{206}Pb and ^{208}Pb. Metallic lead is relatively insoluble in water and dilute acids, but will dissolve in nitric, acetic, and hot, concentrated sulfuric acids. In compounds, lead assumes valence

states of +2 and +4. Inorganic lead compounds may be brightly colored and vary widely in water solubility; several are used extensively as pigments in paints such as lead chromate (yellow) and lead oxide (red). Lead also forms organic compounds, of which two, tetramethyl and tetraethyl lead, were used commercially as gasoline additives.[56] These are essentially insoluble in water, but readily soluble in organic solvents.[104] Lead complexes with ligands containing sulfur, oxygen, or nitrogen as electron donors. It thus forms stable complexes with several ligands common to biologic molecules, including â€“OH, â€“SH, and â€“NH_2. Complexes with sulfhydryl (â€“SH) groups are thought to be of most toxicologic importance. There is no known physiologic role for lead, and any lead found in human body fluids represents environmental contamination.[86]

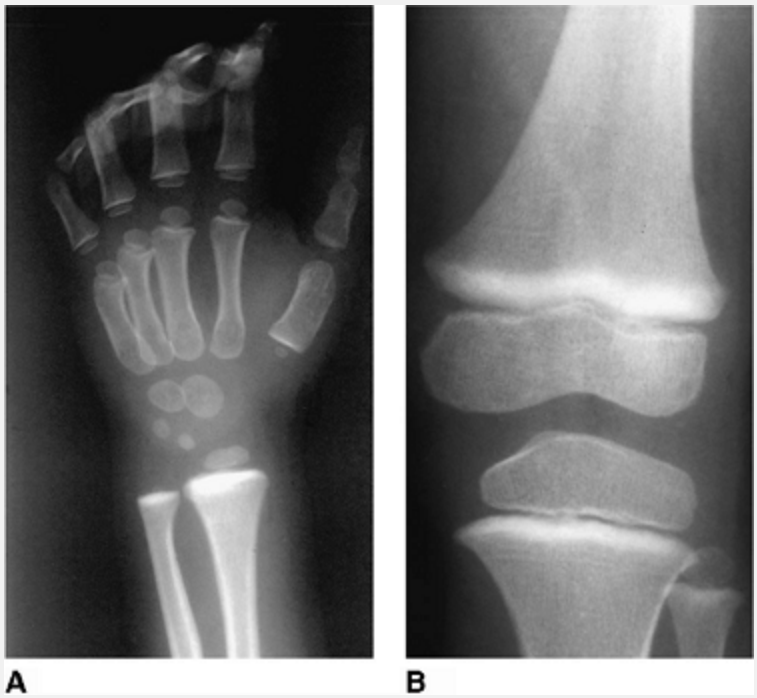

Figure 91-2. A. Radiograph of the wrist reveals increased bands of calcification: â€œlead lines.â€• *(Courtesy of Department of Radiology, St. Christopher's Hospital for Children, Philadelphia, PA.)* B. Similar radiographic findings in another patient at the knee. *(Courtesy of Richard Markowitz, MD, Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, PA.)*

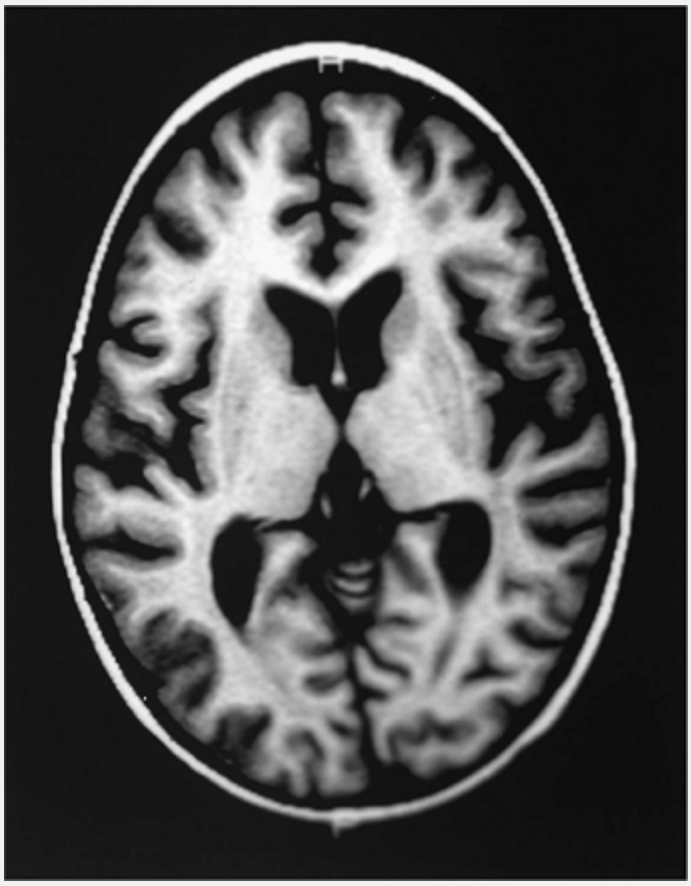

Figure 91-3. Magnetic resonance image of the brain reveals cortical atrophy and multiple areas of cerebral infarction. *(Courtesy of Eric Faerber, MD, Department of Radiology, St. Christopher's Hospital for Children, Philadelphia, PA.)*

History and Epidemiology

Industrial Applications

Lead's low melting point and malleability made it one of the first metals smelted and used by human society. Lead-based ocher paints are believed to date to approximately 40,000 B.C. Ancient Egyptians

and Hebrews used lead, and the Phoenicians established lead mines in Spain circa 2000 B.C. The Greeks and Romans produced lead during the process of extracting silver intended for coinage. Roman society found many uses for lead, including pipes, cooking utensils, and ceramic glazes, and a common practice was to use sapa, a grape syrup simmered down in lead vessels, as a sweetener and preservative.[83] Postindustrial lead use increased dramatically, and today, lead is the most widely used nonferrous metal, with global production on the order of 9 million tons annually.[56] Lead is used widely in industry for its waterproofing and electrical- and radiation-shielding properties. Use of both lead-based paint for house paint and leaded gasoline has been essentially eliminated by regulation in the United States since the 1980s, but persistence of lead paint in older homes still constitutes an enormous environmental challenge.[4]

History of Lead-Related Health Effects

The problem of human poisoning from lead, known as plumbism, dates back to antiquity. Dioscorides, a Greek physician in the 2nd century B.C., observed that lead makes the mind â€œgive way.â€•[167] Pliny cautioned the Romans of the danger of inhaled fumes from lead smelting.[79] Modern authors have suggested that extensive use of sapa in Roman aristocratic society contributed to the downfall of Roman dominance.[83] Lead poisoning was also recognized in Colonial times. Benjamin Franklin observed, in 1763, the â€œdry gripesâ€• (abdominal colic) and â€œdanglesâ€• (wristdrop) that afflicted tinkers, painters, and typesetters, as well as the â€œgripesâ€• caused by rum distillation in leaden condensing coils.[74] Lead salts, particularly lead acetate (sugar of lead), were used medicinally in the early 19th century for control of bleeding and diarrhea. With the 19th-century Industrial Revolution, lead poisoning became a common occupational disease. The reproductive effects of lead poisoning were also noted by the turn of the 20th century, including the high rate of stillbirths, infertility, and abortions among women in the pottery industry, or who were married to pottery

workers.

The modern history of childhood plumbism can be traced to the recognition of lead-paint poisoning in Brisbane, Australia, in 1897.[79] Lead poisoning was reported in US children in 1917, and by 1943 it was established that children who recovered from clinical plumbism were frequently left with neurologic sequelae and intellectual impairment. Symptomatic childhood lead poisoning was a frequent occurrence in US pediatric medical centers throughout the 1950s and 1960s, a period during which research established effective chelation therapy protocols with British anti-Lewisite (BAL) and edetate calcium disodium ($CaNa_2EDTA$).[26] From the 1970s to present, the research thrust in childhood lead poisoning has centered on the recognition and quantification of more subtle neurocognitive impairment caused by subclinical lead poisoning.[12,80] Over this time period, the Centers for Disease Control and Prevention (CDC) have steadily revised downward the definitions of a normal blood lead concentration (BLL) in children. The CDC definition of lead poisoning was 60 Âµg/dL in the early 1960s, whereas the current action level is 10 Âµg/dL.[20]

Sources of Human Exposure

Numerous sources of lead exposure exist, and can be generally classified as environmental, occupational or â€œexotic.â€• *Environmental* exposures affect the entire population, particularly young children. These exposures occur primarily by ingestion or inhalation, though handâ€“mouth exposure to some form of lead paint derivative predominates in most cases of childhood lead poisoning in the United States (Table 91-1). Because of its continuing, major impact in the United States today, lead paint exposure is further detailed here.

Lead pigments (typically lead carbonate) account for 50% by weight of many white house paints from the pre-World War II era. Since 1978, paint intended for interior or exterior residential surfaces,

toys, or furniture in the United States may contain, by law, no more than 0.06% lead.[4] However, an estimated 3 million tons of lead remain in 57 million US homes built prior to 1980 and painted with lead-based paint. This aging housing stock has created an enormous environmental hazard of lead exposure to these children, and to adult homeowners, house painters, and construction workers who become involved in sanding, scraping, and restoration of painted surfaces in these homes. Furthermore, lead-based paint is still allowed for industrial, military, marine, and some outdoor uses, such as structural components of bridges and highways; occasionally, some of this paint is inadvertently used in homes.[20] Attempts to abate lead-painted outdoor structures can pollute entire communities.[59]

TABLE 91-1. Environmental Lead Sources

Source	Comment
Leaded paint	Especially pre-1978 homes
Dust	House dust from deteriorated lead paint
Soil	From yards contaminated by deteriorated lead paint, lead industry emissions, roadways with high leaded gasoline usage
Water	Leached from leaded plumbing (pipes, solder), cooking utensils, water coolers

Air	Leaded gasoline (pre-1976 United States, still prevalent worldwide), industrial emissions
Food	Lead solder in cans (pre-1991 United States, still prevalent in imported canned foods); â€œnaturalâ€• calcium supplements; â€œmoonshineâ€• whiskey; lead-foilâ€“covered wines; contaminated flour, paprika

Although paint-derived lead exposure may result from pica in some children, most lead paint exposure in childhood relates to the crumbling, peeling, flaking, or chalking of aging paint.[20] These fine paint particles are incorporated into household dust and yard soil, where ordinary childhood handâ€“mouth activity results in ingestion.[21] Seasonal variations in house dust lead content occur, with higher levels in the summer months. This correlates well with predictable increases in BLLs in preschool children. This may reflect, in part, increased exposure to leaded street dust and soil while playing outdoors, and/or increased contamination of windowsills and floors by outdoor dust gaining entrance through open windows. Adults, as well as children, may develop paint-related lead poisoning when homeowners renovate Victorian-era homes in rural areas or urban neighborhoods undergoing regentrifying.[5,20]

Adults with *occupational* exposures and persons of all ages with *recreational* or *exotic* exposures to lead constitute another large group of persons at risk. It is estimated that more than 1 million workers in the United States, employed in more than 100 occupations, are exposed to lead.[100] The most important route of absorption in occupational settings is inhalation of lead dust and fumes. In addition, workers may eat, drink, or smoke in lead-dustâ€“contaminated areas, resulting in some ingestion as well

(contaminated cigarettes may provide a source of oral exposure). However, presence of lead in the workplace, per se, does not imply a significant risk of poisoning. The risk is correlated with several factors that contribute to the occurrence of respirable lead fumes or dust particles in the worksite atmosphere.[104] There are three general categories of such factors. The first relates to the degree of hazard inherent in the work process itself, including high temperatures (eg, >1832Â°F [1000Â°C]); significant aerosol, dust, or fume production; and less-mechanized technology. Second, the adequacy of dust elimination, such as local and general ventilation, is critical. The third category is that of worksite and personal hygiene, including proper use of protective clothes and equipment, and thorough housekeeping. In general, small shops employing few workers are more hazardous than large factories with hundreds or thousands of employees. The small, sometimes â€œbackyardâ€• operations are less likely to adhere to industry safety regulations. They are less automated and have less environmental control, and the relatively few workers are less educated about potential risks and protective equipment usage.[32] Despite the risk factors that may be specific to each worksite, there are some types of lead-related work that are more hazardous than others, based on actual surveys of BLLs and reported incidence of clinical poisoning (Table 91-2).[100,104]

For convenience, environmental and occupational/recreational lead exposures have been discussed separately, although there is considerable overlap. For example, workers who fail to change lead-dustâ€“covered work clothes or shoes may bring this occupational lead hazard home and secondarily contaminate their children's environment.[100]

Finally, numerous additional *exotic sources* are also reported sporadically, such as exposures to contaminated folk medications or cosmetics, ingested lead foreign bodies (Fig. 91-4), or retained bullets.[20] These, too, are highlighted separately in Table 91-2.

Prevalence

Several recent national and regional surveys have evaluated current US population-based trends in BLLs and sociodemographic correlates. The CDC recently estimated that BLLs are >9 Âµg/dL in 434,000 children ages 1â€“5 years, and that approximately 10,000 adult workers are reported each year with BLLs >24 Âµg/dL.[16] Although such numbers are impressive, they represent a considerable decrease from prevalence rates done in decades prior, and it is certainly the observed clinical experience that symptomatic pediatric plumbism, in particular, is far less common than it was a generation ago. Nevertheless, for young minority children and the poor who reside in our nation's deteriorating central cities, the battle is far from won.[18] For example, the CDC reported in 2000 that children enrolled in Medicaid had a prevalence of elevated BLLs three times greater than those not enrolled.[14] Refugee, immigrant, and foreign-born adopted children remain at particularly high risk,[13] and remarkable cases of extremely elevated BLLs (>100 Âµg/dL) may still be detected on routine screening.[31]

TABLE 91-2. Occupational and Recreational Lead Sources

High-risk occupations
Automobile radiator repairers
Crystal glass makers
Firing range instructors, bullet salvagers
Lead smelters, refiners
Metal welders, cutters (includes bridge and highway reconstruction workers)
Painters, construction workers (sanding, scraping, or spraying of lead paint; demolition of lead-painted sites)
Polyvinyl chloride plastic manufacturers
Shipbreaking

Storage battery manufacturers, repairers, recyclers

Moderate-risk occupations

Automobile factory workers and mechanics

Enamelers

Glass blowers

Lead miners

Plumbers

Pottery glazers

Ship repairers

Shot makers

Solderers

Type founders

Varnish makers

Wire and cable workers

Low-risk occupations

Electronics manufacturers

Jewelers

Pipefitters

Printers

Rubber product manufacturers

Traffic police officers, taxi drivers, garage workers, turnpike tollbooth operators, gas station attendants (exposed to leaded gasoline exhaust fumes)

Recreational and hobby sources

Crafters of ceramics

Furniture refinishing, restoring

Home remodeling, refinishing

Painting (fine artist's pigments)

Repair of automobiles, boats

Stained glass making

Target shooting, recasting lead for bullets

Exotic sources

Complementary remedies, cosmetics; ingested lead foreign bodies, retained lead bullets; illicit substance abuse (heroin,

methamphetamine, leaded gasoline â€œhuffingâ€•); burning batteries, leaded paper, or wood for fuel; use of lead-glazed ceramics; handâ€“mouth contact with pool cue chalk, glazes, leaded ink; vinyl miniblinds

Toxicology

Pharmacokinetics

Inorganic Lead

Absorption

Gastrointestinal (GI) absorption is less efficient than pulmonary absorption. Adults absorb an estimated 10â€“15% of ingested lead in food, and children have a higher GI absorption rate, averaging 40â€“50%.[1,41] However, it should be noted that fasting and diets deficient in iron, calcium, and zinc enhance GI absorption of lead, factors that are frequent among groups of young children.[41,66] A study of adults under fasting conditions found a lead absorption rate from beverage consumption of almost 60%.[49] The role of essential trace elements in decreasing lead absorption is assumed to be a consequence of competitive absorption processes; an iron-binding protein, mobilferrin, initially identified in rat duodenum, is also found in human duodenal mucosa and competitively binds lead.[27]

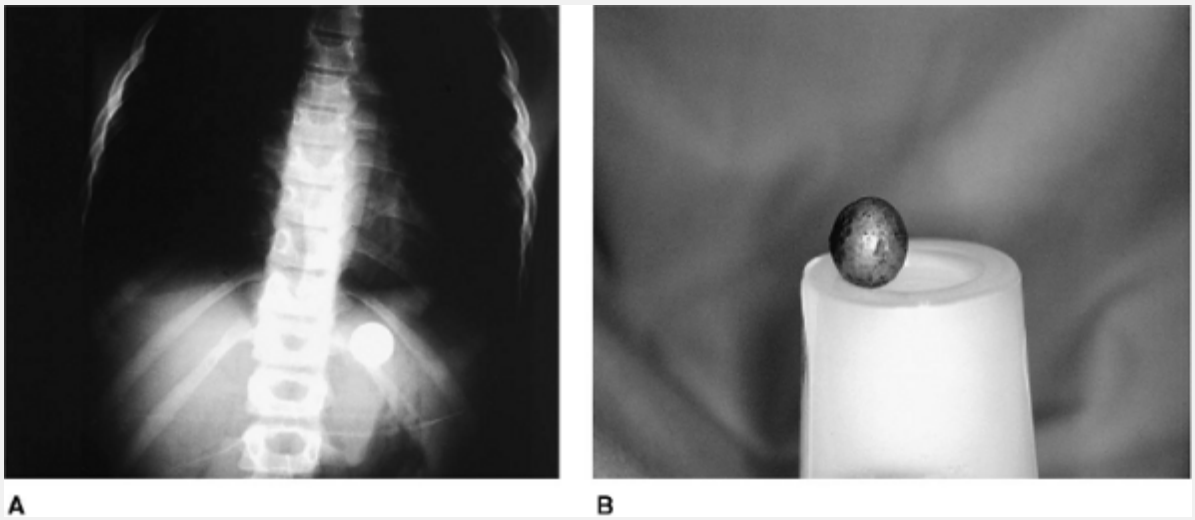

Figure 91-4. An unusual source of lead poisoning. A. Radiograph of the abdomen reveals ingested metallic foreign body. B. The ingested foreign body was a Civil War era musketball from the collection of the patient's father. *(Courtesy of Evaline Alessandrini, MD, Division of Emergency Medicine, Children's Hospital of Philadelphia, Philadelphia, PA.)*

The overall absorption of inhaled lead averages 30â€“40%. Of note, both minute ventilation and the concentration of lead in air determine airborne lead exposure, and thus a worker engaged in vigorous physical activity will absorb considerably more lead than a person in the same atmosphere at rest. Likewise, children, with relatively greater volume of inhaled air per unit of body size because of higher metabolic rates, are proportionally at greater risk in a given degree of atmospheric lead pollution. It is estimated that children have a 2.7-fold higher lung deposition rate of lead than do adults.[1]

Cutaneous absorption of inorganic lead is low; one study found an average absorption of 0.06% through intact skin.[75] Alkyl leads may have appreciable cutaneous absorption that is capable of causing

toxicity.[104]

Transplacental lead transfer is critical in fetal and neonatal lead exposure, which has been under increasing scrutiny in recent years. Lead readily crosses the placental barrier throughout gestation, and lead uptake cumulative until birth. Breast milk from heavily exposed mothers may likewise be a potential source of lead exposure, and may require lead concentration analysis before breast feeding can be safely recommended.[9]

Distribution

Absorbed lead enters the bloodstream where at least 99% is bound to erythrocytes.[40] From blood, lead is distributed into both a relatively labile soft-tissue pool and into a more stable bone compartment. This classic three-compartment model may be somewhat of an oversimplification. Currently, at least two bone compartments are recognized: a more labile pool in trabecular bone and a more stable pool in cortical bone. In adults, approximately 95% of the body lead burden is stored in bone, versus only 70% for children. The remainder is distributed to the major soft-tissue lead-storage sites, including liver, kidney, bone marrow, and brain. Most of the toxicity associated with lead is a result of soft-tissue uptake, so that the relative decrease in bone storage is another comparative disadvantage for lead-poisoned children.

Lead uptake into soft tissues occurs in a complex fashion that depends on numerous factors, including blood lead concentrations, external exposure factors, and specific tissue kinetics.[1] In general, tissue lead content in populations without very excessive exposure averages 200â€“500 parts per billion (ppb) but rises above this with excessive exposure, rapidly producing overt toxicity. For example, brain lead content in humans with overt encephalopathy is on the order of 1â€“2 parts per million (ppm) or less (eg, only twice the above-noted range). BLLs of <100 ppb (10 Âµg/dL) are associated with subtle toxic effects in critical target organs.[12]

Lead in the central nervous system (CNS) is of particular toxicologic importance, and studies have addressed specific storage sites. Lead preferentially concentrates in gray matter and certain nuclei.[40] Fetal brain uptake is relatively higher than with postnatal exposure in animal models. The highest brain concentrations are found in the hippocampus, cerebellum, cerebral cortex, and medulla.

Unlike soft-tissue storage, bone lead accumulates throughout life. Bone storage begins in utero, and occurs across all ranges of exposure, so that there is no threshold for bone lead uptake.[1] Total body accumulation of lead may range from 200â€“500 mg in workers with heavy occupational exposure.[40] Bone lead is thought to be relatively metabolically inert, but it can be mobilized from the more labile compartment, and contributes as much as 50% of the blood lead content. This may be of particular importance during pregnancy and lactation, in elder persons with osteoporosis,[111]

and in children with immobilization because of fracture or neurologic disease.[72] Lead also accumulates in teeth, particularly the dentine of children's teeth, a phenomenon that has been used to quantify cumulative lead exposure in young children.[80]

Excretion

Absorbed lead that is not retained is primarily excreted in urine (approximately 65%) and bile (approximately 35%).[1] A miniscule amount is lost via sweat, hair, and nails. Children excrete less of their daily uptake than adults, with an average retention of 33% versus 1â€“4%, respectively.[132] Biologic half-lives for lead are estimated as follows:[1,68,93] blood (adults, short-term experiments), 25 days; blood (children, natural exposure), 10 months; soft tissues (adults, short-term exposure), 40 days; bone (labile, trabecular pool), 90 days; and bone (cortical, stable pool), 10â€“20 years.

Organic Lead

Alkyl lead compounds have unique pharmacokinetics that are less-well characterized.[10] Tetraethyl lead is lipid soluble, easily absorbed through intact skin, and distributed widely to lipophilic tissues, including the brain. Tetraethyl lead is metabolized to triethyl lead, which is believed to be the major toxic compound. Alkyl leads may slowly release lead as the inorganic form, with subsequent kinetics as noted above.

Pathophysiology

General Effects

Similar to many metals, lead is a complex toxin exerting numerous pathophysiologic effects in many organ systems.[40] Furthermore, genetic polymorphism may impact on individual susceptibility to lead.[84] At the biomolecular level, lead functions in three general ways. First, its affinity for biologic electron-donor ligands, especially sulfhydryl groups, allows it to bind and impact numerous enzymatic, receptor, and structural proteins. Second, lead is chemically similar to calcium and interferes with numerous metabolic pathways, particularly in mitochondria and in second-messenger systems regulating cellular energy metabolism. Lead-induced mitochondrial injury can result in apoptosis, a phenomenon particularly well studied in animal models of retinal cells.[60] Lead may function as an inhibitor or agonist of calcium-dependent processes. For example, lead inhibits neuronal voltage-sensitive calcium channels[8] and membrane-bound Na^{+}â€“K^{+}â€“ATPase (adenosine triphosphatase),[113] but activates calcium-dependent protein kinase C.[70] Third, lead exhibits mutagenic and mitogenic effects in mammalian cells in vitro and is carcinogenic in rats and mice.[189] Evidence for human carcinogenicity, however, is lacking.[34]

Neurotoxicity

Lead's neurotoxicity involves several mechanisms, including

apoptosis, excitotoxicity, adverse influence on neurotransmitter and second-messenger function, mitochondrial injury, cerebrovascular endothelial damage, and impaired development and function of both oligodendroglia and astroglia, although particularly the former, with resultant abnormal myelin formation. In severe cases, pathologic changes may result in cerebral edema and increased intracranial pressure. Lead-induced dysfunction is reported for several neurotransmitter systems, including the classic acetylcholine-, dopamine-, norepinephrine-, Î³-aminobutyrate (GABA)-, glutamate-, and *N*-methyl-D-aspartateâ€“dependent systems.[28,40,60] Many of these phenomena can be linked to lead's ability to substitute for calcium, as noted above.

Peripheral neuropathy is a classic effect of occupational lead poisoning. The neuropathology in humans is poorly characterized, but there is primarily Wallerian degeneration. In animal models, it is associated with Schwann cell destruction, segmental demyelination, and axonal degeneration.[40] Sensory nerves are less affected than motor nerves.

Hematologic

Lead is hematotoxic in several ways, including via potent inhibition of several enzymes in the heme biosynthetic pathway (Chap. 24 and Fig. 24-3). It also induces a defect in erythropoietin function secondary to associated renal damage.[46,99] Shortened erythrocyte life span is believed to be caused by increased membrane fragility. Inhibition of Na^{+}â€“K^{+}â€“ATPase and pyrimidine-5â€²-nucleotidase may impair erythrocyte membrane stability by altering energy metabolism. The inhibition of pyrimidine-5â€²-nucleotidase is also thought to underlie the appearance of basophilic stippling in erythrocytes, representing clumping of degraded RNA, which is normally eliminated by this enzyme.[85]

Renal

Functional changes associated with acute lead nephropathy include decreased energy-dependent transport, resulting in a Fanconilike syndrome of aminoaciduria, glycosuria, and phosphaturia. These changes are believed to be related to disturbed mitochondrial respiration and phosphorylation, and are reversible with discontinuation of exposure and/or treatment.[43] A pathologic finding is characteristic nuclear inclusion bodies in renal tubular cells, composed of leadâ€“protein complex. Lead is a renal carcinogen in rodent models, but its status in humans is uncertain.[34,40]

The association of plumbism with gout (â€œsaturnine goutâ€•) was noted more than 100 years ago. Lead decreases renal uric acid excretion, with resulting elevated blood urate concentrations and urate crystal deposition in joints. Renal function is virtually always impaired in patients with gout. (See ILBASOPHILICSTIPPLING in the Image Library at http://www.goldfrankstoxicology.com)

Cardiovascular

The most important manifestation of lead toxicity on the cardiovascular system is hypertension. This is likely caused by altered calcium-activated changes in contractility of vascular smooth muscle cells, secondary to decreased Na^{+}â€“K^{+}â€“ATPase activity and stimulation of the Na^{+}-Ca^{2+} exchange pump. Lead may also affect vessels by altering neuroendocrine input or sensitivity to such stimuli, or by increasing reactive oxygen species which enhance nitric oxide inactivation.[64] Elevated plasma renin activity is found after periods of modest exposure, although activity may drop to normal or lower in chronic severe exposure.[126] Rarely, cardiotoxicity is reported.[79,95,112] Animal models demonstrate increased sensitivity to norepinephrine-induced dysrhythmias and decreased myocardial contractility, protein phosphorylation, and high-energy phosphate generation.[57] Lead-induced impairment of intracellular calcium metabolism may impact on cardiac electrophysiology.

Reproductive System

Impairment of both male and female reproductive function is associated with overt plumbism. Gametotoxic effects in animals of both sexes and chromosomal abnormalities in workers with BLLs >60 Âµg/dL are reported.[40] Testicular endocrine hypofunction occurs in smelter workers with BLLs in the 60-Âµg/dL range.[97]

Endocrine

Reduced thyroid and adrenopituitary function are found in adult lead workers.[102,103] Children with elevated lead levels have depressed secretion of human growth hormone and insulinlike growth factor.[52]

Skeletal System

In addition to the skeletal system's importance as the largest repository of lead body burden, studies suggest that bone metabolism also is adversely affected by lead.[40] Hormonal response is altered by reduced 1,25-dihydroxyvitamin D_3 levels and by inhibition of osteocalcin. Both new bone formation and coupling of normal osteoblast and osteoclast function may thus be impaired.[39,115] Bands of increased metaphyseal density on radiographs of long bones in young children with heavy lead exposure demonstrate increased calcium deposition in the zones of provisional calcification (Fig. 91-2). Impaired bone growth and shortened stature are associated with childhood lead poisoning. Impaired calcium or cyclic adenosine monophosphate (cAMP) messenger systems may underlie these cellular effects.

Gastrointestinal

Gastrointestinal effects are partly explained by spasmodic contraction of intestinal wall smooth muscle, analogous to that

believed to occur in vascular walls.[104]

Clinical Presentation

Inorganic Lead

The numerous observed lead-induced pathophysiologic effects accurately predict that the clinical manifestations of lead poisoning are diverse. These manifestations of lead toxicity are often characterized as falling into distinct syndromes of acute and chronic symptomatology. In most cases, these distinctions really describe a continuum of severity, with more severely exposed persons manifesting the classic â€œacuteâ€• lead toxicity syndrome. Rarely, patients with massive acute inhalational exposure, intentional overdose of soluble lead compounds, or intravenous administration of lead-contaminated substances of abuse present with clinical findings that are somewhat unique, but overlap considerably with the more severe cases of chronic lead exposure. By far, the most important contexts of lead toxicity in the United States today are related to chronic environmental exposure in children, and chronic occupational exposure in adult workers. These are sufficiently distinct in epidemiology, clinical manifestations, and current recommended management approaches that they are described separately (Tables 91-3 and 91-4). Severe symptomatic poisoning is rare in recent years among persons of all ages, although it is still reported.[19,73,130] In 2000, a Sudanese refugee child died of lead toxicity in New Hampshire.[15] It should be first reemphasized that the occurrence of overt clinical symptoms in lead-exposed persons is in most cases the culmination of a long history of lead exposure. As total dose increases, these symptoms are almost always preceded first by measurable biochemical and physiologic impairment, followed, in turn, by subtle prodromal clinical effects that may only become apparent in hindsight. In general, children are considered to be more susceptible than adults to toxicity for a given dose (eg, measured

blood lead concentration); however, the data for this primarily concern effects on the CNS.

TABLE 91-3. Clinical Manifestations of Lead Poisoning in Children

Clinical Severity	Typical Blood Lead Concentrations (Âµg/dL)
Severe	
CNS: Encephalopathy (coma, altered sensorium, seizures, bizarre behavior, ataxia, apathy, incoordination, loss of developmental skills; papilledema, cranial nerve palsies, signs of increased ICP) GI: Persistent vomiting Heme: Pallor (anemia)	>70â€“100
Mild/moderate	
CNS: Hyperirritable behavior, intermittent lethargy, decreased interest in play, â€œdifficultâ€• child GI: Intermittent vomiting, abdominal pain, anorexia	50â€“70
Asymptomatic	

CNS: Impaired cognition, behavior PNS: Impaired fine-motor coordination Misc: Impaired hearing, growth	0â€“49

CNS = central nervous system; GI = gastrointestinal; Heme = hematologic; ICP = intracranial pressure; Misc = miscellaneous; PNS = peripheral nervous system.

Symptomatic Children

Acute lead encephalopathy is the most severe presentation of pediatric plumbism (Table 91-3). It may be

associated with cerebral edema and increased intracranial pressure. Encephalopathy is characterized by pernicious vomiting and apathy, bizarre behavior, loss of recently acquired developmental skills, ataxia, incoordination, seizures, altered sensorium, or coma. Physical examination may reveal papilledema, oculomotor or facial nerve palsy, diminished deep-tendon reflexes, or other evidence of increased intracranial pressure.[19,130] There may be pallor if there is coexisting anemia in patients with more chronic exposure. Encephalopathy usually occurs in children ages 15â€“30 months, is associated with BLLs >100 Âµg/dL, although it is reported with BLLs as low as 70 Âµg/dL, and tends to occur more commonly in summer months, when BLLs peak.[89] Milder but ominous symptoms that may portend incipient encephalopathy include sporadic vomiting, hyperirritable or aggressive behavior, periods of lethargy interspersed with lucid intervals, and decreased interest in play activities. Many patients seek medical advice for vomiting and lethargy during the 2â€“7 days prior to onset of frank encephalopathy. Additional symptoms include anorexia, constipation, and intermittent abdominal pain.[26,89] Physical examination of such children usually reveals no specific abnormalities.

TABLE 91-4. Clinical Manifestations of Lead Poisoning in Adults

Clinical Severity	Typical Blood Lead Concentrations (Âµg/dL)
Severe	
CNS: Encephalopathy (coma, seizures, obtundation, delirium, focal motor disturbances, headaches, papilledema, optic neuritis, signs of increased ICP) PNS: Footdrop, wristdrop GI: Abdominal colic Heme: Pallor (anemia) Renal: Nephropathy	>100
Moderate	
CNS: Headache, memory loss, decreased libido, insomnia	70â€“100
GI: Metallic taste, abdominal pain, anorexia, constipation	70â€“100
Renal: Nephropathy with chronic exposure Misc: Mild anemia, myalgias, muscle weakness, arthralgias	

Mild	
CNS: Tiredness, somnolence, moodiness, lessened interest in leisure activities Misc: Impaired psychometrics, reproduction; hypertension	40â€“69
CNS = central nervous system; GI = gastrointestinal; Heme = hematologic; ICP = intracranial pressure; Misc = miscellaneous; PNS = peripheral nervous system.	

Death and serious neurologic sequelae occurred frequently when encephalopathy was common. Mortality was 65% in the prechelation era, dropping to <5% with the advent of effective chelation. The incidence of permanent neurologic sequelae, including mental retardation, seizure disorder, blindness, and hemiparesis, is 25â€“30% in patients who develop encephalopathic symptoms prior to onset of chelation.[26]

Subencephalopathic symptomatic plumbism usually occurs in children 1â€“5 years old and is associated with BLLs >70 Âµg/dL, but may occur with concentrations as low as 50 Âµg/dL. Unfortunately, common complaints in well children of this age (â€œterrible twos,â€• with functional constipation and who don't eat as much as parents expect) often overlap with the milder range of reported symptoms of lead poisoning. Not infrequently parents of children diagnosed by routine blood screening recognize milder symptoms only in hindsight, after chelation treatment (â€œit seemed as if the child was going through a phaseâ€•).[37] This is especially true currently, when symptomatic plumbism is rarely reported.[19,20] Other uncommon clinical presentations are described,[26] including isolated

seizures without encephalopathy (indistinguishable from idiopathic epilepsy), chronic hyperactive behavior disorder, isolated developmental delay, progressive loss of cortical function simulating degenerative cerebral disease, peripheral neuropathy (reported particularly in children with sickle-cell hemoglobinopathy),[35] and a syndrome of colicky abdominal pain, vomiting, constipation, and myalgias of trunk and proximal girdle muscles.

Asymptomatic Children

Children with *elevated body lead burdens, but without overt symptoms*, represent the largest group of persons believed to be at risk of chronic lead toxicity. The subclinical toxicity of lead in this population centers around subtle effects on growth, hearing, and neurocognitive development. This last effect, in particular, is the subject of intense research interest and scrutiny. An effort to rigorously evaluate several modern (since 1979), carefully done studies of the low lead and intelligence association (cross-sectional studies with blood or tooth lead, and prospective studies), and combine their results with a statistical meta-analysis technique has been reported.[91] The overall finding was that even though the majority of individual studies failed to achieve statistical significance when taken together, there was a significant inverse association between lead exposure and IQ, on the order of 1â€“2 IQ points for BLL increases from 10â€“20 Âµg/dL. Since that publication, another study evaluated IQ in patients from 6 months to 5 years old and found that BLLs were inversely correlated with IQ at 3 and 5 years of age, and that the magnitude of effect was a 4.6-point decrement in IQ for each 10 Âµg/dL increase in BLL. Of particular concern, this effect was even greater for children in the 1â€“10 Âµg/dL BLL range.[12]

Adults

Adults with occupational lead exposure may manifest numerous signs

and symptoms representing disorders of several organ systems. Severity of symptoms correlates roughly with BLLs (Table 91-4). True acute poisoning occurs rarely, after very high respiratory,[56] large oral,[81] or intravenous exposures.[82] Such patients may present with colic, hepatitis, pancreatitis, hemolytic anemia, and encephalopathy over days or weeks. Most adult plumbism is related to chronic respiratory exposure, although some authors have used the term *acute poisoning* to include patients with such exposure whose symptoms are severe and of relatively recent onset (within 6 weeks of presentation) and whose exposure is relatively brief (average 1 year or less).[30]

The hallmark of severe toxicity is *acute encephalopathy*, which has been rarely reported in adults since the 1920s.[30] The majority of modern cases are actually not associated with occupational exposures, but rather with ingestion of illicit â€œmoonshineâ€• whiskey. Of fatal adult cases in the United States between 1979 and 1988, moonshine was the lead source in 22 of 25 patients for which the lead source was identified.[116] Encephalopathy in adults is usually associated with very high BLLs (typically >150 Âµg/dL) and is manifested by seizures (75% of cases), obtundation, confusion, focal motor disturbances, papilledema, headaches, and optic neuritis.[73,129] Adult patients with severe plumbism often manifest attacks of abdominal colic, are virtually always anemic, and are at significant risk for severe peripheral nerve palsy (eg, wristdrop, footdrop) and nephropathy. Rarely are cardiac dysfunction and electrocardiographic abnormalities reported.[95]

Moderate plumbism in adults typically involves CNS, peripheral nerve, hematologic, renal, gastrointestinal, rheumatologic, endocrine/reproductive, and cardiovascular findings.[56,100,104] At BLLs >80 Âµg/dL such symptoms may include headache, memory loss, decreased libido, and insomnia. Gastrointestinal symptoms may include metallic taste, abdominal pain, decreased appetite, weight loss, and constipation. Musculoskeletal and rheumatologic complaints at this stage include muscle pain and joint tenderness. Peripheral

neuropathy may occur, primarily motor, manifesting as muscle weakness, numbness of the legs, occasional paresthesias, tremor, and hyperreflexia. Many patients at this stage have mild anemia, and those with chronic exposure are at risk for nephropathy.

Mild plumbism may manifest minor CNS findings such as changes in mood and cognition. Subtle neurocognitive abnormalities demonstrable by neuropsychiatric testing are being found in both adults and children with modest elevations in blood lead concentration. Studies have documented abnormal psychometrics and nerve conduction in workers recently exposed to lead as BLLs rose to >30 Âµg/dL.[67] Early symptoms, manifesting at BLLs of 40â€“70 Âµg/dL, may be subtle, and include increased tiredness at the end of the day, disinterest in leisure-time pursuits, falling asleep easily, moodiness, and irritability. Effects on reproductive function and blood pressure may also be apparent in this range of exposure. Historically, infertility and stillbirths were common among heavily exposed women lead workers. More recent studies found reduced

sperm counts, impaired sperm motility, and abnormal morphology in battery workers with BLLs >40 Âµg/dL,[7] and increased incidence of menstrual irregularity and spontaneous abortion in lead-exposed female workers in China.[53] Prematurity is more common in children of pregnancies associated with elevated maternal lead levels.[78] Increased blood pressure is probably the most prevalent adverse health effect observed from lead exposure in adults. Epidemiologic studies document significant associations between hypertension and body lead burdens. The association is particularly strong for adult men ages 40â€“59 years, with an approximate 1.5â€“3.0 mm Hg rise in systolic pressure for every doubling of BLL beginning at 7 Âµg/dL.[90,121] Additional studies have correlated body lead burden with several other disorders of aging, including decline in cognitive ability,[105] electrocardiographic abnormalities,[22] chronic renal dysfunction,[64] and cataract prevalence.[108]

Physical examination findings will vary with degree of severity. Mild

and moderate symptoms usually occur in patients with normal examination findings.[32] In encephalopathic patients, typical changes of stupor, coma, posturing, and papilledema are noted. Milder abnormal neurologic findings include dominant wrist or hand weakness, paresthesia, and tremor. One author described grayish stippling of the retina circumferential to the optic disk,[115] but other authors dispute this finding.[87] A bluish-purple gingival lead line (Burton line), representing lead sulfide precipitation, is described rarely in adult patients with poor oral hygiene. Abdominal guarding and tenderness are occasionally observed. Patients with gout may have typical joint findings of acute arthritis. Severely anemic patients may exhibit pallor. Careful neuropsychologic testing may reveal abnormalities of memory span, rapid motor tapping, visual motor coordination, and grip strength.[30]

Organic Lead

Clinical symptoms of tetraethyl lead (TEL) toxicity are usually nonspecific initially, and include insomnia and emotional instability.[10,104] Nausea, vomiting, and anorexia may occur. The patient may exhibit tremor and increased deep-tendon reflexes. In more severe cases, these symptoms progress to an encephalopathy with delusions, hallucinations, and hyperactivity, which may resolve or deteriorate to coma and, occasionally, death. Severe cases may also develop hepatic and renal injury. Because many reported patients are exposed via intentional abuse of leaded gasoline, much of the literature reporting this syndrome may be confounded by accompanying volatile hydrocarbon toxicity.[118] Of note, in contrast to inorganic lead poisoning, patients with significant TEL toxicity do not consistently manifest hematologic abnormalities or elevations of heme synthesis pathway biomarkers. In addition, there is no close correlation of neurotoxicity severity with measured BLL.[48]

Assessment

Clinical Diagnosis in Symptomatic Patients

For all patients in whom plumbism is considered, based on clinical manifestations, the medical evaluation should first include a comprehensive past medical history, noting only foreign-body ingestions or gunshot wounds with retained bullets. Further inquiry should elicit environmental, occupational or recreational sources of exposure as detailed earlier (Tables 91-1 and 91-2). A child between the ages of 1 and 5 may be at further risk if there is persistent vomiting, lethargy, irritability, clumsiness, or loss of recently acquired developmental skills; afebrile seizures; a strong history of pica, including acute unintentional ingestions,[47] or aural, nasal, or esophageal foreign bodies;[131] residence in a pre-1960sâ€“built home, especially with deteriorated paint, or one that has undergone recent remodeling; a family history of lead poisoning; iron-deficiency anemia; evidence of child abuse or neglect;[36,106] or is foreign-born.[13]

The differential diagnosis of plumbism is broad. Adult patients may be misdiagnosed as having carpal tunnel syndrome, Guillain-BarrÃ© syndrome, sickle-cell crisis, acute appendicitis, renal colic, and infectious encephalitis. Children are often initially considered to have viral gastroenteritis, or even to have insidious symptoms passed off as a difficult developmental phase.

The patient who presents to the ED with acute encephalopathy that may represent lead poisoning presents the physician with a dilemma: severe lead toxicity requires urgent diagnosis, but confirmatory blood lead assays are usually unavailable on an immediate basis.[50] For adults, a history of occupational exposure is often available from past medical records or family members, and lead encephalopathy can be strongly considered with positive supportive laboratory findings (usually available on urgent basis) such as anemia, basophilic stippling, elevated erythrocyte protoporphyrin (especially

>250 Âµg/dL), and abnormal urinalysis. In this context, it might be appropriate to institute presumptive chelation therapy while awaiting lead concentrations. In children, a similar indication for presumptive treatment would be suggested by a constellation of clinical features and ancillary studies, such as age 1â€“5 years, a prodromal illness of several days' to weeks' duration (suggestive of milder lead-related symptoms), occurrence in summer, history of pica and source of lead exposure, the laboratory features noted above, which are equally helpful in young children, radiologic findings of dense metaphyseal â€œlead linesâ€• at wrists or knees (Fig. 91-2), and/or evidence of recent pica for lead paint particles on abdominal radiographs (Fig. 91-5). In both adults and children, the decision to institute empiric chelation treatment should not deter additional emergent diagnostic efforts to exclude or to confirm other important entities while blood lead concentrations are pending. An important consideration in this context may be the suspicion of an acute, potentially treatable CNS infection (eg, bacterial meningitis or herpetic encephalitis). Lumbar puncture may be dangerous in patients with lead encephalopathy because of the risk of cerebral herniation. If immediate lumbar puncture is thought to be highly desirable, a computed tomography scan would allow determination of severe cerebral edema, midline shift, or other evidence of especially high risk for herniation. If performed, the minimal amount of fluid necessary for diagnosis (<1 mL) should be removed using a small-gauge needle. Alternatively, empiric treatment for infectious processes can be initiated while the lead concentration is pending, and delayed lumbar puncture can be performed if the blood lead concentration is normal.

Laboratory Evaluation

In patients suspected of having plumbism, laboratory testing is used to augment the evaluation of both lead exposure and lead toxicity. The *whole BLL* is the principal measure of lead exposure available in clinical practice. In any patient suspected of symptomatic plumbism, whole blood should be collected by venipuncture into special lead-

free evacuated tubes. The BLL is typically determined by atomic absorption spectrophotometry. For asymptomatic children, BLL screening is often performed by capillary blood testing for convenience; however, venous confirmation of elevated capillary lead concentrations, unless extremely high (eg, >69 Âµg/dL) or the patient

is clearly symptomatic, is still considered mandatory prior to chelation or other significant interventions. The *erythrocyte protoporphyrin concentration* test reflects lead's inhibition of the heme synthesis pathway (Chap. 24) and had been used as a screening tool in the past, but is no longer considered sufficiently sensitive. The erythrocyte protoporphyrin concentration test may still be useful for tracking response to therapy and in distinguishing acute from chronic lead exposure, as an adjunct to the emergency diagnosis of symptomatic plumbism, if emergent BLL determination is not available, and, rarely, in the evaluation of suspected factitious plumbism. Routine *serum chemistries, renal function tests, urinalysis*, and *complete blood count* are indicated in patients who are symptomatic or about to undergo chelation therapy. *Radiographic studies* may suggest recent lead ingestion and/or toxicity. Abdominal films may reveal lead paint chips or other ingested lead foreign material (Figs. 91-4 and 91-5). The finding of â€œlead lines,â€• metaphyseal densities at the ends of long bones in young children, may substantiate a clinical diagnosis of plumbism before BLLs are available (Fig. 91-2). Finally, *X-ray fluorescence* technology estimates bone lead,[51] and thus indirectly is a cumulative measure of body lead exposure. The X-ray fluorescence technique has been used in research studies of issues concerning past chronic heavy lead exposure and a variety of current health outcomes.[128]

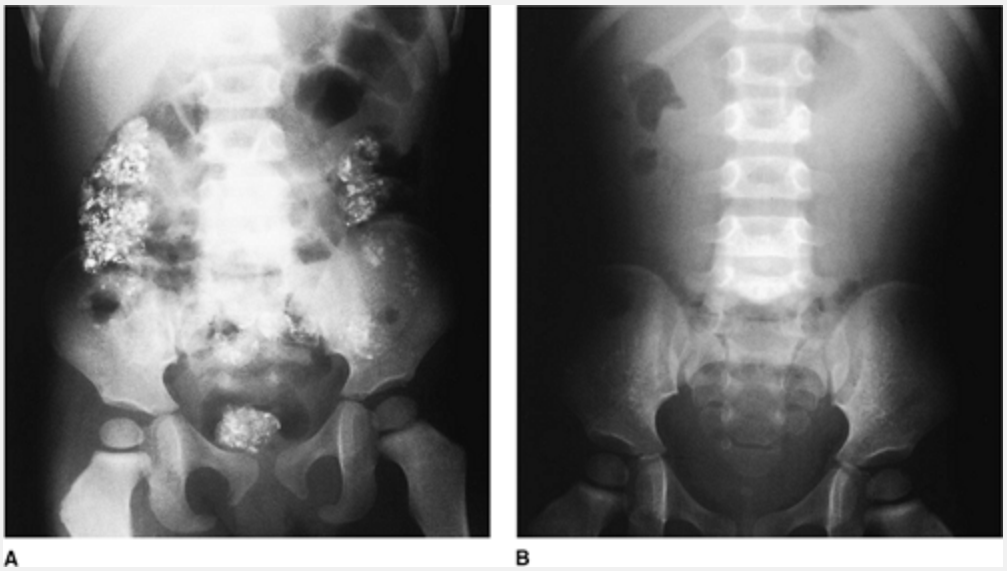

Figure 91-5. A. Abdominal radiograph of a child who had massive paint chip ingestion. B. Followup radiograph after whole-bowel irrigation. *(Courtesy of Department of Radiology, St. Christopher's Hospital for Children, Philadelphia, PA.)*

Screening

Although outside the scope of this discussion, screening is an essential public health practice for the prevention of severe plumbism in both children and adults from high-risk settings. Table 91-5 outlines the current CDC[17] pediatric recommendations, which also are endorsed by the American Academy of Pediatrics.[2] Likewise, the Occupational Safety and Health Administration (OSHA) maintains a lead standard for US workers formulated to reduce workplace exposure to lead, to decrease symptomatic lead poisoning, and to provide quality medical care to workers with elevated blood lead levels.[123,124,125] Table 91-6 summarizes the action BLL values for worker notification, removal, and reinstatement.

Management

There are several caveats about the management of lead poisoning. First, the most important aspect of treatment is removal from further exposure to lead. Unfortunately, effective implementation of this therapy is often beyond the control of the clinician, but rather depends on a complex interplay of public health, social, and political actions. Currently, the ability to control exposure is generally more applicable to adults with occupational exposures than to children exposed to residential hazards. Second, in children for whom some residual lead exposure continues, optimization of nutritional status is vital in order to minimize absorption. Finally, pharmacologic therapy with chelation agents, although a mainstay of therapy for symptomatic patients, is an inexact science, with numerous unanswered questions despite almost 50 years of clinical use.[3,6,58] The rationale for chelation therapy of lead-poisoned patients is that chelating drugs complex with lead, forming a chelate that is excreted in urine, feces, or both. Chelation therapy does increase lead excretion, reduce blood levels, and reverse hematologic markers of toxicity during therapy. Reports from the 1950s found symptomatic improvement in adults chelated for lead colic.[127] The institution of effective combination chelation treatment of childhood lead encephalopathy in the 1960s certainly contributed to the dramatic decline in mortality and morbidity of that devastating degree of plumbism.[26] However, the same era saw major advances in pediatric critical care, in general, and medical management of increased intracranial pressure, in particular. The situation of chelation therapy for asymptomatic patients with mildly to moderately

increased body burdens of lead is even less clear, and many questions regarding efficacy and safety remain.[25,42,58] To date, long-term reduction of target tissue lead content or reversal of toxicity is not demonstrated in human trials.[71,98]

TABLE 91-5. Pediatric Screening and Followup Guidelines

Screening
Screen 1. All high-risk children at ages 1 and 2 y (3â€“6 y if not previously screened) 2. Selected low-risk children (any affirmative answer to risk questions) (high-risk community = 12% of young children with elevated BPb, 27% of homes built before 1950; all children enrolled in Medicaid)
Personal Risk Questionnaire 1. Does your child live in or regularly visit a home built before 1950? 2. Does your child live in or regularly visit a home built before 1978 undergoing remodeling or renovation (or renovated within 6 mo)? 3. Specific exposure questions: Personal, family, or playmate history of lead poisoning Occupational, industrial, hobby exposures Proximity to major roadway Hot tap water for consumption Cultural exposures (complementary remedies, cosmetics, ceramic food containers, trips, residence outside United States, international adoptees) Migrant farm workers, receipt of poverty assistance History of pica for paint chips, dirt History of iron deficiency

Followup	
BPb (Âµg/dL)	*Recommended Action*
â‰¤9	Retest in 1 y
10â€“14	Retest in 3 mo; education
15â€“19	Retest in 2 mo; education; if 15â€“19 twice, refer for case management
20â€“44	Clinical evaluation; education; environmental investigation and control
45â€“69	Clinical evaluation and case management within 48 h; education; environmental investigation and control; chelation therapy
â‰¥ 70	Hospitalize child; immediate chelation therapy; education; environmental investigation and control

BPb = venous blood lead.
Educational interventions as per Table 91-7.
Chelation therapy as per Table 91-8.
Adapted from Centers for Disease Control and Prevention: Screening Young Children for Lead Poisoning: Guidance for State and Local Public Health Officials. US Dept of Health and Human Services, Atlanta, CDC, 1997.

Decreasing Exposure

All patients with significantly elevated lead concentrations warrant identification of the lead exposure source and specific environmental interventions (Table 91-7). In adults, this usually involves changes in their worksite.[32,104] Remedial actions might include improvements in ventilation, modification of personal hygiene habits, and optimal use of respiratory apparatus. It is vital to prohibit smoking, eating, and drinking in a lead-exposed work area. Work clothes should be changed after each shift and should not be lockered together with street clothes.

TABLE 91-6. OSHA General industry[a] Standard for Various Lead Concentrations in Blood (BLLs)

Number of tests	BLL (Âµg/dL)	Action Required
1	â‰¥40	Notification of worker in writing; medical examination of worker and consultation
3 (average)	â‰¥50	Removal of worker from job with potential lead exposure
1	â‰¥60	Removal of worker from job with potential lead exposure

2	<40	Reinstatement of worker in job with potential lead exposure

[a] The construction industry standard is similar for worker notification (at 40 Âµg/dL) and reinstatement (<40 Âµg/dL Ã— 2) but requires worker removal for a single value â‰¥50 Âµg/dL.
Adapted from US Department of Labor, Occupational Safety and Health Administration: Medical surveillance guidelinesâ€”1910.1025 App C. Available at http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS?p_id=10033. Last accessed December 29, 2005; and Leadâ€”1926.62. Available at http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS?p_id=0641. Last accessed December 29, 2005.
See also references 123,124,125.

Table 91-7 also summarizes several specific educational guidelines that may be offered to parents of lead-exposed children.[4,11,20] Overarching principles include home lead paint abatement (done preferably by professionals, with the family out of the home), home dust reduction techniques, decreasing soil lead exposure, and nutritional evaluation and counseling. Clinicians who have primary responsibility for children with elevated lead levels should refer to the CDC's exhaustive monograph, which details such pediatric case mananagement.[20]

Chelation Therapy

The indications for and specifics of chelation therapy are determined by patient age, blood lead concentration, and clinical

symptomatology (Table 91-8). Three chelation agents are currently recommended as drugs of choice for the treatment of lead poisoning: BAL and $CaNa_2EDTA$ are used parenterally for more severe cases, and succimer is available for oral therapy. Pharmacologic profiles of these three agents are detailed in the corresponding Antidotes in Depth. A fourth drug, D-penicillamine, has been used orally for patients with mild to moderate excess lead burdens. Unfortunately, D-penicillamine has a toxicity profile that includes serious, life-threatening hematologic disorders and reversible, but serious, dermatologic and renal effects; consequently, since 1991, its role in lead poisoning treatment has been largely replaced by succimer. Currently, the American Academy of Pediatrics recommends D-penicillamine use only when unacceptable adverse reactions to both succimer and $CaNa_2EDTA$ occur, and it remains important to continue chelation.[3]

TABLE 91-7. Reducing Lead Exposure

Adults
(Evaluate possible sources beyond occupational setting: Tables 91-1 and 91-2)
- Implement OSHA lead standard
- Improve ventilation
- Use respiratory apparatus
- Wear protective clothing; change from work clothes before leaving worksite
- Modify personal hygiene habits
- Prohibit eating, drinking, smoking in worksite

Children
(Consider possible sources beyond lead paint exposure: Tables 91-1 and 91-2)
- Notify local health department

Home lead paint abatement (professional contractors if possible; use plastic sheeting, low dust-generating paint removal; replacement of lead-painted windows, floor treatment; final cleanup with high-efficiency particle air vacuum, wet-mopping)

Avoid most hazardous areas of home, yard

Dust control: wet-mopping, sponging with high-phosphate detergent; frequent hand, toy, pacifier washing

Soil lead exposure reduction by planting grass, shrubs around house

Use only cold, flushed tap water for consumption

Optimize nutrition: avoid fasting; iron, calcium sufficient diet; iron and/or calcium supplementation as necessary

Avoid food storage in open cans

Avoid imported ceramic containers for food, beverage use

Evaluate parental occupations, hobbies

TABLE 91-8. Chelation Therapy Guidelines[a]

Condition, BPb (Âµg/dL)	Dose	Regimen/Comments
Adults		
Encephalopathy	BAL 450 $mg/m^2/d$[a]	75 mg/m^2 IM every 4 h for 5 d
	$CaNa_2EDTA$ 1500 $mg/m^2/d$[a]	Continuous infusion or 2â€“4 divided IV doses for 5 d (start 4 h after BAL)

Symptoms suggestive of encephalopathy or >100	BAL 300â€“450 $mg/m^2/d^a$ $CaNa_2EDTA$ 1000â€“1500 $mg/m^2/d^a$	50â€“75 mg/m^2 every 4 h for 3â€“5 d Continuous infusion or 2â€“4 divided IV doses for 5 d (start 4 h after BAL) Base dose, duration on BPb, severity of symptoms (see text)
Mild symptoms or 70â€“100	Succimer 700â€“1050 $mg/m^2/d$	350 mg/m^2 tid for 5 d, then bid for 14 d
Asymptomatic and <70	Usually not indicated	Remove from exposure (Table 91-7)
Children		
Encephalopathy	BAL 450 $mg/m^2/d^a$ $CaNa_2EDTA$ 1500 $mg/m^2/d^a$	75 mg/m^2 IM every 4 h for 5 d Continuous infusion or 2â€“4 divided IV doses for 5 d (start 4 h after BAL)
Symptomatic or > 69	BAL 300â€“450 $mg/m^2/d^a$ $CaNa_2EDTA$ 1000â€“1500	50â€“75 mg/m^2 every 4 h for 3â€“5 d Continuous infusion or 2â€“4 divided IV doses for 5 d (start 4

	mg/m^2/d[a]	h after BAL) Base dose, duration on BPb, severity of symptoms (see text)
Asymptomatic: 45â€“69	Succimer 700â€“1050 mg/m^2/d or $CaNa_2EDTA$, 1000 mg/m^2/d[a] (*or rarely*, D-penicillamine)	350 mg/m^2 tid for 5 d, then bid for 14 d Continuous infusion or 2â€“4 divided IV for 5 d (see text)
20â€“44	Routine chelation not indicated (see text)	If succimer used, same regimen as per above group
	Attempt exposure reduction	(Table 91-7)
<20	Chelation not indicated	
	Attempt exposure reduction	(Table 91-7)

BPb = blood lead (Âµg/dL); EP = erythrocyte protoporphyrin; IM = intramuscular; IV = intravenous; d = day.

[a] Doses expressed mg/kg: BAL 450 mg/m^2 (24 mg/kg); 300 mg/m^2 (18 mg/kg).
$CaNa_2EDTA$ 1000 mg/m^2 (25â€“50 mg/kg); 1500 mg/m^2 (50â€“75 mg/kg) adult maximum 2â€“3 g/d). Succimer 350 mg/m^2 (10 mg/kg).
Subsequent treatment regimens based on postchelation BPb and clinical symptoms (see text).
Adapted from references 3, 20, 56, 89, and 92

Chelation is not a panacea for lead poisoning. It is a relatively inefficient process, with a typical course of therapy decreasing body content of heavy metal by 1â€“2%.[58,77] Furthermore, there is little evidence that chelating agents have significant access to critical sites in target organs, particularly in the brain.[29] Assumptions that reducing blood lead level will improve subtle neurocognitive dysfunction or other subclinical organ toxicity are appealing theoretically, but unproven.[98,120]

Pediatric Therapy

Lead encephalopathy is an acute life-threatening emergency and should be treated under the guidance of a multidisciplinary team in the intensive care unit of a hospital experienced in the management of critically ill children. Encephalopathy requires treatment by combination parenteral chelation therapy with maximum-dose BAL and $CaNa_2EDTA$, and meticulous supportive care.[3,20,26] Such combination therapy has a dramatic effect on decreasing BLLâ€”to 50% or less of baseline within 15 hours, and to 75â€“80% of baseline by 48â€“72 hours. It is far superior to monotherapy with $CaNa_2EDTA$ in this regard.[26]

Chelation is instituted with intramuscular (IM) BAL 75 mg/m^2/d (or 25 mg/kg/d) in 6 divided doses.[3,20] The second dose of BAL is given 4 hours later, followed immediately by intravenous (IV) $CaNa_2EDTA$, in maximum concentration of 0.5% solution, at 1500 mg/m^2/d (or 50 mg/kg/d) as a continuous infusion over several hours or in divided-dose infusions.[3,20,89] The delay in initiating $CaNa_2EDTA$ infusion is based on past observations of clinical deterioration in encephalopathic patients treated with $CaNa_2EDTA$ alone.[3,26] Therapy is typically continued with both agents for 5 days, although in milder cases with prompt resolution of encephalopathy and decrease of BLL to <50 Âµg/dL, BAL may be discontinued after 3 days, with continuation of $CaNa_2EDTA$ alone for 2 more days.

The presence of radiopaque material in the gastrointestinal tract on radiography has raised concern that parenteral chelation might enhance absorption of residual gut lead. This issue is not settled fully,[25,54] but most experts advocate initiation of chelation without delay in seriously symptomatic patients. It seems reasonable to simultaneously attempt bowel decontamination,[3] as with a whole-bowel irrigation solution. One case report described the successful use of chelation therapy begun with parenteral BAL and $CaNa_2EDTA$ and then enteral succimer (initiated after 3 days of whole-bowel irrigation) for a child with lead encephalopathy and an extraordinarily high BLL of 550 Âµg/dL.[39] Generally, oral fluids, feedings, and medications are withheld for at least the first several days. Careful provision of adequate intravenous fluids optimizes renal function while avoiding overhydration and the risk of exacerbating

cerebral edema. The occurrence of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) may be associated with lead encephalopathy,[26,117] so urine volume, specific gravity, and serum electrolytes should be closely monitored, especially as fluids are gradually liberalized with clinical improvement. In the context of lead encephalopathy, this approach would need to be tempered by the requirement for maintaining good urine output to optimize

chelation efficacy.

Seizure control is usually accomplished with benzodiazepines. Rarely, continuous infusions of midazolam or high-dose pentobarbital therapy may be necessary.[130] Ongoing anticonvulsant therapy is typically continued with phenytoin or phenobarbital.

Recent advances in *management of cerebral edema and increased intracranial pressure* have not as yet been critically evaluated in the currently rare context of lead encephalopathy. Lumbar puncture should be avoided if lead encephalopathy is highly suspected and acute infectious processes are not. It seems reasonable that noninvasive measures such as hyperventilation and steroids might have a salutary effect at minimal risk of increased iatrogenic morbidity.[3,130] Mannitol administration has been suggested as a possible adjunct in the therapy of such patients when cerebral edema is complicated by SIADH and/or impaired renal function.[26] Whether more aggressive measures, such as intracranial pressure monitoring, induced hypothermia, or barbiturate coma, would decrease mortality or morbidity further is unknown.

Children with *milder symptoms, or* who are *asymptomatic with BLL*. >70 Âµ*g/dL*, should be chelated with a regimen similar to that recommended for encephalopathy. It is likely that this group of patients will require only 2â€“3 days of BAL in addition to 5 days of $CaNa_2EDTA$. The asymptomatic patients in this group might also be adequately treated with 2,3-dimercaptosuccinic acid (succimer) plus $CaNa_2EDTA$, or even succimer alone, but these regimens have not been studied in such children. Intensive care monitoring may be prudent for such patients as well, at least during the initiation of chelation therapy.[77]

Chelation therapy is widely recommended for *asymptomatic children with BLLs between* 45 and 70 Âµ*g/dL*.[3,6,20,77] Children without overt symptoms may be treated with succimer alone, which has documented efficacy in lowering BLLs and short-term safety since its FDA approval in 1991.[45,62] Succimer is initiated at 30 mg/kg/d (or

1050 mg/m^2/d) orally in 3 divided doses; this is continued for 5 days, then decreased to 20 mg/kg/d (or 700 mg/m^2/d) in 2 divided doses for 14 additional days.[3,44] The original data establishing this empiric dosing regimen were based on surface area rather than body weight.[44] For younger children, the alternative dosing by body weight results in suboptimal dosing.[96] Although the ability to chelate children orally with succimer makes it tempting to prescribe routinely for outpatient therapy, and some animal evidence suggests succimer does not enhance enteral lead absorption,[55] clinical reports suggest that children must be protected from continued lead exposure during succimer chelation.[23,24] Home abatement and reinspection should be accomplished before initiation of ambulatory succimer therapy; if this is not feasible, hospitalization is still warranted. Alternative regimens (for rare patients with succimer intolerance or allergy, or parental noncompliance) include inpatient parenteral chelation with $CaNa_2EDTA$ at 25 mg/kg/d for 5 days,[3] or an outpatient oral course of D-penicillamine.

After initial chelation therapy, *decisions to repeat treatment* are based on clinical symptoms and followup BLLs. Patients with encephalopathy or any severe symptoms, or initial BLL >100 Âµg/dL, will often require repeated courses of treatment. It is suggested that at least 2 days elapse before restarting chelation. The precise regimen and dosing of chelating agents are determined by ongoing symptomatology and the repeat BLLs (Table 91-8). A third course of chelation should rarely be necessary sooner than 5â€“7 days after the second course ends.[89] For patients with milder degrees of plumbism (eg, asymptomatic, initial BLL <70 Âµg/dL), it is reasonable to allow 10â€“14 days of reequilibration before restarting treatment.[3]

The management of *asymptomatic children with BLLs of* 20â€“44 Âµ*g/dL* is controversial.[23,69,76,120] The National Institutes of Health-sponsored Treatment of Lead-exposed Children (TLC) trial found only modest efficacy of succimer in reducing BLL. Furthermore, at 3 years postenrollment no benefit was noted in treated patients on measures

of cognition, neuropsychiatric function, or behavior.[98] Of note, small, but statistically significant, decrements in growth velocity were noted in the treatment group, which might reflect trace mineral depletion. This study has been criticised, particularly for using a single chelating agent and having failed to lower BLL significantly over time between treated and control groups.[109] Since its initial publication, the primary findings of the TLC trial on lack of cognitive improvement were confirmed in a 7-year followup study.[33] In addition, a reanalysis of the original data found that falling blood concentrations did correlate with improved cognitive scores over the initial 36-month trial period (~ IQ points for each 10 Âµg/dL drop in BLL), but only in the placebo group.[65] Currently, the CDC[20] and the American Academy of Pediatrics[3] recommend aggressive environmental and nutritional interventions with close monitoring of blood lead concentrations, *without routine chelation therapy*, for such children. Nevertheless, there may still be potential indications for occasional chelation treatment in this group, including BLLs at the higher end of the range (eg, 35â€“44 Âµg/dL), especially if BLLs remain the same or rise over several months after rigorous environmental controls are instituted, in younger children (eg, younger than 2 years old), with evidence of biochemical toxicity (an elevated erythrocyte protoporphyrin concentration, after iron supplementation, if necessary), or any hint of subtle symptoms.

BLLs of 10â€“19 Âµg/dL are defined by the CDC as representing excessive exposure to lead, but do not require chelation therapy. Close monitoring (for the 10â€“14 Âµg/dL range) and careful environmental investigation and interventions as necessary (particularly for the 15â€“19 Âµg/dL range) are appropriate and sufficient.[3,20] The educational approaches outlined earlier should be included in the case management of all children with even modestly elevated lead levels (Table 91-7).

Adult Therapy

General Considerations

The first principle in the treatment of adults with lead poisoning is that chelation therapy may not substitute for adherence to OSHA lead standards at the worksite and should never be given prophylactically.[33,56] In addition to the guidelines for decreasing lead exposure noted earlier, chelation therapy is indicated for adults with significant symptoms (encephalopathy, abdominal colic, severe arthralgias, or myalgias) and evidence of target organ damage (neuropathy or nephropathy), and possibly in asymptomatic workers with markedly elevated BLLs and/or evidence of biochemical toxicity or increased chelatable lead.[99,104,107] Table 91-8 outlines chelation therapy regimens for adults. Recent reports support the use of succimer in adult

patients with mild to moderate plumbism after environmental and occupational remedies have been instituted.[63,92] Treatment of patients with tetraethyl lead toxicity is largely supportive, with sedation as necessary. If blood lead concentrations are significantly elevated, chelation as described above may be considered, but it has not been found clinically efficacious.[104,118]

Pregnancy, Neonatal, and Lactation Issues

An area of particular concern in the management of adult plumbism involves decisions regarding therapy during pregnancy. As noted previously, lead freely passes the placental barrier and accumulates in the fetus throughout gestation. Chelation therapy during early pregnancy poses theoretical problems of teratogenicity, particularly that caused by enhanced fetal excretion of potentially vital trace elements, or translocation of lead from mother to fetus (see also the relevant Antidotes in Depth). Symptomatic pregnant women with elevated BLLs certainly warrant chelation therapy, regardless of these concerns. Additionally, of some reassurance regarding fetal health, a recent case series and 25-year literature review of lead

poisoning during pregnancy found no reports of chelation-associated birth defects in the handful of such published cases.[110] It should be noted that despite falls in maternal BLL with chelation therapy, newborn BLLs may be considerably higher and, in some cases, approximated the pretreatment maternal BLL, implying limited efficacy for in utero fetal chelation. However, the newborn's hemoglobin level was generally much higher than the mother's, and thus some of the maternalâ€“neonatal difference in lead concentrations may simply reflect this difference in hemoglobin concentration and hence total blood lead content. In general, there currently seems little support for routine chelation therapy in pregnant women who would not otherwise warrant treatment based on their own symptoms or degree of elevated BLL.

Postnatally, infant BLLs may decline over time without chelation, but this occurs very slowly.[101] In 2 reported neonates exposed to prenatal maternal chelation, who were then monitored for 2 weeks postpartum, the BLL remained stable or rose until chelation therapy was instituted.[88,119] In 2 additional cases of neonates whose mothers were not treated prepartum, BLLs also remained stable or rose for 17 days to 3 weeks.[38,114] Thus, postpartum chelation therapy is warranted for neonates, depending on BLLs, as per the guidelines described above for older children. Lastly, the issue of allowing mothers with elevated BLLs to breast-feed their infants may arise. One small case series found that breast milk from 2 women with BLLs of 34 and 29 Âµg/dL, respectively, had clinically insignificant lead content (<0.01 Âµg/mL).[9] Breast milk analysis may be warranted in such cases, particularly with BLLs of 35 Âµg/dL or greater, before safely advising continued nursing.

Summary

Lead is a ubiquitous element in the earth's crust that has long been used by humans for a variety of purposes. Metallic lead finds many uses for its waterproofing and electrical and radiation shielding

properties. Lead compounds are used as paint pigments and find many applications in the manufacture of plastics, ceramics, glass, and explosives.

Lead poisoning or plumbism has an equally long history, dating back to antiquity. Today, lead poisoning is primarily an important environmental health problem for young children exposed to deteriorated lead paint, and as an occupational exposure for adult workers, although numerous other exotic exposures are continually reported.

Lead has toxic effects on multiple organs, involving especially the hematologic and neurologic systems in patients of all ages, and renal injury with hypertension in adults. This can result in a broad spectrum of clinical effects, ranging from vague constitutional symptoms without overt physical signs to an acute encephalopathy with potentially fatal cerebral edema and increased intracranial pressure. Several techniques have been used to estimate increases in body lead burden, but currently the measurement of whole-blood lead concentration is favored.

The mainstays of treatment are removal from exposure and chelation therapy for those patients with symptoms or significantly elevated body lead burdens. Defining a group of asymptomatic patients that will benefit from chelation therapy has been difficult and controversial. Parenteral chelation with $CaNa_2EDTA$ and BAL is efficacious in lowering BLLs and reducing mortality and morbidity from severe lead poisoning. Succimer, an oral chelator, also has efficacy in reducing BLLs in asymptomatic children.

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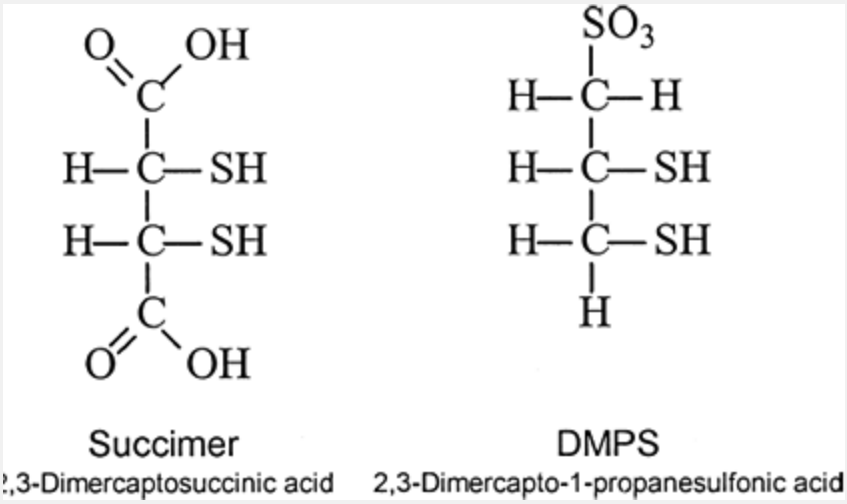
Antidotes in Depth

Succimer (2,3-Dimercaptosuccinic Acid)

Mary Ann Howland

History



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Succimer was initially synthesized in 1949 in England.[66] In 1954, antimony-a,aâ€²-dimercaptopotassium succinate (TWSb) was developed to treat schistosomiasis.[38] TWSb is antimony bound to the potassium salt of succimer in a 2:3 ratio, forming a water-soluble drug with 50 times less toxicity than the previously used antimony compound, tartar emetic. Several years later, a group from Shanghai demonstrated the ability of the sodium salt of succimer to increase the LD_{50} (median lethal dose for 50% of test subjects) of tartar emetic 16-fold in mice.[97] An early review of the Chinese experience with IV succimer in the treatment of occupational lead and mercury poisoning suggested efficacy similar to IV edetate calcium disodium ($CaNa_2EDTA$) in increasing urinary lead and to IM DMPS (racemic-2,3-dimercapto-1-propanesulfonic acid, unithiol) for mercury, with little observed toxicity.[95] This experience, subsequent widespread use in Asia[70,73,83,95,96,99] and Europe,[16,30,36,39,58,91] and the realization that succimer could be used orally,[3,45] led to US-based animal experiments, human trials, and FDA approval in 1991 for the treatment of lead-poisoned children.

Pharmacology

Succimer is a white crystalline powder with a molecular weight of 182 daltons and a characteristic sulfur odor and taste. Succimer is the meso form of 2,3-dimercaptosuccinic acid; the racemic form is being investigated.[33] Because it contains four ionizable hydrogen ions, succimer has four different pK_asâ€”2.31, 3.69, 9.68, and 11.14â€”with the dissociation of the two lower values representing the carboxyl groups and the two higher values the sulfur groups.[4] Lead and cadmium bind to the adjoining sulfur and oxygen atoms, whereas arsenic and mercury bind to the two sulfur moieties,

forming pH-dependent water-soluble complexes[79] (see Fig. A24-1). Succimer is highly protein-bound to albumin through a disulfide bond. Subhuman primate studies of IV and oral ^{20}C succimer indicate that following an IV dose, radiolabel is eliminated almost exclusively via the kidney, with only trace amounts (<1%) excreted via feces or expired air.[66] Following the administration of a single oral dose of 10 mg/kg, succimer is rapidly and extensively metabolized.[61] Approximately 20% of the administered dose is recovered in the urine, presumably reflecting the low bioavailability of the drug. Of the total drug eliminated in the urine, 89% is altered and in the form of disulfides of L-cysteine. The majority of the altered succimer is in the form of a mixed disulfide. The remaining 11% is excreted as unaltered free succimer.[61] Maximal excretion of succimer occurs in urine specimens collected between 2 and 4 hours after administration. Surprisingly, the blood only contains albumin-bound succimer and no evidence of the altered disulfide moieties, which suggests that the kidney may be involved in the biotransformation of succimer.

Lead

In addition to precise analysis of metal elimination kinetics, measures of clinical outcome are essential for an understanding of the utility of this agent. The Treatment of Lead-exposed Children (TLC) trial is a step in that direction.[93] The TLC trial is a randomized, multicenter, double-blind, placebo-controlled, ongoing study to examine the effects of succimer on cognitive development, behavior, stature, and blood pressure in children 1â€“3 years old with blood lead concentrations between 20 and 44 Âµg/dL.

Several groups are studying the efficacy of succimer in reducing blood, brain, and tissue lead by using rat and nonhuman primate models of childhood and adult lead poisoning.[84,85,87] Although monkeys most closely resemble humans in their lead-associated

toxicity, their use is costly;[72] the rat model is economical but of limited use because of the species differences with regard to lead and succimer metabolism and efficacy. The primate experiments are exciting, but one substantial criticism is the lack of comparison groups with regard to dimercaprol and $CaNa_2EDTA$ treatment. Notably that the animal evidence suggests that isolated blood lead concentrations do not accurately reflect brain lead concentrations. If this finding is also true in humans, the importance and ability to interpret blood lead concentrations will be significantly altered.

The validity of using blood lead concentrations as a marker of brain lead was studied in the adult rhesus monkey. Lead was administered orally for 5 weeks to achieve a target blood lead concentration of 35â€“40 Âµg/dL.[28] Five days after lead exposure ceased, succimer chelation was initiated in the currently approved dosage regimen. Two IV doses of radioactive lead tracer were administered prior to succimer chelation to study the kinetics of recent versus chronic lead uptake and distribution. Four areas of the brain, as well as blood and bone, were assayed for lead. Merely stopping further lead exposure significantly reduced blood lead concentrations by 63% and brain lead concentrations by 34% compared to pretreatment concentrations, and was not statistically different than succimer administration after halting exposure. However, when an integrated area under the blood drug concentration versus time curve (AUC) blood analysis was used over the 19-day succimer treatment course, instead of a single blood lead concentration, the differences between succimer and control were statistically significant.

How clinically significant these differences are is unclear. Succimer-treated animals showed the biggest drop in blood lead concentrations over the first 5 days, while a similar end point was gradually achieved in the control. The lead from both the recent exposure (radioactive tracer lead) and chronic exposure declined to the same extent, independent of treatment with succimer. A

better correlation was found between brain prefrontal cortex lead concentrations and an integrated blood lead analysis than with a single blood lead measurement.

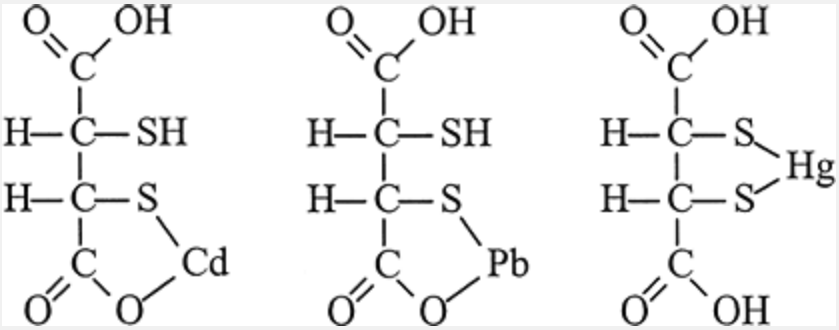

Figure A24-1. The chelation of cadmium, lead, and mercury with succimer.

Similarly, a study in neonatal rats demonstrated that increasing the duration of succimer chelation from 7â€“21 days decreased brain lead concentrations without a corresponding decrease in blood lead concentrations.[84] The authors proposed that a slow rate of egress of brain lead to the blood was responsible for the demonstrable benefit of prolonging therapy to 21 days. In this study, succimer decreased blood lead concentration by approximately 50% when compared to the vehicle as control, and this difference persisted for the 21 days of treatment. With succimer treatment, brain lead concentration decreased by 38% at 7 days and by 68% at 21 days. Previous animal studies demonstrated the ability of succimer to enhance urinary lead elimination [37,45,87] and to reduce blood,[14,26,34,35,50,76,85,87,88,90] brain,[14,26,76,89,90] liver,[87] and kidney lead concentrations,[14,26,35,50,76,90] while reducing[14,50,76,90] or showing

no effect on bone lead concentrations.[26,87] These studies differ in the amounts and duration of lead administration prior to chelation, as well as in route, dose, and duration of chelation. It is noteworthy that several months after a course of succimer chelation, tissue lead concentrations were similar to pretreatment values, indicating that the short-term effects did not persist.[26] Given the limited absolute amount of lead that is actually eliminated by chelation in comparison to the total body burden, particularly bone, these transient effects are not surprising.

Under a variety of experimental conditions in animals, succimer prevents the deleterious effect of lead on heme synthesis,[14,45,76] blood pressure,[54] and behavior.[88]

Published studies of the use of succimer in both children and adults with chronic lead poisoning demonstrate consistent findings.[17,24,46,47,48,59,71] During the first 5 days of succimer chelation (1050 mg/m^2/d in children, 30 mg/kg/d in adults in 3 divided doses), the blood lead concentration dropped precipitously by approximately 60â€“70%. This blood lead concentration remained unchanged during the next 14â€“23 days of continued therapy. Increases in urinary lead excretion coincide with the drop in blood lead concentration, with maximal excretion occurring on day 1.[24,47] Calculations indicate that urinary lead excretion exceeds estimated blood content. This suggests that some lead is being removed from soft tissues as a concentration gradient is established from tissue to blood to urine.[24,48] Typically, 2 weeks after the completion of succimer, blood lead concentration rebounds to values 20â€“40% lower than pretreatment values. In the one randomized, double-blind, placebo-controlled trial of succimer use in children with pretreatment blood lead concentrations of 30â€“45 Âµg/dL, followup at 1 month and at 6 months showed no differences between succimer-treated children and controls.[71] Succimer restores red blood cell D-aminolevulinic acid dehydratase (ALA-D) activity, decreases erythrocyte protoporphyrin, and decreases urinary excretion of D-

aminolevulinic acid and coproporphyrin.[17,24,47,48,71]

There is a large body of evidence reporting on the usage and safety profile of succimer in adults with chronic lead poisoning.[11,16,36,39,43,92,94] The published experience outside the United States with the use of oral succimer for metal poisoning includes nearly 100 adult cases and contributes considerably to the supporting evidence. At least 74 additional individuals have been successfully treated parenterally (IM or IV) with the sodium salt of succimer.[11,16,36,39]

Lead Encephalopathy

The experience with the use of succimer in severely lead-poisoned subjects, including those with encephalopathy, is very limited.[36,39,47] Three children with mean blood lead concentrations of >70 Âµg/dL who were treated with 5 days of succimer achieved comparable declines in blood lead concentration to two similar children who had been treated previously with a combination of British anti-Lewisite (BAL) for 3 days and $CaNa_2EDTA$ for 5 days.[47] Three adult patients with encephalopathy achieved significant improvement following succimer chelation.[36] A 3-year-old child with a massive lead exposure superimposed on chronic lead poisoning and a blood lead concentration of 550 Âµg/dL was given BAL and $CaNa_2EDTA$ for 5 days, with whole-bowel irrigation (WBI) performed on the first 3 days and succimer following WBI beginning on day 3 and continuing for 19 days. The blood lead concentration dropped from 550 Âµg/dL to 70 Âµg/dL on day 5, but rebounded to 99 Âµg/dL 2 days after BAL and $CaNa_2EDTA$, but not the succimer, were discontinued.[42]

Arsenic

Succimer has been used for arsenic toxicity in China and the Soviet Union since 1965.[3,11] Animal studies with sodium arsenite

and lewisite demonstrate the ability of succimer to improve the LD_{50} with a good therapeutic index, lack of redistribution of arsenic to the brain as compared to BAL or control, and reduced kidney and liver arsenic concentrations.[3,11,57,80] A few case reports attest to the ability of succimer to enhance the urinary excretion of arsenic.[27,81] A randomized, placebo-controlled trial of succimer in treating 21 patients with chronic arsenic poisoning in India, demonstrated improved clinical results and enhanced urinary excretion in both the treatment and placebo groups, but no statistical differences could be demonstrated.[65] A comparison of BAL, succimer, and DMPS as arsenic antidotes, demonstrated higher therapeutic indices for succimer and DMPS over BAL in chronic arsenic poisoning.[69] The authors speculated that the lipophilic nature of BAL might make it preferable for use in acute toxicity, especially with lipophilic organoarsenicals. This issue needs further investigation.

Mercury

Succimer enhances the elimination of mercury and has been used to treat patients poisoned with inorganic, elemental, and methyl

mercury. It improves survival, decreases renal damage, and enhances elimination of mercury following inorganic mercury[4,20,50,53,62,78,98] and methylmercury exposure in animals.[1,2,7,63] However, one study in mice subjected to intraperitoneal mercuric chloride demonstrated an enhanced deposition of mercury in motor neurons following chelation with succimer or DMPS.[32] Of 53 construction workers who were exposed to mercury vapor, 11 received succimer and *N*-acetyl-*d,l*-penicillamine in a crossover study.[19] Mercury elimination was increased during the period of succimer administration compared to the period of *N*-acetyl-*d,l*-penicillamine administration. Because the chelators were administered for only 2 weeks late in the clinical course, therapeutic benefit could not be evaluated. When

succimer was given to victims of an extensive Iraqi methylmercury exposure, blood methylmercury half-life decreased from 63 days to 10 days.[3]

Pharmacokinetics

The pharmacokinetics of a single oral dose of succimer were determined in 3 children and 3 adults with lead poisoning, and in 5 healthy adult volunteers.[29] Children received 350 mg/m^2 of succimer, and adults received 10 mg/kg of succimer. The peak concentration and the time to peak blood concentration of total succimer (parent vs. altered oxidized metabolites) were similar for all three groups. The half-life of total succimer was 1.5 times longer in the children than in either adult group. The renal clearance of total succimer was greater in healthy adults than in lead-poisoned patients. Distribution of succimer (parent and/or oxidized metabolites) into erythrocytes appeared greater in poisoned patients than in the healthy adults.[29]

The metabolism of succimer was studied in lead-poisoned children and in normal adults.[13] The results indicate that succimer undergoes an enterohepatic circulation facilitated by gastrointestinal (GI) microflora. Similar to the previous pharmacokinetic study, moderate lead exposure impaired the renal elimination of succimer.

Adverse Effects and Safety Issues

Succimer is generally well tolerated with few serious adverse events reported.[24,25] Common adverse effects are gastrointestinal in nature, including nausea, vomiting, flatus, diarrhea, and a metallic taste in 10â€“20% of patients. Mild elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are reported.[23,25,48,59,74] A single patient developed severe hyperthermia and hypotension reportedly related to succimer

administration.[74] Rarely, chills, fever, urticaria, rash, reversible neutropenia, and eosinophilia are reported.[17,24,25,43] During the latest open-labeled prospective study in children, apparently unrelated adverse events included an elevation in bone-derived alkaline phosphatase, eosinophils, and elevated serum aminotransferases.[24]

The Chinese have reported a high incidence of more serious adverse effects (including dizziness and weakness) in response to IV or IM succimer.[96,99] This discrepancy is undoubtedly related to the relatively low (approximately 20%)[66] oral bioavailability of succimer as a result of first-pass metabolism. Therefore, parenteral administration delivers a substantially greater dose.

Incidental chelation of essential elements is always a concern with the use of chelating agents. A number of studies using succimer demonstrate no rise in urinary zinc, copper, iron, or calcium.[24,36,39,46,47,48] Urinary excretion of essential elements was the focus of a study in a primate model of childhood lead exposure.[85] Infant rhesus monkeys were exposed to lead for the first year of life to achieve blood lead concentrations of 40â€“50 Âµg/dL. Succimer was administered in the standard dosage regimen and complete urine collections over the first 5 days were analyzed for calcium, cobalt, copper, iron, magnesium, manganese, nickel, and zinc. Only when the data were analyzed collectively for all 8 elements for all 5 days was there a statistically significant increased urinary elimination. These results raise concern that children with repeated succimer chelation may be at risk for enhanced elimination of essential elements.[24,85,87] An obvious concern regarding the safety of succimer is that there is still relatively limited clinical experience with the drug, particularly with regard to long-term administration.

One concern with administering succimer orally is that outpatient management might permit continued unintentional lead exposure and the possibility for succimer-facilitated lead absorption. Studies

with D-penicillamine, dimercaprol,[51] and $CaNa_2EDTA$ demonstrate enhanced lead absorption and elevated blood lead concentrations.

Most blood lead concentrations are measured by graphite furnace atomic absorption spectrophotometry, in which case succimer does not interfere with the measurement. However, if blood lead concentrations were to be measured by anodic stripping voltammetry, succimer would affect the results by chelating the mercury in the electrode.[24]

Animal studies suggest that succimer does not promote lead retention in the face of continued exposure unless lead exposure is overwhelming.[45,52,76] A radiolabeled lead tracer administered to adult volunteers suggested that succimer increased the net absorption of lead from the gastrointestinal tract and may have distributed it to other tissues, as well as having enhanced urinary elimination.[86] Absorption is bimodal and consistent with an initial phase, followed by a delayed increase attributable to an enterohepatic effect. It may be that succimer-enhanced urinary lead elimination often exceeds enhanced lead absorption. One study reported 2 children with environmental exposure and dramatic rises in blood lead concentration while receiving succimer.[24] In the event of unintentional exposure to a new lead source, decontamination of the gastrointestinal tract should complement oral succimer.[67]

Although iron supplementation cannot be given concomitantly with BAL, because the BALâ€“iron complex may be a potent emetic, iron has been given concomitantly to patients receiving oral succimer without any adverse effects.[49] The prevalence of both iron deficiency and elevated blood lead concentrations is highest among poor, inner-city children.[60] Because heme is a constituent of all cells, including those of the brain, it appears clinically prudent to provide iron supplementation during chelation therapy, when the heme pathway is freed of the inhibitory effects of lead. The timing of administration of the iron should be separate from

administration of the succimer.[24]

A case report describes a 3-year-old child who reportedly ingested 185 mg/kg of succimer and was asymptomatic.[82] There was a dose-dependent effect of succimer on early and late fetal resorption and on fetal body weight and length when succimer was administered to pregnant mice during organogenesis. No observed teratogenic effects were noted when 410 mg/kg, or approximately 5% of the acute LD_{50}, of succimer was administered subcutaneously.[31] Succimer 30â€“60 mg/kg/d was administered by gavage to lead-poisoned rats from day 6 to day 21 of gestation.[22] These doses

of succimer decreased embryonic and fetal blood lead concentrations and normalized offspring body weight at 13 weeks. Although succimer was able to reverse some lead-induced immunotoxic effects, succimer itself caused problems with the immune system that persisted into adulthood.[22] The use of succimer in pregnancy is restricted to women who warrant therapy based on their symptoms.[24]

Combined Chelation Therapy

Succimer could be combined with $CaNa_2EDTA$ to take advantage of the ability of succimer to remove lead from soft tissues, including the brain, while capitalizing on the ability of $CaNa_2EDTA$ to mobilize lead from bone.[26] A number of rodent models have examined this combination and found it to be superior in enhancing the elimination of lead, in reducing tissue concentrations of lead, and in restoring some lead-induced biochemical abnormalities.[34,35,89] Although the addition of succimer to $CaNa_2EDTA$ prevented the redistribution of lead to the brain caused by $CaNa_2EDTA$ alone, the combination also increased urinary excretion of zinc, calcium, and iron.[89,90] A retrospective review comparing dimercaprol plus CaEDTA to succimer plus

$CaNa_2EDTA$ in children with blood lead concentrations >45 Âµg/mL, demonstrated a similar reduction in blood lead concentrations at the end of treatment and at 14 and 33 days following the termination of treatment.[18] Blood lead concentration reductions were approximately 75%, 40%, and 37% at the end of therapy, and at 14 and 33 days posttreatment, respectively. The succimer plus $CaNa_2EDTA$ combination was better tolerated.[18]

DMPS

DMPS (racemic-2,3-dimercapto-1-propanesulfonic acid, Na salt) is an investigational metal chelator that, like succimer, is a water-soluble analog of BAL.[3,7,21] A dose of 15 mg/kg of DMPS is equimolar to 12 mg/kg of succimer. DMPS was used in the former Soviet Union since the late 1950s and continues to be used in Russia and other former Soviet countries. DMPS also is marketed in both oral and parenteral forms in Germany as Dimaval. DMPS seems promising in mercury and arsenic poisoning.[3,7,9,12,21,41] DMPS is associated with an increase in the urinary excretion of copper and the development of Stevens-Johnson syndrome.[23] Like succimer, DMPS does not appear to redistribute mercury or lead to the brain. More research needs to be done to determine whether DMPS is more advantageous than succimer, given its lower LD_{50} in rodents (5.22 mmol/kg vs. 16.5 mmol/kg for succimer).

Dosing

Succimer (Chemet) is available as 100-mg bead-filled capsules. For patients who cannot swallow the capsule whole, it can be separated immediately prior to use and the contents sprinkled into a small amount of juice or on apple sauce, ice cream, or soft food, or placed on a spoon and followed by a fruit drink. The dosage is 350 mg/m^2 in children, 3 times a day for 5 days, followed by 350 mg/m^2 twice a day for 14 days. In adults, the dosage is 10 mg/kg in the same regimen as above. However, using 10 mg/kg in

children rather than dosing based on body surface area, as was done during the premarketing trials, might result in patient underdosing.[68]

Unanswered Questions

In spite of the epidemic of lead poisoning, there is a paucity of rigorous data defining the role of succimer. There are many unanswered questions regarding clinical efficacy, pharmacokinetics, and dosage regimens, for example:[56,68] How exactly does succimer bind lead in the blood? Is it succimer, its active disulfide cysteine metabolites, or both that bind lead? What happens to the cysteine conjugates? How do the kidneys handle the lead chelate? What exactly is reabsorbed in the enterohepatic circulation, succimer, the cysteine metabolites, and the lead chelated form? Should a longer succimer-dosing regimen be used? And, the most important question of all, does succimer chelation improve clinical outcome?

Summary

Succimer (meso-2,3-dimercaptosuccinic acid) is an orally active metal chelator that is FDA approved for the treatment of lead poisoning in children with blood lead concentrations >45 Âµg/dL. Succimer is also being used to treat lead-poisoned adults, children with blood lead concentrations <45 Âµg/dL, and patients poisoned with arsenic and organic and inorganic mercury. Succimer has many advantages over dimercaprol and $CaNa_2EDTA$, the two other agents used for the same clinical problems. The advantages of succimer use include oral administration, limited effects on trace metals such as zinc, enhanced patient tolerance, limited toxicity, the ability to coadminister iron, if needed, and no contraindication in glucose-6-phosphate dehydrogenase-deficient individuals.[24] In contrast to $CaNa_2EDTA$, succimer does not redistribute lead to the brain of poisoned animals.[9,26] The role of succimer alone and in

conjunction with other chelators to treat lead encephalopathy continues to be defined.[56,68]

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Antidotes in Depth

Edetate Calcium Disodium ($CaNa_2EDTA$)

Mary Ann Howland

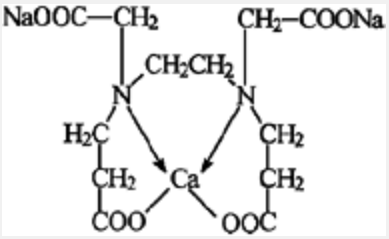

Figure. No Caption Available.

Edetate calcium disodium ($CaNa_2EDTA$) is a chelating agent that is primarily used for the management of lead poisoning. $CaNa_2EDTA$

has been replaced by succimer (2,3-dimercaptosuccinic acid) for the treatment of patients with lead levels between 45 and 70 Âµg/dL Although, in conjunction with dimercaprol, $CaNa_2EDTA$ retains a role in the management of serious lead poisoning and lead encephalopathy, even this role is being challenged by succimer.

Chemistry

Edetate calcium disodium belongs to the family of polyaminocarboxylic acids. Although it is capable of chelating many metals, its current use is almost exclusively in the management of lead poisoning. The term *chelate* has its origin in the Greek word *chele*, which means â€œclaw,â€• implying an ability to tightly grasp the metal.[38] Implicit in chelation is the formation of a ring-structured complex. When $CaNa_2EDTA$ chelates lead, the calcium is displaced and the lead takes its place, forming a stable ring compound.[23]

Pharmacokinetics

$CaNa_2EDTA$ is an ionic, water-soluble compound with a molecular weight of 374 daltons. The volume of distribution is small (0.05â€“0.23 L/kg) because of its polar nature and approximates that of the extracellular fluid compartment in normal individuals,[19,23] but is smaller in patients with renal dysfunction.[29] $CaNa_2EDTA$ appears to penetrate cells such as erythrocytes poorly,[2,19] and <5% of $CaNa_2EDTA$ gains access to the spinal fluid.[19,23] Oral administration of $CaNa_2EDTA$ is not practical because of an oral bioavailability of <5%. The half-life is about 20â€“60 minutes.[3,19,23] Renal elimination approximates the glomerular filtration rate,[28] which correlates with creatinine clearance,[29] and results in the excretion of 50% of $CaNa_2EDTA$ in the urine within 1 hour, and more than 95% within 24 hours.[19,23] When $CaNa_2EDTA$ combines with lead, it forms a stable, soluble,

nonionized compound that is subsequently excreted in the urine. Following $CaNa_2EDTA$ administration, urinary lead excretion is increased 20â€“50-fold.

Lead

Animals

Animal studies demonstrate a decrease in tissue lead stores, including brain concentrations, when measurements are performed following $CaNa_2EDTA$ therapy.[21] One study concluded that $CaNa_2EDTA$ failed to reduce lead levels in the rat model.[13] Furthermore, another rat study that examined the effect of $CaNa_2EDTA$ on brain lead concentrations following a single dose demonstrated a significant increase in brain lead concentrations,[14] suggesting that $CaNa_2EDTA$ may initially mobilize lead and facilitate redistribution to the brain. Additional doses enhance lead elimination, reduce blood lead concentrations, and subsequently reduce brain lead concentrations. This phenomenon may explain why some human case reports demonstrate worsening lead encephalopathy when $CaNa_2EDTA$ is used without concomitant dimercaprol (British anti-Lewisite [BAL]) therapy.

Humans

$CaNa_2EDTA$ is capable of reducing blood lead concentrations, enhancing renal excretion of lead, and reversing the effects of lead on hemoglobin synthesis.[11] With chronic exposure blood lead concentrations rebound considerably, days to weeks following the cessation of $CaNa_2EDTA$, as is the case after terminating other chelators.[1,2,20] Although $CaNa_2EDTA$ has been used clinically since the 1970s, no rigorous clinical studies have ever been performed to evaluate whether $CaNa_2EDTA$ is capable of reversing the neurobehavioral effects of lead.[12] Chelators, including $CaNa_2EDTA$, are incapable of dramatically decreasing the body burden of lead,

because only several milligrams of lead are eliminated during chelation.[8,9,31] A study of children with blood lead concentrations of 25â€“50 Âµg/dL who were given 5 days of $CaNa_2EDTA$ revealed very little difference in blood lead, bone lead, or erythrocyte protoporphyrin concentrations, when compared to pretreatment values.[25] Another study in children demonstrated no additional benefits of $CaNa_2EDTA$ on cognitive performance beyond that which was achieved by limiting further lead exposure and correcting an iron deficiency anemia.[30] A followup study in children with initial blood lead concentrations of approximately 30 Âµg/dL suggested an improvement in perceptual motor performance over a 6-month period beyond that which was achieved by the treatment of the iron-deficiency anemia.[33]

$CaNa_2EDTA$ Mobilization Test

The $CaNa_2EDTA$ mobilization test was once widely recommended as a diagnostic aid for assessing the potential benefits of chelation therapy.[24,26] When scrutinized,[7] it can only be considered obsolete and is therefore no longer recommended.[11,14] Criticisms include difficulties with administration, unreliability as a predictor of total-body lead burden, expense, and the risk of worsening toxicity through redistribution of lead to either the kidney or brain.[11]

Adverse Effects and Safety Issues

The principal toxicity of $CaNa_2EDTA$ is related to the metal chelate. In mice, the intraperitoneal (IP) LD_{50} (median lethal dose for 50% of test subjects) values of various $CaNa_2EDTA$ metal chelates are $CaNa_2EDTA$, 14.3 mmol/kg; lead EDTA, 3.1 mmol/kg; and mercury EDTA, 0.01 mmol/kg.

When $CaNa_2EDTA$ is given to patients with lead poisoning, the

sites of major renal toxicity are the proximal convoluted tubule, the distal convoluted tubule, and the glomeruli.[23] This toxicity may be caused by the release of lead in the kidneys during excretion.[23] Of 210 children who received dimercaprol and $CaNa_2EDTA$, 21% had biochemical evidence of nephrotoxicity, and 3% developed acute oliguric renal failure, which resolved over time without the need for hemodialysis.[24] Other studies failed to demonstrate any cases of renal failure in more than 1000 patient courses of therapy, when $CaNa_2EDTA$ was given in divided daily doses of 1000 mg/m^2 IV over 1 hour, every 6 hours.[26] Because lead toxicity causes renal damage independent of chelation, it is important to monitor renal function closely during $CaNa_2EDTA$ administration and to adjust the dose and schedule appropriately.[28,29] Nephrotoxicity may be minimized by limiting the total daily dose of $CaNa_2EDTA$ to 1 g in children or to 2 g in adults, although higher doses may be needed to treat lead encephalopathy. Continuous infusion while maintaining good hydration seems to increase efficacy and decrease toxicity.[28] Because the administration of disodium EDTA can lead to life-threatening hypocalcemia $CaNa_2EDTA$ has become the preparation of choice and hypocalcemia is no longer a clinical concern. Other adverse effects of $CaNa_2EDTA$, most of which are uncommon, include malaise, fatigue, thirst, chills, fever, myalgias, dermatitis, headache, anorexia, urinary frequency and urgency, sneezing, nasal congestion, lacrimation, glycosuria, anemia, transient hypotension, increased prothrombin times, and inverted T waves.[23] Mild increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (usually reversible), and decreases in alkaline phosphatase, are frequently reported. Extravasation may result in the development of painful calcinosis at the injection site.[34] Depletion of endogenous metals, particularly zinc, iron, and manganese, can result from chronic therapy.[5,37] A decrease in serum dopamine Î²-hydroxylase, a copper-dependent enzyme, without any demonstrable decrease in

serum copper occurred after a single injection of $CaNa_2EDTA$ in 3 adult lead welders.[15] Although the clinical relevance of this is unknown, it merits further investigation.[15]

An animal study suggests that gastrointestinal lead absorption may be enhanced by either intraperitoneal or oral administration of $CaNa_2EDTA$;[20] consequently, removal of lead from the environment should always remain the first strategy in the management of lead toxicity. In the event of unintentional exposure to a new lead source, decontamination of the gastrointestinal tract must complement chelation.[27]

The safety of $CaNa_2EDTA$ has not been established in pregnancy, and a risk-to-benefit analysis must be made if its use is considered. In a model of lead poisoning in pregnant rats, fetal resorption decreased and the number of live fetuses increased when $CaNa_2EDTA$ was used, although the placental levels of lead were increased.[17] Zinc levels were not affected. Another study, however, found that when $CaNa_2EDTA$ was given to pregnant rats not poisoned with lead, increases in submucous clefts, cleft palate, adactyly/syndactyly, curly tail, and abnormal ribs and vertebrae resulted.[4] These teratogenic effects occurred with doses of $CaNa_2EDTA$ comparable to human doses and without causing noticeable changes in the mother except for weight gain. Use of zinc calcium EDTA and zinc EDTA preparations in pregnant rats caused no teratogenic effects at low dose but resulted in the development of submucous cleft palates in 30% of the offspring receiving the higher dose of zinc calcium EDTA.[4]

Dosing and Administration

The dose of $CaNa_2EDTA$ is determined by the patient's body surface area or weight (up to a maximum dose) and the severity of the poisoning and renal function (Chap. 91 and Table 91-8).[11,25,30] For patients with lead encephalopathy, the dose of $CaNa_2EDTA$ is 1500 $mg/m^2/d$ by continuous IV infusion, starting 4

hours after the first dose of dimercaprol and after an adequate urine flow is established.[10] Simultaneous dimercaprol and $CaNa_2EDTA$ therapy is administered for 5 days, followed by a rest period of at least 2â€“4 days, which permits lead redistribution. Dosage adjustments limiting the daily dose to 50 mg/kg are necessary when $CaNa_2EDTA$ is used in patients with renal dysfunction.[19,28,29] There is limited evidence to suggest that folic acid, pyridoxine, and thiamine increase the antidotal properties of $CaNa_2EDTA$.[35] A blood lead concentration should be measured 1 hour after the $CaNa_2EDTA$ infusion is discontinued, to avoid falsely elevated blood lead concentration determinations.

In symptomatic children without manifestations of lead encephalopathy, the dose of $CaNa_2EDTA$ is 1000 $mg/m^2/d$, in addition to dimercaprol at 50 mg/m^2 every 4 hours. However, with FDA approval, and the demonstrated ability to reduce brain lead concentrations in animals, succimer is increasingly replacing $CaNa_2EDTA$ as the chelator of choice in lead-poisoned children without encephalopathy.[9]

Because of the pain associated with IM administration, most clinicians recommend that $CaNa_2EDTA$ be administered at concentrations of approximately 0.5% by continuous IV infusion over 24 hours in 5% dextrose or 0.9% NaCl. Concentrations greater than 0.5% may lead to thrombophlebitis and should be avoided. $CaNa_2EDTA$ is incompatible with other solutions. Careful attention to total fluid requirements in children and patients who have or who are at risk for, lead encephalopathy is paramount.[23,30] Rapid intravenous infusions in patients with lead encephalopathy may increase intracranial pressure and cerebral edema. In children with acute lead encephalopathy, starting BAL 4 hours prior to $CaNa_2EDTA$ appears to be more effective than starting $CaNa_2EDTA$ prior to and simultaneously with BAL.[6,12] In addition, treating with two chelators also reduces the blood lead concentration significantly faster than does $CaNa_2EDTA$ alone, while maintaining a better molar ratio of chelator to lead.[6]

If $CaNa_2EDTA$ is to be administered IM to avoid the use of an IV and fluid overload, then procaine is added to the $CaNa_2EDTA$ in a dose sufficient to produce a final concentration of 0.5%. This can be accomplished by mixing 1 mL of a 1% procaine solution with each mL of chelator.[23] The procaine minimizes pain at the injection site.

Combination Therapy with Succimer or DMPS

The possible benefit of combining $CaNa_2EDTA$ with succimer or 2,3-dimercapto-1-propane-sulfonic acid (DMPS) is under investigation in animals.[16,18,36] The combination of $CaNa_2EDTA$ with succimer appears more potent than either individual agent in promoting urine and fecal lead excretion, and decreasing blood and

liver lead concentrations. However, this approach might increase nephrotoxicity and zinc depletion.

Availability

Calcium disodium EDTA is available as calcium disodium versenate in 5-mL ampules containing 200 mg of $CaNa_2EDTA$ per milliliter (1 g per ampule).[23] Disodium edetate (sodium EDTA) should not be considered an alternative to $CaNa_2EDTA$ because of the risk of life-threatening hypocalcemia associated with sodium EDTA use.

Summary

$CaNa_2EDTA$ reduces blood lead concentrations, enhances urinary lead excretion, and reverses lead-induced hematologic effects. Studies evaluating long-term effects in reversing lead-induced neurotoxicity have not been performed. $CaNa_2EDTA$ remains the

standard of care for patients with lead encephalopathy when used in conjunction with dimercaprol. A $CaNa_2EDTA$ challenge test is no longer recommended as a diagnostic gesture.[11,14] Recommended doses and dosage schedules should not be exceeded and should be reduced when the creatinine clearance is reduced. Patients should be well hydrated to achieve an adequate urine flow prior to and during $CaNa_2EDTA$ therapy.

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Chapter 92
Mercury

Young-Jin Sue

Mercury (Hg)
Atomic number
=
80
Atomic weight
=
200.59
Normal concentrations
Whole blood
=
< 10 Âµg/dL (<50 nmol/L)
Urine
=
< 20 Âµg/L (<100 nmol/L)
=
<5 Âµg/g creatinine

A 16-year-old boy presented to the emergency department approximately 40 minutes after having intentionally ingested

â€œseveral teaspoonsâ€• of mercuric oxide (HgO) from his chemistry set. On arrival, he was alert and oriented, but diaphoretic and vomiting. He complained of midepigastric pain and a metallic taste in his mouth. Initial vital signs were: blood pressure, 130/80 mm Hg; pulse, 110 beats/min; respiratory rate, 18 breaths/min; and rectal temperature, 99.7Â°F (37.6Â°C). Physical examination revealed an anxious, somewhat pale young man who was repeatedly vomiting blood-tinged, nonbilious material. He had no respiratory distress or drooling. Other than a grayish discoloration of the buccal mucosa, examination of the oropharynx was unremarkable. The lungs were clear. The cardiac examination was normal, except for a sinus tachycardia. The abdominal examination revealed a nondistended, soft abdomen, moderately tender to deep palpation in the epigastric region; no masses or organomegaly were appreciated. Rectal examination was negative for blood. Examination of the skin was unremarkable. The neurologic examination was normal, except for mild tremulousness. The patient was attached to a cardiac monitor, and he was given 1 L of 0.9% sodium chloride solution (IV) over the subsequent 15 minutes. Results of a complete blood count (CBC), electrolytes, blood urea nitrogen (BUN), creatinine, glucose, prothrombin time, partial thromboplastin time (PTT), and liver enzymes were within normal limits. Blood was obtained for whole-blood mercury concentrations, and the bladder was catheterized to collect urine for 24-hour urine mercury quantification. Initial spot urinalysis revealed 2+ proteinuria.

The electrocardiogram (ECG) was normal, except for sinus tachycardia. Upright chest and abdominal radiographs revealed the presence of a radiopaque substance scattered throughout the GI tract, but no extraluminal air. Figures 92-1A and B are abdominal radiographs of a patient with a similar exposure.

Endoscopic examination of the upper gastrointestinal (GI) tract was considered but rejected based on the patient's clinical presentation. Instead, the patient underwent gastric lavage and

received 1 g/kg of activated charcoal. Whole-bowel irrigation with polyethylene glycol electrolyte lavage solution was begun. The rectal effluent contained flecks of blood. A subsequent abdominal radiograph after whole-bowel irrigation revealed no radiopaque densities.

History and Epidemiology

The toxicologic manifestations of mercury are well known as a result of thousands of years of medicinal applications, industrial use, and environmental disasters.[54 , 85] Mercury occurs naturally in small amounts as the elemental silver-colored liquid (quicksilver); as inorganic salts such as mercuric sulfide (cinnabar), mercurous chloride (calomel), mercuric chloride (corrosive sublimate), and mercuric oxide; and as organic compounds (methylmercury and dimethylmercury). In recent centuries, mercury preparations were widely used to treat both syphilis and constipation. The musician Paganini was one of several famous persons whose gingivitis, dental decay, ptyalism (excessive salivation), and erethism (pathologic shyness) were attributed to mercury therapy.[62] In the 1800s, the United States witnessed an epidemic of â€œhatters' shakesâ€• or â€œDanbury shakesâ€• and â€œmercurial salivationâ€• in hat industry workers.[95] Danbury, CT, was a US center of felt hat manufacturing in which mercuric nitrate was used to mat animal furs to make felt.[85 , 95]

In the early 1900s, acrodynia, or â€œpink disease,â€• was described in children who received calomel for ascariasis or teething discomfort.[10] Vividly described in a series of 41 children, the development of acrodynia was more common in younger children, did not seem to correlate with mercury dose, and was not necessarily related to urine concentrations of mercury.[94]

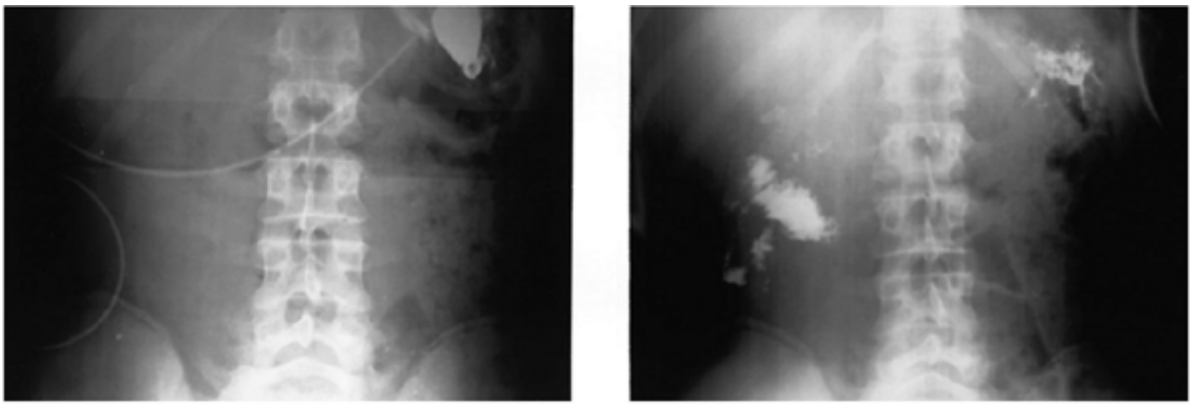

Figure 92-1. A chemist ingested mercuric oxide in a suicide attempt. A. Initial plain abdominal radiograph reveals the radiopaque liquid in the stomach. B. A second radiograph shows progression of the toxin through the bowel. The patient was followed radiographically as the mercuric oxide was expelled into the feces.

One of the most devastating epidemics of mercury poisoning occurred as the result of a decade of contamination of Minamata Bay in Japan by a nearby vinyl chloride plant during the 1940s. Methylmercury accumulated in the bay's marine life and poisoned the inhabitants of the local fishing community. Although officially only 121 victims were initially counted, thousands more are believed to have been affected by what has subsequently been named Minamata disease.[67, 87] The largest outbreak of methylmercury poisoning to date occurred in Iraq in late 1971. Approximately 95,000 tons of seed grain intended for planting and treated with methylmercury as a fungicide were baked into bread for direct consumption, resulting in widespread neurologic symptoms, 6530 hospital admissions, and more than 400 deaths.[4, 16, 72]

In 1990, the EPA banned mercury-containing compounds from interior paints.[2] However, mercury-containing paints manufactured prior to that ruling may still be on the interior walls and mercury

containing paint can still be sold for outdoor use. In 1997, a scientist succumbed to delayed, progressive neurologic deterioration following dermal exposure to a minute quantity of dimethylmercury.[59]

Amalgam
Disinfectants
Bactericide makers
Barometers
Dye makers
Drug makers
Bronzers
Explosives
Embalmers
Ceramic workers
Fireworks makers
Farmers
Chlorine workers
Fur processors
Fungicides
Dentists
Laboratory workers
Histology technicians
Electroplaters
Tannery workers
Pesticides
Jewelers
Taxidermists
Seed handlers
Mercury refiners
Vinyl chloride makers
Wood preservatives
Paint makers
Paper pulp workers
Photographers

Thermometers

Elemental Salts Organic

TABLE 92-1. Potential Occupational Exposures to Mercury

Contemporary exposures occur in the form of mercury-tainted seafood and mercury-based preservatives (thimerosal). However, a once widely feared source of potential poisoning, mercury-containing dental amalgam, does not appear to result in clinically important poisoning. Occasionally, exposure to mercury from thermometers leads to poisoning in the home. Tables 92-1 and 92-2 show the potential occupational and nonoccupational risks for mercury exposure.

Forms of Mercury and Kinetics

The three important classes of mercury compounds (elemental, inorganic, and organic) differ with respect to toxicodynamics and toxicokinetics (Table 92-3). Each of the three classes of mercurials produces distinct clinical patterns of poisoning stemming in part from their unique kinetic features (Table 92-4). Within each class, the specific poisoning, manifestations are determined by route of exposure, rate of exposure, distribution, and biotransformation of mercury within the body, and relative accumulation or elimination of mercury by the target organ systems.

Antiseptics
Fish
Button batteries
Calomel teething powders
Dental amalgam
Grains and seed, treated
Livestock, fed treated grain

Chemistry sets
Home amalgam extraction
Diuretics
Laxatives

Lightbulbs (fluorescent)
Sphygmomanometers
Self-injection
Stool fixatives
Preservatives
Thermometers
Weighted nasogastric tubes
Ritualistic use

Medicinal Food Other

TABLE 92-2. Nonoccupational Exposures to Mercury

Elemental mercury
Hg^0
Quicksilver
Inorganic mercury salts
Hg^+
Mercurous ion
HgCl
Calomel, mercurous chlorine
Hg^{2+}
Mercuric ion
$HgCl_2$
Mercuric chloride
Organic mercury compounds
Short-chain, alkyl-mercury compounds
Methylmercury
Ethylmercury

Long-chain, aryl-mercury compounds
Methoxyethylmercury
Phenylmercury

Chemical Formula Example

TABLE 92-3. Classes of Mercury Compounds

Absorption

Elemental Mercury

Elemental mercury (Hg^0) is absorbed primarily via inhalation of vapor, although slow absorption following aspiration, subcutaneous deposition, and direct intravenous embolization is reported.[45, 56, 92, 98] Although elemental mercury is moderately volatile at room temperature, volatilization increases significantly when it is heated. Vaporization may also be hastened by aerosolization. Both occur when elemental mercury is vacuumed.[77] When inhaled by human volunteers, 75â€“80% of a stable, radioactive mercury vapor mixture is absorbed.[33] However, as elemental mercury is negligibly absorbed from a normally functioning gut, it is usually considered nontoxic when ingested. Abnormal gastrointestinal (GI) motility prolongs mucosal exposure to elemental mercury and increases subsequent ionization to more readily absorbed forms. Similarly, anatomic GI abnormalities such as fistulae or perforation may be associated with extravasation of mercury into the peritoneal space where elemental mercury is oxidized to more readily absorbed inorganic forms.

Inorganic Mercury Salts

The principal route of absorption for inorganic mercury salts is the

GI tract. Approximately 10% of inorganic mercury salts are absorbed after dissociation of ingested soluble divalent mercuric salts such as mercuric chloride ($HgCl_2$).[51] Absorption of a relatively insoluble monovalent mercurous compound, such as calomel (HgCl), is thought to depend on its oxidation to the divalent form.[60] Inorganic mercury salts are also absorbed across skin and mucous membranes, as evidenced by urinary excretion of mercury following the dermal application of mercurial ointments and powders containing HgCl.[94] The degree of dermal absorption varies by concentration of mercury, skin integrity, and the lipid solubility of the vehicle. With substantial dermal exposures to inorganic mercury salts, skin absorption may be difficult to distinguish from concomitant absorption via other routes, such as ingestion.

Primary route of exposure
Inhalation
Oral
Oral
Primary tissue distribution
CNS, kidney
Kidney
CNS, kidney, liver
Clearance
Renal, GI
Renal, GI
Methyl:GI
Aryl: renal, GI
Clinical effects
CNS
Tremor
Tremor, erethism
Paresthesias, ataxia, tremor, tunnel vision, dysarthria
Pulmonary
+++

â€”
â€”
Gastrointestinal
+
+++(caustic)
+
Renal
+
+++(ATN)
+
Acrodynia
+
++
â€”
Therapy
BAL, succimer
BAL, succimer
Succimer (early)

Elemental Inorganic (Salt) Organic (Alkyl)

TABLE 92-4. Differential Characteristics of Mercury Exposure

Organic Mercury Compounds

As in the case of inorganic mercury salts, organic mercury compounds are primarily absorbed from the GI tract. Methylmercury, considered the prototype of the short-chain alkyl compounds, is approximately 90% absorbed from the gut.[51] Aryl and long-chain alkyl compounds have greater than 50% gastrointestinal absorption.[60] Although both dermal and inhalational absorption of organic mercury compounds are reported, precise quantitation and exclusion of concomitant

absorption by ingestion are difficult to determine.[20, 24, 96, 97]

Distribution and Biotransformation

After it is absorbed, mercury distributes widely to all tissues, predominantly the kidneys, liver, spleen, and central nervous system (CNS). The initial distributive pattern into nervous tissue of elemental and organic mercury differs from that of the inorganic salts because of their greater lipid solubility.

Elemental Mercury

Although peak levels of elemental mercury are delayed in the CNS as compared to other organs (2â€“3 days vs. 1 day),[31] significant accumulation in the CNS may occur following an acute, intense exposure to elemental mercury vapor. Conversion of elemental mercury to the charged mercuric cation within the CNS favors retention and local accumulation of the metal. As elemental mercury does not covalently bind to other compounds, its toxicity depends on its oxidation initially to the mercurous ion (Hg^{+}) and then to the mercuric ion (Hg^{2+}) by the enzyme catalase.[51] Because this oxidation-reduction reaction favors the mercuric cation at steady state, the distribution and late manifestations of metallic mercury toxicity eventually resemble those of inorganic mercury salt poisoning. Conversely, and to a lesser extent, inorganic mercuric ions are reduced to the elemental state, although the site and mechanism of this reaction are not well understood.[60]

Inorganic Mercury Salts

The greatest concentration of mercuric ions is found in the kidneys, particularly within the renal tubules. Very little mercury is found as free mercuric ions. At least in animal studies, administration of mercury induces the renal synthesis of

metallothionein, a compound that binds to and detoxifies mercuric ions.[7] In blood, mercuric ions are found within the red blood cells and are bound to plasma proteins in approximately equal proportions. Blood concentrations are greatest immediately following inorganic mercury exposure, with rapid waning as distribution to other tissues occurs. Although penetration of the bloodâ€“brain barrier is poor because of low lipid solubility, slow elimination and prolonged exposure contribute to consequential CNS accumulation of mercuric ions. Within the CNS, mercuric ions are concentrated in the cerebral and cerebellar cortices. Although inorganic mercurials undergo organification in marine life, as in the Minamata

Bay disaster, the importance of this conversion in humans is unknown.[20] Animal studies demonstrate that the placenta functions as an effective barrier to mercuric ions.[60]

Organic Mercury Compounds

Once absorbed, aryl and long-chain alkyl mercury compounds differ from the short-chain organic mercury compounds (ie, methylmercury) in an important way. The former possess a labile carbon-mercury bond, which is subsequently cleaved, releasing the inorganic mercuric ion. Thus, the distribution pattern and toxicologic manifestations produced by the aryl and long-chain alkyl compounds beyond the immediate postabsorptive phase are comparable to those of the inorganic mercury salts, but the organification has facilitated absorption and reduced the caustic effects.[61] In contrast, short-chain alkyl mercury compounds possess relatively stable carbon-mercury bonds that survive the absorptive phase, although conversion to the inorganic mercuric cation at a rate of less than 1% per day may occur following absorption.[96] Because it is lipophilic, methylmercury readily distributes across all tissues, including the bloodâ€“brain barrier and placenta.[33] An important consequence of this property is the

devastating neurologic degeneration that develops in prenatally exposed infants with Minamata disease.

After methylmercury is distributed to brain tissue, its fate is uncertain. Animal evidence indicates that methylmercury is converted to inorganic mercury in brain tissue.[48] Primates fed oral methylmercury daily for periods exceeding 1 year and then killed within a few days of the last exposure, demonstrated an average brain inorganic mercury fraction of only 19%. When the postexposure period was extended to between 150 and 650 days, the inorganic mercury fraction increased to 88%. Similarly, long-term survivors of methylmercury poisoning had a higher ratio of inorganic mercury to total mercury in their brains.[22] In one patient who survived 22 years following methylmercury ingestion, autopsy revealed that the brain mercury was nearly completely in the inorganic form.

Methylmercury concentrates in red blood cells (RBCs) to a much greater degree than do mercuric ions, with an RBC-to-plasma ratio of about 10:1 (contrast with 1:1 RBC-to-plasma ratio for inorganic mercury).[42, 60, 96] However, despite this apparent affinity for nervous tissue and red blood cells, the greatest methylmercury concentrations are found in the kidneys and liver. Also, because of the extensive sulfhydryl bonds in hair, methylmercury deposits in hair at concentrations approximately 250 times that found in whole blood.[41, 86]

Elimination

Elemental Mercury/Inorganic Mercury Salts

Mercuric ions are excreted through the kidney by both glomerular filtration and tubular secretion, and in the GI tract by transfer across gut mesenteric vessels into feces. Small amounts are

reduced to elemental mercury vapor and volatilized from skin and lungs. The total-body half-life of elemental mercury and inorganic mercury salts is estimated at approximately 30â€“60 days.[15 , 51]

Organic Mercury Compounds

In contrast to elemental mercury and inorganic mercury salts, the elimination of short-chain alkyl mercury compounds is predominantly fecal. Enterohepatic recirculation contributes to its somewhat longer half-life of about 70 days. Less than 10% of methylmercury is excreted in urine and feces as the mercuric cation.[96]

Pathophysiology

The pervasive disruption of normal cell physiology by mercury is believed to arise from its avid covalent binding to sulfur, replacing the hydrogen ion in the body's ubiquitous sulfhydryl groups. Mercury also reacts with phosphoryl, carboxyl, and amide groups, resulting in widespread dysfunction of enzymes, transport mechanisms, membranes, and structural proteins. The role of mercury is being investigated in a variety of cellular alterations including oxidant stress, microtubule disruption, protein and DNA synthesis, and cell membrane integrity.

Mercury deposits in all tissues. Not surprisingly, the clinical manifestations of mercury toxicity involve multiple organ systems with variable features and intensity. Necrosis of the gastrointestinal mucosa and proximal renal tubules, which occurs shortly after mercury salt poisoning, is thought to result from direct oxidative effect of mercuric ions. An immune mechanism is attributed to the membranous glomerulonephritis and acrodynia associated with the use of mercurial ointments.[8] Postmortem examination of the kidneys from two women who died following chronic abuse of mercurous chloride-containing laxatives, revealed severe proximal tubular atrophy and mercury deposition within the

cortical interstitium and renal macrophages.[93]

Neurologic manifestations of methylmercury poisoning correlated with pathologic findings in the brains of both adults and children believed to have been prenatally exposed.[53, 87] Grossly, atrophy of the brain is more severe in children who had prenatally or postnatally acquired methylmercury, when compared with the brains of those exposed as adults. In the adult brain, neuronal necrosis and glial proliferation are most prominent in the calcarine cortex of the cerebrum and in the cerebellar cortex. In fetal Minamata disease, similar lesions are present, but in a more diffuse and severe form. Atrophy of the cerebellar hemispheres, postcentral gyri, and calcarine area of the brain on magnetic resonance images in organic mercury-poisoned patients, correlate with clinical findings of ataxia, sensory neuropathy, and visual field constriction, respectively.[44] Neuropathologic examination of the brain of a woman who died after dermal exposure to dimethylmercury revealed lesions in the cerebellum, temporal lobe, and visual cortex.[80]

In rats neuronal cytotoxicity of methylmercury may result in part from muscarinic receptor mediated calcium release from smooth endoplasmic reticulum of cerebellar granule cells.[47] There is animal evidence that methylmercury may trigger reactive oxygen species production. In addition, methylmercury inhibits astrocyte uptake of cysteine, the rate-limiting step in the production of glutathione, a major antioxidant in mammalian cell systems.[79]

Clinical Syndromes

Elemental Mercury

Symptoms of *acute elemental mercury inhalation* occur within hours of exposure and consist of cough, chills, fever, and shortness of breath. Gastrointestinal complaints include nausea,

vomiting, and diarrhea, accompanied by a metallic taste, dysphagia, salivation, weakness, headaches, and visual disturbances. Chest radiography during the acute phase may reveal interstitial pneumonitis and both patchy atelectasis and emphysema. Symptoms may resolve or progress to acute lung injury, respiratory failure, and death. Survivors of severe pulmonary manifestations may develop

interstitial fibrosis and residual restrictive pulmonary disease. The acute respiratory symptoms may occur concomitantly with or lead to the development of, subacute inorganic mercury poisoning, manifested by tremor, renal dysfunction, and gingivostomatitis.[11, 40, 70] Thrombocytopenia may also occur during the acute phase.[27]

While acute exposure to elemental mercury vapor occurs most commonly in the occupational setting, poisonings caused by mishandling of the metal in the home are well reported.[13, 36, 55, 82] In fact, attempts at home metallurgy employing metallic mercury have resulted in fatalities with ambient air concentrations of mercury as high as 0.9 mg/m^3 (National Institute for Occupational Safety and Health [NIOSH] recommended exposure level [REL] 8-hour time-weighted average [TWA] 0.05 mg/m^3 for mercury vapor).[14] The lethal dose of inhaled elemental mercury has not been determined. As with other inhaled toxins, younger individuals may be more sensitive to the pulmonary toxicity of mercury vapor.[55] Although pulmonary toxicity from elemental mercury usually results from inhalation of vapor, massive endobronchial hemorrhage followed by death has occurred secondary to direct *aspiration of metallic mercury* into the tracheobronchial tree.[100]

Gradual volatilization of elemental mercury results in chronic toxicity, both in the occupational setting and in the home, from improper handling, such as vacuuming spilled mercury.[77]

The clinical importance of volatilized metallic mercury from dental

amalgams for both the dentist and patient has been a point of contention for years. The preponderance of evidence currently refutes the idea that dental amalgam causes mercury poisoning. Several comprehensive reviews of the subject conclude that (a) occupational exposure to mercury from dental amalgam is acceptably low, provided that recommended preventive measures such as adequate ventilation are adhered to; (b) the quantity of mercury vaporized from dental amalgam by mechanical forces, such as chewing is clinically insignificant; and (c) only in very rare cases will immunologic hypersensitivity to mercury amalgam (manifested as cutaneous signs and symptoms and confirmed by patch testing) necessitate removal of the amalgam.[23 , 25 , 26 , 46 , 81]

Unusual cases of chronic toxicity have resulted from intentional *subcutaneous or intravenous injection of elemental mercury* (Figs. 6-6 and 92-2).[35 , 56] Aside from management of local and systemic mercury toxicity, local wound care and excision of deposits of mercury were additional therapeutic challenges presented by these cases. Serial or repeat radiographs are useful in guiding the removal of the radiopaque deposits.

Inorganic Mercury Salts

Acute *ingestion of mercuric salts* produces a characteristic spectrum from severe irritant to caustic gastroenteritis. Immediately following the ingestion, a grayish discoloration of mucous membranes and metallic taste may accompany local oropharyngeal pain, nausea, vomiting, and diarrhea, followed by abdominal pain, hematemesis, and hematochezia. The lethal dose of mercuric chloride is estimated to be 30â€“50 mg/kg.[88] The hallmarks of severe acute mercuric salt ingestion are hemorrhagic gastroenteritis, massive fluid loss resulting in shock, and acute tubular necrosis.[75]

Oropharyngeal injury, nausea, hematemesis, hematochezia, and

abdominal pain were the most prominent symptoms in a series of 54 patients who presented after ingesting up to 4 g of mercuric chloride.[88] In this series, a fatal outcome was associated with the early development of oliguria (within 3 days). The development of anuria appeared to be related to the dose of mercuric chloride ingested. The histopathologic finding of proximal tubular necrosis following mercuric salt poisoning results from both direct toxicity to renal tubules by mercuric ions and renal hypoperfusion caused by shock. Consequently, aggressive fluid therapy is useful.[76]

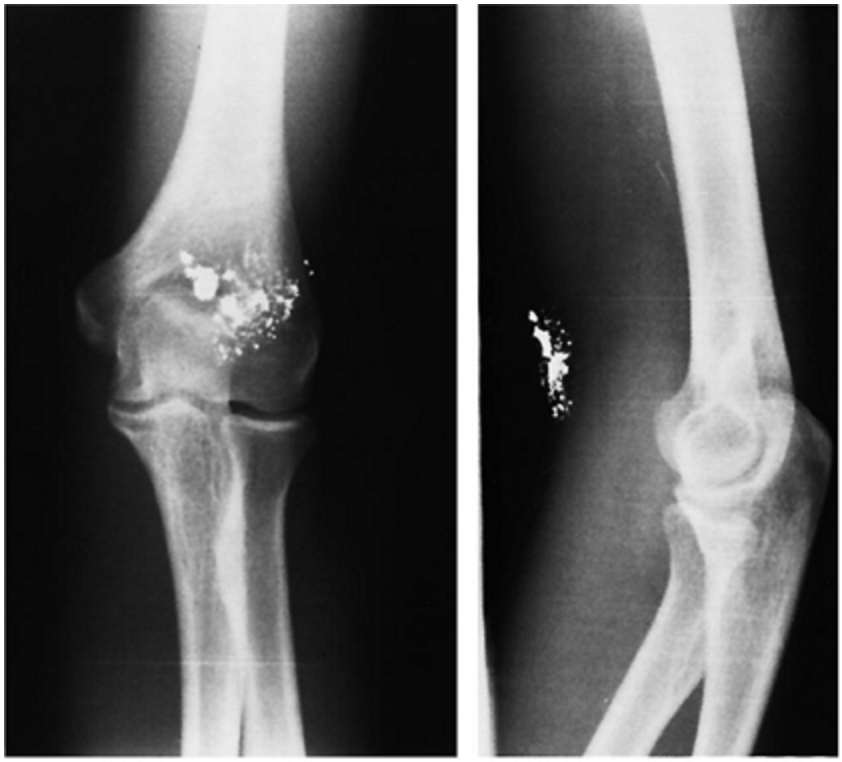

Figure 92-2. Anteroposterior (A) and lateral (B) view of the elbow after an unsuccessful suicidal gesture involving an attempted intravenous injection of mercury in the antecubital fossa. Note extensive mercury deposition, which was partially removed by surgical intervention. *(Courtesy of Diane Sauter, MD.)*

Acute ingestion of mercuric salts is usually intentional, but

unintentional ingestion occurs sporadically in both children and adults.[37] Although ingestion of button batteries containing mercuric oxide is associated with a greater incidence of fragmentation than with other batteries, clinically significant systemic mercury toxicity by this route has not been reported.[49, 52]

Mercuric chloride-containing stool preservatives are another potential source of unintentional inorganic mercury poisoning. Ingestion of 10â€“20 mL of a polyvinyl alcohol preservative that contained 4.5% mercuric chloride resulted in bloody gastroenteritis and proteinuria.[78] Ethnic medicines are also associated with unintentional inorganic mercury poisoning.[39] Not subject to FDA regulation and available without prescription, these xenobiotics are often inadequately labeled and of variable composition (Chap. 43).

Subacute or chronic mercury poisoning occurs after (a) inhalation, aspiration, or injection of elemental mercury; (b) ingestion or application of inorganic mercury salts; or (c) ingestion of aryl or long-chain alkyl mercury compounds. Slow in vivo oxidation of elemental mercury and dissociation of the carbonâ€“mercury bond of aryl or long-chain alkyl mercury compounds result in the production of the inorganic mercurous and mercuric ions.

The predominant manifestations of subacute or chronic mercury toxicity include gastrointestinal symptoms, neurologic abnormalities, and renal dysfunction. Gastrointestinal symptoms consist of a metallic taste and burning sensation in the mouth, loose teeth and gingivostomatitis, hypersalivation (ptyalism), and nausea.[94] The neurologic manifestations of chronic inorganic mercurialism

include tremor, as well as the syndromes of neurasthenia and erethism. Neurasthenia is a symptom complex that includes fatigue, depression, headaches, hypersensitivity to stimuli,

psychosomatic complaints, weakness, and loss of concentrating ability. Erethism, derived from the Greek word *red* , describes the easy blushing and extreme shyness of the afflicted. Other symptoms of erethism include anxiety, emotional lability, irritability, insomnia, anorexia, weight loss, and delirium. The mercurial tremor is well described in numerous case reports as a central intention tremor (Chap. 19) that is abolished during sleep. In the most severe forms of mercury-associated tremor, choreoathetosis and spasmodic ballismus may be present. Other neurologic manifestations of inorganic mercurialism include a mixed sensorimotor neuropathy, ataxia, concentric constriction of visual fields (â€œtunnel visionâ€•), and anosmia.

Chronic poisoning with mercuric ions is associated with renal dysfunction, which ranges from asymptomatic, reversible proteinuria, to nephrotic syndrome with edema and hypoproteinemia. An idiosyncratic hypersensitivity to mercury ions is thought to be responsible for acrodynia, or â€œpink disease,â€• which is an erythematous, edematous, and hyperkeratotic induration of the palms, soles, and face, and a pink papular rash that was first described in a subset of children exposed to mercurous powders.[94] The rash is described as morbilliform, urticarial, vesicular, and hemorrhagic. This symptom complex also includes excessive sweating, tachycardia, irritability, anorexia, photophobia, insomnia, tremors, paresthesias, decreased deep-tendon reflexes, and weakness. The acral rash may progress to desquamation and ulceration. The prognosis is favorable, after withdrawal from mercury exposure. Childhood acrodynia has become uncommon since the abandonment of mercurial teething powders and diaper rinses. Occasional case reports are still noted, however, with fluorescent light bulbs and phenylmercuric-acetateâ€“containing paint implicated.[2 , 89]

Thimerosal is an example of an aryl or long-chain alkyl mercury compound that results in chronic inorganic mercury toxicity. It is a compound that is widely used as a preservative in the

pharmaceutical industry (Chap. 53). Although initial kinetics suggest a stable ethylâ€“mercury bond, the later elimination phase more closely resembles that of the inorganic mercury compounds. Thimerosal is approximately 50% mercury by weight. Generally considered safe, toxicity and death can nevertheless occur following both intentional overdose and excessive therapeutic application of merthiolate (0.1% thimerosal or 600 Âµg/mL mercury).[66 , 71]

Recent concern that the cumulative dose of thimerosal in childhood immunizations may exceed federally recommended maximum mercury doses (Environmental Protection Agency, 0.1 Âµg/kg/d; Agency for Toxic Substances and Disease Registry, 0.3 Âµg/kg/d; Food and Drug Administration, 0.4 Âµg/kg/d) led to a call by the American Academy of Pediatrics to reduce or eliminate thimerosal from vaccines.[3] In particular, controversy exists whether thimerosal causes autism. Although sensitization following use in vaccinations has been reported in atopic children,[65] clinical mercury toxicity has not been reported in appropriately immunized children. Moreover, a number of studies suggest that the incidence of autism is unrelated to use of thimerosal-containing vaccines.[50 , 64 , 83] At the present time, there is clearly more evidence for risk to child health from the diseases targeted for prevention by the vaccines, than from thimerosal. Nevertheless, since 2001, routinely administered childhood vaccines in the United States, with the exception of injectable influenza vaccine, contain only trace amounts of thimerosal.[34]

Organic Mercury Compounds

In contrast to the inorganic mercurials, methylmercury produces an almost purely neurologic disease that is usually permanent, except in the mildest of cases. Although the predominant, syndrome associated with methylmercury is that of a delayed neurotoxicity, acute gastrointestinal symptoms, tremor,

respiratory distress, and dermatitis may occur.[20, 96] In addition, electrocardiographic abnormalities (ST segment changes) and renal tubular dysfunction are associated with this poisoning.[24, 32]

The lipophilic property and slower elimination of methylmercury may contribute to its profound neurologic effects.[24] Characteristically, clinical manifestations follow the initial poisoning by a latent period of weeks to months. Consequently, the lethal dose of methylmercury is difficult to determine. As noted previously, infants exposed prenatally to methylmercury were the most severely affected individuals in Minamata. Often born to mothers with little or no manifestation of methylmercury toxicity themselves, exposed infants exhibited decreased birth weight and muscle tone, profound developmental delay, seizure disorders, deafness, blindness, and severe spasticity. The development of neurologic symptoms in infants exclusively breast-fed by women exposed to methylmercury after delivery, and the detection of mercury in the milk of lactating women, implies a risk for mercury poisoning via breast milk.[43] In one series of lactating women, mercury concentrations in milk were approximately 30% of concentrations found in blood.[63] The rapid decline of blood mercury concentrations in both suckling rats and breast-feeding human infants is attributed to rapid growth of body volume combined with limited transport of mercury by milk.[58, 73, 74]

Several weeks after methylmercury-contaminated grain was ingested in Iraq, patients began to appear with paresthesias involving the lips, nose, and distal extremities. Symptomatic patients also noted headaches, fatigue, and tremor. More serious cases progressed to ataxia, dysarthria, visual field constriction, and blindness. Other neurologic deficits included hyperreflexia, hearing disturbances, movement disorders, salivation, and dementia. The most severely affected patients lay in a mute rigid posture punctuated only by spontaneous crying, primitive reflexive movements, or feeding efforts.[72]

While the outlook for methylmercury neurotoxicity is generally considered dismal, observations over the subsequent two years, in 49 Iraqi children poisoned during the 1971 outbreak, revealed complete resolution or partial improvement in all but the most severely affected.[4] Of 40 symptomatic children, 33 mildly to severely affected children showed partial to complete resolution of symptoms, but the seven children classified as â€œvery severely poisonedâ€• remained physically and mentally incapacitated.

The extreme toxicity of dimethylmercury was tragically demonstrated by the delayed fatal neurotoxicity that developed in a chemist who inadvertently spilled dimethylmercury on a break in the gloves on her hands. Over a period of several days, she developed progressive difficulty with speech, vision, and gait. Despite chelation and exchange transfusion, she died within several months of the exposure.[59]

An important route of organic mercury exposure is through seafood consumption. The safe level of methylmercury in seafood remains controversial. The FDA's action level of 1 ppm for methylmercury in fish was set to limit consumption of methylmercury to less than one-tenth of levels found in cases of symptomatic poisoning. The Environmental Protection Agency (EPA) established a reference dose for methylmercury of 0.1 Âµg/kg/d.[68 , 90]

Although elevated blood concentrations (19â€“53 Âµg/L) of mercury were found in one group of self-reported high consumers of seafood, increased incidence of cognitive and gastrointestinal complaints were not.[38] Even so, concentrations at which fetuses suffer adverse effects are unknown. Longitudinal studies of fish-eating populations are conflicting. No effect of a high prenatal fish diet was found on developmental markers in children followed to nine years of age in the Seychelles Islands. In the Faroe Island and New Zealand studies, however, a subtle but significant effect on neuropsychological development was seen.[19 , 29 , 84] One

reason for the discrepancy seen between the populations may be the different concentrations of methylmercury in the seafood consumed by each. The mean concentration of methylmercury in the whale meat consumed in the Faroe Islands was 1.6 Âµg/g, and mean mercury concentration of mercury found in New Zealand shark was 2.2 Âµg/g. In contrast, mean methylmercury content of Seychellois fish was 0.3 Âµg/g.[57] The threshold concentration for neuropsychological effects may lie between these levels. The FDA recommends that at-risk populations (ie, pregnant women and women who may become pregnant, nursing mothers, and young children) avoid the large predator fish (eg, shark, swordfish, tilefish, and king mackerel) that contain levels of methylmercury approaching 1 ppm.[91] The FDA has ruled that consumption advice is not indicated for the top 10 seafood species, which make up 80% of all seafood consumed: canned (nonalbacore) tuna, shrimp, pollack, salmon, cod, catfish, clams, flatfish, crabs, and scallops. These species contain levels of mercury less than 0.2 ppm and are rarely consumed in quantities in excess of the recommended weekly limit of 2.2 pounds. The recommendations are not as clear for albacore tuna, which may have levels of mercury as high as 0.34 ppm. The FDA-recommended limit of albacore tuna consumption by at-risk populations is less than 6 ounces per week, but some consumer advocacy groups feel that the limit should be lower.[18]

Laboratory

The dual findings of unexplained neuropsychiatric and renal abnormalities in an individual should alert the clinician to the possibility of mercurialism, as should an at-risk occupation or access by the patient to a mercurial product (Tables 92-1 and 92-2).

Occupational or environmental exposure and a consistent clinical scenario may be suggestive of mercury poisoning, but

demonstration of mercury in blood, urine, or tissues is necessary for confirmation of exposure. Of the many methods available to measure mercury, cold atomic absorption spectrometry is rapid, sensitive, and accurate, but cannot distinguish the various forms of mercury. Thin-layer and gas chromatographic techniques can be used to distinguish organic from inorganic mercury.[20] Blood should be collected into a trace element collection tube obtained from the laboratory performing the assay. Urine should be collected for 24 hours into an acid-washed container obtained from the laboratory. Spot collections must be adjusted for creatinine concentration. Attempts to measure or otherwise handle the specimen should be avoided to prevent contamination.

There is considerable overlap among concentrations of mercury found in the normal population, asymptomatic exposed individuals, and patients with clinical evidence of poisoning. There is no definitive correlation between either blood or urine mercury levels and mercury toxicity. However, mercury serves no useful role in human physiology, and concentrations less than 10 Âµg/L and 20 Âµg/L for whole blood and urine, respectively, are generally considered to reflect background exposure in nonpoisoned individuals. Following long-term exposure to elemental mercury vapor, levels as low as 35 Âµg/L for blood and 150 Âµg/L for urine may be associated with nonspecific symptoms of mercury poisoning.[28]

For inorganic mercury poisoning, urine mercury levels may correlate roughly with exposure severity and neuropsychiatric symptoms,[69] but the relationship to total-body burden is probably poor. Urine mercury values have their greatest usefulness in confirming exposure and monitoring the efficacy of chelation therapy. Whole-blood mercury concentrations may reflect intense, acute inorganic mercury exposure, but become less reliable as redistribution to tissues takes place.

Because organic mercury is eliminated via the fecal route, urine

mercury levels are not useful in methylmercury poisoning. Because methylmercury concentrates in red blood cells, the total-body methylmercury burden is best reflected acutely by whole-blood levels.[20, 42] As methylmercury distributes to and accumulates in brain, the severity of clinical manifestations probably more closely reflects the degree of the irreversible neuronal destruction that has taken place, rather than the current body burden of mercury. Correlation of increasing blood mercury concentrations with prevalence of paresthesias was suggested in a population of Iraqis studied early in the course of methylmercury poisoning.[17] However, in another group of patients, blood concentrations did not correlate with severity of methylmercury poisoning.[72] This apparent discrepancy may have resulted from the finding that paresthesias are among the earliest reported symptoms of methylmercury poisoning.

Because mercury accumulates in hair, hair analysis has been employed as a tool for measuring mercury burden. However, because metal incorporation reflects past exposure and hair avidly binds mercury from the environment, the reliability of this method is questionable and is not recommended. In addition to mercury assays, neuropsychiatric testing, nerve conduction studies, and urine assays for *N* -acetyl-Î²-D-glucosaminidase and $Î²_2$ -microglobulin are advocated for early detection of subclinical inorganic and organic mercury toxicity.[25, 32, 69]

Initial Management

After initial assessment and stabilization, the early toxicologic management of mercury poisoning includes termination of exposure by removal from vapors; washing exposed skin; gastrointestinal decontamination; supportive measures, such as hydration and humidified oxygen; baseline diagnostic studies, such as complete blood count, serum chemistries, arterial blood gas, radiographs, and electrocardiogram; specific analysis of blood and

urine for mercury; consideration of possible cointoxicants; and meticulous monitoring.

Elemental Mercury

Inhalation of mercury vapors or aspiration of metallic mercury can result in life-threatening respiratory failure; in this situation, stabilization of cardiorespiratory function is the initial priority. Postural drainage and endotracheal suction may be effective in removing aspirated metallic mercury. Parenteral deposition of subcutaneous or intramuscular mercury may be amenable to surgical excision, if well localized (Fig. 92-2).

An adjunct to the initial management of patients with mercury poisoning is consideration for environmental decontamination. Elemental mercury that spills onto solid surfaces should be adsorbed to sand and the resulting mixture then swept into tightly sealed containers. Ideally, a mercury decontamination kit should be used. The kit consists of calcium polysulfide, which contains excess sulfur to convert mercury to water-insoluble mercuric sulfide (cinnabar). Absorbent surfaces, such as carpets, should be removed. Spilled mercury compounds should not be vacuumed because vacuuming could volatilize the substances.[12] Guidance for decontamination of major spills and disposal of materials can be provided by local and federal hazardous materials agencies.

Inorganic Mercury Salts

Ingestion of inorganic mercuric salts may lead to cardiovascular collapse caused by severe gastroenteritis and third-space fluid loss. Fluid resuscitation is a priority. Gastrointestinal decontamination of ingested inorganic salts of mercury is particularly problematic because of their causticity and risk for perforating injury. Nevertheless, one series of mercuric chloride

ingestion of up to 4 g reported recovery without long-term gastrointestinal sequelae in patients who did not succumb to renal failure.[88] Therefore, unless there is high suspicion for penetrating gastrointestinal mucosal injury, removal of mercury from absorptive surfaces should take priority over endoscopic evaluation. The prominence of vomiting makes gastric lavage unnecessary for most patients with inorganic mercury poisoning.

Metals are among the substances that are often considered to be poorly adsorbed to activated charcoal. Nevertheless, the serious nature of late sequelae following mercury absorption, the typically small quantities of mercury ingested, and evidence that inorganic mercuric salts in fact have substantial adsorption to activated charcoal (800 mg mercuric chloride to 1 g activated charcoal in one in vitro study) justify administration of activated charcoal.[5] Whole-bowel irrigation with polyethylene glycol solution may also be useful in removing residual mercury and should be considered, following its progress with serial radiographs.

Organic Mercury Compounds

Organic mercury exposures do not typically present as single, acute ingestions but rather as chronic or subacute ingestion of contaminated food. Therefore, gastrointestinal decontamination is generally moot with respect to organic mercury poisoning. Nevertheless, its irreversible toxicity coupled with unsatisfactory treatments calls for aggressive decontamination when acute ingestions do occur.

Treatment: Chelation

After initial stabilization and decontamination, early institution of chelating agents may minimize or prevent the widespread effects of poisoning. A high degree of protein binding and distribution to the brain are responsible for the lack of efficacy of other measures

to increase mercury clearance, such as peritoneal dialysis and hemodialysis.[75] In one report of the use of continuous venovenous hemodiafiltration (CVVHDF) in combination with a chelating agent, in a patient with severe inorganic mercury poisoning, 12.7% of the ingested dose was recovered in the ultrafiltrate.[21] Hemodialysis may nevertheless ultimately be necessary, because of the acute renal failure that often follows mercuric chloride poisoning.

Chelating agents have thiol groups that are believed to compete with endogenous sulfhydryl groups for the binding of mercury, thereby preventing inactivation of sulfhydryl-containing enzymes and other essential proteins (see Antidotes in Depth: Dimercaprol [British Anti-Lewisite or BAL] and Antidotes in Depth: Succimer [2,3-Dimercaptosuccinic Acid] for further discussion). A history of significant mercury exposure, combined with the presence of typical symptoms of mercury poisoning, is an appropriate indication for the institution of chelation therapy. Elevated blood and urine mercury concentrations can help support the decision to begin chelation therapy in unclear cases, and may also be used to guide duration of therapy. Provocative chelation, in which urinary mercury excretion before and after a chelating dose is compared to determine degree of mercury poisoning, is of dubious value.[38] Chelation tends to increase urinary elimination of mercury, regardless of exposure history and baseline excretion.

Elemental Mercury and Inorganic Mercury Salts

For clinically significant acute inorganic mercury poisoning, dimercaprol (BAL) should be administered for 10 days in decreasing dosages of 5 mg/kg/dose every 4 hours IM for 48 hours, then 2.5 mg/kg every 6 hours for 48 hours, followed by 2.5 mg/kg every 12 hours for 7 days. This dosing regimen of BAL, derived from the use of BAL in lead poisoning, may be adjusted according to clinical response and the occurrence of adverse

reactions.

When a patient is able to take oral medications, BAL therapy can be replaced with 2,3-dimercaptosuccinic acid (succimer) at 10 mg/kg orally 3 times a day for 5 days, then twice a day for 14 days if the GI tract is clear. As headache, nausea, vomiting, abdominal pain, and diaphoresis may result from BAL chelation therapy, oral succimer is recommended in patients who are not acutely ill or who have been chronically poisoned.

Either BAL or succimer are considered the treatments of choice for inorganic mercury poisoning in the United States, but a few other chelating agents deserve mention. DMPS (2,3-dimercapto-1-propanesulphonate) is a water-soluble dimercaprol derivative that is used in Europe. It can be administered both IV and orally. D-Penicillamine is an orally administered monothiol. Its adverse effectsâ€”gastrointestinal distress, rashes, leukopenia, thrombocytopenia, and proteinuriaâ€”although uncommon in therapeutic doses, seriously limit the usefulness of the drug. *N*-acetyl-D,L-penicillamine (NAP), an investigational analog of D-penicillamine, is thought to be a more effective chelator of mercury than is D-penicillamine, perhaps because of its greater stability.[6 , 30]

Organic Mercury Compounds

The neurotoxicity of methylmercury and other organic mercury compounds is resistant to treatment, and therapeutic options are less than satisfactory. In rats, both BAL and D-penicillamine effectively reduced tissue mercury and prevented neurologic toxicity if administered within the first day of a methylmercury injection.[99] Neither agent reversed neurologic toxicity when administered 12 days after methylmercury injection. DMPS, D-penicillamine, NAP, and a thiolated resin all led to a marked reduction of blood half-life of mercury (ie, 10, 24, 23, and 19 days, respectively, vs. 60 days) during the outbreak of

methylmercury poisoning in Iraq in 1971.[17] Clinical improvement was not observed in any treatment group, but it is reasonable to postulate that reducing the total-body burden of methylmercury may prevent or limit progression of

disease. When studied in mice poisoned with methylmercury,[1] succimer was superior to NAP, DMPS, and a thiolated resin in decreasing brain mercury and increasing urinary excretion. Brain mercury was decreased to 35% of control, and total-body burden fell to 19%. Some animal evidence suggests that BAL may increase mercury mobilization into the brain.[9] For this reason and the lack of serious GI symptoms necessitating parenteral chelation, BAL should not be used for the treatment of organic mercury poisoning.

As the neurologic impairment associated with methylmercury is both profound and essentially irreversible, early recognition of poisoning and prevention of neurotoxicity are essential to a successful outcome. Although further investigation is necessary, succimer may prove to be the treatment of choice for methylmercury poisoning because of its apparently low toxicity and reported efficacy in animal trials.

Summary

Mercury poisoning by any of the three major formsâ€”elemental, inorganic, and organicâ€”presents a complex toxicologic problem associated with a large variety of clinical presentations. An ever-present awareness of the problems, coupled with the knowledge of the differing clinical forms is essential for both early recognition and effective treatment. Although some chelating agents do show promise in the treatment of mercury poisoning, neurologic sequelae, particularly those resulting from organic mercury exposures, remain largely irreversible. Promotion of public education regarding the dangers of mercury, its avoidance, and

proper disposal may aid in the prevention of mercury poisoning.

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Chapter 93
Nickel

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Nickel (Ni)

Atomic number = 28

Atomic weight = 58.7

Normal concentrations

Serum = < 1 Âµg/dL (<17 nmol/L)

Urine = < 6 Âµg/L (<100 nmol/L)

A 16-year-old woman presented to her physician complaining of a pruritic rash that began around her umbilicus. She had first noticed small papules several months earlier and over the past 2 weeks the rash had worsened and spread to involve the skin on the anterior neck and flexural areas of the arms. Her physical examination was notable for small areas of erythema and

lichenification on the earlobes, which she stated had begun a year earlier, after she had pierced her ears. There was no fever and no involvement of mucous membranes, joints, palms, or soles. She reported no prescription or nonprescription medications or recreational drug use. Dimethylgloxime spot tests of her belt buckle and earrings were positive for free nickel. A diagnosis of nickel allergy was made, and the patient was treated with topical corticosteroids and antihistamines. She was instructed to avoid exposure to nickel in clothing and jewelry and given a dimethylgloxime test to detect free nickel on metal surfaces. At a followup 1 month later she reported complete resolution of her symptoms.

History and Epidemiology

Nickel is a white, lustrous metal whose name is derived from the German word â€œkupfernickelâ€• or â€œdevil's copper.â€• It was first identified in 1751 in a mineral known as niccolite. Nickel comprises 0.008% of the earth's crust and is found in diverse locations, ranging from meteorites and soil to bodies of fresh- and saltwater.

First produced by the Chinese, nickel has been used as a component in a variety of metal alloys for more than 1700 years. The first malleable nickel was produced by Joseph Wharton following the American Civil War. Wharton went on to sell bulk quantities of nickel to the US government for the minting of 3-cent coins, and later donated the equivalent of 3.3 million of these coins to help fund what is today known as the Wharton School of Business.[65] The modern United States 5-cent piece, the â€œnickel,â€• is actually only approximately 25% nickel by weight.[73]

Nickel ores typically consist of accumulations of nickel sulfide minerals of relatively low nickel content. Although a variety of technical methods for extracting nickel from ore have been

developed, one method of special note was developed in 1890 by Ludwig Mond. He is credited with the discovery of nickel carbonyl. The Mond process for the extraction of nickel involves passing carbon monoxide over smelted ore. This creates nickel carbonyl, which then decomposes at high temperatures to produce purified nickel and carbon monoxide.[65] Nickel has not been mined in the United States since 1993,[14] and despite an increasing worldwide demand, as of 2002 there were still no active domestic nickel mines.[34] Nickel is imported into the United States from other nickel-rich countries such as Canada, Russia, and Australia, while production of nickel in the United States is essentially limited to the recycling of nickel-containing metals.

Nickel is a siderophoric material that forms naturally occurring alloys with iron, a property that has made it useful for many centuries in the production of coins, tools, and weapons. Today, most nickel is used in the production of stainless steel, a highly corrosion-resistant alloy containing 8â€“15% nickel by weight.[79]

Occupational exposure to nickel and nickel-containing compounds occurs in a variety of industries, including nickel mining, refining, reclaiming, and smelting. Chemists, magnet makers, jewelry makers, oil hydrogenator workers, battery manufacturers, petroleum refinery workers, electroplaters, stainless steel and alloy workers, and welders are at increased risk for exposure to nickel and nickel-containing compounds.[41] The vast majority of nonindustrial

human exposures to nickel are usually from dietary and environmental sources. Cigarette smoke also contains nickel and may contribute to human exposure.[26] In the occupational setting, nickel carbonyl is responsible for the great majority of acute nickel toxicity, while in clinical practice, the most common health issue related to nickel is the development of allergic dermatitis from jewelry and clothing. Nickel ranks behind poison ivy and poison oak as the second most common cause of allergic contact

dermatitis;[24] in a recent patch testing study, more than 30% of adolescents demonstrated an allergy to nickel.[20]

Toxicology and Pharmacokinetics

Exposure

Nickel occurs naturally in soil, volcanic dust, fresh- and saltwater, but also enters the environment from the combustion of fuel oil, municipal incineration, nickel refining processes, and the production of steel and other nickel alloys that may allow aerosolized nickel to be disseminated into the environment.

The specific form of nickel emitted to the atmosphere depends on the source. Complex nickel oxides, nickel sulfate, and metallic nickel are associated with combustion and incineration, as well as smelting and refining processes. Consequently, ambient air levels of these forms of nickel tend to be higher in urban areas, and concentrations of nickel in urban household dust may be elevated under certain circumstances and thus may pose some variable exposure risk for young children who crawl or sit on floors.

Nickel carbonyl, $Ni(CO)_4$, deserves special mention. This highly volatile, highly useful, and very deadly liquid nickel compound is commonly used in nickel refining and petroleum processing, and as a chemical reagent. Its high vapor pressure and high lipid solubility lead to rapid systemic absorption through the lungs. In the air and in the body, it decomposes into metallic nickel and carbon monoxide and its toxicity has been compared to that of hydrogen cyanide.[35] Employees are commonly screened for low-level exposure to nickel carbonyl, but disasters such as the Gulf Oil Company refinery incident in 1953, and the Toa Gosei Chemical company incident in 1969, resulted in hundreds of inhalational exposures.[65]

Levels of metallic nickel in drinking water in the United States are

generally below 20 Âµg/L.[42] Elevated levels of nickel in household and other potable and nonpotable water sources may result from corrosion and leaching of nickel alloys present in various plumbing fixtures, including valves and faucets.[2] Although many water suppliers in the United States monitor nickel levels in their water, there is currently no US Environmental Protection Agency (EPA) regulation regarding how much nickel is permissible in drinking water.

Dietary intake is a recognized source of nickel exposure for humans. Foods high in nickel include nuts, legumes, cereals, and chocolate. Although evidence exists for uptake and accumulation of nickel in certain plants, nickel does not seem to bioaccumulate along the food chain.[79] Nickel is not considered an essential element for human health and dietary recommendations for nickel have not been established. Although estimates vary widely, one author estimated that a 70-kg reference human contains 0.5 mg of nickel, giving an average body concentration of 7 ppb.[7] No clear biologic function has been determined for nickel in humans. However, it may serve as a cofactor for various enzymes, or it may facilitate iron absorption or metabolism in microorganisms, as in certain nickel-dependent blue-green algae.[75]

Absorption

Nickel enters the body through the skin, lungs, and gastrointestinal tract. The amount of absorption depends strongly on the solubility of the nickel compound in water. Once in the body nickel exists primarily as the divalent cation. Thus, regardless of the particular nickel compound, it is elemental nickel that is measured in the serum or urine.

Following inhalational exposure, nickel tends to accumulate in the lungs, and only 20â€“35% of nickel deposited in the human lung is systemically absorbed into the bloodstream.[7,25] The remainder of the inhaled material is swallowed, expectorated, or deposited in

the upper respiratory tract. Subsequent systemic absorption from the respiratory tract is dependent on the solubility of the specific nickel compound in question. Soluble nickel salts (nickel sulfate and nickel chloride) are more easily absorbed, whereas the less-soluble oxides and sulfides of nickel have much lower levels of absorption.

A man who died of adult respiratory distress syndrome 13 days after being exposed to fumes containing high concentrations of metallic nickel (approximately 380 mg/m^3) had very high levels of nickel in his urine (700 Âµg/L).[52] This case report demonstrates that metallic nickel can be systemically absorbed from the lungs; however, many authorities believe that pulmonary levels must be high enough to result in local lung tissue injury before systemic absorption occurs following inhalational exposure.

Because soluble nickel compounds tend to be more readily absorbed from the respiratory tract when compared with nonsoluble or poorly soluble nickel,[72] exposure to the soluble nickel chloride or nickel sulfate results in higher urinary nickel concentrations than does exposure to less-soluble nickel oxide or nickel subsulfide. The half-life of nickel in the lungs of rats exposed by inhalation is reported to be 32 hours for nickel sulfate,[28] 4.6 days for nickel subsulfide, and 120 days for green nickel oxide,[8] a fact that probably reflects slow dissolution and absorption from the lungs.

Following ingestion, approximately 27% of the total nickel in nickel sulfate given to humans in drinking water is absorbed, whereas only approximately 1% is absorbed when given in food.[66] Serum nickel concentrations peak between 1.5 and 3 hours following ingestion of nickel.[15,49,66] The bioavailability of nickel increased when nickel was administered in a soft drink, but decreased when nickel was given with whole milk, coffee, tea, or orange juice.[59] The presence of food appears to reduce the absorption of nickel, and most ingested nickel remains in the gut and is excreted in the

feces.

Human studies show that several nickel compounds are capable of penetrating the skin.[23,46] In one study, radioactive nickel sulfate was applied to occluded skin.[46] It was determined that 55â€“77% of the applied nickel was absorbed within 24 hours, with most of the nickel being absorbed in the first few hours. It could not be determined, however, if the nickel had been absorbed into the deep layers of the skin or into the bloodstream. In a study using excised human skin, only 0.23% of an applied dose of nickel chloride permeated skin after 144 hours when the skin was not occluded, whereas 3.5% permeated occluded skin.[23]

Distribution

In human serum, the exchangeable pool of primarily divalent nickel is bound to albumin, L-histidine, and Î±$_2$-macroglobulin.[45] A

nonexchangeable pool of nickel that is tightly bound to a transport protein known as nickeloplasmin also exists in the serum. Nickel crosses the placenta,[56] and may accumulate in breast milk, resulting in the potential for nickel exposure to offspring.[19]

Nickel also appears to be concentrated in various solid organs rather than in serum. An autopsy study of individuals not occupationally exposed to nickel reports the highest concentrations of nickel in the lungs, followed by the thyroid, adrenals, kidneys, heart, liver, brain, spleen, and pancreas.[53] Nickel concentrations in the nasal mucosa are higher in workers exposed to less-soluble nickel compounds relative to soluble nickel compounds,[72] indicating that, following inhalation exposure, less-soluble nickel compounds remain deposited on the nasal mucosa.

Elimination

In humans, most ingested nickel is excreted in the feces; however,

because more than 90% of ingested nickel does not leave the gut,[63] most of the nickel found in feces represents this unabsorbed fraction rather than the elimination of body nickel.[49,66]

Regardless of the route of exposure, absorbed nickel is excreted in the urine and workers occupationally exposed to nickel have increased urinary concentrations of nickel.[4,22,25,29,72] Following inhalational exposure to green nickel oxide, nickel was only excreted in the feces, implying that the removal of nickel oxide from the lungs is macrophage mediated rather than through mechanisms dependant on dissolution and absorption.[8] Following exposure to nickel subsulfide, nickel was excreted in both the urine and the feces, with greater amounts in the urine on days 6â€“14 postexposure. These results indicate that dissolutionâ€“absorption plays an important role in the removal of nickel subsulfide from the lungs; thus, in the lungs, nickel subsulfide behaves essentially like a soluble compound.[8]

The elimination half-life of nickel depends on the source of exposure. It is important to note that prolonged elevation of serum and urine nickel concentrations from inhalational exposure to insoluble nickel represents continued slow absorption.

In nickel workers, urinary excretion increased from the beginning to the end of the shift, indicating that a fraction is rapidly eliminated.[25,72] Similarly, urinary excretion increased as the workweek progressed, indicating a fraction that was excreted more slowly.[25]

Studies with radioactive nickel chloride injected into rats show that 68% of administered nickel is eliminated in the urine during the first day,[48] and urine nickel concentration is commonly assumed to measure exposure over the past 2â€“3 days.[15]

In workers who unintentionally ingested water contaminated with nickel sulfate and nickel chloride, the mean serum half-life of nickel was 60 hours.[64] This half-life reportedly decreased

substantially (to 27 hours) when the workers were treated with intravenous fluids.

There are no data regarding excretion of nickel in humans or animals after dermal exposure.

Clinical Manifestations

Acute

The most important source of acute, nondermatologic nickel toxicity is nickel carbonyl. Exposure to this compound is associated with pulmonary, neurologic, and hepatic dysfunction.[65]

The specific clinical manifestations associated with acute exposure to other forms of nickel depend on the specific compound and route of exposure. Inhalation of nickel-containing aerosolized particles tends to affect the lungs and upper airways directly whereas ingestion and intravenous administration may result in systemic toxicity, usually involving the neurologic system. By far the most common disorder associated with acute exposure to nickel is an allergic dermatitis.

Nickel Dermatitis

Nickel dermatitis was first reported in the late 1800s in nickel-plating workers and was recognized as an allergic reaction in 1925. Since then, nickel has been recognized as a common cause of allergic contact dermatitis. One population survey reported that 3% of males and 15% of females demonstrated evidence of allergy to nickel.[39] The 5-fold greater prevalence of nickel allergy in females is presumably a consequence of their higher rates of body piercing and more frequent wearing of jewelry, both of which are risk factors for nickel sensitization.[37,54]

Nickel dermatitis is classified into two types: primary and

secondary. The more common primary dermatitis presents as a typical eczematous reaction in the area of skin that is in contact with nickel. It is characterized initially by erythematous papules that may proceed to lichenification. Areas typically involved are the wrists, as a result of wearing watches and bracelets, pierced ears, and periumbilical eruptions at the site of contact with nickel-containing buttons on jeans or nickel-containing belt buckles. (See ILNICKEL in the Image Library at http://www.goldfrankstoxicology.com) Approximately 50% of all belt buckles and 10% of buttons on blue jeans contain nickel.[13]

The secondary form involves a more widespread dermatitis as a result of other exposures, such as ingestion, transfusion, inhalation, and implantation of metal medical devices, and may be regarded as a systemic contact dermatitis elicited by nickel. Secondary eruptions are typically symmetrically distributed and may localize in the elbow flexure, on the eyelids, on the sides of the neck and face, and can become widespread. Nickel in foods, excessive skin contact, and certain orthodontic appliances with high nickel content are all linked to this eczematous eruption. Nonetheless, more recent research indicates that standard stainless steel orthodontic appliances do not increase the rate of nickel sensitivity.[50,51]

The most common cause for nickel dermatitis in women is direct contact from jewelry, garments, wristwatches, and occupational contact in the metal, hairdressing, tailoring, hotel, and restaurant industries. In men, nickel dermatitis is often occupational but may also, in some individuals, be related to jewelry, body piercing, and garments.

It is reported that the bimetallic core structure of the 1 euro and 2 euro coins creates an electrical potential that results in the release of nickel when in contact with sweat.[44] Although studies report no increase in the prevalence of nickel sensitivity before and after the switch to the euro in the general population,[37] positive patch tests

to euro coins[47] and cases of dermatitis in certain high-risk patients have been reported.[55]

One study[36] showed that following skin application, nickel salts are retained in the skin for an extended period of time, which could lead to prolonged antigen processing and consequent immune responses in dermal tissue. Additionally, when in contact with the skin, nickel is oxidized to form soluble, stratum corneum-diffusible compounds that may penetrate the intact stratum and have the potential to elicit allergic reactions.[30,31]

The allergic reaction caused by contact with nickel is a type IV delayed hypersensitivity immune response that typically occurs in two phases. In the first phase, sensitization occurs when nickel enters the body. The second phase occurs when the body is reexposed to nickel, at which time allergy manifests. The diagnosis of nickel allergy is suggested by specific historical findings listed in Table 93-1.

TABLE 93-1. Findings Suggestive of Nickel Dermatitis

Previous history of allergic response to jewelry
Multiple piercings
Eruptions at the site of metal contact, or flexural areas if generalized
Eruptions following placement of orthodontic appliances containing high concentrations of nickel (unusual)
Seasonal dermatitis in warm months (increased metalâ€“skin contact and increased sweating)

Nickel Carbonyl

Perhaps the most important cause of acute toxicity from nickel exposure is nickel carbonyl. Nickel carbonyl is a volatile liquid compound that dissociates into carbon monoxide and metallic nickel. It is the most potentially harmful form of nickel and the majority of acute occupational nickel exposures involve nickel carbonyl. Once dissociated, nickel carbonyl can be oxidized in tissues to Ni^{2+}. Nickel carbonyl is described as having a â€œmustyâ€• or â€œsootyâ€• odor, although thresholds for detection vary considerably and potentially harmful exposures cannot be excluded simply by a reported lack of odor. Exposure to concentrations <100 mg/m^3 is fatal in rats after 20 minutes.[61,67]

Nickel carbonyl exposure may cause symptoms rapidly or symptoms may be delayed. In a series of 179 exposures, approximately 40% of patients reported symptoms within 1 hour of exposure. It is important to note however that symptoms were delayed for approximately 1 week in 20% of patients, and even patients with mild initial symptoms could develop severe delayed symptoms, although usually, within the next 2 days.[58] In patients who developed symptoms shortly following exposure, the initial manifestations involved nonspecific complaints, including respiratory tract irritation, chest pain, cough, dyspnea, frontal headache, dizziness, weakness, and nausea. Cases manifesting only these initial signs are categorized as mild intoxication.[58]

Symptoms of severe acute nickel carbonyl poisoning generally develop over the course of several hours to days and may be associated with acute lung injury and interstitial pneumonitis. Myocarditis, marked by prolonged ECG changes, including ST- and T-wave changes, as well as QTc interval prolongation, are reported.[58] Neurologic symptoms associated with severe poisoning include altered mental status, seizures, and extreme weakness that sometimes necessitates mechanical ventilation. A moderate leukocytosis (10,000â€“15,000 white blood cells/mm^3), nonspecific opacities on chest radiography, and elevation of transaminases may occur, but these tend to resolve over the

course of several weeks. Deaths from nickel carbonyl exposures are typically caused by interstitial pneumonitis and cerebral edema occurring within 2 weeks of initial exposure.[67] Survivors usually recover completely, although the development of a prolonged neurasthenic syndrome can occur and may last in some cases for up to 6 months.[58]

Parenteral Administration

Acute parenteral toxicity from nickel-containing compounds was associated with water used in hemodialysis which was heated in a nickel-plated tank.[77] The concentration of nickel in the delivered water was 0.25 mg/L, and serum concentrations reportedly reached over 3 mg/L. Through back-extrapolation, serum concentrations were estimated to have been as high as 9 mg/L. These patients developed nonspecific symptoms, including headache, nausea, and vomiting, similar to nickel carbonyl poisoning, although no respiratory complaints were reported. The effects resolved after several hours, and the patients recovered without sequelae.[77]

Acute ingestions of contaminated water containing 1.63 g Ni^{2+}/L as nickel salts caused nausea, vomiting, diarrhea, weakness, and headache, as well as pulmonary symptoms, including cough and dyspnea, lasting up to 48 hours.[64] Estimated ingested doses of nickel (as Ni^{2+}) were 0.5â€“2.5 g and serum concentrations as high as 13.4 Âµg/L were reported. The death of a 2-year-old female followed ingestion of 2.2â€“3.3 g Ni in the form of nickel sulfate crystals. Following ingestion, this child reportedly developed depressed mentation, nuchal rigidity, mydriasis, erythema, tachycardia, and acute lung injury.[21]

Although transdermal absorption is typically of minor clinical significance, disruption of the normal integument may allow for more efficient systemic absorption. A metal refinery worker suffered a 40% body surface area partial-thickness chemical injury

resulting from exposure to a chemical mixture that included nickel carbonate and nickel sulfate. Preincident, this individual's measured serum nickel concentration was 0.023 Âµmol/L (1.33 Âµg/L). On postinjury day 6 the serum concentration was 0.490 Âµmol/L (28 Âµg/L). Chelation with $CaNa_2EDTA$ was begun for concomitant cobalt poisoning, and the patient recovered without manifesting signs of nickel toxicity.[43]

Chronic Nickel Exposure

Chronic inhalational exposure to nickel is associated with injury as well as specific histologic changes in the nasopharynx and upper respiratory tract, including atrophy of the olfactory epithelium,[27] rhinitis, sinusitis, nasal polyps, and septal damage.[11] More distal pulmonary effects may include asthma[38] and pulmonary fibrosis.[9,27]

Although evidence of the effects of chronic nickel exposure on reproduction remains limited, a study of Indian welders occupationally exposed to nickel and cadmium showed reduced sperm count and quality, with a positive correlation between sperm tail defects and serum nickel concentrations.[18]

The International Agency for Research on Cancer (IARC) classifies nickel compounds as a group 1 carcinogen.[32] The potential for and mechanisms of carcinogenesis of nickel depend heavily on the specific compounds studied. Animal studies show a threshold doseâ€“response curve for inflammation with soluble compounds (nickel sulfate), and similar curves describing the risks of pulmonary cancers with the less-soluble nickel oxides and nickel subsulfide.[57] Although earlier studies of occupationally exposed workers, primarily electroplaters and refinery workers, also showed increased rates of nasal and pulmonary tumors, more recent studies of refinery workers in more modern environments with lower levels of nickel exposure do not show increased risks of cancer or any cause of mortality.[60]

Soluble compounds such as nickel sulfate cause a threshold-dependent inflammatory response, and may act as promoters of malignancies without a directly genotoxic effect. Insoluble nickel oxides and nickel sulfide bind to chromatin and nucleic acids[16] and also affect expression of various mRNAs.[76] Thus under some conditions, these compounds may be carcinogenic through genetic

and/or epigenetic mechanisms. The more potent carcinogenic effects of insoluble nickel compounds may be a consequence of their increased cellular uptake.[17]

Diagnostic Testing

Although nickel is widely distributed to many body fluids and tissues, urine and blood are the most commonly analyzed samples. Urine collection should ideally use acid-washed, metal-free containers. Some authors recommend correcting urinary nickel concentration per gram of urine creatinine, but it is not clear that this offers any particular advantage in clinical decision making. The average nickel concentration in serum is 0.3 Âµg/L, whereas the value in urine ranges from 1â€“3 Âµg/L.[70] Concentrations among workers occupationally exposed to nickel may be substantially higher and serum concentrations of more than 8 Âµg/L are indicative of excessive exposure.[40]

Nickel concentrations rise in urine, serum, and whole blood following oral administration. In these studies, serum concentrations were slightly higher than, but correlated well with whole blood. Urine and blood concentrations primarily reflect exposure in the past 2 days.[15]

Urine nickel concentrations are used more commonly than blood for monitoring of workplace exposures and for prognostic and therapeutic decision making in nickel carbonyl exposures. An 8-hour collection is typically performed, and the average urinary excretion of nickel (in these nickel workers) is 2 Âµg/L, with an

upper limit of normal of 5 Âµg/L. In cases of nickel carbonyl poisoning, concentrations of <100 Âµg/L in the initial 8-hour specimen may imply mild toxicity. Concentrations of 100â€“500 Âµg/L are classified as moderate, while concentrations >500 Âµg/L are categorized as severe poisonings.[67] These guidelines are often used in guiding treatment decisions. Urine nickel concentrations rise prior to the onset of symptoms in nickel carbonyl poisoning, making this a potentially useful screening tool for both workforce surveillance and acute exposures.

Testing metal surfaces for free nickel is possible and sometimes necessary in the evaluation and treatment of nickel dermatitis. Patients with clinically important sensitivity or suspect medical histories can order an inexpensive, commercially packaged dimethylgloxime spot test, allowing them to test metal objects for the presence of free nickel.[13]

Treatment

The first step in treatment of nickel-related medical problems is eliminating the exposure, which includes detection and removal of the source. In the case of acute exposures to nickel carbonyl, removal of clothing to prevent continued exposure and thorough skin decontamination may be necessary.

Symptomatic treatment for pulmonary symptoms associated with hypoxia includes the administration of supplemental oxygen. The use of bronchodilators and corticosteroids may also be necessary for the treatment of concomitant bronchospasm. Mechanical ventilation will be required in the most severe cases.

The administration of intravenous fluids to promote diuresis reduces the half-life of orally ingested nickel chloride by approximately 50%.[64] It is important to note, however, that hemodialysis does not effectively remove nickel from the serum.[77]

Chelation

Because there are no controlled human trials, specific recommendations for the use of chelation to treat nickel toxicity are not currently supported by the literature. As a result, extrapolation from animal studies and case reports are the bases for most treatment regimens. Most studies and reports involving treatment have focused on workers exposed to nickel carbonyl.

Several drugs are proposed as potential treatments for nickel carbonyl exposures. Studies in rats with various chelating agents show some protection by administration of British anti-Lewisite (BAL) and D-penicillamine,[78] whereas calcium EDTA had no protective effect.[62] Although BAL was been used in the past,[67] the most recent literature has focused on the use of diethyldithiocarbamate (DDC) (Chaps. 77 and 96).

DDC is a chelating chemical formerly used as the color reagent for urine nickel measurements. Rats exposed to several times the LD_{50} (median lethal dose for 50% of test subjects) for nickel carbonyl had dramatically reduced mortality when pretreated with DDC; the antidotal efficacy, however, decreased with increasing delay to treatment.[6] A proposed treatment regimen for exposed workers focused on analysis both of the exposure and of the initial 8-hour urine collection.[67] Patients with suspected severe poisonings are typically given the first gram of DDC in divided oral doses. When less-severe exposures are suspected, treatment decisions are based on the urinary nickel concentration. At concentrations <10 Âµg/dL, no initial therapy is given as delayed symptoms are unlikely to develop. At concentrations between 10 and 50 Âµg/dL, an oral regimen consisting of 1 g DDC initially, 0.8 g at 4 hours, 0.6 g at 8 hours, and 0.4 g at 16 hours is used. DDC is continued at a dose of 0.4 g every 8 hours until there is symptomatic improvement and urine nickel concentration is normal. Severe exposures with urinary nickel concentrations >50 Âµg/dL can be treated using the same regimen, although these

patients frequently require closer monitoring. Critically ill patients are given parenteral DDC starting at a dose of 12.5 mg/kg. However, given the animal data that the route and timing of administration are important to survival, some authors recommend that parenteral DDC be given as soon as possible following nickel carbonyl poisoning.[12] Although typically well-tolerated, DDC is capable of inducing a disulfiram reaction (Chap. 77) if taken with alcohol, and there are concerns about using DDC when there is concurrent cadmium exposure.[3]

Disulfiram is metabolized into two molecules of DDC. Given that DDC is not pharmaceutically available in the United States, there is some interest in the use of disulfiram as an antidote for nickel carbonyl. Although case reports describe successful treatment of nickel carbonyl toxicity with disulfiram,[35] concern exists because of animal studies showing that disulfiram increased nickel concentration in brain tissue.[5] One treatment regimen was 750 mg PO every 8 hours for 24 hours, followed by 250 mg every 8 hours.[35]

Considering that the majority of the literature and almost all human case reports of nickel carbonyl refer to the use of DDC, it is considered the treatment of choice for nickel toxicity. Although commonly available as a reagent, pharmaceutical-grade DDC is not produced commercially. It is recommended that the regional poison control center be contacted if necessary to assist with treatment decisions.

Treatments evaluated for divalent nickel exposure are D-penicillamine and *N*-benzyl-D-glucamine dithiocarbamate (NBG-DTC), which, while not commonly available, more effectively lowers brain nickel concentrations than does DDC, perhaps because of its lower lipid solubility.[68]

Contact dermatitis from nickel is treated using standard measures, including avoidance, topical steroids, and oral antihistamines.

Some patients have benefited from dietary alteration to reduce nickel intake. Although sometimes advised, there does not appear to be a role for avoiding stainless steel cookware to reduce the nickel content of food.[1]

Summary

Nickel is an important metal that is ubiquitous in the human environment and vital to the functioning of an industrialized society. This constant exposure to nickel is reflected by high rates of nickel sensitivity and dermatitis in the public. Although systemic toxicity from nickel is rare, it is a potentially important cause of occupational illness. Acute toxicity from nickel carbonyl and the potential cancer risk posed by chronic inhalation of nickel-containing dusts and fumes remain important concerns in many industries.

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Chapter 94
Selenium

Diane P. Calello

Selenium (Se)

Atomic number = 34

Atomic weight = 78.96

Normal concentrations

Whole Blood = 0.1â€“0.34 mg/L

Serum = 0.04â€“0.6 mg/L

Urine = <0.03 mg/L

Hair = 0.36 ng/g

A 30-year-old corrections officer was brought to the emergency department by his girlfriend 2 hours after a suicidal ingestion of gun bluing solution. The label on the empty bottle revealed that it

contained 2% selenious acid and copper nitrate. On physical examination, his vital signs were: blood pressure, 80/30 mm Hg; pulse, 120 beats/min; respiratory rate, 18 breaths/min; temperature 98.6Â°F (37Â°C), and pulse oximetry revealed 100% oxygen saturation on room air. He was somnolent but arousable, and complained of abdominal pain followed by several episodes of bloody emesis. Further evaluation revealed an ECG with diffuse T-wave flattening and ST changes, creatinine of 1.5 mg/dL, and the following arterial blood gas values: pH, 7.1; PCO_2, 28 mm Hg; PO_2, 100 mm Hg. His urinalysis was positive for blood but negative for erythrocytes; the creatine phosphokinase was 1430 IU. His hepatic aminotransferases were also elevated.

Because of the delay in presentation and the suspicion of caustic esophageal injury, he did not receive gastrointestinal decontamination. Two large-bore IV lines were inserted and 3 L of 0.9% sodium chloride was administered. Despite aggressive volume resuscitation, his blood pressure fell to 70/26 mm Hg, prompting the administration of IV dopamine (15 Âµg/kg/min) and subsequently epinephrine via a central venous line. He developed ectopy with multiple premature ventricular complexes, and his mental status deteriorated further. Cardiac arrest followed soon thereafter, with ventricular fibrillation progressing quickly to asystole. Further resuscitation attempts were unsuccessful, and he expired 12 hours after ingestion. A serum selenium concentration was later reported as 46 mg/L. Postmortem pathologic examination revealed severe corrosive gastritis and red pigmentation of all viscera.

Selenium was discovered by JÃ¶ns Berzelius in 1817 as a contaminant of sulfuric acid vats that was causing illness in Swedish factory workers. He originally believed it to be the element tellurium (from the Latin *tellus*, â€œearthâ€•), but on finding it to be an entirely new, yet similar, element, he named it for the Earth's satellite (from the Greek *selene*, â€œmoonâ€•). Selenium has unusual light-sensitive electrical conductive

properties, leading to its widespread use in industry. It is both an essential component of the human diet, as well as a potentially deadly poison.

History and Epidemiology

Much of what is known about selenium centers around its role as an essential trace element required in the diet of living things, not around its toxic properties. In the 1970s, it was discovered to be an essential cofactor of the enzyme glutathione peroxidase. Keshan disease, an endemic cardiomyopathy associated with multifocal myonecrosis, periacinar pancreatic fibrosis, and mitochondrial disruption, was described in 1979 in Chinese women and children who consumed a selenium-poor diet over several years.[11] Kashin-Beck disease, a disease causing shortened stature as a result of chondrocyte necrosis, is described in young children in Russia, China, and Korea; although other factors are also likely involved, people with this disease show some improvement with selenium supplementation.[1]

These observations prompted the establishment, in 1980, of the United States' recommended daily allowance (RDA) of selenium. Taking into account the level of supplementation required to

achieve optimal glutathione peroxidase activity in selenium-deficient study populations, as well as the amounts required to cause toxicity, the recommendation calls for 55 Âµg/d. Deficiency occurs below 20 Âµg/d.[11]

Chronic selenium toxicity, or selenosis, has occurred throughout history. Described first in animals, the acute syndrome of â€œblind staggersâ€• and the more chronic â€œalkali diseaseâ€• affected livestock eating highly seleniferous plants, causing blindness, walking in circles, anorexia, weight loss, blindness, ataxia, and dystrophic hooves. Humans in seleniferous areas of China and Venezuela develop similar integumentary symptoms

(dermatitis, hair loss, and nail changes) at an intake >100 times the RDA, approximately 6000 Âµg/d.[5,37]

Selenium is found in abundance and widely distributed throughout the earth's crust, usually as a metal selenide in sulfide ores such as marcasite, arsenopyrite, and chalcopyrite. It is found in the soil where it has leached from bedrock, in groundwater, and in volcanic gas. The highest soil levels of selenium in the United States are in the midwest and west. Dietary selenium is easily obtained through meats, grains, and cereals. Brazil nuts, grown in the foothills of the highly seleniferous Andes Mountains, contain the highest concentration measured in food, but chronic selenium toxicity from Brazil nuts has not been reported and would only be expected after massive ingestion.[1]

In industry, selenium is generated primarily as a byproduct of electrolytic copper refining, and in the combustion of rubber, paper, municipal waste, and fossil fuels. In general, selenium compounds are used in glass manufacture and coloring, photography and xerography, rubber vulcanization, and as insecticides and fungicides. Selenium sulfide is the active ingredient in many antidandruff shampoos. Gun bluing solution, used by law enforcement for cleaning of the exterior surface of firearms, is composed of selenious acid, as well as other compounds, such as cupric sulfate in hydrochloric acid, nitric acid, copper nitrate, and methanol. Table 94-1 lists industrial uses of selenium compounds. Table 94-2 lists common acceptable selenium exposure concentrations.

Chemical Principles

Selenium is a nonmetal element of group VIA of the periodic table, which also contains oxygen, sulfur, and tellurium. Selenium exists in elemental, organic and inorganic forms, with important oxidation states of 0 (elemental), â€“2 (selenide, Se^{2+}), +2 (selenite, SeO_3^{2+}) and +4 (selenate, SeO_4^{2+}). Solubility in water

generally increases with oxidation state, so elemental selenium and metal selenides are insoluble, whereas alkali selenites and selenates are highly water soluble. Selenium behaves similarly to sulfur both in its tendency to form compounds and in biologic systems.[1] Selenium is both photovoltaic (able to convert light to electricity) and photoconductive (conducts electricity faster in bright light), which has led to its use in photography, xerography, and solar cells.

TABLE 94-1. Selenium Compounds and Their Uses

Chemical Formula	Name	Uses
Se	Selenium, elemental	Photography, catalyst, xerography
SeS_2	Selenium sulfide	Antidandruff shampoo
SeO_2	Selenium dioxide	Catalyst, photography, xerography, glass decolorizer, vulcanization of rubber
$SeOCl_2$	Selenium oxychloride	Solvent, plasticizer
SeF_6	Selenium hexafluoride	Gaseous electrical insulator

H_2SeO_3	Selenious acid	Gun bluing solution
H_2Se	Hydrogen selenide, selenium hydride	â€”
Na_2SeO_3	Sodium selenite	Glass and porcelain manufacture
Na_2SeO_4	Sodium selenate	Insecticide

TABLE 94-2. Selenium Regulations and Advisories

Oralâ€”recommended intake and exposure limits		
RDA (2000)	55 Âµg/d[a]	(0.8 Âµg/kg/d)
NAS-TUL ATSDR-chronic oral MRL[b]	400 Âµg/d 5 Âµg/kg/d	(5.7 Âµg/kg/d)
Waterâ€”limits		

WHO	Drinking water	0.01 mg/L
FDA	Bottled water	0.01 mg/L
EPA	MCL, Drinking	0.05 mg/L
Airâ€”limits[c]		
NIOSH		
REL (TWA)		0.2 mg/m^3
IDLH		1.0 mg/m^3
OSHA		
PEL (TWA)		0.2 mg/m^3

ATSDR = American Toxic Surveillance and Disease Registry; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; MCL= maximum contaminant level; MRL = minimal risk level; NAS = National Academy of Sciences; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; RDA = recommended daily allowance; REL = recommended exposure limit; TUL = tolerable upper limit; TWA = time-weighted average; WHO = World Health Organization.

[a]Values differ for pregnant and lactating women, children,

and neonates.
[b]No acute or intermediate MRL has been established. Chronic = >365 days.
[c]Ambient background air concentrations are usually in the ng/m^3 range.

At least three allotropes of elemental selenium are described: a gray substance, which predominates at room temperature, red crystals, and a red amorphous powder.[1] In general, toxicity from elemental selenium is rare and only occurs from long-term exposure. Hydrogen selenide (H_2Se) is formed from the reaction of water or acids with metal selenides, or from the reaction of hydrogen with soluble selenium compounds; at room temperature it exists in gaseous form and results in industrial inhalation exposures. The organic alkyl compounds (dimethylselenide, trimethylselenide) are the least toxic and are byproducts of endogenous selenium detoxification (methylation). Selenious acid (H_2SeO_3) is the most toxic form of selenium, generated from the reaction of selenium dioxide with water; ingestion of selenious acid is usually fatal.

Pharmacology and Pathophysiology

There are 3 categories of selenium normally found in the body. First, selenium-specific proteins, or selenoproteins, contain selenocysteine residues and play specific roles primarily in redox (reduction-oxidation) physiology. Second, there are a number of nonspecific proteins containing selenium, for example as selenomethionine in place of methionine, in which selenium appears to have no specific role but which may represent a storage form of selenium; other examples include nonspecific proteins containing selenocysteine, and ubiquitous plasma proteins, such as albumin, which bind selenium. Third, selenium has several

inorganic forms throughout the body, such as selenate, alkyl selenides, and elemental selenium (Se^0).

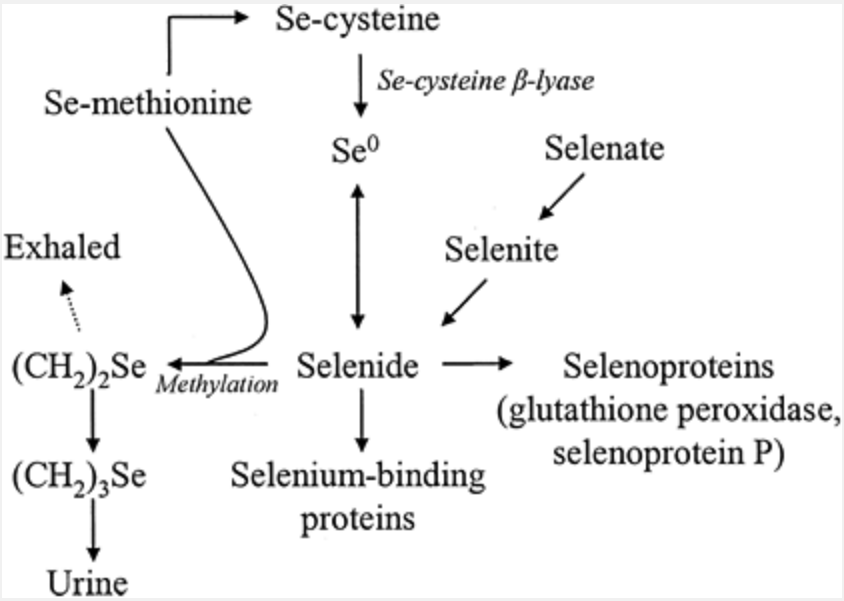

Figure 94-1. Metabolism of selenium. The selenide anion is central in selenium metabolism. Organic selenocysteine is converted via the Î²-lyase enzyme to elemental selenium, then to selenide. Selenomethionine may either undergo transsulfuration to selenocysteine or methylation to excretable metabolites. The selenate and selenite salts are reduced to selenide. Selenide then undergoes one of three processes: methylation, incorporation into selenoproteins, or binding by nonspecific plasma proteins.[1,13]

The known specific selenoproteinsâ€”glutathione peroxidase, iodothyronine 5-deiodinases, and thioredoxin reductaseâ€”each contain a selenocysteine residue at the active site. The most well-studied selenoprotein is glutathione peroxidase, responsible for detoxification of reactive oxygen species. Using reduced

glutathione (GSH) as a substrate, glutathione peroxidase catalyses the reduction of hydrogen peroxide to water and oxidized glutathione (GSSG, or glutathione disulfide) (Fig. 94-1); the reaction is made possible by oxidation of the selenocysteine unit on the enzyme.[4,30] Other selenocysteine-containing proteins also appear to have antioxidant properties, such as thioredoxin reductase. The thyroid hormone deiodinases are responsible for the conversion of thyroxine (T_4) to the active triiodothyronine (T_3) form.

In selenium deficiency, glutathione peroxidase activity is decreased, and GSH and glutathione-S transferases are increased.[30] Consequently, selenium-deficient rats are much less vulnerable to substances detoxified by glutathione-S transferase, such as acetaminophen and aflatoxin B.[6] However, selenium deficiency potentiates toxicity to prooxidants such as nitrofurantoin, diquat, and paraquat.[6] In animal studies of metal toxicity, selenium also appears to either increase or decrease (depending on the individual metal) the effects of silver, cadmium, arsenic, copper, zinc, mercury, and fluoride; conversely, vanadium, tellurium, and arsenic modify the effects of selenium deficiency or excess.[14,20,27,32] Although it is proposed that this is accomplished through the formation of insoluble seleniumâ€“metal complexes, these relationships are not entirely understood.[13]

Less is known about the biochemical mechanism of selenium toxicity, and what is known is not from overdose data, but from in vitro studies. Paradoxically, excess selenium causes oxidative stress, presumably as a result of prooxidant tendencies of selenide (RSe^-) anions. In addition, the replacement of selenium for sulfur in enzymes of cellular respiration may cause mitochondrial disruption, and the substitution of selenomethionine in place of methionine may interfere with protein synthesis. Selenium's integumentary effects are also most likely a result of interpolation of selenium into disulfide bridges of structural proteins such as keratin.[35]

Pharmacokinetics and Toxicokinetics

Gastrointestinal absorption varies with the species of selenium, and human data are limited. Elemental selenium is the least bioavailable (up to 50%), followed by inorganic selenite and selenate salts (75%);[23] selenious acid is quite well absorbed in the lungs and gastrointestinal tractâ€”approximately 85% in animal studies.[10] Organic selenium compounds are the most absorbed at approximately 90% as determined by isotope tracers in human volunteer studies.[2,23]

Inhalational absorption was documented in a group of workers exposed to selenium dioxide and hydrogen selenide gas,[2,17] but quantitative inhalation studies in humans are not available. Dermal absorption appears to be limited. Selenium disulfide shampoos are not systemically absorbed as measured by urinary selenium levels,[10] except in cases of repeated use on excoriated skin.[29]

The toxic dose of selenium varies widely between selenium compounds, as demonstrated by LD_{50} (median lethal dose for 50% of test subjects) animal studies,[32] and parallels gastrointestinal bioavailability. Elemental selenium has no reported adverse effects in acute overdose, although long-term exposure can be harmful. The selenium salts, particularly selenite, are more acutely toxic, as is selenium oxide (SeO_2) through its conversion to selenious acid in the presence of water. Selenious acid may be lethal with as little as a tablespoon of 4% solution in children.

The metabolic fate of selenium centers on the selenide anion (Fig. 94-1), which has 1 of 3 final processes: (a) incorporation into selenoproteins such as glutathione peroxidase and triiodothyronine; (b) binding by nonspecific plasma proteins such as albumin or globulins; or (c) hepatic methylation into nontoxic, excretable metabolites. Trimethylselenide is the primary metabolite and is excreted by the kidneys, the major elimination

pathway for selenium. Fecal elimination also occurs. Dimethylselenide production is usually minor, but increases with dose or exposure; this compound is volatilized through exhalation and sweat, and is responsible for the garlic odor of patients exposed to excess selenium. The remaining selenium in the body is >95% protein-bound within 24 hours.[1,32] Toxicokinetic data are limited and vary by compound.

Clinical Manifestations

Acute Overdose

Dermal and Ophthalmic Exposure

Dermal exposure to selenium dioxide, which is converted to selenious acid, and to selenium oxychloride, a vesicant that is hydrolyzed to hydrochloric acid, causes significantly painful caustic burns, although the tissue destruction is not usually severe.[12] Excruciating pain may result from accumulation under fingernails. Unsurprisingly, selenious acid can also produce a pustular and ulcerative caustic burn.

Corneal burns with severe pain, lacrimation, and conjunctival edema are reported after exposure to selenium dioxide sprayed unintentionally into the face.[24] In chronic exposures, â€œrose eye,â€• a red discoloration of eyelids with palpebral conjunctivitis, is also described.

Inhalational Exposure

When inhaled, all selenium compounds have the potential to be respiratory irritants. In general, inhaled elemental selenium dusts are less systemically toxic than those compounds that are converted to selenious acid. Hydrogen selenide inhalation toxicity

is reported repeatedly throughout the industrial literature.[8] Hydrogen selenide is oxidized to elemental selenium, so acutely toxic exposures are limited to confined spaces where the hazardous gas may accumulate; however, like hydrogen sulfide (H_2S), its ability to cause â€œolfactory fatigue,â€• which renders the exposed persons anosmic to the toxic fumes, can be very hazardous (Chap. 21).[8] Acute exposure to high concentrations of hydrogen selenide gas produces throat and eye pain, rhinorrhea, wheezing, and pneumomediastinum, with residual restrictive and obstructive disease that can remain on pulmonary function testing years later.[31]

In contrast, selenium dioxide and selenium oxide fumes form selenious acid in the presence of water in the respiratory tract. Twenty-eight workers in a selenium rectifier plant were inadvertently exposed to smoke and high concentrations of selenium oxide in an enclosed area. Initial symptoms included bronchospasm with upper respiratory irritation and burning. Some acutely developed hypotension, tachycardia, and tachypnea, which resolved over 2 hours. Patients went on to develop chemical pneumonitis, fever, chills, headache, vomiting, and diarrhea. Five patients required hospitalization for respiratory support, with fever, leukocytosis, and bilateral infiltrates. All patients recovered without sequelae.[36]

Selenium hexafluoride is a caustic gas used in industrial settings as an electrical insulator. Its caustic properties are derived from its conversion, in the presence of water, to elemental selenium and hydrofluoric acid. Severe pain and burning of the eyes, skin, and respiratory tract similar to that seen with hydrofluoric acid exposure can occur following inhalation of selenium hexafluoride (Chap. 101).

Oral Exposure

There are no reported cases of acute overdose with elemental

selenium. All reported cases of acute oral selenium poisoning have occurred with selenium salts, their corresponding acids, and selenium oxides, and the mechanism remains unclear. Gastrointestinal symptoms predominate at low doses, with attendant minor abnormalities in hepatic aminotransferases serum bilirubin and alkaline phosphatase. More severely poisoned patients develop weakness, elevation in creatine phosphokinase (CPK) concentrations, and renal insufficiency as a result of direct tissue injury, myoglobinuria, and hemolysis. Caustic esophageal and gastric burns, myocardial and mesenteric infarction, and metabolic acidosis all contribute to poor outcome in these patients.[25,28] The unifying feature in all serious cases of selenium poisoning is refractory hypotension, a combined product of decreased contractility from acute toxic cardiomyopathy and decreased peripheral vascular resistance. Multisystem organ failure often results, with the acute respiratory distress syndrome, cerebral edema, and death.[9,19,34] The underlying mechanism for this clinical syndrome is not well understood. Postmortem red pigmentation of viscera is also consistently reported and is likely caused by the accumulation of selenium compounds, some of which have a red or rust color (see Chemical Principles above).

Ingestion of the selenium salts is associated with the above symptoms, but usually with good outcome.[9,34] A 15-year-old female survived a suicidal ingestion of approximately 22 mg/kg selenium as sodium selenate, possibly because of near-immediate induction of emesis. She presented with strong garlic odor, diarrhea, and diffuse T-wave flattening on ECG, which progressed to T-wave inversions and a prolonged QTc interval that resolved over 2 weeks. Her serum selenium concentration was 3.1 mg/L on admission (normal: 0.04â€“0.6 mg/L), with a 24-hour urine concentration of 0.8 mg/L (normal: <0.03 mg/L). She underwent treatment with vitamin C and British anti-Lewisite (BAL) and recovered.[9]

Ingestion of even small quantities of selenious acid, however, is

almost invariably fatal. As little as 15 mL of a 4% selenious acid gun bluing solution can be fatal in a child. Selenium oxide and dioxide are also highly toxic via the oral route, presumably because of their conversion to selenious acid. A 17-year-old boy who ingested, in a suicide attempt, an estimated 10 g of selenium dioxide used as a chemistry reagent was found apneic and pulseless, and failed resuscitation; pathology revealed orange-brown discoloration of all viscera.[19] In a similar scenario, 2 g of selenium dioxide produced a severe but nonfatal caustic (grade III) gastric ulceration.[18]

Chronic

Elemental selenium is implicated in a number of long-term exposure cases. Many descriptions of chronic selenium toxicity, or selenosis, come from inhabitants of the Hubei province of China from 1961â€“1964, the majority of whom developed clinical signs after an estimated average consumption of 5 mg of selenium per day (but as little as 910 Âµg/d) derived from local crops and vegetation. Inhabitants of a seleniferous area of Venezuela, consuming approximately 300â€“400 Âµg/d, also develop symptoms of selenium excess; however, the low socioeconomic and poor dietary status of the subjects may also contribute to their symptoms. In contrast, US residents in a seleniferous area with a high selenium intake (724 Âµg/d) over 2 years who were compared to a control population and monitored for symptoms and laboratory abnormalities, remained asymptomatic, with only a clinically insignificant elevation of hepatic aminotransferases in the high-selenium group.[22] Average selenium levels were serum, 0.215 mg/L; whole blood, 0.322 mg/L; and urine 0.17 mg/L.

Selenosis is similar to arsenic toxicity, with its most consistent manifestations being nail and hair abnormalities. The hair becomes very brittle, breaking off easily at the scalp, with regrowth of discolored hair, and the development of an intensely pruritic scalp

rash. The nails are also brittle, with white or red ridges that can be either transverse or longitudinal; the thumb is usually involved first, and paronychia can develop. The skin becomes erythematous, swollen, and blistered, slow to heal, and with a persistent red discoloration. Increased dental caries may occur.[15] Neurologic manifestations include hyperreflexia, peripheral paresthesia, anesthesia, and hemiplegia. Although cardiotoxicity is described with both selenium deficiency and acute poisoning, no such cases are reported with human selenosis. Aside from one case described in the Chinese series, in which there is insufficient postmortem data, there are no reported deaths from intermediate or chronic exposure. Selenium concentrations in these populations averaged 3.2 mg/L (range: 1.3â€“7.5) in whole blood, 2.68 mg/L (0.88â€“6.63) in urine, and 32.2 ng/g in hair.[37]

Selenosis may also occur as a result of overzealous dietary supplement use. In 1983, a 57-year-old woman taking a selenium supplement labeled as 150-Âµg tablets developed progressive symptoms of alopecia, nail streaking, paronychia, and fingernail loss. Three months into her course the manufacturer recalled the lot for superpotency; analysis revealed the tablets contained instead 31 mg of selenium, a dose 200 times higher than labeled. Subsequently, 12 other individuals on the same supplement developed symptoms. All patients recovered after discontinuation of the supplement.[7,16]

Selenosis also is reported in the industrial setting. Copper refinery workers demonstrate garlic odor and gastrointestinal and respiratory symptoms coincident with exposure to selenium dust and fumes.[17] Long before regulatory workplace standards were in place, intense garlic odor of the breath and secretions was recognized as a reason to remove a worker from selenium until the odor subsided. Neuropsychiatric findings such as fatigue, irritability, and depression are reported throughout the industrial literature and are difficult to quantify. Early reports exist such as

the factory worker being â€œunable to tolerate his children about himâ€• at the end of the day when working with selenium.

Although carcinogenicity is suggested by a number of animal studies, in humans the data available suggest, if anything, an inverse correlation between selenium intake and cancer risk. The International Agency for Research on Cancer (IARC) does not list selenium as a suspected carcinogen.[2] Animal studies also suggest that selenium has embryotoxic and teratogenic properties.[13]

Diagnostic Testing

Over time, selenium is incorporated into blood and erythrocyte proteins. As a result, whole-blood and erythrocyte selenium concentrations are more useful for quantifying chronic exposure than plasma and serum concentrations, which change rapidly in relation to selenium intake and are better measures following acute exposure. In general, a serum concentration >1 mg/L is associated with mild toxicity, and a concentration >2 mg/L is associated with serious toxicity.[2] However, concentrations do not demonstrate a predictable relationship with exposure, toxicity, or time course.

Urine concentrations reflect very recent exposure, as urinary excretion of selenium is maximum within the first 4 hours. In addition, urine concentrations are an imperfect measure as they can be affected by the most recent meal and hydration status. However, in general a normal urinary concentration is <0.03 mg/L.

Hair concentrations of selenium were measured in the Chinese populations of interest, and may be a useful measure of exposure.[33,37] However, the usefulness of hair selenium is limited in countries such as the United States where the use of selenium sulfide shampoos is widespread.

Freezing of liquid biologic specimens following collection is recommended to retard the enzymatic formation of difficult-to-

detect volatile metabolites. Other ancillary tests to assess selenium toxicity include ECG, thyroid function, platelet counts, hepatic transaminases, creatinine, and serum creatine phosphokinase. These are abnormal in some patients, for example, in patients with selenious acid poisoning, and are not indicated in cases not expected to cause systemic toxicity.

Management

Pain Management

Treating painful skin, nail bed burns, or ocular pain with 10% sodium thiosulfate solution or ointment may provide relief of symptoms as the result of a reduction of selenium dioxide to elemental selenium.[12] In one series, workers exposed to selenium dioxide fumes reported similar relief from inhalation of fumes from ammonium hydroxide soaked sponges; the mechanism of this is unclear, and further study is required before this practice can be recommended.[36]

Workers exposed to selenium hexafluoride gas can be treated with calcium gluconate gel to affected areas. This is the same treatment as in hydrofluoric acid exposures, which is discussed in Chap. 101.

Decontamination

As with any toxic exposure, prompt removal from the source is required if possible. Patients with dermal exposure should be irrigated immediately. There are limited data to support the use of aggressive gastrointestinal decontamination following the ingestion of most selenium substances as there is little expected acute toxicity. However, in compounds with the potential for producing systemic toxicity, such as the selenite salts, decontamination with orogastric lavage or activated charcoal may be warranted.

Although there are no charcoal adsorption data to guide this therapy, it should be given in light of potential benefit until further information is available.

Special consideration should be given to the ingestion of selenious acid, which is both a caustic agent with attendant decontamination difficulties and a serious systemic poison. The judicious use of orogastric lavage may be indicated based on time since ingestion, amount ingested, presence or absence of spontaneous emesis, and the clinical condition of the patient.

Chelation and Antidotal Therapy

There are no proven antidotes for selenium toxicity. Animal studies and scant human data suggest that chelation with dimercaprol (BAL),[21] $CaNa_2EDTA$ (edetate calcium disodium), or succimer form nephrotoxic complexes with selenium, do not speed clinical recovery and may, in fact, worsen toxicity.[20,21,28] Arsenical compounds appear to ameliorate selenium toxicity through enhanced biliary excretion,[8,13,17,20] but there are no studies to guide this potentially toxic therapy. Vitamin C is hypothesized to limit oxidative damage, but has not been studied. Bromobenzene may accelerate urinary excretion of selenium,[8] but its inherent toxicity would limit its use, regardless of efficacy.

Extracorporeal removal techniques such as hemodialysis or hemofiltration decrease selenium concentrations in patients undergoing the procedure regularly for renal failure, so theoretically this could be of use in lowering toxic serum selenium concentrations. However, because of extensive protein binding, this benefit may be only minor and only relevant to patients undergoing frequent dialysis. Although there are reports of using hemodialysis in patients with acute selenium poisoning, further study must occur before this can be recommended.[18,19]

Supportive Care

This is the mainstay of therapy in selenium poisoning. In particular, patients with selenious acid toxicity require intensive monitoring and multisystem support to survive.

Summary

Selenium is an essential trace element and is required in the diet of both animals and humans. However, in overdose or with excessive exposure, toxicity can result. In particular, ingestion of selenious acid is often fatal. Other selenium compounds cause variable toxicity, usually in the setting of occupational exposure. Elemental selenium can cause symptoms with excess long-term exposure. Although it is

possible to obtain blood, urine, and hair selenium concentrations to confirm exposure, there is no clear relationship between levels and clinical outcome. Supportive therapy remains the standard of care.

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Chapter 95
Silver

Melisa W. Lai
Michele Burns Ewald

Silver (Ag)
Atomic number
=
47
Atomic weight
=
107.87
Normal concentrations
Serum
=
â‰¤1 Âµmg/L
Urine (24 hour)
=
â‰¤2 Âµmg/L

A 46-year-old woman who was status post breast biopsy was wheeled fro
(OR) to a recovery bay where she was attached to cardiac and pulse oxi
was extubated without complication in the OR and still remained lightly s

vital signs from the OR recorded as: blood pressure, 116/72 mm Hg; puls respiratory rate, 16 breaths/min; temperature, 99Â°F (37.2Â°C); and O_2 2 L nasal canula. Minutes after her arrival, a staff member became conce dusky-cyanotic appearance and called for assistance and a cardiac arrest caused the patient to open her eyes and then sit upright. Her oxygen sat oximetry remained at 99% on room air despite what appeared to be her the patient's resident arrived she confirmed to the recovery room staff th standing history of argyria, which she developed as a teenager after usin nasal spray to treat allergies.

Silver is a so-called precious metal that has been used for thousands of y impressive array of applications including coinage, an abstract financial and tool material, chemical catalyst, electrical conductor, and medicinal naturally occurs throughout the earth's crust at an average concentration and at 0.1 ppb in seawater. Consequential toxicity of silver is uncommon can lead to permanent disability.

Second only to gold in weakness of interaction with oxygen, silver has c malleability, and both thermal and electrical conductivity. These propertie widespread use throughout the health, science, and engineering industries key component in batteries, mechanical bearings, catalysts, coins, electr coatings, photography, medical bactericidal agents, and water purificatio

The prevalence of silver notwithstanding, silver poisoning is rare and is o occupational exposure or self-administration of silver-containing products medicinal purposes. Since the mid-20th century, the use of silver for me infrequently resulted in iatrogenic overuse and subsequent argyria, which bluish-gray discoloration of skin that is the primary manifestation of chro overexposure.[6]

History and Background

Although the symbol of silver, Ag, is derived from the Latin and Greek wo silverâ€”*argentum* and *argyros* â€”the word we use in English is derived Germanic *Silubr* and *Sirebro* .[52] Even the alchemist symbol of silver (a cr dalton symbol (a coinlike circumscribed letter S) etch the impression of si

precious element.

In Asia Minor and on islands in the Aegean Sea, dumps of slag (scum for surface oxidation) demonstrate that silver was being separated from lead B.C.[26] The use of silver as a precious metal with trade value appears to 600 B.C., when weighed pieces of silver were exchanged for goods. Silve circa 550 B.C. in the Mediterranean, and was adopted by various empires nation-states thereafter. Today, only Mexico uses silver in circulating coir States incorporates silver purely in commemorative and proof coins.

A traded commodity on the world's markets, silver has been used as an standard for various economies throughout modern banking history until

Beyond the economic role of silver, the electrical and thermal conductive element make it an invaluable material for scientific instrument manufac It is ubiquitous and is found in commonly used electronic devices and ap silver contacts neither corrode nor overheat. Silver propelled the dawn of telecommunicationsâ€”it was the choice

for Morse's first telegraph contacts in 1844â€”and made the jet age possi plated bearings have the adequate dry lubricity necessary for safe engine volatile oil lubricants. Today, washing machines, cars, personal digital as electronics all use small amounts of silver in their functional parts. Silver clouds to cause precipitation.

Epidemiology

Humans are exposed to varying minute amounts of silver on a daily basis most closely related to occupation. Silver is released into the environmen manufacture for use in photography, mirrors, plating, inks and dyes, and for germicides, antiseptics, caustics, and analytical reagents. Silver-salt c oxidation-reduction and polymerization reactions, provide a source of silve silver powder pigments and paints.[31] Workplace exposure is often via tra transmucosal (eg, oral and nasal mucosa), or inhalational routes from si during various mining, refining, and manufacturing processes. Both the N Occupational Safety and Health (NIOSH) and the Occupational and Safety

Administration (OSHA) have established the safe occupational exposure li and soluble compounds as 10 Âµg/m^3 air per 8-hour work shift. The estir silver from average environmental exposure for humans not working in industries ranges from 10â€“88 Âµg/d.[15]

Medical Use of Silver Salts

Silver has a 1^+ (Ag^+) valence when bonding with other elements and co complex ions and salts. Because of the microcidal effects of silver cations concentrations,[47] silver has been used as a simple medicinal and bacteric Phoenicians and early Greeks knew to store water, wine, and vinegar in during long sea voyages, just as later American pioneers added silver coi and jugs of milk to keep them fresh.[42] The phrase â€œborn with a silver mouthâ€• referred originally to health and not wealth, as silver pacifiers were used to help ward off childhood illnesses. Today silver is used in w cartridges and supermarket products for washing vegetables, and is even sterilize recycled drinking water on the MIR space station and NASA spac

Silver nitrate (1% $AgNO_3$)
Silver nitrate
Ophthalmic
Prevention of gonorrheal ophthalmia neonatorum
Silver nitrate (10% $AgNO_3$)
Silver nitrate
Cutaneous
Chemical cautery of mucosa and exuberant granulations (eg, in podiatry impetigo vulgaris, plantar warts, and papillomatous growths)
Silver sulfadiazine (0.2%, 1% micronized silver sulfadiazine)

1. Silvadene
2. Thermazene
3. Silver sulfadiazine
4. SSD
5. SSD AF
6. SSD RP

Cutaneous
Antimicrobial adjunct for prevention and treatment of wound infection for second- and third-degree burns

Product Name Trade Name(s) Route of Administration Applica

TABLE 95-1. Medicinal Silver-Containing Products[14,24,50]

The antibacterial activity of silver is related to both direct binding to bioti disruption of hydrogen ions and thus, pH balance. Silver ions bind to elec proteins (sulfhydryl, amine, carboxyl, phosphate, and imidazole) to inhib and provoke protein denaturation and precipitation.[19] Silver also intercala destroying the double helix, thereby inhibiting fungal DNAse.[16] Silver ions leakage through a bacterial (*Vibrio cholerae*) membrane, leading to loss force in oxidative phosphorylation, with subsequent energy loss and cell resistance to silver was not reported until the mid-1970s, followed shortly identification of the genes for silver resistance in bacteria.[47]

Although banned from routine administration by intravenous, intramuscula the United States, silver salts are approved for use in topical medications, styptic or as a key component of burn care. Approved medicinal uses for States apply only to silver salts and compounds (Table 95-1).

Silver sulfadiazine added to burn dressings kills bacteria and increases the reepithelialization across partial-thickness wounds.[9] Concerns of long-terr use of these products by some clinicians.[8] Central venous catheters impre sulfadiazine and silver-impregnated Foley catheters are used to lower the

Colloidal Silver Controversy

The medicinal triumphs of silver are greatly exaggerated, with the elemer some as a â€œcure-all.â€• Claims have been made that oral administra treat, among other things, acne, allergies, appendicitis, arthritis, bubonic cholera, diabetes, gonorrhea, herpes, HIV, leprosy, systemic lupus erythe disease, malaria, meningitis, pneumonia, rheumatism, trench foot, and c Colloidal silver proteins (CSPs) (gelatinous suspensions of finely divided

used as oral medications in the late 19th and early 20th century to treat including syphilis, epilepsy, and nasal allergies.[16] However, in 1960, the Dispensary declared that â€œthere is no justification for

this internal use, either theoretically or practically,â€• and silver was ba nonprescription drugs.[16] In 1999, the US Food and Drug Administration i declaring that all nonprescription drug products containing colloidal silver â€œnot recognized as safe and effective and are misbranded.â€•[18] Howe reintroduced for use as health and dietary supplements.[19] After the anth 2001, the mayor of Tampa, Florida, called for CSPs to be mixed into the as a protective â€œelixirâ€• without any scientific justification.[2]

Oral[20]
1
Inhalation[40]
1.7
Intravenous[16]
2.4

Route of Administration $t_{1/2}$ in Days

TABLE 95-2. Initial (Phase One) Elimination Half-Life of Silver

Pharmacology

Silver that is absorbed into the body is transported by globulins in blood skin and liver, with average daily intake excreted in the bile and eliminate 30â€“80 Âµg/d) and urine (up to 10 Âµg/d).[16] Silver elimination through two phases: phase one has a relatively short $t_{1/2}$ ranging from 1â€“2.4 d route of administration (Table 95-2), and phase two elimination has a t_1 thought to represent liver deposition and clearance.[34 , 41]

Although one study on a single human subject showed 18% of a single do administered silver acetate salt was retained after 30 weeks, animal stud absorption along the GI tract, with 90% of ingested silver excreted within

ingestion.[15]

Humans retain 0â€“10% of their daily silver exposure of 10â€“88 Âµg/d.[5] silver can accumulate in humans throughout life, with a possible estimate accumulation of 230â€“480 mg by 50 years of age.[15]

Pathophysiology

When used as intended in electronic devices or as coinage (ie, when not and under average exposure conditions, silver is not considered to be tox quantities, however, silver manifests cardiovascular, hepatic, and hemat Acutely, administration of 50 mg or more of metallic silver intravenously pulmonary edema, hemorrhage, and necrosis of bone marrow, liver, and mechanism for this acute toxicity was studied only in the water flea (*Dapl* silver blocks Na^+ -K^+ -adenosine triphosphate (ATPase) activity.[4] Toxicity by system, in Table 95-3 .

Cardiovascular

Rats given 0.1% silver nitrate in drinking water for 218 days developed hypertrophy that was not attributable to silver deposition in the heart de pigmentation in other body organs.[38]

Hepatic

Vitamin E and selenium-deficient rats developed hepatic necrosis with u after being given silver salts.[7 , 11 , 53] Silver can induce selenium deficie inhibits synthesis of seleno-enzyme glutathione peroxidase.

Hematologic

Topical application of silver correlated with bone marrow depression with leukopenia or aplastic anemia.[8]

Renal

Tubular lesions are demonstrated in animals, and acute tubular necrosis (identified in humans.[32]

Neurologic

Silver deposits in peripheral nerves, basal membranes, macrophages, and found in one reported case of a 55-year-old female with progressive vert hypoesthesia, and weakness after self-administration of silver salts to trea

years.[55]

Seizures were reported in a schizophrenic patient who ingested >20 mg s years. Serum silver concentrations were elevated (12 Âµg/L). Seizures r with discontinuation of silver ingestion and a subsequent decrease in silv concentration to nondetectable levels 3 months later.[37]

Dermatologic

Generalized argyria, localized argyria, and argyrosis (silver deposition in after chronic administration of silver.

TABLE 95-3. Silver Toxicity: Systemic Manifestations

Argyria

The most significant effect of silver overexposure or ingestion in humans permanent bluish-gray discoloration of skin resulting from silver throughc (See ILARGYRIA1 and ILARGYRIA2 in the Image Library at http://www.goldfrankstoxicology.com).

Cases of argyria have been reported in the medical literature since at leas century. One of the most famous cases of argyria is that of the Barnum a â€œBlue Manâ€• who died at New York's Bellevue hospital in 1923 and v autopsy as follows: â€œThe color of the skin was of an unusually deep blu distance appeared almost black. This deep color was almost uniform thro body, although it was more intense over the exposed skin areas.â€•[23] Si Jacobs, an American woman who developed argyria as a teenager during of a nasal CSP for allergies, has shared her story on the World Wide Web others of the effects of prolonged contact with, or ingestion of, silver salt also featured as an Image in Clinical Medicine in the *New England Journal* 2000, a Montana legislator running for reelection made headlines as the lawmaker who promoted the use of colloidal silver health supplements.[3]

Pathophysiology of Argyria

Generalized argyria can result from either simple mechanical impregnation

particles or inhalational and oral absorption of particulate silver. Local ro absorption may be through the conjunctiva or oral mucous membranes a treatment with silver salts. As recently as 2002, a 42-year-old European argyria after weekly application for 4 years of a topical nasal vasoconstr manufactured by Siegfried, Sweden) available in Austria. The patient usec treat his drug-induced rhinopathy; each drop of medication contained 0.8 protein.[49] More directly,

colloidal silver protein ingestion for â€œhealth supplementationâ€• leads silver that can produce argyria. In 1933, argyria was reported in a 33-ye had ingested 48 mg/d of elemental silver (from silver nitrate capsules) d week periods over 1 year to treat chronic gastrointestinal symptoms.[5] He concentrations remained at 500 Âµg/L for 3 months after discontinuation indicating significant silver deposition in tissues.

Mechanical impregnation of silver produces localized argyria or argyrosis eyes) following repeated contact with metallic silver or silver salts.[29] Loca reported from both implanted acupuncture needles and short-contact acu particle deposition may occur from silver needles used repeatedly during sessions.[30] Silver sulfadiazine use produces localized argyria in and arour Localized argyria of the tongue and gingiva is described in patients with amalgams.[28 , 43] These patients may also have elevated tissue concentra there are no known cases of significant absorption resulting in generalize long-standing wearing of silver earrings has resulted in local contact arg Corneal argyrosis was frequently reported from prolonged use of colloida eyedrops, but as these drops are no longer used, the condition has beco disease caused by both inadequate eye protection and workers rubbing ey contaminated by silver particles.[44 , 46 , 59] Additionally, industrial exposur involved in silver mining and manufacturing increases the workplace risk argyria, although development of signs of argyria from uninterrupted oc takes a minimum of 24 years.[12] Employees are susceptible to localized ar argyrosis from working with smaller amounts of silver in specific applicatio of metallic films on glass and china, manufacture of electroplating solutio processing, preparation of artificial pearls, and simple cutting and polishir

Histopathology of Argyria

Surprisingly, there are no pathologic changes or inflammatory reactions v level from silver deposition or impregnation. Rather, the skin discoloration from the silver itself and from the induction of increased melanin produc are initially found within fibroblasts and macrophages, then extracellularly membrane of blood vessels, sweat glands, dermoepidermal junction, and muscles (Chap. 29). Patients with argyria commonly manifest increased sun-exposed skin. The proposed mechanism for this process is that silver are reduced to their elemental form via photoactivation, similar to photo development. Silver plus light then further stimulates melanogenesis, inc light-exposed areas.

Argyria develops in stages, beginning with an initial gray-brown staining progressing to hyperpigmentation and bluish-gray discoloration in sun-ex sclerae, nail beds and mucous membranes become hyperpigmented; on a noted to be blue. Confirmation of the diagnosis of argyria is through skin hematoxylin and eosin staining, showing brown-black clusters of silver g

Argyria occurs at exposure levels much lower than those associated with of silver; the degree of discoloration is directly proportional to the amour or ingested.[22] The threshold dose for silver accumulation and retention r generalized argyria varies considerably. Discoloration has been reported i as little as a cumulative 1 g of metallic silver administered intravenously (arsphenamine used to treat syphilis over a 2-year period in the early 19 tolerated infusions containing up to 5 g of elemental silver over 9 months change was noted.[22]

Diagnostic Testing

Urine and serum concentrations of silver can be measured as indices of s also tested for silver, but airborne silver particles may bind to hair and

In individuals without a history of medicinal silver ingestion or occupation normal serum silver concentration is â‰¤1 Âµg/L and normal urinary sil â‰¤2 Âµg/L (24-hour urine collection).[54] Workers who smelt and refine prepare silver salts for use in the photographic industry have mean serur

11 Âµg/L and urine silver concentrations of 2.6 Âµg/L (in single â€œspot

Treatment of Argyria

Chelators such as British anti-Lewisite and D-penicillamine are ineffective silver toxicity and argyria.[16] Topical hydroquinone 5% may reduce the nu granules in the upper dermis and around sweat glands, as well as diminis melanocytes.[39] Sunscreens and opaque cosmetics are used to prevent fu darkening from sun exposure.

As oxidant deficiencies may enhance silver toxicity, antioxidants, such as vitamin E, may play a role in reversing effects of silver exposure. Seleni glutathione peroxidase synthesis is diminished when silver binds to, and intracellular selenium.[7 , 53] Supplemental vitamin E and selenium increas in rats and chickens.[7] Selenium and sulfur are being considered as possib argyria. Selenium may act to precipitate or chelate silver: silver selenide and should reduce the availability of monovalent silver to interfere with activities.[1 , 36 , 45] Hence, increased selenium intake is theorized to bind rather than skin deposition. Silverâ€“sulfur complexes may be investigate although the silverâ€“sulfur complex is not as stable.[45]

Carcinogenicity of Silver

Silver is not classified as a human carcinogen and no data link therapeutic human cancer, nor has silver been found to be mutagenic.[15] Although ani that silver implanted subcutaneously can lead to local sarcoma formation, been deemed uninterpretable in regard to carcinogenicity as implantation solids, such as, plastic and smooth ivory, produce similar results.[15] Colloi into rats induces growths at injection sites, but intramuscular injections c not induced cancer.[21] Local inflammatory responses notwithstanding, silve inert substance and not a human carcinogen.

Emergency Management

Although systemic toxicity of silver is predominantly a result of chronic rarely encounter a patient who has

ingested a CSP, a silver-containing medicinal product, or a silver salt. Bu cautery should be managed as burns. Silver ingestion should be manage salt ingestion should be treated as a caustic ingestion (Chap. 100).

Summary

Silver toxicityâ€”primarily argyria and burnsâ€”is still occasionally encou the workplace environment and health supplementation products are the exposure. Despite frequent therapeutic use of silver and silver compounds evidence of silver acting as a mutagen or carcinogen. Significant toxicity argyria from chronic silver use is essentially a permanent manifestation. T effective means for removing accumulated silver and reversing argyria.

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Chapter 96
Thallium

Maria Mercurio

Robert S. Hoffman

Thallium (T1)
Atomic number
=
81
Atomic weight
=
204.37
Normal concentrations
Whole bolood
=
<2Âµg/L (<9.78 nmol/L)
Urine (24 hour)
=
<5 Âµg/L (<24.5 nmol/L)

A 21-year-old woman developed mild, but persistent abdominal pain with intermittent, severe, colicky pain. Three days after the initial painful episode, her hair began to fall out. She became

constipated and noted a delay in the onset of her menses. Within 5 days of her initial symptoms, she was completely bald. On day 18, she was hospitalized. Physical examination was only remarkable for horizontal white (Mees) lines on her fingernails. Her routine blood studies and several special studies for autoimmune disease were all normal. Her overall condition responded to nutritional support, her symptoms gradually resolved, her hair regrew, and she was discharged almost 2 months after the onset of symptoms, but without a clear diagnosis.

The patient returned to school. One month later, she felt pain in both her hands and feet, and developed difficulty speaking, blurred vision, tremulousness, and vertigo. Again, she was taken to the hospital. On admission, her blood pressure was 140/110 mm Hg; other vital signs were normal. Examination of her extremities showed good muscular strength in her legs but poor muscle coordination, and hyperesthesias in a stocking-and-glove distribution. Her deep-tendon reflexes were hypoactive in both legs, but normal in her upper extremities. Cranial nerve examination revealed horizontal and vertical nystagmus, and palsies of the abducens (VI) and facial (VII) cranial nerves. Electrolyte, hepatic enzymes and analysis of cerebrospinal fluid were all normal.

Four days later, still without a diagnosis, her symptoms of vertigo and tremulousness worsened. She developed an oculogyric crisis, and her mental status deteriorated. Her alopecia returned. A magnetic resonance image of her brain was interpreted as normal, and an electroencephalogram was nondiagnostic. Her condition progressed very rapidly with the development of bulbar palsy, involuntary chewing movements of her mouth, and spastic clonus of both upper limbs. Her level of consciousness changed from mild agitation to lethargy. Tonic movements of both upper extremities and episodic oculogyric crises were noted.

Five days after her hospitalization, she became comatose.

Investigative studies for arsenic, antinuclear antibody, antidouble-stranded DNA antibody, rheumatoid factor, HIV, and Lyme disease were negative. Routine urinalysis was normal. She was treated with several broad-spectrum antibiotics, antiviral agents, hormones, and intravenous injections of Î³-globulin, none of which had any appreciable effect on her clinical manifestations.

Because her spontaneous respiratory efforts became progressively weaker and irregular, a tracheostomy was performed and she was placed on a ventilator. At that point, the diagnosis of acute disseminated encephalomyelitis was considered. Plasmapheresis was initiated and 7 exchanges, for a total of 10 L, were completed over the following 3 weeks. No change in her condition was noted.

Ultimately, the diagnosis of thallium toxicity was considered. Blood, urine, and cerebrospinal fluid thallium concentrations were reported as 275, 532, and 31 Âµg/L, respectively. Nail and hair concentrations were 22, 824, and 532 Âµg/kg, respectively. A regimen of intravenous potassium (100 mEq/d), oral Prussian blue (250 mg/kg/d divided q4h in 50 mL of 15% mannitol), and daily hemodialysis was initiated. Her symptoms slowly improved. About 2 months after hospitalization she began to intermittently regain consciousness.

One year after her initial presentation, her orientation and memory improved and her IQ was estimated at 128, with good mathematical and verbal abilities. The patient was able to sit in a wheelchair for a prolonged period of time and could move herself 20â€“30 meters. She still could not move her legs. Her vision remained poor, but periodically she was able to see clearly.

History and Epidemiology

Thallium, a metal with atomic number 81, is located between mercury and lead on the periodic table. It is a commonly found constituent

of granite, shale, volcanic rock, and pyrites used to make sulfuric acid, and is also recovered as flue dust from iron, lead, cadmium, and copper smelters.[23] Thallium is a soft, pliable metal that melts at 572Â°F (300Â°C), boils at 2699.6Â°F (1482Â°C), and is essentially nontoxic. However, thallium forms univalent thallous and trivalent thallic salts, which are highly toxic. Thallium has been used in alloys as an anticorrosive, in optical lenses to increase the refractive index, in artists' paints, in lamps to improve tungsten filaments, in extreme cold thermometers, in imitation jewelry, as a catalyst, and in fireworks.

In the early 1900s, thallium salts were used medicinally to treat syphilis, gonorrhea, tuberculosis, and ringworm of the scalp, and as a depilatory.[5 , 62] Although the usual oral dose given for epilation in the treatment of ringworm of the scalp was 7â€“8 mg/kg, fatal doses ranged from 6â€“40 mg/kg.[13 , 51] Many cases of severe thallium poisoning (thallotoxicosis) resulted from the treatment of ringworm, with one author summarizing nearly 700 cases and 46 deaths.[65]

Because thallium sulfate is odorless and tasteless, it was also successfully used as a rodenticide. Commercially available as Thalgrain, Echol's Roach Powder, Mo-Go, Martin's Rat Stop liquid, and Senco Corn Mix, thallium sulfate was a very efficient rodenticide. As a consequence of numerous case reports of unintentional poisonings,[64 , 65 , 76] the use of thallium salts as a household rodenticide was restricted in the United States in 1965. Ultimately, even the commercial use of thallium salts as a rodenticide was banned in the United States in 1972, because of continued reports of human toxicity.

Life-threatening unintentional poisoning continues in other countries where thallium salts are still commonly used as rodenticides.[12 , 74 , 82 , 97] Additional cases of thallium poisoning are reported in the United States and other countries as a result of

the use of thallium as a homicidal agent,[19,56,60,68,70,79,86] and through contamination of herbal products[83] and illicit drugs such as heroin[73] and cocaine.[38] Although occupational exposures to consequential amounts of thallium salts are uncommon, toxicity is well described in this setting.[32] Diagnostically, trace amounts of thallium salts are used as a radioactive contrast agent to image tumors and to visualize cardiac function.[62]

The following discussion of thallium toxicity refers to toxicity resulting from exposure to inorganic thallium salts, because this source represents virtually the entire literature on thallium poisoning. Although exceedingly rare, cases of poisoning with organic thallium compounds are reported,[1] and should be assessed and managed in a fashion similar to that used for patients with inorganic exposures.

Toxicokinetics

Exposures usually occur via one of three routes: *inhalation* of dust, *ingestion*, and *absorption* through intact skin. Thallium is rapidly absorbed following all routes of exposure. Bioavailability is greatest following ingestion, and exceeds 90%.[35] Distribution follows 3-compartment toxicokinetics[75] (Chap. 9), into a final volume of distribution that is estimated to be about 3.6 L/kg.[18] Thallium can be found in all organs, but it is distributed unevenly, with the highest concentrations found in the large and small intestine, liver, kidney, heart, brain, and muscles.[5,46] In animals, the highest concentrations of thallium are found in the kidneys.[2,46]

The toxicokinetics of thallium can be described in the following 3-phase model. The first phase, occurs rapidly in the 4 hours following exposure during which thallium is distributed to a central compartment and to well-perfused peripheral organs such as the kidney, liver, and muscle. In the second phase, which can last between 4 and 48 hours, thallium is distributed into the central

nervous system.[75] Whereas previous literature suggests that this distribution phase is generally completed within 24 hours of ingestion,[75] a recent human case suggests slower distribution into the CNS as evidenced by increasing cerebrospinal fluid (CSF) concentrations days following exposure when blood concentrations were declining.[86] The third, or elimination, phase starts within 24 hours after ingestion. The primary mechanism of thallium elimination is secretion into the intestine, but enteral reabsorption of thallium that is present in the bile subsequently reduces the fecal elimination.[18, 60] Thallium is excreted primarily via the feces (51.4%) and the urine (26.4%).[50] It is filtered by the glomerulus, with approximately 50% being reabsorbed in the tubules. Thallium is also secreted into the tubular lumen in a manner similar to potassium.[3] The duration of the elimination phase depends on the route of exposure, dose, and treatment. Unlike many other metals, thallium does not have a major anatomic reservoir. As such, reported elimination half-lives are as short as 1.7 days in humans with thallium poisoning.[36]

Pathophysiology

The mechanism of thallium toxicity is not well established. Thallium behaves biologically in a manner similar to potassium because they have similar ionic radii (0.147 nm for thallium and 0.133 nm for potassium). Because cell membranes cannot differentiate between thallium and potassium ions, thallous ions accumulate in areas with high potassium concentrations, such as central and peripheral nervous system and hepatic and muscle tissue.[57, 97] This accumulation is the fundamental principle that governs the use of radioactive thallium in cardiac imaging studies. Thallium replaces potassium in the activation of potassium-dependent enzymes.[57] In low concentrations, thallium stimulates these enzyme systems, but in high concentrations, it inhibits them.[7, 59] Thallium also inhibits several potassium-dependent systems. Pyruvate kinase, a magnesium-dependent glycolytic

enzyme that requires potassium to achieve maximum activity, has 50 times greater affinity for thallous ions than potassium ions.[42] Succinate dehydrogenase, an essential enzyme in the Krebs cycle, is inhibited by small doses of thallium in rats.[31] Sodium-potassium adenosine triphosphatase (ATPase), which is responsible for active transport of monovalent ions across cell membranes, can use thallous ions at extremely low concentrations because of an affinity that is 10-fold greater than that of potassium ions,[8,26] but is inhibited by thallium at higher concentrations.[39] Thallium also impairs depolarization of muscle fibers.[62] Mitochondrial energy is decreased as a result of the inhibition of pyruvate kinase and succinate dehydrogenase, resulting in a decrease of adenosine triphosphate (ATP) generation via oxidative phosphorylation. Enzymatic destruction results in swelling and vacuolization of the mitochondria after exposure to thallium.[87] At low levels, thallium can activate other potassium-dependent enzymes such as phosphatase, homoserine dehydrogenase, vitamin B_{12} -dependent diol dehydrogenase, L-threonine dehydrogenase, and adenosine monophosphate (AMP) deaminase.[62] The net result of these processes is a failure of energy production.

Thallous ions have been used to isolate riboflavin from milk in the form of a reversible precipitate. Thallous ions may also form insoluble complexes and cause intracellular sequestration of riboflavin in vivo.[10] Riboflavin is the vitamin precursor of the flavin coenzyme FAD (flavin adenine dinucleotide). Because of a decrease in riboflavin, metabolic reactions dependent on flavoproteins will decrease, causing disruption of the electron transport chain and a subsequent further decrease or impairment in the generation of cellular energy.[10] This decrease in cellular energy may lead to a decrease in mitotic activity and cessation of hair follicle formation resulting in the clinical sign of alopecia. Subsequent hair loss is the result of combined arrested formation and local destruction of hair shaft cells in the hair bulb.[10,76]

Unfortunately, riboflavin supplementation was not beneficial in one animal model of thallium poisoning.[4] Data also demonstrate that the dermatologic, neurologic, and cardiovascular effects of thallium toxicity mirror the side effects of thiamine deficiency (beriberi), highlighting the inhibitory effect of thallium on glycolytic enzymes.[10, 62] It is unclear whether thiamine administration has any beneficial effect in patients with thallium poisoning.

Thallium has a high affinity for the sulfhydryl groups present in many other enzymes and other proteins. Keratin, a structural protein, consists of many cysteine residues that cross-link and form disulfide bonds. These disulfide bonds add strength to keratin. Thallium interferes with the formation of disulfide bonds, which may lead to the development of alopecia and defects in nail growth resulting in Mees lines.[28, 62, 68, 81, 82] Additionally, the complexation of sulfhydryl groups with thallium results in a decrease in glutathione production secondary to a decrease in cysteine. This results in the accumulation of lipid peroxides in the brain, which is most prominent in the cerebellum, and appears as dark, pigmented, lipofuscinlike areas.[30] The complexity and presumable multifactorial nature of thallium poisoning are again highlighted by the inability of *N* -acetylcysteineâ€“induced augmentation of glutathione stores to protect against toxicity in an animal model.[4]

Thallium also adversely affects protein synthesis in animals by damaging ribosomes, particularly the 60S subunit.[37] Although ribosomes are primarily dependent on potassium and magnesium, thallium will be used if present. In an experimental model, low concentrations of thallium are protective against hypokalemia-induced ribosomal inactivation. As thallium concentrations increase, the protective effects diminish, resulting in progressive destabilization and destruction of the ribosomes. Ribosomal destruction can also be produced with exposure to potassium concentrations of 4.5â€“20 times higher than the thallium

concentrations necessary to achieve the same effect.[37]

Pathologic studies of the central nervous system in patients with thallium poisoning reveal localized areas of edema found in the cerebral hemispheres and brainstem. Chromatolytic changes are prominent in neurons of the motor cortex, third-nerve nuclei, substantia nigra, and pyramidal cells of the globus pallidus. In chronic exposures, there are signs of edema of the pial and arachnoidal membranes, and changes in the ganglion cells of the ventral and dorsal horns of the spinal cord, consisting of chromatolysis, swelling, and fatty degeneration.[5 , 76]

The peripheral nervous system, which is usually clinically affected before the central nervous system, develops a diffuse axonopathy in a classic dying back or Wallerian degeneration pattern.[5 , 6 , 15 , 21 , 58] Fragmentation and degeneration of associated myelin sheaths are accompanied by activation of Schwann cells.[5 , 10 , 11] Because thallium affects the longer peripheral fibersâ€”first sensory, then motor, and finally the shorter fibersâ€”toxic effects occur initially in the lower extremities.[49 , 67 , 101]

Clinical Manifestations

Many of the effects of thallium poisoning are somewhat nonspecific and occur over a variable time course.[47] When combined, however, a clear toxidrome can be defined (Table 96-1). Alopecia and painful ascending peripheral neuropathy are the most characteristic findings.[6 , 24 , 60 , 67] Because of the delayed development of alopecia, the diagnosis of thallotoxicosis is often delayed. In fact, with acute exposures, a dose-dependent latent period of hours to days may precede initial symptoms.[47 , 62] When death occurs, it is usually the result of coma with loss of airway-protective reflexes, respiratory paralysis, and cardiac arrest.

Unlike most other metal salt poisonings, gastrointestinal symptoms are usually modest or even absent in thallium toxicity.[13] The most

common symptom is abdominal pain, which may be accompanied by vomiting and either diarrhea or constipation.[19, 44, 47, 59, 81, 98, 99] Constipation may be a result of decreased intestinal motility and peristalsis caused by direct involvement of the vagus nerve.[13, 62] Rarely, severe symptoms, such as hematemesis, bloody diarrhea, or ulceration of the mucosal lining, occur.

Pleuritic chest pain was described in a small series of poisoned patients.[56] Another patient was reported to have developed â€œchest tightnessâ€• shortly after drinking thallium-poisoned tea.[60] There is no known etiology for this finding, although it may relate to involvement of the vagus nerve.

Tachycardia and hypertension frequently occur in patients with thallotoxicosis and usually develop during the first or second week following an acute ingestion. A poor prognosis may be associated with a persistent and pronounced tachycardia. No exact mechanism has been determined for these cardiovascular effects of thallium toxicity. Some authors theorize that they result from autonomic neuropathic dysfunction directly related to involvement of the vagus nerve,[67] but others have noted early electrocardiographic changes, such as prolongation of the QTc interval, T-wave flattening or inversion, and nonspecific ST-segment abnormalities, which might suggest direct myocardial damage.[6, 11, 59, 62, 78] Another theory suggests that thallium's stimulation of ATPase in the chromaffin cells can lead to increased output of catecholamines, resulting in sinus tachycardia.[3, 60]

Neurologic symptoms usually appear 2â€“5 days postexposure. Patients may develop severely painful, rapidly progressive, ascending peripheral neuropathies.[5, 6, 21, 56] Pain and paresthesias are present in lower extremities (especially the soles of the feet), and although numbness is present in fingers and toes, there is also decreased sensation to pinprick, touch, temperature, vibration, and proprioception.[6, 83] The weight of the bedsheets on the lower extremities may be sufficient to cause excruciating

pain.[56 , 58] Motor weakness is always distal in distribution, with the lower limbs more affected than the upper limbs.[11 , 62]

Symptoms of confusion, delirium, psychosis, hallucinations, seizures, headache, insomnia, anxiety, tremor, ataxia, and choreoathetosis are common. Onset is variable, and most likely dependent on dose. Ataxia can develop within 48 hours after ingestion. Insomnia occurs in almost every patient and may progress to total reversal of sleep rhythm. Coma may occur, especially with larger exposures.[11 , 47 , 62 , 81] All cranial nerves can probably be affected by thallium, although abnormalities of cranial nerves I, V, and VIII have

not been reported. Cranial nerve III involvement, as evidenced by ptosis, is common, and may be present asymmetrically.[11] Nystagmus, another common finding, demonstrates involvement of cranial nerves IV and VI.[11] Cognitive abnormalities may persist for months after exposure.[53]

Gastrointestinal

Nausea

â€

Vomiting

â€

Diarrhea

â€

Constipation
â€
â€

Cardiovascular
Nonspecific ECG changes
â€
â€

Hypertension

â€

Tachycardia

â€

Respiratory
Pleuritic chest pain
â€
â€

Respiratory depression

â€
â€

Renal
Albuminuria

â€

Renal insufficiency

â€

â€¡
Dermatologic
Dry skin

â€

Alopecia

â€

â€¡
Mees lines

â€
â€¡
Neurologic
Painful ascending sensory neuropathy

â€
â€
â€¡
Motor neuropathy

â€

â€
â€¡
Cranial nerve abnormalities

â€

Altered mental status

â€

â€¡
Seizures

â€
â€

Optic neuritis

â€¡
Memory and cognitive deficits

â€¡
â€ = Typical onset of symptoms.
The time course outlined above may be accelerated with extremely large doses.
When â€œâ€ â€• appears in two adjacent columns, the time course is highly variable and may be dose dependent.
With small ingestions, many of the effects listed above may not be evident.
â€¡ = Effects that may persist long after exposure, and possibly permanently.

Organ System	Onset of Effects			Residual Effects
	Immediate (<6 h)	Intermediate (Rarely in the first few days; within 2 wk)	Late (>2 wk)	

TABLE 96-1. Clinical Manifestations of Acute Thallium Poisoning

Thallium is toxic to both the retinal fibers and the neural retina.[84] In cases of a large, single ingestion of thallium, approximately 25% of patients may develop severe lesions of the optic nerve.[62, 81] Optic neuropathy can lead to optic atrophy and a permanent decrease in visual acuity. In early stages, the optic disk shows signs of neuritis, which is red and poorly defined, and later develops pallor from resultant optic nerve atrophy. In patients exposed to multiple small doses, nearly 100% suffer optic nerve injury.[59] Visual complaints may be delayed in comparison to other neurologic findings,[84] and can include decreased acuity and central scotomata. Other described ophthalmic effects are noninflammatory keratitis, cataracts, and the color vision defect of tritanomaly (blue color defect).[90, 91]

Renal function may remain normal in mild cases of thallium poisoning, even though the kidney bioaccumulates thallium more than any other organ. Changes in renal function in patients with severe thallotoxicosis include oliguria, diminished creatinine clearance, elevated blood urea nitrogen, and albuminuria.[3, 56, 59, 62] These findings correlate with morphologic studies in thallium-poisoned rats, demonstrating abnormalities in the renal medulla, mainly in the thick ascending limb of the loop of Henle, that occur by the 2nd day after exposure and resolve by the 10th

day.[3]

Alopecia is the most common and classic manifestation of thallium toxicity.[60 , 94] Typically occurring as the presenting symptom in patients with chronic exposures following an acute exposure, epilation begins in approximately 10 days and total hair loss usually occurs within a month.[24 , 60 , 65] Facial and axillary hair, especially the inner one-third of the eyebrows, may be spared, but in some cases, full beards, as well as all scalp hair, are lost.[76] Microscopic studies show thallium deposition as dark brown or black pigmentation located in the roots of hair samples. (See ILTHALLIUM in the Image Library at http://www.goldfrankstoxicology.com) These deposits can be found within 3â€“5 days of initial exposure.[9 , 59] In patients with chronic exposures, several bands may be noted on the hair shaft, demonstrating multiple exposures. Initial hair regrowth is very fine and unpigmented, but usually returns to normal following mild exposure.[59] In patients with severe exposures, alopecia may be permanent. Dermatologic effects that have been observed include acne, palmar erythema, and dry scaly skin that results from damage to the

sebaceous glands.[94] Mees lines appear within 2â€“4 weeks after exposure.[60 , 68 , 81] (See ILMEESLINES in the Image Library.)

Other less common findings include hepatotoxicity,[38] hypochloremic metabolic acidosis,[81] and anemia and thrombocytopenia.[48 , 81]

Teratogenicity

In animal models, thallium is teratogenic.[27 , 29] One study evaluated 297 children born in a region in which thallium levels were higher than normal because of industrial contamination.[20] Urine thallium levels in the exposed children were as high as 76.5 Âµg/L. Although these children had a slightly higher than expected

incidence of congenital abnormalities, no causal relationship could be established with regard to thallium exposure.[20]

There are few human reports of acute thallium poisoning during pregnancy. A comprehensive literature review demonstrated 25 cases, which included acute and chronic exposures that occurred during all trimesters.[34] Thallium slowly crosses the placenta and is able to cause characteristic fetal toxicity,[22,66] which manifests initially as decreased fetal movement, possibly as a consequence of fetal paralysis. The classic clinical signs and symptoms of thallium poisoning have been described in the neonate following delivery and the fetus following abortion.[22,59,66,74] However, outcome of the pregnancy may be normal despite significant maternal toxicity.[22,40] The only consistent finding is a trend toward prematurity and low birth weight, especially in those children exposed during the first trimester.[34] One author recommends continuing the pregnancy as long as the mother is clinically improving.[22] It is reasonable to conclude that a fetus exposed to thallium during organogenesis has the potential for permanent injury. Those exposed later in the pregnancy may recover without deficit if their exposures are limited and the mother recovers. If the exposure occurs closer to term, the child may be born with overt toxicity such as alopecia, dermatitis, nail growth disturbances, and permanent central nervous system lesions.[59]

These few case reports and animal studies provide confusing and sometimes contradictory results. It seems that fetal outcome is determined both by the stage of pregnancy and the extent of maternal toxicity. However, because there are insufficient data to predict the outcome of pregnancy complicated by maternal thallium poisoning, no specific course of action can be recommended other than extensive fetal monitoring and aggressive treatment for the mother. If a viable child is delivered, it is important to note that thallium is eliminated in breast milk, such that nursing provides ongoing exposure.[34]

Assessment

Most patients with acute thallium toxicity seek healthcare soon after exposure because of alterations in their gastrointestinal, cardiovascular, and neurologic function. Establishing the correct diagnosis at this early stage is essential to assure a satisfactory outcome. Unfortunately, many patients with either smaller acute exposures or chronic thallium poisoning first present days to weeks after their initial exposure, and diagnosis is often further delayed. In these instances, obtaining valuable aspects of the exposure history may be difficult. Gastrointestinal symptoms may not have occurred, or their consequence or etiology may have gone unrecognized because of their nonspecific, mild, and transient nature. Many patients with small acute or chronic exposures usually seek care because of alopecia or neuropathy.

The differential diagnosis of the neuropathy includes disorders such as poisoning by arsenic, colchicine, and vinca alkaloids; botulism; thiamine deficiency; and Guillain-BarrÃ© syndrome. Both the sensory neuropathy and the preservation of reflexes help differentiate thallium-induced neuropathy from Guillain-BarrÃ© syndrome and most other causes of acute neuropathy.[11] When gastrointestinal symptoms are present along with neuropathy and other end-organ effects, poisoning with metal salts such as arsenic and mercury should be considered (Chaps. 85 and 92). The differential diagnosis of abrupt and complete alopecia is more restricted and includes arsenic, selenium, colchicine, and vinca alkaloid poisoning (Chap. 29). When present, Mees lines indicate past exposure to metals, mitotic inhibitors, or antimetabolites, and as such are nonspecific for thallium (Chaps. 29 , 85 , and 92).

Diagnostic Testing

Radiographs of tampered food products[56] and the abdomen[28] can document the presence of a heavy metal such as thallium, which is

radiopaque. Although abdominal radiography may be useful shortly after a suspected exposure, the sensitivity and specificity of this test is unknown. Similarly, the yield from other routine studies, such as the complete blood count, electrolytes, urinalysis, and ECG, is limited in that these other studies are often normal, or, at most, merely demonstrate nonspecific abnormalities.

Microscopic inspection of the hair reveals a diagnostic pattern of black pigmentation of the hair roots of the scalp in approximately 95% of poisoned patients.[9, 60, 81, 94] However, for the inexperienced observer, this test is likely to be inconclusive.

The definitive clinical diagnosis of thallium poisoning can only be established by demonstrating elevated thallium concentrations in various body fluids or organs. Thallium can be recovered in the hair, nails, feces, saliva, CSF, blood, and urine, and standard assays and normal values for most of these sources can be found.[62] Urine spot tests notoriously give false-negative results and require the use of dangerous chemicals that are not routinely available (20% nitric acid), and therefore should be avoided.[81] The standard toxicologic method is to obtain a 24-hour urine sample for thallium to be assayed by atomic absorption spectroscopy.[14, 100] Normal urine values are below 5 Âµg/L. Some authors suggest a potassium mobilization test to enhance urinary elimination (similar to the ethylenediaminetetraacetic acid [EDTA] mobilization test) to assist in the diagnosis of thallium exposure.[9, 38, 81] We advise against this practice because of its lack of proven usefulness and its potential to exacerbate neurologic toxicity (see Potassium below).

Management

The treatment goals for a patient with thallium poisoning are initial stabilization, prevention of absorption, and enhanced elimination. Following the initial assessment and stabilization of the patient's airway, breathing, and circulatory status, gastrointestinal

decontamination should be instituted in all patients with suspected thallium ingestions because of the morbidity and mortality associated with a significant exposure.

Decontamination

Patients who present shortly after ingestion should be considered candidates for orogastric lavage (Chap. 8). If the patient presents more than a few hours after ingestion, or has had considerable spontaneous emesis, gastric emptying is unnecessary. Thallium

salts are substantially adsorbed to activated charcoal in vitro.[33, 44] Additionally, because thallium undergoes enterohepatic recirculation, activated charcoal may be useful both to prevent absorption following a recent ingestion and to enhance elimination of thallium in patients who present in the postabsorptive phase.[93] In fact, a rat model of thallium poisoning demonstrated that multiple-dose activated charcoal (given as 0.5 g/kg twice daily for 5 days) increased the fecal elimination of thallium by 82% and produced a substantial improvement in survival.[50] Other data demonstrate that activated charcoal alone is superior to either forced diuresis or potassium chloride therapy.[45] In patients with severe thallium toxicity, constipation is common, such that the addition of mannitol[52, 88, 98] or another cathartic to the first dose of activated charcoal seems logical. Although no studies address the usefulness of whole-bowel irrigation with polyethylene glycol electrolyte lavage solution, this technique may prove useful, especially when radiopaque material is demonstrated in the gastrointestinal tract by an abdominal radiograph.

Potassium

The similarities between the cellular handling of potassium ions and thallium ions led to the investigation of a role for potassium in the treatment of thallium poisoning. In humans, potassium

administration is associated with an increase in urinary thallium elimination.[13,25,69] The magnitude of this increase is reported to be on the order of 2â€“3-fold.[69] This is supported by animal models that demonstrate some benefit in terms of either enhanced thallium elimination or survival.[26,45,50] It is believed that potassium administration both blocks tubular reabsorption of thallium and mobilizes thallium from tissue stores, thereby raising thallium levels available for glomerular filtration.[63,81] However, it is this second mechanism that is of concern. Many authors report either the development of acute neurologic toxicity or the significant exacerbation of neurologic symptoms during potassium administration.[6,25,56,69,78,95] Others cite data demonstrating that potassium's augmentation of thallium elimination in humans is quite limited.[43] Additionally, animal models demonstrate that potassium loading enhances lethality[55] and permits thallium redistribution into the CNS.[31] For these reasons, the routine use of potassium should be considered potentially dangerous. Some authors recommend forced diuresis, especially in conjunction with potassium chloride.[17,93] However, no convincing experimental or clinical evidence can support the use of forced diuresis with or without potassium at this time.

Again, the similarities between thallium and potassium might suggest a role for administration of sodium polystyrene sulfonate (SPS) as a sodiumâ€“thallium exchange resin. Although in vitro binding between thallium and SPS is excellent, it is unlikely to be clinically useful because of preferential binding between potassium and SPS.[33] Consequently, neither the use of potassium nor of SPS is recommended.

Chelation

Thallium toxicity does not respond to traditional chelation therapy. Studies demonstrate that the use of EDTA and diethylenetriamine pentaacetic acid are without benefit.[62,81] Dimercaprol (British

anti-Lewisite, BAL) and D-penicillamine also fail to enhance thallium excretion in experimental models.[62,81] In one model in which D-penicillamine was able to enhance thallium elimination, it did so at the cost of substantial thallium redistribution into vital organs.[77] Similarly, sulfur-containing compounds such as cysteine or *N* -acetylcysteine (NAC) have not been demonstrated to be beneficial.[50,54] Another chelator, diphenylthiocarbazone (dithizone), forms a minimally toxic complex with thallium, resulting in a 33% increase in fecal elimination of thallium in rats.[85] Unfortunately, dithizone is goitrogenic and diabetogenic in animal studies.[50,61,93] Dithiocarb (sodium diethyldithiocarbamate), an intermediate metabolite of tetraethylthiuram disulfide (disulfiram, or Antabuse) (Chap. 77), also increases the urinary excretion of thallium.[85,89] Prior to thallium elimination, however, the formation of a lipophilic thalliumâ€“diethyldithiocarbamate complex can result in the redistribution of thallium into the central nervous system.[41,89] After decomposition of the chelate complex, thallium may remain in the central nervous system, potentially exacerbating neurologic symptoms.[41,89] Because of the significant adverse effects of dithizone and the redistribution of thallium following dithiocarb use, neither agent is recommended in the treatment of patients with thallium toxicity. Currently there is renewed interest in the water-soluble analogs of BAL (DMPS [dimercaptopropane sulfonate] and succimer). In an animal model, DMPS failed to decrease tissues levels of thallium.[61] Similarly, in another animal model, although succimer improved survival over control, the benefit was less than that achieved for Prussian blue (see below) and was at the cost of an increase in brain thallium concentrations.[80] In conclusion, the above data fail to support a role for any traditional metal chelators in thallium-poisoned patients.

Prussian Blue

Prussian blue is an FDA-approved antidote for thallium toxicity (see Antidotes in Depth: Prussian Blue).[92] When given orally, Prussian blue acts as an ion exchanger for univalent cations, with its affinity increasing as the ionic radius of the cation increases. As such, Prussian blue interferes with the enterohepatic circulation by exchanging potassium ions, from its lattice, for thallium ions in the gastrointestinal tract. This results in the formation of a concentration gradient causing an increased movement of thallium into the gut.

Humans with thallium poisoning are routinely given Prussian blue, which appears to result in clinical benefits, enhanced fecal elimination, and falling thallium concentrations.[14 , 16 , 56 , 72 , 88 , 95 , 96 , 98 , 99] One series of 11 thallium-poisoned patients demonstrated both the safety of Prussian blue and its ability to substantially increase fecal thallium elimination.[88] Unfortunately, because there are no controlled trials in humans that compare Prussian blue to other drugs, and many of the patients reported above received multiple therapies, the actual efficacy of Prussian blue is unknown.

The dose of Prussian blue is 250 mg/kg/d orally via a nasogastric tube in 2â€“4 divided doses.[88] For patients who are constipated, the Prussian blue may have greater benefit if dissolved in 50 mL of 15% mannitol.[93] Although any cathartic may be appropriate, most authors have used mannitol, possibly because of concerns regarding repeated magnesium use in patients with neurologic findings and sorbitol in patients with poor gastrointestinal mobility. (Other dosing regimens are discussed in Antidotes in Depth: Prussian Blue .)

Extracorporeal Drug Removal

Extracorporeal drug removal may have a limited beneficial role in patients with thallium toxicity, especially if begun shortly after the initial exposure while serum concentrations remain high prior to

effective tissue distribution. Because a frequently quoted review attests to the benefits of hemodialysis,[59] many patients still receive this therapy.[58] The actual data, however, show that hemodialysis, at

various stages of poisoning, is no better than forced diuresis.[16, 71] Reported thallium removal rates by hemodialysis are trivial: 143 mg of thallium were removed by 120 hours,[72] 222.8 mg were removed by 121 hours,[16] and 128 mg were removed by 54 hours of hemodialysis.[16] These values can be placed in perspective knowing that the minimum lethal adult dose of thallium is estimated to be on the order of 1 g,[62] and that many reported cases involve ingestions 10 times greater than the minimum lethal dose. Data from a more recent hemodialysis experience suggest that by using high blood-flow rates (300 mL/min), clearances as high as 90â€“150 mL/min could be obtained.[52] Although clearances seem encouraging, this should be interpreted with an appreciation of the large volume of distribution of thallium. With lower blood-flow rates, charcoal hemoperfusion may be 2â€“3 times more efficient than hemodialysis, providing clearance rates as high as 139 mL/min.[16] Furthermore, combined hemoperfusion and hemodialysis were used in several cases,[1, 16, 18] and were reported to remove as much as 93 mg of thallium within 3 hours of therapy.[1] While extracorporeal therapy alone is probably insufficient for patients with significant poisoning, and unnecessary in those with small exposures, it may have some benefit when used in combination with other therapies, especially in patients with renal insufficiency and those with early massive, and presumed lethal, exposures. As is the case with other xenobiotics, the use of peritoneal dialysis is probably ineffective in removing thallium.[43] Table 96-2 summarizes the suggested therapy for thallium-poisoned patients.

Early (patients who present in the first hours postexposure)

- Stabilize airway, breathing, and circulation if necessary
- Consider orogastric lavage if the patient has not vomited
- Consider whole-bowel irrigation with polyethylene glycol electrolyte lavage solution for patients with large ingestions or the presence of radiopaque material on abdominal radiograph
- Begin multiple-dose activated charcoal therapy; add a cathartic to the first dose if the patient does not have diarrhea
- Give Prussian blue 250 mg/kg/d in 2 or 4 divided doses, dissolved in water, or 50 mL of 15% mannitol if the patient does not have diarrhea
- Consider simultaneous charcoal hemoperfusion and hemodialysis, especially if the patient has renal insufficiency

Late (patients who present more than 24 hours postexposure or with chronic toxicity)

- Stabilize airway, breathing, and circulation if necessary
- Begin multiple-dose activated charcoal therapy; add a cathartic to the first dose if the patient does not have diarrhea
- Give Prussian blue 250 mg/kg/d in 2 or 4 divided doses, dissolved in water, or 50 mL of 15% mannitol if the patient does not have diarrhea

TABLE 96-2. Treatment for Thallium Poisoning

Summary

The elimination of thallium salts from common use as depilatories and rodenticides substantially reduced the incidence of both intentional and unintentional thallium toxicity in the United States. Despite this fact, cases of significant poisoning still occur in countries where thallium-containing rodenticides remain in use, as well as in this country, from attempted homicide and by personal injury from contamination of foods and illicit drugs. Early

recognition of the characteristic signs and symptoms of thallium poisoning and prompt initiation of safe and appropriate therapy will substantially improve the patient's prognosis. When recognition and subsequent treatment are delayed, morbidity and mortality can be consequential.

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Antidotes in Depth

Prussian Blue

Robert S. Hoffman

Prussian blue, the first artificially synthesized pigment, was discovered unintentionally by Diesbach, in 1704, while he was attempting to make cochineal red lake. Although it immediately became popular in art and later in printing, it took approximately 250 years to recognize that Prussian blue was able to attract monovalent alkali metals into its crystal lattice. Subsequently, in 1963, Nigrovic was the first investigator to demonstrate that Prussian blue enhanced cesium elimination from the gut of rats.[33] In 2003, the FDA approved Prussian blue (Radiogardase) for the treatment of thallium and radioactive cesium poisoning.

The literature associated with Prussian blue is complicated by many confusing chemical and physical terms. The product synthesized by Diesbach, $Fe_4[Fe(CN_6)]_3$, commonly known as insoluble Prussian blue, is assigned the Chemical Abstracts Service (CAS) number 14038-43-8, and is the FDA-approved product Radiogardase (Fig. A26-1). Synonyms for Prussian blue include Berlin blue, Hamburg blue, mineral blue, Paris blue, and Pigment

blue 27, to name a few.[50] These names are often used interchangeably to refer to both insoluble Prussian blue and a soluble (colloidal) Prussian blue that has either the molecular formula $KFe[Fe(CN)_6]_3$ or $K_3Fe[Fe(CN)_6]_3$. Thus â€œPrussian blueâ€• also carries two additional CAS numbers: 25869-98-1 and 12240-15-2.[34] Compounds containing the same basic core structure, such as $NH_4Fe[Fe(CN)_6]_3$ (ammonium ferric ferrocyanide or Chinese blue) and sodium ferric ferrocyanide, may have similar efficacy in binding monovalent cations, and are also sometimes incorrectly called Prussian blue. For the purpose of clarity, general statements that follow use the term Prussian blue. In many instances the terms â€œinsolubleâ€• and â€œsolubleâ€• are specified to highlight differences between the compounds. Unfortunately, because many studies do not specify which Prussian blue is used, some inherent ambiguity persists.

Typically, the crystal lattice of Prussian blue takes up cationic potassium ions from the surrounding environment. However, because its affinity increases as the ionic radius of the monovalent cation increases, Prussian blue preferentially binds cesium (ionic radius: 0.169 nm) and thallium (ionic radius: 0.147 nm) over potassium (ionic radius: 0.133 nm).[6,15] Additionally, binding for rubidium (ionic radius: 0.148 nm) has been demonstrated.[43] Thus, when given orally, Prussian blue binds unabsorbed thallium or cesium in the gastrointestinal tract, preventing absorption as well as reversing the concentration gradient to enhance elimination through gut dialysis. In addition, in the gastrointestinal tract Prussian blue can interfere with enterohepatic circulation, causing a further reduction in tissue stores.

Pharmacology

Insoluble Prussian blue is essentially not absorbed from the gastrointestinal tract and is eliminated in the feces at a rate determined by gastrointestinal transit time. In a radiolabeled

study of healthy pigs, 99% of a single ingested dose was recovered unchanged in the stool.[29] In contrast, soluble Prussian blue is probably minimally absorbed based on the clinical finding of a blue discoloration that develops in the sweat and tears of patients undergoing prolonged therapy.[11] This discoloration appears to be benign and resolves when therapy is stopped. No significant food or drug interactions are known to exist. Animal studies show no adverse effects of therapeutic doses[38] and oral lethal doses are not known. The only significant adverse effects reported in humans from therapeutic doses are constipation and hypokalemia,[49] and the constipation may be related more to the xenobiotic than to the Prussian blue. Although there is some concern regarding cyanide liberated from Prussian blue, this release appears to be quantitatively minimal. In simulated gastric fluid, cyanide release from soluble Prussian blue was <3 mg/24 h; the insoluble form released even less.[55] When three human volunteers were given 500 mg of radiolabeled soluble Prussian blue, only 2 mg of cyanide were absorbed.[31]

In Vitro Adsorption of Thallium

In vitro and, presumably, in vivo binding of thallium to Prussian blue are influenced by its chemical formulation. An early investigation demonstrated that the soluble form more effectively adsorbs thallium than the insoluble form.[8] In a more rigorous study, the in vitro adsorptions of both forms were similar when thallium concentrations remained low.[14] However, as thallium concentrations increased, the colloidal (soluble) form demonstrated far greater adsorptive capacity. Although not proven, this difference may occur because the soluble form contains more potassium and can therefore exchange proportionally more cation. Furthermore, the actual size of the crystal lattice alters its efficacy. Laboratory synthesized Prussian blue (with a crystal size of 17.68 nm) was compared with a commercial preparation (with a crystal size of 31.19 nm). The

laboratory synthesized product adsorbed more thallium in vitro, because its smaller size increased its surface area.[15]

Thallium Poisoning

A thorough analysis of the efficacy of Prussian blue in thallium poisoning is severely hampered by many factors. First, and most importantly, there are no controlled human trials. Second, although multiple patients have received Prussian blue in the setting of thallium poisoning, many were simultaneously treated with a variety of therapies, including forced potassium diuresis, single- or multiple-dose activated charcoal, and either hemodialysis or hemoperfusion. Thus, it is impossible to determine the specific effects of Prussian blue on mortality or other clinical outcomes, and even toxicokinetic data must be interpreted with caution. Third, many of the in vitro and animal investigations fail to specify the exact type of Prussian blue used. Those investigations that do specify the type of Prussian blue used typically used the soluble form, which is presently unavailable as a pharmaceutical preparation. Discussions of the available data in the following sections are limited by these considerations.

In Vitro Comparison of Prussian Blue with Activated Charcoal

In one in vitro study, thallium was well adsorbed to Norit brand activated charcoal.[14] Although numerical data are not supplied in the body of the paper, the 10â€“20% adsorption to activated charcoal demonstrated in a figure was far less than the results achieved with several different forms of Prussian blue tested simultaneously.[14] Two other binding studies showed different results from the Norit study. An early investigation determined that the maximal adsorptive capacity (MAC) of activated charcoal

was 124 mg of thallium/g, whereas the MAC for Prussian blue was only 72 mg of thallium/g.[16] More recently, a MAC of only 59.7 mg of thallium/g was calculated for CharcoAid activated charcoal, compared to a higher MAC for insoluble Prussian blue of 72.7 mg of thallium/g.[12] Although the MACs for Prussian blue in these two studies are nearly identical, the variable results for activated charcoal may be a function of the study pH or the different types of activated charcoal used.

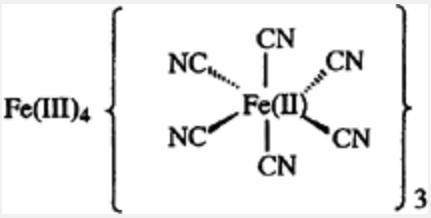

Figure A26-1. The chemical structure of insoluble Prussian Blue. The Roman numerals II and III denote the valence state of iron. Although in the most current nomenclature this would be expressed as Fe^{2+} and Fe^{3+}, the figure is drawn this way to be consistent with most available references, which use the older nomenclature.

Animal Data: Kinetics, Tissue Concentrations, and Survival

Sublethal doses of thallium were used to evaluate the effects of various antidotes in rats over an 8-day period.[16] Although the control group only eliminated 53% of the administered dose of

thallium, 93% of the dose was eliminated in the activated charcoal and 82% was eliminated in the insoluble Prussian blue groups. Although other investigators only demonstrated a modest increase in thallium elimination in rats treated with oral activated charcoal, a consistent benefit of Prussian blue is noted.[17]

Multiple studies clearly demonstrate that Prussian blue not only decreases the half-life of thallium in animals but also lowers thallium content in critical organs such as the brain and the heart.[10,26,27,42,44] Half-lives are typically reduced by approximately 50% when Prussian blue is given with or without a cathartic. The rationale for the cathartic is that constipation is invariably present in humans and animals with severe thallium poisoning.

Only a few studies evaluate the effects of Prussian blue on survival. In these studies, a statistically significant survival advantage has been shown in thallium-poisoned rats[15,44] and mice[21] treated with Prussian blue. The experimental benefit is on the order of a 31% increase in the LD_{50} (median lethal dose for 50% of test subjects) in poisoned animals.[45]

Radioactive Thallium

There is no published experience describing human poisoning with radioactive thallium. As would be expected, because the ionic radius of isotopes is generally very similar, Prussian blue has demonstrable efficacy in an animal model of radiothallium poisoning. In one small study, insoluble Prussian blue decreased the biologic half-life of radioactive thallium in rats by approximately 40%.[2]

Human Data

Three patients, in 1971, were the first to receive Prussian blue as a treatment for thallium poisoning.[14] Although daily fecal

determinations were not possible in 2 of the 3 patients because of severe constipation, an approximately 7-fold increase in fecal elimination over baseline was attributed to Prussian blue therapy in the third patient. Subsequently, many humans with thallium poisoning have received Prussian blue, with or without a cathartic, as part of their therapy.[1,3,5,6,9,14,37,40,48,52,53,57] Unfortunately, other components of therapy that may have confounded the effects of Prussian blue in these cases include single- or multiple-dose activated charcoal, D-penicillamine, dimercaprol, ethylenediaminetetraacetic acid (EDTA), succimer, 2,3-dimercaptopropane-1-sulphate (DMPS), forced potassium diuresis, and either hemodialysis or hemoperfusion. Again, there have been no controlled trials of any of these modalities alone or in combination, and most of the data are based on single case reports or small case series.

One of the largest series was composed of eleven thallium-poisoned patients who were treated with soluble Prussian blue.[48] This report not only demonstrated the tolerability of Prussian blue, but also was the first to systematically evaluate fecal elimination. In all individuals studied, fecal elimination remained high, even when urinary elimination fell, suggesting selective redistribution of thallium into the gut.[48] Although the authors commented on clinical improvement in these patients, the lack of controlled data make these subjective observations difficult to interpret. Similarly, a substantial reduction in half-life was demonstrated when Prussian blue was compared to no therapy at all in patients with thallium poisoning.[6]

Dosage and Administration

The dosage of Prussian blue has never been investigated systematically in either humans or animals. In most of the case reports and series mentioned above, a total dose of 150â€“250 mg/kg/d was administered orally or via a nasogastric tube in

2â€“4 divided doses.[48] Because constipation or obstipation is often present or expected, Prussian blue is generally dissolved in 50 mL of 15% mannitol.[49] Although any cathartic may be appropriate, mannitol is used most frequently, possibly because of concerns over the risks associated with repeated does of magnesium or sorbitol (see Antidotes in Depth: Whole-Bowel Irrigation and Other Intestinal Evacuants). The manufacturer of Radiogardase recommends that adults and adolescents with thallium poisoning receive a total dose of 9 g divided daily (3 g every 8 hours) and that children receive a total dose of 3 g divided daily (1 g every 8 hours). Although the manufacturer does not suggest the use or benefit of a cathartic, the use of a high-fiber diet is advocated when constipation is present. Because Prussian blue is well tolerated, the editors continue to favor the 150â€“250 mg/kg/d dosing because it provides more antidote. In addition, because many severely poisoned patients cannot eat, the use of a cathartic should be considered when constipation is consequential.

The end point of therapy is similarly poorly defined. By convention, Prussian blue is usually continued until urinary thallium concentrations fall below 0.5 mg/d. This end point may not be a meaningful measurement of thallium burden, as fecal elimination may continue, even when urinary elimination has diminished.[48] However, because most laboratories are not equipped to measure fecal thallium concentrations, the use of some urinary end point seems reasonable as the reported residual amounts of fecal elimination are small.

Cesium Poisoning

The radioactive isotope of cesium (^{137}Cs), a common byproduct of nuclear fission reactions, is a strong Î² and Î³ emitter with a physical half-life of more than 30 years and a biologic half-life of about 110 days. Another isotope (^{134}Cs) is only produced by

neutron activation of the stable isotope (^{133}Cs) and has a physical half-life of about 2 years and a biologic half-life comparable to ^{137}Cs. Like thallium, cesium is absorbed in the small bowel, distributes like potassium, and undergoes enteric recirculation.[25] Approximately 80% of a given dose is eliminated in the urine, with 20% cleared in the feces.

The isotope ^{137}Cs is used clinically as a radiation source in nuclear medicine. Although uncommon, radiologic disasters such as Chernobyl and GoiÃ¢nia (see Human clinical Trials below) have resulted in lethal incorporation exposures. Additionally, concerns over the use of ^{137}Cs in â€œdirty bombsâ€• have increased the awareness of, and the potential need to treat, patients with radiocesium poisoning. Toxicity from nonradioactive cesium is also reported. Many cases of QTc prolongation and torsade de pointes are reported in patients who take cesium chloride either as a dietary supplement or for its alleged antineoplastic effects.[4,19,36,41,46] To date, there have been no reports of Prussian blue therapy for nonradioactive cesium poisoning, but the following discussion is most likely applicable.

In Vitro Adsorption of Cesium

Standard binding studies compared the ability of activated charcoal, sodium polystyrene sulfonate (SPS), and both soluble and insoluble Prussian blue to bind ^{137}Cs over a range of gastrointestinal pHs.[54] Unlike thallium, the adsorption of cesium to activated charcoal was negligible. Comparable to thallium, SPS offered no benefit, likely because of preferential effects on potassium. Although both forms of Prussian blue adsorbed cesium, the insoluble form was consistently superior. A pH of 7.5 was selected to represent the pH of the small bowel lumen, the location where most adsorption would occur. At this pH, a MAC of 238 mg of ^{137}Cs/g of insoluble Prussian blue was determined. In an interesting extension, when the same authors bound insoluble

Prussian blue to a hemoperfusion column, they demonstrated a clearance of approximately 100 mL/min of ^{137}Cs from plasma, and projected that a 4-hour treatment would adsorb about 0.3 terra becquerel (TBq) of radiocesium.[56]

Animal Data: Kinetics, Tissue Concentrations, and Survival

Small animal investigations with either ^{134}Cs or ^{137}Cs consistently demonstrate that Prussian blue therapy reverses the urine-to-stool-elimination ratio from 8:1 to 0.3:1, and reduces the biologic half-life and the total body area under the curve by as much as 60%.[28,32,33,43,47] For example, rats given oral ^{134}Cs retained 84.7% of the ingested dose at 7 days. Treatment with insoluble and soluble Prussian blue, as well as Chinese blue, produced significant reductions in retained cesium (only 6.36%, 2.63%, and 2.43% of the dose was retained at 7 days, respectively).[7]

In addition to human toxicity, concern over radiocesium incorporation into cattle milk and meat has resulted in a number of large animal investigations. Daily Prussian blue therapy reduced radiocesium concentrations in sheep by as much as 42%.[13,39] Likewise, radiocesium transfer to milk was reduced by 85% in cows.[51] When dogs were contaminated with ^{137}Cs, Prussian blue reduced total-body burden by as much as 51%.[23] Similar efficacy in reducing the amount of cesium was demonstrated in meat from pigs fed ^{134}Cs-contaminated whey, with insoluble Prussian blue reducing activity from 359 Bq/kg to 11 Bq/kg.[7]

Human Volunteer Studies

Two human volunteers ingested meals contaminated with ^{134}Cs to compare the efficacy of both the soluble and insoluble forms of Prussian blue with controls.[7] At 14 days after loading and without therapy, the volunteers retained 94.7% of the ingested dose as

compared to a retention of only 5.1% following therapy with insoluble Prussian blue and 4.9% following soluble Prussian blue. In another study, two volunteers demonstrated that Prussian blue decreased the biologic half-life of ingested radiocesium by approximately 33%.[20] Finally, in two volunteers, the effects of pretreatment were compared to simultaneous posttreatment Prussian blue. When a single dose of Prussian blue was administered 10 minutes before ^{134}Cs, absorption decreased from 100% (without therapy) to 3â€“10%. However, simultaneous administration of 0.5 or 1 g of Prussian blue with ^{134}Cs resulted in 38â€“63% absorption. Finally, when Prussian blue was given daily at a dose of 0.5 g every 8 hours in the postabsorptive phase, the biologic half-life of ^{134}Cs was reduced from 106 to 44 days.[30]

Human Clinical Trials

There are no controlled trials of Prussian blue in radiocesium poisoning. Experience is derived exclusively from treating disaster victims. In 1987, a number of people in GoiÃ¢nia, Brazil, were contaminated with radiocesium from a discarded radiotherapy unit.[35] Although the reported total number of individuals treated is uncertain because of multiple reports that probably include overlapping patients, one group describes 37 patients who were given insoluble Prussian blue in doses ranging from 3g/d in children up to 10g/d in adults. Untreated, elimination kinetics were first order and half-lives varied extensively from 39 to 106 days in adults (mean: 65.5 days in women and 83 days in men). Half-lives were shorter in children. Therapy with insoluble Prussian blue reduced half-lives by a mean of 32%[18] and reduced the retained cesium dose 51â€“84%.[22]

The nuclear disaster at Chernobyl, Ukraine, resulted in many cases of acute radiation exposure as well as incorporation into the population of radioactive iodine, cesium, and strontium. In one trial, insoluble Prussian blue was given to three victims of

radiocesium incorporation many weeks after their exposure. The reported reduction in biologic half-life ranged from 12â€“52%.[24] The authors of this paper include data from the Chinese literature describing another six patients that demonstrate a similar reduction in cesium's biologic half-life following Prussian blue therapy.

Dosage and Administration

The manufacturer of Radiogardase recommends that for radiocesium poisoning, adults receive a total daily dose of 9 g divided into 3 g, 3 times per day. Children should receive a total daily dose of 3 g divided into 1 g, 3 times per day. Although these are the same doses used for thallium poisoning, therapy for cesium poisoning should be continued for least 30 days. Even though there are no recommendations of other criteria to determine the end point of therapy, quantitative and radiologic evaluations of cesium elimination should be performed.

Pregnancy Category

Insoluble Prussian blue is listed as pregnancy category C. Because of the severe consequences of poisoning from radiocesium and thallium and the lack of systemic absorption of insoluble Prussian blue, a risk-to-benefit analysis favors the use of the antidote in all poisoned pregnant patients.

Availability

Insoluble Prussian blue (Radiogardase) is available as a 0.5-g blue powder in gelatin capsules for oral administration manufactured from Haupt Pharma Berlin GmbH for distribution by HEYL Chemisch-pharmazeutische Fabrik GmbH & Co. KG, Berlin.

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Chapter 97
Zinc

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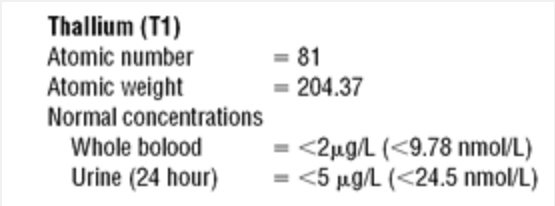

Figure. No Caption Available.

A 39-year-old woman presented to the emergency department with retrosternal chest pain and weakness. She had no history of cardiac or pulmonary disease, but had auditory hallucinations for

several years. She denied any trauma, nausea or vomiting, travel, or recent illnesses. Her vital signs were: blood pressure, 95/60 mm Hg; pulse, 120 beats/min; respiratory rate, 16 breaths/min; and temperature, 98.6Â°F (37Â°C) Oxygen saturation on room air was 100% by pulse oximetry. Her physical examination was notable for pale conjunctiva and mild erythema of the posterior pharynx without exudates, petechiae, or tonsillar enlargement. Auscultation of the chest revealed clear breath sounds with good air exchange. Her heart had a rapid, regular rhythm and no murmurs were appreciated. Her abdomen was slightly distended, but it was soft, and no masses, involuntary guarding, or rebound was noted. Her stool was negative for occult blood. The neurologic examination was within normal limits. Her skin was noted to be pale but without any rashes. She had full range of motion of all joints.

Intravenous fluid therapy was initiated with 0.9% sodium chloride and the patient was attached to a cardiac monitor. With the exception of sinus tachycardia, the electrocardiogram was normal and did not show any evidence of ischemia. A chest radiograph revealed a normal cardiac silhouette and no abnormal pulmonary lesions. However, the stomach was visualized on the chest film and appeared to contain circular foreign bodies. An abdominal radiograph showed the foreign bodies traversing the entire gastrointestinal tract. Upon further questioning, the patient admitted that for more than a year â€œherâ€• voices had instructed her to ingest coins. The patient described a preference for pennies because of their small size.

Laboratory evaluation was significant for a hematocrit of 16% and a blood smear showed ringed sideroblasts. No other abnormal cells were visualized on the peripheral smear. Hemoglobin electrophoresis excluded thalassemia, and a venous lead concentration was 1.2 Âµg/dL (normal: <10 Âµg/dL). A whole-blood zinc concentration was 298 Âµg/dL and her serum copper concentration was 50 Âµg/dL (normal: 70â€“140 Âµg/dL). A blood

transfusion was given, as well as whole-bowel irrigation to facilitate passage of the coins. The patient received chelation therapy with intravenous $CaNa_2EDTA$ (edetate calcium disodium). Two weeks later, the hematocrit, zinc, and copper concentrations had normalized, and the patient was transferred to an inpatient psychiatric hospital.

History and Epidemiology

The Babylonians used zinc alloys more than 5000 years ago[1] and references to zinc oxide can be found in the Ebers papyrus, written in 1500 B.C.[17] This papyrus is the oldest preserved medical document and it contains magical formulas and folk remedies to cure various diseases. Topical zinc is listed as a calamine lotion to heal lesions around the eye. Zinc oxide and zinc sulfate were used in Western Europe during the late 1700s and early 1800s for gleet (urethral discharge), vaginal exudates, and convulsions. In the late 1800s, brass workers who inhaled zinc oxide fumes were noted to develop â€œzinc fever,â€• â€œbrass founders' ague,â€• and â€œsmelter shakes,â€• all of which are now identified as metal fume fever (Chap. 119).[55]

Throughout history, humans have contaminated the environment with zinc. For example, release of zinc and other metals from mines produces elevated levels of zinc in the local water supply and vegetation, and may lead to elevated tissue zinc concentrations and clinical effects in the nearby population.[41,48]

Medicinal Exposures

Zinc salts have several medicinal uses, including enhancing the solubility of pharmaceutical agents such as insulin (eg, rapid

insulin zinc, extended insulin zinc, and protamine zinc insulin). The salts are used in baby powder (zinc oxide), sun blocks, and topical

burn preparations (zinc oxide). Furthermore, zinc oxide powders are used on some latex and latex-free gloves. Given zinc's antiinflammatory effects, zinc sulfate was studied in the late 1970s for acne vulgaris with mixed results. However, a double-blinded controlled group found no difference between zinc and placebo.[60]

Zinc gluconate-containing lozenges are sold as dietary supplements with conflicting evidence that they can shorten the duration of the common cold.[37,51] One placebo-controlled study found that zinc nasal gel shortened the duration of the common cold when applied within 24 hours of the onset of symptoms.[32]

The FDA approved zinc acetate in 1997 for maintenance therapy of Wilson disease.[11,46] Its use in this disorder is related to the ability of zinc to induce the formation of metallothionein, which assists in the elimination of copper from the blood and body tissues (Chap. 90).[6]

Occupational Exposures

Occupational exposures during coin production may involve contact with zinc. The United States penny has been made with a zinc coating since the introduction of the Lincoln penny in 1943. Its composition was altered in 1982 from 95% copper and 5% zinc to the current 97.5% zinc and 2.5% copper. The reason for this change was 2-fold: it reduced both production costs and the weight of the coin.[78]

Zinc is widely used in industry because it enhances the durability of iron and steel alloys; it also is commonly used in construction. Inhalational zinc oxide exposure commonly occurs in those who weld galvanized steel (galvanization involves coating metal with zinc to protect the metal from rust). Zinc is routinely encountered by electroplaters, smelters, jewelers, in yellow paint production, artists working on stained glass or sculpting metal, as well as aircraft manufacturing workers. The United States mines only a

small percentage of the world's zinc, with the state of Alaska being the main producer.[2]

Chemistry

Zinc is a divalent cation that, like iron and cadmium, is a transition metal. Zinc is among the most common elements comprising the earth's crust and is present in air, soil, and water. It has two common oxidation states, Zn^0 (elemental or metallic) and Zn^{2+}. The pure element exists as a blue to white shiny metal, but it also combines with other elements to form many familiar compounds: zinc chloride ($ZnCl_2$), zinc oxide (ZnO), zinc sulfate ($ZnSO_4$), and zinc sulfide (ZnS). Once the metal is exposed to moisture, it becomes coated with zinc oxide or carbonate ($ZnCO_3$).[2]

Like other transition metals, zinc is able to participate in reactions that result in the generation of reactive oxygen species. As with other transition metals, such as iron (Chap. 40) and copper (Chap. 90), the liberation of superoxide radicals or hydroxyl radicals results in toxicity to the tissues in which it is generated.

Physiology

Zinc is an essential nutrient and found in more than 200 metalloenzymes, including acid phosphatase, alkaline phosphatase, alcohol dehydrogenase, carbonic anhydrase, superoxide dismutase, and DNA and RNA polymerases.[2] Zinc contributes to gene expression and chelates with either cysteine or histidine in a tetrahedral configuration, forming looped structures known as â€œzinc fingers,â€• which bind to specific DNA regions.[10,81] Other functions of zinc include a role in membrane stabilization, vitamin A metabolism, and the development and maintenance of the nervous system. Zinc and copper concentrations generally have an inverse relationship in the plasma (Chap. 90).

Zinc is important in maintaining olfactory and gustatory function.

Serum, urine, and salivary zinc concentrations are lower in patients with dysfunctional senses of smell or taste. This is supposedly related to an abnormality in a salivary growth factor known as gustin/carbonic anhydrase VI.[30] Because this enzyme is zinc dependent, oral zinc produces some subjective improvement in taste and smell in patients with a known decrease in salivary growth factor and increased parotid saliva gustinâ€“carbonic anhydrase VI complex.[31] Oral zinc sulfate also improved subjective findings in a group of 25 patients with posttraumatic olfactory disorders.[4]

Zinc is important for fetal growth. Accordingly, when 29 pregnant mothers were given zinc citrate, sulfate, or aspartate because they were at risk for small-for-gestational age babies, no intrauterine growth retardation was observed.[72] Similarly, no reproductive effects were observed in a rodent model exposed to inhalational zinc oxide.[52]

The role of zinc within the immune system is undefined. Zinc may be effective in the treatment of infectious diarrhea generically and specifically in the management of Shigella by improving the shigellacidal antibody response and increasing circulating B lymphocyte and plasma cells.[66,67] Zinc deficiency, or hypozincemia, is a well-described clinical entity. It can either be inherited in an autosomal recessive pattern known as acrodermatitis enteropathica that was first described in 1973, or it can be an acquired deficiency.[61] A defect in zinc absorption in the GI tract is thought to be responsible for the disorder, and those patients at risk for acquiring the disorder include patients who receive total parenteral nutrition without adequate zinc supplementation, patients who have undergone intestinal bypass procedures, those with Crohn disease, and premature infants with low zinc storage. Physical findings that suggest the diagnosis, regardless of etiology, include the triad of dermatitis (acral and perioral), diarrhea, and alopecia. Zinc gluconate, acetate, or sulfate in initial doses of 5â€“10 mg/kg/d followed by maintenance

doses of 1â€“2 mg/kg/d is highly effective; in fact, skin lesions typically heal within 2â€“4 weeks and hair growth also restarts during this time frame.

Pharmacokinetics and Toxicokinetics

The average daily intake of zinc in the United States is 5.2â€“16.2 mg; foods that contain zinc include leafy vegetables (2 ppm), meats, fish, and poultry (29 ppm).[2] The recommended daily allowance is 11 mg/d for men and 8 mg/d for women. Pregnant and nursing women require 12 mg/d. Zinc is present in drinking water, and beverages stored in metal containers or that flow through pipes coated with zinc. Zinc levels in air are typically low; average zinc levels in the United States are <1 Âµg/m^3. Air near industrial areas can be higher, and may be greater in certain occupational settings (see Occupational Exposures above).

The main site of oral zinc absorption is the jejunum, although absorption is reported to occur throughout the intestine by binding to a metallothionein as a zincâ€“protein complex in the luminal cells.[80]

Metallothioneins are specific metal-binding proteins with diverse functions considered essential to metal homeostasis. The metallothioneins are of low molecular weight (6000 daltons) and are rich in thiol ligands; it is these ligands that allow high-affinity binding to metals such as zinc, copper, cadmium, mercury, and silver. The primary route of excretion of the complex is fecal. Albumin binds about two-thirds of zinc in the plasma and the remainder is bound to Î±$_2$-globulins. Zinc concentrations in the body show a great variability by organ, with the prostate having the highest amount of the zinc-containing enzyme acid phosphatase.[8]

Clinical Manifestations

Acute

The hallmark of acute zinc toxicity is gastrointestinal (GI) distress, including nausea, vomiting, abdominal pain and gastrointestinal bleeding.[8] In initial studies that evaluated the oral use of zinc sulfate as an acne therapy, epigastric distress was noted,[22,27] One patient developed GI bleeding within a week of therapy initiation with zinc sulfate at a therapeutic dose of 220 mg twice a day.[58] Zinc chloride in concentrations greater than 20% are particularly corrosive when ingested. Partial- and full-thickness burns to the oral mucosa, pharynx, esophagus, and stomach, as well as to the laryngotracheal tree, can occur following unintentional ingestions of zinc chloride by children.[20,43,56] Delayed gastric stricture may occur after acute[56] or chronic zinc chloride consumption.[19] Pancreatitis was noted in a piglet model[26] and in a 24-year-old male who inadvertently ingested liquid zinc chloride.[20] Finally, hyperamylasemia, vomiting, diarrhea, and jaundice occurred following an intentional intravenous injection of zinc sulfate.[12]

Acute inhalation of zinc chloride from smoke bombs produces lacrimation, rhinitis, dyspnea, stridor, and retrosternal chest pain. Upper respiratory tract inflammation, acute lung injury (ALI), and acute respiratory distress syndrome (ARDS) may occur, generally with no suggestions of systemic absorption such as pathologic changes in the liver or kidneys.[34,36,53] Morbidity and mortality increases when the exposure to a zinc chloride smoke bomb is in an enclosed space.[69] Of 70 individuals exposed to a zinc chloride smoke bomb in a tunnel during World War II, 10 died within 4 days.[23] Ambient zinc concentrations in the tunnel were measured at 33,000 mg zinc/m^3 (33,000 times greater than the currently accepted occupational threshold limit value [TLV]- time-weighted average [TWA] of 1 mg zinc/m^3). Inhalation of zinc oxide, a far less water soluble zinc salt, is associated with metal fume fever and not pneumonitis despite similar ambient zinc concentrations.[8]

Animal research suggests that intranasal zinc sulfate use can cause at least transient anosmia as a consequence of disruption of functional connections between the main olfactory bulb and the olfactory epithelium.[54] Topical zinc sulfate is used experimentally in both the rat and mouse model to eliminate olfactory input so that further nerve fiber density and behavioral discrimination testing can be performed.[79] A case report describes a 55-year-old patient who developed an immediate burning sensation after intranasal zinc gluconate application with subsequent anosmia that had persisted for 23 months at the time of publication.[40] Five other patients, ages 31â€“55 years, are described where application of zinc gluconate to the olfactory epithelium resulted in either long-lasting or permanent olfactory dysfunction.[40]

US pennies lodged in the distal esophagus release reactive zinc ions following exposure to gastric acids[16] and can damage the local esophageal tissue. The phenomenon of acid dissolution is demonstrated in animal[3] and in vitro models.[59]

Rare reports of renal complications exist. Microhematuria was observed in a 24-year-old male who ingested liquid zinc chloride but whose renal function did not deteriorate.[20] Intentional intravenous zinc sulfate administration can result in acute tubular necrosis and renal failure as manifestations of systemic zinc poisoning.[12]

Certain zinc salts, as found in baby powders and calamine lotion, are nonirritating.[5] Although older studies suggested the possibility of pruritic, pustular rashes in workers who are exposed to zinc oxide, other causative factors, including personal hygiene, were not considered.[77] One case report describes urticaria and angioedema in a 34-year-old welder following contact with zinc fumes at a smelting plant.[24] The patient was asymptomatic once he was removed from the environment and was able to return to work once full protective gear was used during the welding process.

Chronic

Chronic zinc toxicity can produce a reversible sideroblastic anemia, as well as a reversible myelodysplastic syndrome; 2 patients with zinc exposures, one from nutritional supplements and the other from ingested coins, each had a reversible myelodysplastic syndrome.[13] Both anemia and granulocytopenia occur with the bone marrow showing vacuolated precursors and ringed sideroblasts; the mechanism appears to be a zinc-induced copper deficiency.[25] A 54-year-old schizophrenic patient with a 15-year history of pica (typically metal objects) presented with pancytopenia, including a hemoglobin of 3 g/dL and a white blood cell count of 1300/mm^3.[44] A serum zinc concentration of 280 Âµg/mL and low serum copper concentration of <0.05 Âµg/mL reflected his ingestion of zinc-containing coins over many years. The patient refused surgery to remove the coins from his GI tract. Meat tenderizer and pancreatin were given in an unsuccessful to attempt to loosen the objects. During his medical therapy, he continued to ingest coins. Despite treatment efforts, he died of sepsis and multiorgan failure; an autopsy revealed a coin mass weighing 1870 g in his stomach and another bezoar at the site of a sigmoid volvulus. A 17-year-old boy used megadoses of oral vitamins and mineral supplements containing zinc to treat acne over a 6â€“7 month period.[68] He developed copper deficiency and anemia, leukopenia, and neutropenia. Hemolysis requiring blood transfusions is described in a dog model.[75]

It is suggested that zinc and other transition metals may be important in the pathogenesis of demyelinating diseases.[45,64] Clusters of cases of multiple sclerosis (MS) were described in northern New York in a factory where zinc was the primary substance to which workers were exposed. One hypothesis is that the allele frequency for transferrin (an iron- and zinc-binding protein) may differ in these MS subjects.[70,74] Another cluster was found in Canada where excess metals, including zinc, were found

in the soil and water.[28,38,39] A conclusive link to MS, however, has not been established. Finally, a mutation of one of the copper-zinc superoxide dismutase forms may play a role in a familial forms of amyotrophic lateral sclerosis.[50]

Since the prostate contains the highest concentration of zinc in the human body, the role of zinc in the development of prostate cancer has been investigated. Specifically, American men participating in the Health Professionals Follow-Up Study were followed for 14 years, from 1986â€“2000. Of the 46,974 in the cohort, 2901 new cases of prostatic cancer were diagnosed, with 434 of them considered to be in an advanced stage.[47] Men who used zinc

supplementation at a dose >100 mg/d had a relative risk of advanced prostate cancer of 2.29, and those using zinc for longer than 10 years had a relative risk of 2.37. To date, neither the International Agency for Research on Cancer (IARC) or the Environmental Protection Agency (EPA) have classified zinc as a carcinogen.

A zinc overload syndrome has been described.[29] A 46-year-old male presented with evidence of bone marrow suppression followed by sensory ataxia and a progressive myelopathy. The neuroimaging evaluation was normal. His only remarkable laboratory studies included an elevated serum zinc concentration of 184 Âµg/dL (28.2 Âµmol/L) and a low copper concentration of <10 Âµg/dL (<12.6â€“18.9 Âµmol/L). There was no known exposure to or supplementation of zinc by history. Although his copper deficit improved with copper therapy, hyperzincemia persisted for more than three years that he was followed. This report and three others suggest the possibility of an inherited zinc overload syndrome;[64,65,73] researchers believe the pattern of inheritance is either autosomal recessive or autosomal dominant, with reduced penetrance or new mutations. Whether the pathophysiology is analogous to the iron overload of

hematochromatosis or to the copper overload with subsequent decreased zinc excretion of Wilson disease, remains to be determined.

Metal Fume Fever

Metal fume fever (MFF) typically occurs within 12 hours after an exposure to zinc fumes. Patients develop fever, chills, cough, chest pain, dyspnea, dry throat, and a metallic taste in the mouth. Although exposure to zinc oxide fume is most commonly associated exposure with this syndrome, other zinc compounds and other metal oxides may be implicated. The chest radiograph is often normal, but may show an infiltrate. Hypoxia and tachycardia are rare, but may be noted. Overall, however, the syndrome is relatively benign, with tolerance developing within days. An immune mechanism is suggested, and chronic exposure is needed for sensitization (Chap. 119).

Diagnostic Testing

Because zinc is ubiquitous in the environment and laboratory, great care must be taken to avoid contamination of any samples for investigation.[2] Because elevated zinc concentrations cause copper deficiency, a serum copper concentration should always be obtained simultaneously. Whole-blood zinc concentrations exceed serum concentrations by a ratio of approximately 6â€“7:1 because the metal accumulates in erythrocytes.[57]

Urine zinc concentrations are not well defined. In a cohort of nonoccupationally exposed Italians, the mean urine concentrations were 0.45 mg/L, with a range up to 0.85 mg/L.[57] In the United States, normal urine values are generally accepted as <0.5 mg/d. The National Institute for Occupational Safety and Health states the detection limits in urine are as low as 0.1 Âµg per sample, with extraction of the urine with polydithiocarbamate resin

required prior to digestion and analysis.[2]

Errors can be caused by incorrect sample collection, equipment malfunction or miscalibration, inadequate reagent purity, and atmospheric deposition. Zinc oxide powder in some gloves can contaminate specimens, as can the rubber stopper in the blood collection tubes. Specific tubes are recommended with negligibly low concentrations of trace elements.[18] During sample analysis, laminar flow is recommended to prevent airborne particles from interfering.

Management

Treatment for acute oral zinc toxicity is primarily supportive. Efforts should be focused on hydration, as well as on antiemetic therapy. H_2 receptor antagonists or proton pump inhibitors may relieve abdominal discomfort when given for several days following the zinc salt ingestion.[8]

Gastrointestinal decontamination after zinc salt ingestions may include whole-bowel irrigation (WBI). A radiograph in a 16-year-old boy who ingested 50 zinc sulfate tablets noted no change in their position 4 hours after gastric evacuation. Within 1 hour of institution of WBI therapy, zinc tablets were present in the rectal effluent.[15]

The data regarding the efficacy of chelation therapy for zinc is limited in humans. Edetate calcium disodium ($CaNa_2EDTA$) was used successfully in several cases, including in a child who was exposed to zinc chloride that was a component of soldering flux[63] and in a 24-year-old man exposed to liquid zinc chloride.[20] The combination of $CaNa_2EDTA$ and BAL (British anti-Lewisite) was used successfully in a 16-month-old toddler 74 hours after ingestion.[56] Both DTPA (diethylenetriaminepentaacetic acid) and EDTA (ethylenediaminetetraacetic acid) were effective in enhancing the urinary excretion of zinc in a rodent model of zinc

acetate poisoning.[21] DTPA had its greatest antidotal efficacy when given within 30 minutes of the intraperitoneal injection of zinc acetate.[49] The urinary excretion of zinc increased 1.6â€“44-fold following a 3 mg/kg intravenous dose of DMPS (sodium 2,3-dimercaptopropane-1-sulfonate) in one human study where metal toxicity in patients with dental amalgams was the focus.[76] Two potential zinc-selective chelators, DPESA (4-{[2-(bis-pyridin-2-ylmethylamino)ethylamino]-methyl}phenylmethanesulfonic acid) sodium salt, as well as TPESA (4-{[2-bis-pyridin-2-ylmethylamino)ethyl]pyridine-2-ymethylamino}-methyl)phenyl]methanesulfonic acid) sodium salt,[42] rapidly chelate zinc in vitro, but further detailed in vivo studies are needed before its clinical use can be considered. Finally, an iron-chelating agent, deferiprone, was incidentally noted to cause decreased serum zinc concentrations in a transfusion overload study.[33] A subsequent prospective trial showed enhanced urinary excretion of zinc in children with thalassemia major who had been transfused with blood multiple times.[9]

Intravenous *N*-acetylcysteine (NAC) increased the urinary zinc excretion in a patient who had inhaled zinc chloride smoke.[62] Two individuals with inhalational zinc chloride-induced ARDS[34] had simultaneous transient decreases in plasma zinc concentrations and increases in urinary zinc excretion with intravenous and nebulized NAC. However, they succumbed at days 25 and 32 after inhalation. Although an increase in urinary zinc excretion was noted in one rat model,[7] 10 healthy volunteers who were treated with oral NAC for 2 weeks had no significant change in either their serum or urine zinc concentrations.[35]

Supportive care is used for patients with inhalational zinc exposures, including oxygen therapy and bronchodilators as clinically indicated, but these patients may necessitate ventilatory support in severe cases. Exposure to zinc oxide vapors by rescuers is minimal, although respiratory protective equipment should be worn.[71] In a case series of five soldiers exposed to zinc chloride

during military training, the two individuals not wearing gas masks developed ARDS;[34] the others remained clinically well.

Metal fume fever is typically self-limited. Nonsteroidal antiinflammatory drugs should be sufficient to relieve the transient discomfort. Personal protection equipment and/or adequate engineering strategies may allow the individual to continue to work in this setting.

Dermal decontamination is paramount to prevent direct epidermal effects or systemic absorption of zinc salts.[14] However, water should not be used to perform dermal decontamination of patients exposed to metallic zinc because of concerns that zinc metal will ignite when wet. Treatment in these situations includes mechanical removal of any metallic particles with forceps and the application of mineral oil to the affected skin to protect the metal from ambient moisture.

Summary

Zinc is a ubiquitous element found throughout the environment. Exposures to humans occur as part of the diet, medicinal uses, nutritional supplements, and in certain occupational settings. Clinical manifestations include acute, life-threatening gastrointestinal and pulmonary effects, which are generally treated with supportive care. Systemically poisoned patients should receive chelation therapy. Care must be taken to avoid specimen contamination during laboratory analysis.

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Chapter 98

Antiseptics, Disinfectants, and Sterilants

Paul M. Wax

A 60-year-old woman with a history of ethanol abuse was brought to the emergency department (ED) from home, 3 hours after drinking a few ounces of a liquid from an old liquor bottle that was stored in her garage. In the ED, the patient was unresponsive to voice but responded to deep pain. Her vital signs were: blood pressure, 80/40 mm Hg; pulse, 130 beats/min and regular; respiratory rate, 14 breaths/min; and temperature, 98.6Â°F (37Â°C). An unusual, somewhat sweetish odor was noted on her breath. The patient was comatose with normal muscle tone and symmetrical reflexes. Her physical examination was otherwise unremarkable. Her initial electrocardiogram (ECG) showed sinus tachycardia with normal conduction and no evidence of ischemia.

In the ED, the patient continued to vomit. She underwent endotracheal intubation for airway protection and was treated with aggressive fluid resuscitation. Her blood pressure gradually improved, but she exhibited episodic atrial fibrillation and was

admitted to the intensive care unit (ICU). Her electrolytes, renal function tests, and glucose were normal. The arterial blood gas on room air showed: pH, 7.28; PCO_2 , 50 mm Hg; and PO_2 , 70 mm Hg. A urine toxicology screen was negative for drugs of abuse. Serum ethanol concentration was 30 mg/dL. The old liquor bottle that the patient had drunk from was noted to have a disinfectantlike odor that resembled formaldehyde and was sent to the medical examiners office for a formaldehyde analysis.

In the ICU, the patient remained comatose for the first 48 hours. Esophagogastroscopy revealed gastric inflammation, but no burns. There were no further dysrhythmias. The patient was extubated and fully awake within 96 hours of the ingestion and admitted that she had run out of liquor in her house and had gone out to the garage, looking for other sources of ethanol. She believed that she had been drinking from an old rum bottle. The medical examiner's report of the analysis of the liquid from the old bottle revealed the presence of phenol. No formaldehyde, ethanol, or other chemicals were detected.

Antiseptics, disinfectants, and sterilants are a diverse group of antimicrobials used to prevent infection (Table 98-1). Although these terms are sometimes used interchangeably and some of these xenobiotics are used for both antisepsis and disinfection, the distinguishing characteristics between the groups are important to emphasize. An antiseptic is a chemical that is applied to living tissue to kill or inhibit microorganisms. Iodophors, chlorhexidine, and the alcohols (ethanol and isopropanol) are commonly used antiseptics. A disinfectant is a chemical or physical agent that is applied to inanimate objects to kill microorganisms. Bleach (sodium hypochlorite), phenolic compounds, and formaldehyde are examples of currently used disinfectants. Neither antiseptics nor disinfectants have complete sporicidal activity. A sterilant is a chemical or physical process that is applied to inanimate objects to kill all microorganisms as well as spores. Ethylene oxide and glutaraldehyde are examples of sterilants. Unsurprisingly, many of

the xenobiotics used to kill microorganisms also demonstrate considerable human toxicity.[15 , 55]

The use of these xenobiotics evolved during the 20th century as their toxicity and the principles of microbiology became better understood. Two of the more toxic antisepticsâ€”iodine and phenolâ€”were gradually replaced by the less toxic iodophors and substituted phenols. The use of mercuric chloride was superseded by the organic mercurials (eg, merbromin, thimerosal), which also proved toxic. In recent years, newer compounds, such as quaternary ammonium compounds, ethylene oxide, and glutaraldehyde, are used extensively.

Antiseptics

Chlorhexidine

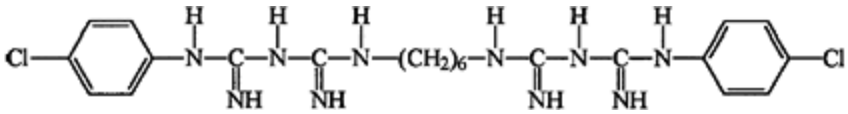


Figure. No Caption Available.

This cationic biguanide compound has been in use as an antiseptic since the early 1950s. It is found in a variety of skin cleansers, usually as a 4% emulsion (eg, Hibiclens), and may also be found in mouthwash. Chlorhexidine is reported to have low toxicity.

Acids
  Boric acid
Borax
Antiseptic
Blue-green emesis and diarrhea

GI decontamination

Sodium perborate
Mouthwash
Boiled lobster appearance
Hemodialysis (rare)

Dobell's solution
Eyewash
Roach killer
CNS depression; renal failure
Alcohols (Chaps. 75 and 103)
Ethanol
Rubbing alcohol (70% ethanol)
Antiseptic
Disinfectant
CNS depression
Respiratory depression
Dermal irritant
Supportive
Isopropanol
Rubbing alcohol (70% isopropanol)
Antiseptic
Disinfectant
CNS depression
Respiratory depression
Ketonemia, ketonuria
GI irritation/bleeding
Hemorrhagic tracheobronchitis
Hemodialysis (rare)
Aldehydes
Formaldehyde
Formalin
Disinfectant

Caustic
Gastric lavage

37% formaldehyde
Fixative
CNS depression
Hemodialysis

12â€“15% methanol
Urea insulation
Carcinogen
Sodium bicarbonate
Endoscopy
Folinic acid
Glutaraldehyde
Cidex (2% glutaraldehyde)
Sterilant
Mucosal and dermal irritant
Supportive
Chlorhexidine
Hibiclens
Antiseptic
GI irritation
Supportive
Chlorinated Compounds
Chlorates
Sodium chlorate
Antiseptic
Hemolytic anemia
Exchange transfusion

Potassium chlorate
Matches
Methemoglobinemia

Hemodialysis

Herbicide
Renal failure

Chlorine

Disinfectant
Irritant
Supportive
Chlorophors (sodium hypochlorite)
Clorox bleach (5% NaOCl)
Disinfectant
Mild GI irritation
Endoscopy (rare)

Dakin solution (1 part 5% NaOCl, 10 parts H_2O)
Decontaminating solution

Ethylene Oxide

Sterilant
Irritant
Supportive

Plasticizer
Peripheral neuropathy
Carcinogen?
CNS depression

Mercurials (Chaps. 53 and 92)

Merbromin 2% (mercurochrome)
Thimerosal (merthiolates)
Antiseptic (obsolete)
CNS
Renal
Gastric lavage AC, BAL, succiner
Iodinated Compounds
Iodine
Tincture of iodine
2% free iodine
2% sodium iodide
50% ethanol
Lugol solution (5% I_2)
Antiseptic
Caustic
Milk, starch, sodium thiosulfate
Endoscopy
Iodophors
Povidone-iodine
(Betadine) (0.01% I_2)
Antiseptic
Limited
Same as iodine if symptomatic
Oxidants
Hydrogen peroxide
H_2O_2 3%â€”household
Disinfectant
Oxygen emboil
Lavage

H_2O_2 30%â€”industrial

GI caustic
Radiographic evaluation

Endoscopy				
Potassium permanganate				
Crystals solution				
Antiseptic				
Oxidizing agent, caustic, manganese elevation				
Decontamination				
Endoscopy as needed				
Phenols				
Nonsubstituted				
Phenol (carbolic acid)				
Disinfectant				
Caustic				
Dermal burns				
Cutaneous absorption				
CNS effects				
Decontamination: polyethylene glycol or water				
Endoscopy as needed				
Substituted				
Hexachlorophene				
Disinfectant				
CNS effects				
Supportive				
Quaternary Ammonium Compounds				
Benzalkonium chloride				
Zephiran				
Disinfectant				
GI caustic at high concentrations				
Endoscopy if significant GI symptoms				

Chemical	Commercial Product	Use	Toxic Effects	Therapeutics and Evaluation

TABLE 98-1. Antiseptics, Disinfectants, Sterilants, and Related Compounds

Clinical

Few cases of deliberate oral ingestion of chlorhexidine are reported. Symptoms are usually mild and gastrointestinal irritation is the most likely effect after oral ingestion.[21] Chlorhexidine has poor enteral absorption. In one case, ingestion of 150 mL of a 20% chlorhexidine gluconate solution resulted in oral cavity edema and significant irritant injury of the esophagus.[107] In the same case, liver enzymes rose to 30 times normal on the fifth day after ingestion. Liver biopsy showed lobular necrosis and fatty degeneration. Subsequently, the liver enzymes normalized. In another case, the ingestion of 30 mL of a 4% solution by an 89-year-old woman did not result in any GI injury.[40] An 80-year-old woman with dementia ingested 200 mL of a 5% chlorhexidine solution and subsequently aspirated.[65] She rapidly developed hypotension, acute respiratory distress, and coma, and died 12 hours after ingestion.

Intravenous administration of chlorhexidine is associated with hemolysis, although this may be caused by the hypotonicity of the injected solution,[23] and acute respiratory distress syndrome.[75] Inhalation of vaporized chlorhexidine is reported to cause methemoglobinemia as a consequence of the conversion of chlorhexidine to *p* -chloraniline.[173] In one patient, the rectal administration of 4% chlorhexidine resulted in acute colitis with ulcerations.[54]

Topical absorption of chlorhexidine is negligible. Contact dermatitis is reported in up to 8% of patients who received repetitive topical applications of chlorhexidine.[55] More ominously, anaphylactic reactions, including shock, are associated with dermal application.[5 , 121] Some of these cases of chlorhexidine-related anaphylaxis occurred during surgery, appearing 15â€“45 minutes after application of the antiseptic prep.[11] Eye exposure may result in corneal damage.[168]

Management

Treatment guidelines for chlorhexidine exposure are similar to those for other potential caustics. Patients with significant symptoms may require endoscopy, but the need for such extensive evaluation is quite uncommon.

Hydrogen Peroxide

Hydrogen peroxide, an oxidizer with weak antiseptic properties, has been used for many years as an antiseptic and a disinfectant. This oxidizer is generally available in two strengths: dilute hydrogen peroxide, with a concentration of 3â€“9% by weight (usually 3%), sold for home use, and concentrated hydrogen peroxide, with a concentration greater than 10%, used primarily for industrial purposes. Commercial-strength hydrogen peroxide is most commonly found as a 27.5â€“70% solution. Home uses for dilute hydrogen peroxide include ear cerumen removal, mouth gargle, vaginal douche, enema, and hair bleaching. Dilute hydrogen peroxide is also sometimes used as a veterinary emetic. Commercial uses of the more concentrated solutions include bleaching and cleansing textiles and wool, and producing foam rubber and rocket fuel. A 35% hydrogen peroxide solution is also available to the general public in health food stores and is sold as â€œhyperoxygenation therapyâ€• and as a health food additive to aerate health food drinks.[71] This potentially dangerous therapy is touted as a treatment for a variety of conditions, including AIDS and cancer.[72]

Hydrogen peroxide has two main mechanisms of toxicity: local tissue injury and gas formation. Toxicity from hydrogen peroxide may occur after ingestion or wound irrigation. The extent of local tissue injury and amount of gas formation is determined by the strength of the hydrogen peroxide. Dilute hydrogen peroxide is an irritant and concentrated hydrogen peroxide is a caustic. Gas

formation results when hydrogen peroxide interacts with tissue catalase, liberating molecular oxygen and water. At standard temperature and pressure, 1 mL of 3% hydrogen peroxide liberates 10 mL of oxygen, whereas 1 mL of the more concentrated 35% hydrogen peroxide liberates more than 100 mL of oxygen. Gas formation can result in life-threatening embolization. Gas embolization may be a result of dissection of gas under pressure into the tissues or of liberation of gas in the tissue or blood following absorption. The use of hydrogen peroxide in closed spaces, such as operative wounds, or its use under pressure during wound irrigation, increases the likelihood of embolization.

Clinical

Determining the concentration of hydrogen peroxide is important as the more toxic manifestations from ingestion are usually associated with the more concentrated formulations. The combination of local tissue injury and gas formation from the ingestion of concentrated hydrogen peroxide may cause GI disturbances, such as abdominal bloating, abdominal pain, vomiting, and hematemesis.[72, 102] Endoscopy may show esophageal edema and erythema and significant gastric mucosal erosions.[146] Airway compromise manifested by stridor, drooling, apnea, and radiographic evidence of subepiglottic narrowing may occur.[37]

Symptoms consistent with sudden oxygen embolization include rapid deterioration in mental status, cyanosis, respiratory failure, seizures, and ischemic ECG changes.[44] A 2-year-old boy died after ingesting 120â€“180 mL of 35% hydrogen peroxide.[25] Antemortem chest radiography showed gas in the right ventricle, mediastinum, and portal venous system. Portal vein gas is also a prominent feature in other cases.[71, 102] Arterialization of oxygen gas embolization may result in cerebral infarction.[150] Encephalopathy with cortical visual impairment[19] and bilateral hemispheric

infarctions detected by MRI imaging may occur after ingestion of concentrated hydrogen peroxide.[74]

Clinical sequelae from the ingestion of dilute hydrogen peroxide are usually much more benign.[37, 62] Nausea and vomiting are the most common symptoms.[37] A whitish discoloration may be noted in the oral cavity. Gastrointestinal injury is usually limited to superficial mucosal irritation, but multiple gastric and duodenal ulcers, accompanied by hematemesis, are reported.[62] Portal venous gas embolization may occur as a result of the ingestion of 3% hydrogen peroxide.[26, 136] Death from intravenous injection of 35% hydrogen peroxide is also reported.[92]

The use of 3% hydrogen peroxide for wound irrigation may result in significant complications. Extensive subcutaneous emphysema occurred after a dog bite to a human's face was irrigated under pressure with 60 mL of 3% hydrogen peroxide.[153] Systemic oxygen embolism, causing hypotension, cardiac ischemia, and coma, resulted from the intraoperative irrigation of an infected

herniorrhaphy wound.[10] Gas embolism, resulting in intestinal gangrene, was reported to occur following colonic lavage with 1% hydrogen peroxide during surgical treatment of meconium ileus.[149] Multiple cases of acute colitis are reported as a complication of administering 3% hydrogen peroxide enemas.[109] The use of 3% hydrogen peroxide as a mouth rinse is associated with the development of oral ulcerations.[138] Ophthalmic exposures may result in conjunctival injection, burning pain, and blurry vision.[37, 108]

A careful examination should be performed to detect any evidence of gas formation. A chest radiograph might reveal gas in the cardiac chambers, mediastinum, or pleural space. An abdominal radiograph might show gas in the GI tract or portal system and define the extent of bowel distension. MRI and CT scan might be useful for detecting brain lesions secondary to gas embolism.[4, 74]

Endoscopic evaluation might be necessary in patients who ingest concentrated hydrogen peroxide to determine the extent of mucosal injury.

Management

The treatment of patients with hydrogen peroxide ingestions depends, to a large degree, on whether the patient has ingested a diluted or concentrated solution. Those with ingestions of concentrated solutions require expeditious evaluation. Dilution with milk or water, although unstudied, is unlikely to be helpful. Nasogastric aspiration of hydrogen peroxide might be helpful if the patient presents immediately after ingestion. Induced emesis is contraindicated and activated charcoal offers no antidotal benefit. Patients with abdominal distension from gas formation should be treated with nasogastric suctioning. Those with clinical or radiographic evidence of gas in the heart should be placed in the Trendelenburg position to prevent gas from blocking the right ventricular outflow tract. Careful aspiration of intracardiac air through a central venous line may be attempted in patients in extremis.[25] Case reports suggest that hyperbaric therapy may be useful in cases of life-threatening gas embolization after hydrogen peroxide ingestion.[71, 102, 114, 174] Asymptomatic patients who unintentionally ingest small amounts of 3% hydrogen peroxide can be safely observed at home.

Iodine and Iodophors

Iodine usually refers to molecular iodine, also known as I_2, free iodine, and elemental iodine. This chemical is the active ingredient of iodine-based antiseptics. The use of ethanol as the solvent, such as tincture of iodine, allows substantially more concentrated forms of I_2 to be available. I_2 and tincture of iodine ingestions are much less common than in the past as a result of the change in antiseptic use from iodine to iodophor antiseptics.[38]

Iodophors have molecular iodine compounded to a high-molecular-weight carrier or to a solubilizing agent. Povidone-iodine (Betadine), a commonly used iodophor, consists of iodine linked to polyvinylpyrrolidone (povidone). Iodophors, which limit the release of molecular iodine and are generally less toxic, are the standard iodine-based antiseptic preparations. Iodophor preparations are formulated as solutions, ointments, foams, surgical scrubs, wound-packing gauze, and vaginal preparations. The most common preparation is a 10% povidone-iodine solution that contains 1% â€œavailableâ€• iodine (referring to all oxidizing iodine species), but only 0.001% free iodine (referring only to molecular iodine).[15, 55]

Iodine is one of the oldest topical antiseptics.[147] It is also used to disinfect medical equipment and drinking water. Iodine is an effective antiseptic against bacteria, viruses, protozoa, and fungi, and is used both prophylactically and therapeutically.[35] Iodine is cytotoxic and an oxidant. It is thought to work by binding amino and heterocyclic nitrogen groups, oxidizing sulfhydryl groups, and saturating double bonds. Iodine also iodinates tyrosine groups.[55]

There may be significant systemic absorption of iodine from topical iodine or iodophor preparations.[128] Markedly elevated iodine concentrations do occur in patients who receive topical iodophor treatments to areas of dermal breakdown, such as burn injuries.[90] Significant absorption occurs when iodophors are applied to the vagina, perianal fistulas, umbilical cords, and the skin of low-birth-weight neonates.[175] A fatality following intraoperative irrigation of a hip wound with povidone-iodine is reported.[32] In this case, the postmortem serum iodine concentration was 7000 Âµg/dL (normal: 5â€“8 Âµg/dL).

Clinical

Problems associated with the use of iodine include unpleasant odor, skin irritation, allergic reactions, clothes staining, and poor

stability. Ingestion of iodine may cause abdominal pain, vomiting, diarrhea, GI bleeding, delirium, hypovolemia, anuria, and circulatory collapse. Severe caustic injury of the GI tract may occur.

Reports of adverse consequences from iodophor ingestions are rare. In one case report, a 9-week-old infant died within 3 hours of receiving povidone-iodine by mouth.[87] In this unusual case, the child was administered 15 mL of povidone-iodine mixed with 135 mL of polyethylene glycol by nasogastric tube over a 3-hour period for the treatment of infantile colic. Postmortem examination showed an ulcerated and necrotic intestinal tract. A blood iodine concentration of 14,600 Âµg/dL was recorded. Significant toxicity from intentional ingestions of iodophors in adults is not documented.

Acidâ€“base disturbances are among the most significant abnormalities associated with iodine and iodophors. Metabolic acidosis occurred in several burn patients after receiving multiple applications of povidone-iodine ointment.[90 , 129] These patients had elevated serum iodine concentrations and normal lactate levels. The exact etiology of the acidosis remains unclear. Postulated mechanisms for the acidosis include the povidone-iodine itself (pH 2.43), bicarbonate consumption from the conversions of I_2 to NaI, and decreased renal elimination of H^+ as a consequence of iodine toxicity.[129] Metabolic acidosis associated with a high lactate level after iodine ingestion likely reflects tissue destruction.[35]

Electrolyte abnormalities also may occur following the absorption of iodine. A patient with decubitus ulcers who received prolonged wound care with povidone-iodineâ€“soaked gauze developed hypernatremia, hyperchloremia, metabolic acidosis, and renal failure.[35] The hyperchloremia was thought to be caused by a spurious elevation of measured chloride ions as a consequence of iodine's interference with the chloride assay. This interference

occurs on the Technicon STAT/ION autoanalyzer, but does not occur when the silver halide precipitation assay is used.[35] Spurious hyperchloremia from iodine (or iodide) may result in the calculation of a low or negative anion gap (Chap. 17).[20 , 42]

Other problems associated with topical absorption of iodine-containing preparations are hypothyroidism (particularly in neonates),[20 , 154] hyperthyroidism,[137 , 140] elevated liver enzymes, neutropenia, and hypoxemia.[35] Because of the lack of consistency between iodine concentrations and symptomatology, and because many of these patients had significant secondary medical problems that may have accounted for their symptoms, the exact relationship

between iodine absorption and the development of a specific clinical syndrome remains speculative. However, a clinical controlled trial that compared preterm infants exposed to either topical iodinated antiseptics or to chlorhexidine-containing antiseptics showed that the infants exposed to topical iodine-containing antiseptics were more likely to have higher thyrotropin levels and elevated urine iodine concentrations than was the chlorhexidine group.[96]

Contact dermatitis can result from repetitive applications of iodophors.[104] A dermal burn may result from the trapping of an iodophor solution under the body of a patient in a pooled dependent position or under a tourniquet.[99 , 117] Anaphylaxis after vaginal application of povidone-iodine solution is also reported.[1]

Management

The patient who ingests an iodine preparation requires expeditious evaluation, stabilization, and decontamination. Careful nasogastric aspiration and lavage may be performed to limit the caustic effect of the iodine if signs of perforation are absent. Irrigation with a starch solution will convert iodine to the much less toxic iodide

and, in the process, turn the gastric effluent dark blue-purple. This change in color may serve as a useful guide in determining when lavage can be terminated. If starch is not available, milk may be a useful alternative. Instillation of 100 mL of a solution of 1â€“3% sodium thiosulfate can also be used to convert any remaining iodine to iodide. Activated charcoal binds iodine and may be useful.[34] Early endoscopy may help assess the extent of the gastrointestinal injury.

Most patients with iodophor ingestion require only supportive management. The use of starch or sodium thiosulfate may be considered in symptomatic patients. Hemodialysis and continuous venovenous hemodiafiltration was used successfully to enhance elimination of iodine in patient with renal insufficiency who had become iodine toxic after undergoing continuous mediastinal irrigation with povidone-iodine.[83] The role of hemodialysis or continuous venovenous hemodiafiltration is unknown in patients with normal renal function and therefore not recommended.

Potassium Permanganate

Potassium permanganate ($KMnO_4$) is a violet water-soluble compound that is usually sold as crystals or tablets or as a 0.01% dilute solution.[80] Historically, it was used as an abortifacient, urethral irrigant, lavage fluid for alkaloid poisoning, and snakebite remedy. Currently, potassium permanganate is most often used in baths and wet bandages as a dermal antiseptic, particularly for patients with eczema.

Potassium permanganate is a strong oxidizing agent and poisoning may result in local and systemic toxicity.[156] Upon contact with mucous membranes, potassium permanganate reacts with water to form manganese dioxide, potassium hydroxide, and molecular oxygen. Local tissue injury is the result of contact with the nascent oxygen, as well as the caustic effect of potassium hydroxide. A brown-black staining of the tissues occurs from the manganese

dioxide. Systemic toxicity may occur from free radicals generated by absorbed permanganate ions.[182]

Clinical

Following ingestion, initial symptoms include nausea and vomiting. Laryngeal edema and ulceration of the mouth, esophagus, and, to a lesser extent, the stomach, may result from the caustic effects. Airway obstruction and fatal gastrointestinal perforation and hemorrhage may occur.[36 , 110 , 123] Esophageal strictures and pyloric stenosis are potential late complications.[85]

Although potassium permanganate is not well absorbed from the GI tract, systemic absorption may occur, resulting in life-threatening toxicity. Systemic effects include hepatotoxicity, renal damage, methemoglobinemia, hemolysis, hemorrhagic pancreatitis, airway obstruction, acute respiratory distress syndrome, disseminated intravascular coagulation, and cardiovascular collapse.[94 , 103 , 110 , 123] Elevation in blood or serum manganese concentration may also occur, confirming systemic absorption (normal levels: blood manganese 3.9â€“15.0 Âµg/L; serum manganese 0.9â€“2.9 Âµg/L).

Chronic ingestion of potassium permanganate may result in classic manganese poisoning (manganism) characterized by behavioral changes, hallucinations, and delayed onset of parkinsonianlike symptoms. A 66-year-old man who mistakenly ingested 10 g of potassium permanganate over a 4-week period (because of medication mislabeling) developed impaired concentration and autonomic and visual symptoms. He also developed abdominal pain, gastric ulceration, and alopecia. Serum manganese was elevated. Nine months later, the patient's neurologic examination displayed extrapyramidal signs consistent with parkinsonism (Chap. 19).[69]

Management

Because the consequential effects of potassium permanganate ingestion are a result of its liberation of strong alkalis, the initial treatment of such a patient should include assessment for evidence of airway compromise. Dilution with milk or water may be useful. Patients with symptoms consistent with caustic injury should undergo early endoscopy. Corticosteroid agents along with antibiotics may be warranted if laryngeal edema is present. Analysis of liver enzymes, BUN, creatinine, lipase, serum manganese, and methemoglobin concentrations should be performed when systemic toxicity is suspected. Methemoglobinemia, if clinically significant, should be treated with methylene blue. Dermal irrigation with dilute oxalic acid may be successful in removing cutaneous staining.[156] The administration of *N* -acetylcysteine (see Antidotes in Depth: *N* -Acetylcysteine) to increase reduced glutathione production, thereby limiting free radical-mediated oxidative injury in cases of systemic potassium permanganate poisoning, has been suggested, but clinical trials have not been performed.[182]

Other Antiseptics

Alcohols

Isopropanol and ethanol are commonly used as skin antiseptics. Sold as rubbing alcohol, the standard concentration for these solutions is usually 70%. Their antiseptic action is thought to be a result of their ability to coagulate proteins. Isopropanol is slightly more germicidal than ethanol.[55] These agents have limited efficacy against viruses or spores. Isopropanol tends to be more irritating than ethanol and may cause more pronounced central nervous system depression.[176] The greater toxicity of isopropanol has caused some emergency departments to switch rubbing alcohol formulations from isopropanol to ethanol (Chaps. 75 and 103).

Chlorine and Chlorophors

Chlorine, one of the first antiseptics, is still used in the treatment of the community water supply and in swimming pools. Chlorine

is a potent pulmonary irritant that can cause severe bronchospasm and acute lung injury. Chapter 119 further discusses chlorine.

Sodium hypochlorite, found in bleach (eg, Clorox) and Dakin solution, remains a commonly used disinfectant. First used in the late 1700s to bleach clothes, its usefulness arises from its oxidizing capability, measured as â€œavailable chlorine,â€• and its ability to release hypochlorous acid slowly. It is used to clean blood spills and to sterilize certain medical instruments. A 0.5% hypochlorite solution is sometimes recommended for dermal and soft-tissue wound decontamination after exposure to biologic and chemical warfare agents (Chaps. 126 and 127).[73] Toxicity from hypochlorite is mainly a result of its irritant effects. The ingestion of large amounts of household liquid bleach (5% sodium hypochlorite) on rare occasions can result in esophageal burns with subsequent stricture formation.[43] In a cat model of bleach ingestion, a high incidence of mucosal injury and stricture formation was noted.[178] However, the vast majority of household bleach ingestions in humans do not cause significant GI injuries.[130] Accordingly, endoscopic evaluation is usually not warranted when assessing most patients with household liquid bleach ingestions. The ingestion of a more concentrated â€œindustrial strengthâ€• bleach preparation (eg, 35% sodium hypochlorite) increases the likelihood of local tissue injury and should be managed accordingly (Chap. 100).

Mercurials

Both inorganic mercurials, such as mercuric bichloride, and organic mercurials, such as merbromin (mercurochrome) and thimerosal

(merthiolate), which contains 49% mercury, were used in the past as topical antiseptic agents. The usefulness of mercurials is significantly limited because of their relatively weak bacteriostatic properties and the many problems associated with mercury toxicity (Chap. 92). Repeated application of topical mercurials may result in significant absorption and systemic toxicity.[115 , 141] The use of high-dose hepatitis B immunoglobulin (HBIg) may cause mercury toxicity because of the use of thimerosal as a preservative in the HBIg preparation.[101] In one case, a 44-year-old male patient received 250 mL of HBIg (containing about 30 mg of thimerosal) over 9 days following liver transplantation.[150] He developed speech difficulties, tremor, and chorea. His whole blood mercury concentration was 104 Âµg/L (normal >10 Âµg/L). Increased mercury concentrations in both preterm and term infants, following immunizations with thimerosal-containing hepatitis B vaccine, have also generated much concern and led to the call to reduce or eliminate the mercury content of vaccines (Chaps. 53 and 92).[52 , 158]

Disinfectants

Formaldehyde

Formaldehyde is a water-soluble, highly reactive gas at room temperature. Formalin consists of an aqueous solution of formaldehyde, usually containing approximately 37% formaldehyde and 12â€“15% methanol. Formaldehyde is irritating to the upper airways, and its odor is readily detectable at low concentrations. Lethality in adults begins to occur following ingestion of 30â€“60 mL of formalin.[39]

Formerly used as a disinfectant and fumigant, its role as a disinfectant is now largely confined to the disinfection of hemodialysis machines. Nonetheless, formaldehyde has many other applications. Healthcare workers are probably most familiar

with the use of formaldehyde as a tissue fixative and embalming agent.

Exposure to formaldehyde, a potent caustic, may result in both local and systemic symptoms, causing coagulation necrosis, protein precipitation, and tissue fixation. Ingestions of formalin may result in significant gastric injury, including hemorrhage, diffuse necrosis, perforation, and stricture.[3,9] The most extensive damage appears in the stomach, with only occasional involvement of the small intestine and colon. Chemical fixation of the stomach may occur. Esophageal involvement is not very prominent, and, if present, is usually limited to its distal segment.

The most striking and rapid systemic manifestation of formaldehyde poisoning is metabolic acidosis, resulting both from tissue injury and from the conversion of formaldehyde to formic acid. The patient may present with profound acidemia, accompanied by a large anion gap metabolic acidosis. Although the methanol component of the formalin solution is readily absorbed and has resulted in methanol levels of 40 mg/dL,[18,39] the rapid metabolism of formaldehyde to formic acid appears to be responsible for much of the acidosis (Chap. 103). Blindness as a consequence of the accumulation of formate, a retinal toxin, is not reported.

Clinical

Patients presenting after formaldehyde ingestions complain of the rapid onset of severe abdominal pain, which may be accompanied by vomiting and diarrhea. Altered mental status and coma usually follow rapidly. Physical examination may demonstrate epigastric tenderness, hematemesis, cyanosis, hypotension, and tachypnea. Hypotension may be profound with decreased myocardial contractility, as well as hypovolemic shock, contributing to the cardiovascular instability.[64,167] Early endoscopic findings include ulceration, necrosis, perforation, and hemorrhage of the stomach,

with infrequent esophageal involvement. Chemical pneumonitis occurs after significant inhalational exposure.[132] Intravascular hemolysis is described in hemodialysis patients whose dialysis equipment contained residual formaldehyde after undergoing routine cleaning.[124, 135]

Occupational and environmental exposure to formaldehyde receives considerable attention. In particular, there is concern over the potential off-gassing of formaldehyde from the widely used urea formaldehyde building insulation and particle boards.[122] Headache, nausea, skin rash, sore throat, nasal congestion, and eye irritation are associated with the use of these polymers.[31] Formaldehyde, at concentrations as low as 1 ppm, may cause significant irritation to mucous membranes of the upper respiratory tract and conjunctivae.[68, 100] Formaldehyde is also a potential sensitizer for immune-mediated reversible bronchospasm.[61] The exact immunologic mechanism is not yet elucidated, although it is likely that formaldehyde acts as a hapten. In addition, formaldehyde is thought to be a dermal sensitizer.[155]

Both animal and human data suggest that formaldehyde exposure is associated with an increased incidence of nasopharyngeal carcinoma.[2, 57, 127, 142] Although its role in the pathogenesis of cancer in humans is the subject of much debate,[28, 105] in 2004 the International Agency for Research on Cancer (IARC) reclassified formaldehyde from a Group 2 *probable* to a Group 1 *known* carcinogen.

Management

The immediate management of a patient who has ingested formaldehyde includes dilution with water. Although such an approach may be useful in reducing the caustic effect,

strong evidence for a beneficial result is lacking. Careful gastric

aspiration with a small-bore nasogastric tube may limit systemic absorption. The role of activated charcoal is not studied and it probably should not be used if endoscopy is considered likely. Significant acidemia should be treated with sodium bicarbonate and folinic acid (Chap. 103). Immediate hemodialysis may remove the accumulating formic acid as well as the parent molecules, formaldehyde and methanol.[39] Independent treatment for methanol toxicity may be indicated. Early endoscopy is recommended for all patients with significant GI symptoms to assess the degree of burn injury. Surgical intervention may be required for those with severe burns. Emergent gastrectomy, as well as late surgical intervention to relieve formaldehyde-induced gastric outlet obstruction, is infrequently required.[58 , 86]

Phenol

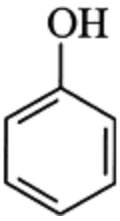


Figure. No Caption Available.

Phenol, also known as carbolic acid, is one of the oldest antiseptic agents. It is rarely used as an antiseptic today, secondary to its toxicity, and has been replaced by the many phenolic derivatives. Currently, phenol is used as a disinfectant, chemical intermediary, and nail cauterizer. The last application uses a highly concentrated 89% solution. Phenol is also a component (0.1â€“4.5%) of various lotions, ointments, gels, gargles, lozenges, and throat sprays.[55] Campho-Phenique and Chloraseptic contain 4.7% and 1.4% phenol, respectively. Although many cases of phenol poisoning were reported in the past, acute oral overdoses of phenol-containing solutions are relatively uncommon today.[49]

Phenol acts as a caustic causing cell wall disruption, protein denaturation, and coagulation necrosis. It also acts a central nervous system stimulant. Intentional ingestion of concentrated phenol, ingestion of phenol-containing water, occupational exposure to aerosolized phenol, dermal contact, and parenteral administration may all result in symptomatic phenol poisoning. Phenol demonstrates excellent skin penetrance.[13] Severe dermal burns from phenol have resulted in systemic toxicity, even death within minutes to hours.[13, 93] Parenteral administration of phenol has also resulted in death.[97] The lethal dose may be as little as 1 g.[70]

Clinical

Clinical manifestations can be divided into local and systemic symptoms. Systemic symptoms from gastrointestinal (GI) or dermal absorption of phenol are usually more dangerous than the local effects and can result in significant morbidity and mortality. Manifestations of systemic toxicity include central nervous system (CNS) and cardiac symptoms. CNS effects include central stimulation, seizures, lethargy, and coma.[51] In a study of patients who had ingested Creolin (26% phenol), CNS symptoms predominated.[157] Of the 52 patients who were evaluated at the hospital, 9 developed lethargy and 2 developed coma. Seizures were not reported. Cardiac symptoms from phenol include tachycardia, bradycardia, and hypotension.[51] Excessive dermal absorption of phenol during chemical peeling procedures is associated with dysrhythmias.[177]

Other systemic symptoms that may develop include pulmonary disturbances, hypothermia, metabolic acidosis, methemoglobinemia, and rabbit syndrome.[70, 81] Rabbit syndrome is most commonly observed as a distinctive extrapyramidal effect from antipsychotic drugs and is characterized by fine rapid repetitive movements of the perioral musculature resembling a

rabbit's chewing movements. Increased acetylcholine release and a relative dopaminergic hypofunction may explain the development of rabbit syndrome after phenol exposure.[81]

Local toxicity to the GI tract from the ingestion of phenol may result in nausea, vomiting, bloody diarrhea, and severe abdominal pain. Serious GI burns are uncommon, and strictures are rare. White patches in the oral cavity may be detected. In the Creolin study cited above, only 1 of 17 patients who underwent endoscopy had a significant esophageal burn.[157] Ingestions of phenol-contaminated water are associated with the development of nausea, vomiting, diarrhea, burning sensation in the mouth, mouth sores, and dark urine.[6, 79] Dermal exposures to phenol usually result in a light-brown staining of the skin.

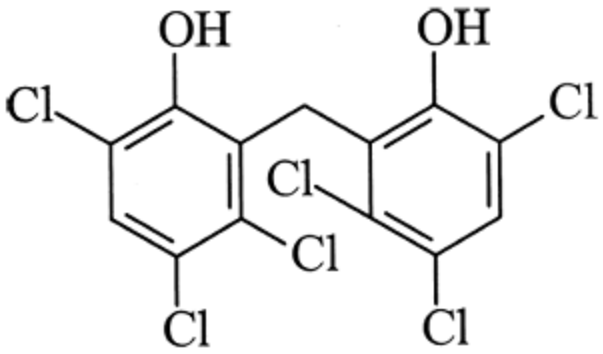
Markedly elevated blood and urine levels of phenol may be detected after ingestion, or dermal absorption, of phenol and phenol-containing compounds (eg, Campho-Phenique).[13, 70, 88]

Management

A variety of treatments have been suggested for dermal and gastric decontamination of phenol. A study employing a rat model showed that cutaneous decontamination with a low-molecular-weight polyethylene glycol solution decreased mortality, systemic effects, and dermal burns.[17] Although this study suggested that polyethylene glycol (PEG) was superior to water as a decontamination agent, a subsequent study using a swine model could not demonstrate a difference between these two therapies.[134] In another swine model, PEG 400 and 70% isopropanol were both superior to water washes and equally effective in decreasing dermal burn.[112] Given the lack of definitive efficacy data, either low-molecular-weight PEG, for example, PEG 300 or 400 (not to be confused with high-molecular-weight PEG that is used for whole-bowel irrigation), or water is currently recommended for dermal irrigation and careful gastric

decontamination. Isopropanol could also be considered as another treatment for dermal decontamination. Endoscopic evaluation, as needed to determine the extent of GI injury, and good supportive care are also recommended.

Substituted Phenols and Other Related Compounds



Hexachlorophene

Hexachlorophene (pHisoHex), a trichlorinated *bis* -phenol, is one of the best known substituted phenols. Hexachlorophene, considered generally less tissue-toxic than phenol, was formerly used extensively as a disinfectant in hospitals. During the 1970s, an association was observed between repetitive whole-body washing of premature infants with 3% hexachlorophene and the development of vacuolar encephalopathy and cerebral edema.[106] There were also multiple reports of significant neurologic toxicity and death in children who became toxic after ingesting hexachlorophene.[63] In addition, fatalities

also occurred after patients absorbed substantial amounts of hexachlorophene during the treatment of burn injuries.[24] The use of hexachlorophene has declined significantly.

Clinical

pHisoDerm, contains sodium octylphenoxyethoxyethyl ether sulfonate and lanolin, and is a safe antiseptic. Irritative effects (nausea, vomiting, diarrhea) would be the main adverse effects with oral ingestions.

In a study of poisoning admissions to Hong Kong hospitals, the ingestion of Dettol liquid, a household disinfectant that contains 4.8% chloroxylenol, 9% pine oil, and 12% isopropanol, accounted for 10% of admissions.[22] Aspiration (perhaps, in part, because of the pine oil) occurred in 8% of these patients, resulting in upper airway obstruction, pneumonia, and acute respiratory distress syndrome. More common symptoms included nausea, vomiting, sore mouth, sore throat, drowsiness, abdominal pain, and fever. Dermal contact with Dettol may result in full-thickness chemical burns.[33]

Cresol, a mixture of three isomers of methylphenol, has better germicidal activity than phenol and is a commonly used disinfectant. Exposure to concentrated cresol may result in significant local tissue injury, hemolysis, renal injury, hepatic injury, and CNS and respiratory depression.[33,56,82,181] Phenol concentrations, as well as cresol concentrations, serve as markers of exposure.[181]

Management

Treatment is mainly supportive.

Quaternary Ammonium Compounds

Quaternary ammonium compounds are a type of cationic surfactant (surface-active agent); they are used as disinfectants, detergents, and sanitizers. Chemically, the quaternary ammonium compounds are synthetic derivatives of ammonium chloride, and structurally similar to other quaternary ammonium derivatives,

such as cholinesterase inhibitors and neuromuscular blockers. Other cationic surfactants include the pyridinium compounds and the quinolinium compounds. Benzalkonium chloride (Zephiran) was one of the most commonly employed quaternary ammonium compounds in the past. Many newer quaternary ammonium compounds have supplanted its use. However, nebulized solutions used for the treatment of asthma, including albuterol and ipratropium bromide, may contain small amounts of benzalkonium chloride. Newer quaternary ammonium compounds are currently used as hospital disinfectants, including Coverage 256, which contains 6% alkyl dimethyl ammonium chloride and 5% octyldecyldimethyl ammonium chloride, and Render, which contains 5% alkyl dimethyl benzyl ammonium chloride.

Clinical

Quaternary ammonium compounds are less toxic than phenol or formaldehyde. Most of the infrequent complications that are described result from ingestions of benzalkonium chloride. Complications of these ingestions include burns to the mouth and esophagus, CNS depression, elevated liver enzymes, metabolic acidosis, and hypotension.[66, 172, 179] Paralysis is also occasionally described as a complication of these ingestions and is presumably a result of cholinesterase inhibition at the neuromuscular junction.[49] Chronic inhalational exposure is associated with occupational asthma.[14] Topical use of the quaternary ammonium compounds can cause contact dermatitis.[151] Few data are available on the toxicity of the newer quaternary ammonium compounds.

Ingestions of other cationic surface-active agents, such as the pyridinium agent cetrimonium bromide (Cetrimide), are associated with caustic burns to the mouth, lips, and tongue.[113] Peritoneal irrigation with cetrimonium bromide can produce metabolic abnormalities, hypotension, and methemoglobinemia.[7, 111]

Intravenous administration of cetrimide produced cardiac arrest, hemolysis, and muscle paralysis.[45]

Management

Treatment recommendations following the ingestion of the quaternary ammonium compounds and other cationic surface-active agents are similar to those for other potentially caustic ingestions. Emergency department evaluation should be considered for all patients who ingest more than a taste of a dilute (less than 1%) solution. Therapy is mainly supportive. Endoscopy may be warranted if symptoms suggest the possibility of a burn injury.

Sterilants

Ethylene Oxide

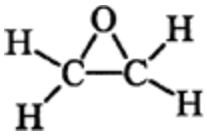


Figure. No Caption Available.

Ethylene oxide is a gas that is commonly used to sterilize heat-sensitive material in healthcare facilities. Unlike antiseptics and disinfectants, which generally do not exhibit full sporicidal activity, sterilants, such as ethylene oxide, inactivate all organisms. Ethylene oxide is also used in the synthesis of many chemicals, including ethylene glycol, surfactants, rocket propellants, and petroleum demulsifiers, and has been used as a pesticide fumigant. Ethylene oxide has a cyclic ester structure that acts as an alkylating agent, reacting with most cellular components, including DNA and RNA.

Medical attention regarding ethylene oxide toxicity has centered on its mutagenic and possible carcinogenic effects.[89] Approximately 270,000 workers (including 96,000 hospital workers) in the United States are at risk for occupational exposure to ethylene oxide.[161] Retrospective studies suggest a possible excess incidence of leukemia and gastric cancer in ethylene oxide-exposed workers.[67, 161] These studies are inconclusive, and the carcinogenicity of ethylene oxide remains subject to debate. It is also suggested that an increased incidence of spontaneous abortions may be associated with occupational exposure to ethylene oxide.[60]

Clinical

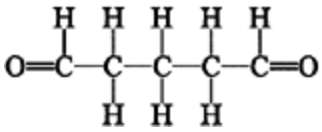
The acute toxicity of ethylene oxide is mainly the result of its irritant effects. Conjunctival, upper respiratory tract, GI, and dermal irritation may occur. Dermal burns from acute exposure to ethylene oxide are reported. Acute exposure to a broken ethylene oxide ampule by a 43-year-old recovery room nurse resulted in nausea, light-headedness, malaise, syncope, and recurrent seizures.[145] There were no long-term complications. In another case of acute exposure, coma was followed by an irreversible parkinsonism.[8]

Chronic exposure to high levels of ethylene oxide may cause mild cognitive impairment and motor and sensory neuropathies.[50, 16, 120] The risk of cancer with occupational exposure is low.[27, 160]

Management

Treatment for patients with ethylene oxide exposure is supportive.

Glutaraldehyde



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Glutaraldehyde is a liquid solution used in the cold sterilization of nonautoclavable endoscopic, surgical, and dental equipment. It is also employed as a tissue fixative, embalming fluid, preservative, and tanning agent, in radiographic solutions, and in the treatment of warts.[47] Glutaraldehyde is a dialdehyde with two active carbonyl groups that is less volatile than formaldehyde. It kills all microorganisms, including viruses and spores. The germicidal ability of glutaraldehyde results from the alkylation of sulfhydryl, hydroxyl, carboxyl, and amino groups, within microbes interfering with RNA, DNA, and protein synthesis.[144] It is prepared as a 2% alkaline solution in 70% isopropanol (Cidex). Healthcare workers may be exposed to glutaraldehyde vapors when equipment is processed in poorly ventilated areas, or in open immersion baths or after spills. Under these circumstances, the evaporation of glutaraldehyde may result in the increase in ambient air levels that may easily exceed recommended limits. Approximately 35,000 workers are occupationally exposed to glutaraldehyde.[131] Patients may be exposed when diagnostic instruments are inadequately rinsed following cold sterilization with glutaraldehyde.

Clinical

Clinical signs and symptoms are thought to be comparable to those of formaldehyde exposure although human toxicity data is limited. Animal studies show that glutaraldehyde's inhalational and dermal toxicity is comparable to formaldehyde at equivalent doses.[166]

Glutaraldehyde is a mucosal irritant. Coryza, epistaxis, headache, asthma, chest tightness, palpitations, tachycardia, and nausea are all associated with glutaraldehyde vapor exposure.[12 , 29 , 118 , 126]

Contact dermatitis and ocular inflammation may also occur.[30, 148] Proctitis has been reported following the use of endoscopes contaminated with residual glutaraldehyde solution.[53] The IARC has not ranked the carcinogenic potential of glutaraldehyde.

Management

Treatment recommendations are similar to those for patients with formaldehyde exposure. Prompt removal from the exposure is essential. Copious irrigation with water provides adequate dermal decontamination. Severe inhalational exposures may require hospital admission for observation, supportive care, and treatment of bronchospasm.

Other Products

Boric Acid

Boric acid is an odorless, transparent crystal, although it is most commonly available as a finely ground white powder. It is also commonly found as a 2.5â€“5% aqueous solution. Boric acid (H_3BO_3), prepared from borax (sodium borate; $Na_2B_4O_7 Â·10 H_2O$), was first used as an antiseptic agent by Lister in the late 19th century. Although used extensively over the years for antisepsis and irrigation, boric acid is only weakly bacteriostatic. As a result of its germicidal limitations and its inherent toxicity, boric acid is nearly obsolete in modern antiseptic therapy. Nonetheless, it continues to be used as an antimicrobial to treat such conditions as vulvovaginal candidiasis.[133] Boric acid is also employed in the treatment of cockroach infestation and as a soap, contact lens solution, toothpaste, and food preservative.

Boric acid is readily absorbed through the GI tract, wounds, abraded skin, and serous cavities. Absorption does not occur through intact skin. Boric acid is predominantly eliminated

unchanged by the kidney. Small amounts are also excreted into sweat, saliva, and feces.[46] Boric acid is concentrated in the brain and liver.

The exact mechanism of action of boric acid's toxicity remains unclear. Although it is an inorganic acid, it does not behave as a caustic. Local effects are limited to tissue irritation.

Over the years, boric acid has developed a reputation as an exceptionally potent toxin. This reputation was derived in great part from a series of reports involving neonatal exposures to boric acid resulting in high morbidity and mortality. Life-threatening toxicity resulted from the repetitive topical application of boric acid for the treatment of diaper rash or the use of infant formulas unintentionally contaminated with boric acid.[46 , 180] Fatality rates greater than 50% were reported in some series.[180] Although infants appear to be the most sensitive to the toxic effects of boric acid, many cases of significant adult toxicity are also reported. These cases date predominantly from the time when boric acid was widely used as an irrigant. Routes of exposure to boric acid, resulting in fatalities, include wound irrigation, pleural irrigation, rectal washing, bladder irrigation, and vaginal packing.[171]

Clinical

Classic boric acid poisoning usually involves multiple exposures over a period of days. Gastrointestinal, dermal, CNS, and renal manifestations predominate. The initial symptomsâ€”nausea, vomiting, diarrhea, and occasionally crampy abdominal painâ€”may be confused with an acute gastroenteritis. At times, the emesis and diarrhea are greenish blue.[180] Following the onset of GI symptoms, the majority of patients develop a characteristic intense generalized erythroderma.[180] This rash, described as producing a â€œboiled lobsterâ€• appearance, may appear indistinguishable from toxic epidermal necrolysis or staphylococcal scalded skin syndrome in the neonate.[143] The rash may be

especially noticeable on the palms, soles, and buttocks.[46] Typically, extensive desquamation takes place within 1â€“2 days. On occasion, prominent mucous membrane involvement of the oral cavity and conjunctivae is also apparent.[180] At about the time of the development of the erythroderma, patients, particularly young infants, may develop prominent signs of CNS irritability, resembling meningeal irritation. Seizures, delirium, and coma can occur.[46] Renal injury is common, both a result of the renal elimination of this compound and prerenal azotemia from GI losses.[46] Other complications of boric acid poisoning include hepatic injury, hyperthermia, and cardiovascular collapse. The abandonment of boric acid as an irrigant and particularly its removal from the nursery setting have led to a marked decrease in the incidence of significant boric acid poisoning.

Two retrospective studies on boric acid ingestions suggest that a single acute ingestion of boric acid is generally quite benign.[95, 98] In these studies, 79â€“88% of patients remained asymptomatic. Symptoms, when present, primarily consist of GI irritative symptoms, such as nausea and vomiting. None of the 1184 patients in these two studies manifested the generalized erythroderma so commonly described in previous reports. Central nervous system manifestations of acute overdose were infrequent and limited to occasional lethargy and headache. Renal toxicity did not occur following single acute ingestions.

Several reports suggest, however, that significant toxicity from massive acute ingestion of boric acid can occur. Fatality resulted from a single ingestion of 2 cups (280 g) of boric acid crystals by a 45-year-old man.[139] Symptoms on presentation (2 days after ingestion) included nausea, vomiting, green diarrhea, lethargy, hypotension, renal failure, and a prominent â€œboiled lobsterâ€• rash on his trunk and extremities. In another case, the ingestion of 30 g of boric acid by a 77-year-old man resulted in similar symptoms and death 63 hours postingestion, despite

hemodialysis.[76] The diagnosis of boric acid poisoning can be confirmed with the measurement of blood or serum boric acid levels (normal = 1.4 nmol/mL), but this test is not routinely available.

Long-term chronic exposure to boric acid results in alopecia in adults and seizures in children.[125] A 32-year-old woman who chronically ingested mouthwash containing boric acid over a 7-month period developed progressive hair loss.[165, 166] The chronic application of a borax and honey mixture to pacifiers resulted in the development of recurrent seizures in 9 infants, which resolved after the mixture was withheld.[48, 125]

Management

Treatment of boric acid toxicity is mainly supportive. Activated charcoal is not recommended because of its relatively poor adsorptive capacity for boric acid.[34] In cases of massive oral overdose or renal failure, hemodialysis, or perhaps exchange transfusion in infants, may be helpful in shortening the half-life of boric acid.[98, 169, 180] In patients with normal renal function, forced diuresis enhances renal elimination.[170]

Chlorates

Sodium chlorate is a strong oxidizing agent. At one time, the chlorate salts, sodium chlorate and potassium chlorate, were used as medicinal agents to treat inflammatory and ulcerative lesions of the oral cavity and could be found in various mouthwash, toothpaste, and gargle preparations.[159] Although their use as local antiseptics is obsolete, chlorates are used as herbicides and in the manufacture of matches, explosives, and dyestuffs.[77] More recent cases of chlorate poisoning resulted from the ingestion of the sodium chlorate-containing weed killers, or dispensing errors that confused sodium chlorate with sodium sulfate or sodium chloride.[77] Sodium chlorate in the form of white crystals has also

been mistaken for table sugar.[59] A case of significant toxicity from the inhalation of atomized chlorates is also reported.[77]

Sodium chlorate is rapidly absorbed from the GI tract and eliminated predominantly unchanged from the kidneys.[78] Its systemic effects are chiefly hematologic and renal. Chlorate's major mechanism of toxicity is its ability to oxidize hemoglobin and increase red blood cell membrane rigidity.[152] Consequently, significant methemoglobinemia and hemolytic anemia may result. Chlorates may also be directly toxic to the proximal renal tubule.[91] The hemolytic anemia and the resultant hemoglobinuria may secondarily cause disseminated intravascular coagulation and potentiate renal toxicity. The worsening renal function is especially problematic because of its adverse effect on chlorate elimination. The methemoglobinemia may be severe and cause significant hypoxic stress. Methemoglobinemia may occur prior to or after the development of hemolytic anemia.[119 , 162] Chlorates may also act locally as a GI irritant, and cause mild CNS depression after absorption.[49]

Clinical

Clinical signs and symptoms of chlorate poisoning usually begin 1â€“4 hours after ingestion.[84] The earliest symptoms are GI, including nausea, vomiting, diarrhea, and crampy abdominal pain. Subsequently, the patient may exhibit cyanosis from the methemoglobinemia and black-brown urine from the hemoglobinuria. Obtundation and anuria may ensue. Laboratory studies may show methemoglobinemia, anemia, Heinz bodies, ghost cells, fragmented spherocytes, metabolic acidosis, decreased platelet count, and abnormal coagulation.[41] Hyperkalemia may be particularly problematic if the patient ingests potassium chlorate preparations.[116] In a recent case of chlorate poisoning from the ingestion of 120 potassium chlorate-containing matchsticks, an MRI revealed symmetric abnormal signal intensity within the deep

gray matter and medial temporal lobes.[116] This finding can be explained by the basal ganglia's increased vulnerability to oxygen deprivation. Followup MRI 2 months later was normal.

Management

Treatment of a patient with a significant chlorate ingestion should include orogastric lavage and the use of activated charcoal.[59] It has been suggested that administration of sodium thiosulfate may inactivate the chlorate ion by reducing it to the chloride ion,[59] but an in vitro study did not confirm this hypothesis.[164] Although methylene blue is used in the treatment of symptomatic methemoglobinemia, its efficacy in the treatment of chlorate-induced methemoglobinemia may be limited, as compared to its efficacy in the treatment of other oxidant-induced methemoglobinemias.[119 , 163] This may be a consequence of the inactivation by chlorates of glucose-6-phosphate dehydrogenase, an enzyme that is required for methylene blue to effectively reduce methemoglobin.[152] Exchange transfusion, peritoneal dialysis, and hemodialysis have all been advocated in the treatment of patients with severe chlorate poisoning.[119 , 162] Because the chlorate ion is easily dialyzable, hemodialysis is capable of removing this xenobiotic as well as treating any concomitant renal failure that may have developed.[77 , 84 , 91]

Summary

A chemically diverse group of antiseptic, disinfectant, and sterilant agents exist. Many of the more toxic xenobioticsâ€”such as iodine, phenol, and chloratesâ€”are no longer commonly used as cleansing agents but may still be available in some settings. Formaldehyde exposures, although also uncommon, can also cause significant problems. Frequently employed antiseptics, such as chlorhexidine, pHisoDerm, and many of the currently used quaternary ammonium compounds, have a relatively limited toxicity. Ingestions of the

iodophors do not usually cause significant toxicity, but absorption through other routes may produce significant adverse effects. Ingestions of hydrogen peroxide, particularly the more concentrated formulations, may result in life-threatening injuries.

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Chapter 99
Camphor and Moth Repellents

Edwin K. Kuffner

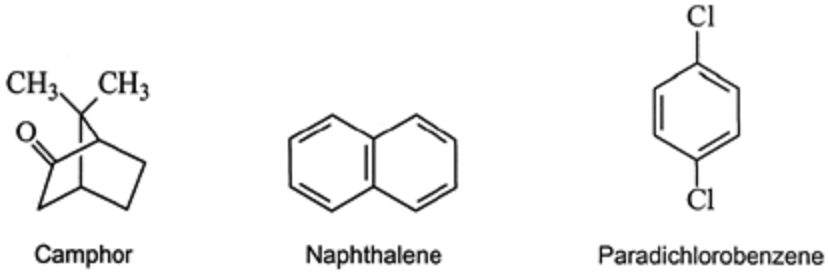

Figure. No Caption Available.

A healthy 3-year-old boy was brought, to the emergency department (ED) with approximately 24 hours of fever as high as 101Â°F (38.3Â°C), nonbloody vomiting, dark urine, yellow eyes, and lethargy. No rhinorrhea, cough, difficulty breathing, diarrhea, or bleeding was reported. He was not taking any medications, and other family members were well. His family history was negative for blood dyscrasias. No history of a toxic exposure was provided.

There was no history of toxic exposure. Physical examination revealed

a pale, jaundiced, and lethargic child. His vital signs were: blood pressure, 72/42 mm Hg; pulse, 138 beats/min; respiratory rate, 44 breaths/min; rectal temperature, 101.5Â°F (38.6Â°C); and an O_2 saturation of 100% on supplemental oxygen. A rapid-bedside blood glucose analysis was 92 mg/dL. There was no evidence of trauma. Ocular examination revealed 4-mm, equally reactive pupils, icteric sclerae, and pale conjunctivae. Mucous membranes were dry. Cardiopulmonary and abdominal examination were normal except for tachycardia and tachypnea. The stool tested negative for occult blood. Strength, sensation, and reflexes were normal.

Initial laboratory evaluation included a complete blood count: white blood cell count of 16,800 cells/mm^3 with 59% neutrophils, 34% lymphocytes, 3% monocytes and 3% eosinophils, a hemoglobin of 10.2 g/dL, a hematocrit of 33% and a platelet count of 314,000 cells/mm^3 . The reticulocyte count was 6.8%. The peripheral smear revealed spherocytosis, anisocytosis, microspherocytosis, Heinz bodies, and red blood cell fragmentation. Methemoglobin level was 2.3%. Both direct and indirect Coombs tests were negative. The serum electrolytes were normal. The total bilirubin was 19 mg/dL with a direct bilirubin of 1.2 mg/dL. Hepatic aminotransferases and alkaline phosphatase were normal. Serum acetaminophen was undetectable. The urine was brown with 0â€“3 red blood cells and, 0â€“3 white blood cells/high power field, and positive for urobilinogen and hemoglobin. A chest radiograph was clear. Cerebrospinal fluid analysis was normal.

The child was treated with intravenous fluids and ceftriaxone and admitted to the intensive care unit. Over the first 2 days of hospitalization, the white blood cell count dropped to 8,800 cells/mm^3 , the hemoglobin to 5.2 g/dL, and the hematocrit to 17%. After 2 units of packed red blood cells were transfused, the hemoglobin increased to 10.5 g/dL and the hematocrit increased to 34%. Blood, urine, and cerebrospinal fluid cultures ultimately showed no growth. The boy's bilirubin gradually decreased over the first week. Both his red blood cell count and his bilirubin normalized after 3 weeks.

A child care provider eventually admitted that the boy was found playing with mothballs 2â€“3 days prior to the onset of illness. The number of mothballs, if any, that the child may have ingested could not be determined. After the additional history was obtained, a urine specimen obtained on the day of the boy's presentation was analyzed and naphthol, a metabolite of naphthalene, was detected, supporting the diagnosis of naphthalene-induced hemolysis. Glucose-6-phosphate dehydrogenase activity, tested 3 months after the exposure, was normal.

Many different products have historically been used as moth repellents. In the United States, paradichlorobenzene has largely replaced both camphor and naphthalene as the most common active component of moth repellent and moth flakes because of its decreased toxicity. However, because paradichlorobenzene is widely available and because life-threatening camphor and naphthalene

toxicity still occur, all of these xenobiotics need to be considered in evaluating possible exposure moth repellent.

Camphor

History and Epidemiology

Camphor (2-bormanone, 2-camphonone), a cyclic ketone of the terpene group, is an essential oil distilled from the bark of the camphor tree, *Cinnamomum camphora.* Today, most camphor is synthesized from the hydrocarbon pinene, a derivative of turpentine oil. Camphor has been used as an aphrodisiac, contraceptive, abortifacient, suppressor of lactation, analeptic, cardiac stimulant, antiseptic, cold remedy, muscle liniment, and drug of abuse.[23 , 28 , 33 , 38 , 50]

Camphorated oil and camphorated spirits contain varying concentrations of camphor. Historically, most camphorated oil was

20% weight (of solute) per weight (of solvent) (w/w) camphor with cottonseed oil, and most camphorated spirits contained 10% w/w camphor with isopropyl alcohol. Toxicity and death following ingestion of camphorated oil, which was confused with castor oil and cod liver oil, prompted the FDA to ban the nonprescription sale of camphorated oil in the United States in 1983.[3,17,33,53,69] Today, based on the 1983 FDA ruling, nonprescription camphor-containing products may not have greater than an 11% concentration of camphor. Camphorated oil is still used as an herbal remedy and muscle liniment, and products containing greater than 11% camphor can still be purchased outside of the United States.[66]

Common camphor-containing products include cold sore ointments (usually <1% camphor), muscle liniments, rubefacients (usually 4â€“7% camphor), and camphor spirits (usually 10% camphor). Paregoric, camphorated tincture of opium, contains a combination of anhydrous morphine (0.4 mg/mL), alcohol (46%), and benzoic acid (4 mg/mL) but only a small amount of camphor.[36] Camphor for industrial use can be purchased legally in the United States and contains up to 100% camphor. Occupational exposures to camphor occur during the manufacture of plastic, celluloid, lacquer, varnish, explosives, embalming fluids, and numerous pharmaceuticals and cosmetics.[29]

Although products containing lower concentrations of camphor are implicitly safer, life-threatening toxicity and death still result, usually from misuse or intentional overdose. Most reported cases of acute camphor poisoning are unintentional ingestions of camphor-containing liquids mistaken for other medications.[3,33,52,67] According to data obtained by the American Association of Poison Control Centers (AAPCC), between 1998 and 2003 there were fewer than 50 reports of â€œmajorâ€• toxicity secondary to camphor. Over the past 20 years, according to the AAPCC, only 5 reported deaths were attributable to camphor, all in adults, at least 2 of which occurred in the setting of an intentional suicidal overdose. Chapter 130 contains complete references and discussion of the AAPCC data.

Pharmacology

Camphor is a colorless glassy solid. Camphor's pharmacologic activity is not well studied and its mechanism of action remains unclear. It is unlikely that camphor has therapeutic benefit as an expectorant or an antiinfective agent. Camphor may provide some local analgesic and antipruritic effects, but much safer drugs are available for these indications. No therapeutic benefit of camphor has been proven in any well-controlled clinical trials.

Pharmacokinetics and Toxicokinetics

There are limited data on the pharmacokinetics and toxicokinetics of camphor. Toxicity is reported following ingestion, dermal application, inhalation, intranasal instillation, intraperitoneal administration, and transplacental transfer.[11, 54, 57, 63, 64, 71] Camphor from liquid preparations is rapidly absorbed from the gastrointestinal tract and camphor can be detected in the blood within 15â€“20 minutes postingestion.[54] Camphor is highly lipid soluble and is predominantly metabolized in the liver where it undergoes hydroxylation followed by conjugation with glucuronic acid. Inactive metabolites, including campherol, borneol, hydroxy-camphor, and camphoglycuronic acid, are excreted by the kidneys.[55]

As with many xenobiotics, the toxic dose of camphor reported in the medical literature is highly variable.[25, 33, 62] As little as 1 teaspoon (1 g) of 20% camphorated oil caused death in an infant.[62] Workplace standards include the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL), which is 2 mg/m^3, the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV), which is 12 mg/m^3 (2 ppm), and the ACGIH short-term exposure limit (STEL), which is 19 mg/m^3 (3 ppm).

Pathophysiology

The mechanism of toxicity of camphor is unknown. Camphor is an

irritant. Pathologic changes following ingestion include cerebral edema, neuronal degeneration, fatty changes, centrilobular congestion of the liver, and hemorrhagic lesions in the skin, gastrointestinal tract, and kidneys.[34 , 62 , 71]

Clinical Manifestations

Exposure to camphor can often be detected by its characteristic aromatic odor (Chap. 21). Ingestion of camphor typically produces oropharyngeal irritation, nausea, vomiting, and abdominal pain. Generalized tonicâ€“clonic seizures may be the first sign of camphor toxicity, usually occurring within 1â€“2 hours postingestion.[5 , 7] Most seizures are brief and self-limited, although some patients may have a more protracted course.[5 , 40 , 63] Central nervous system (CNS) depression is common, but rarely compromises respiratory function.[11 , 39] Other neurologic effects include headache, lightheadedness, transient visual changes, confusion, myoclonus, and hyperreflexia.[37 , 54 , 57] Psychiatric effects include agitation, anxiety, and hallucinations.[25 , 37 , 39] Dermal effects include flushing and petechial hemorrhages.[11 , 28 , 64] Camphor does not cause life-threatening cardiovascular effects.[28] Death is reported secondary to respiratory failure or seizures.[11]

Case reports suggest that acute ingestion of camphor can cause transient elevations of the hepatic aminotransferases.[3 , 34 , 62 , 54 , 57] Chronic administration of camphor to a child caused altered mental status and elevated hepatic aminotransferases suggestive of Reye syndrome.[34] When hepatotoxicity occurs, however, camphor does not typically produce morphologic changes of the liver characteristic of Reye syndrome. Albuminuria can also occur.[62]

Camphor crosses the placenta. Both fetal demise and delivery of healthy neonates are reported in mothers who develop camphor toxicity within 24 hours of term delivery.[8 , 54 , 71] Specific dose-related toxicity could not be determined from these case reports.

Inhalational and dermal exposure from camphor usually produces only mucous membrane and dermal irritation, respectively.[24]

Diagnostic Testing

When managing most patients with camphor toxicity, no specific toxicologic diagnostic testing is indicated. Although camphor and its metabolites can be identified in blood and urine, concentrations are not useful in most cases of acute toxicity because they are not readily available and have not been proven to correlate with clinical toxicity.[28 , 38 , 55]

Management

The patients who should be evaluated in a healthcare facility after an acute ingestion include those who have signs or symptoms consistent with camphor toxicity, those who have ingested more than 1 g of camphor (1 teaspoon of 20% camphorated oil or approximately 2 teaspoons of 11% camphorated oil), suicidal patients, and any patient with a high occupational exposure.

Gastric decontamination is not well studied in patients who have ingested camphor. If lavage is deemed necessary following recent ingestion of a camphor-containing solution, nasogastric suctioning and lavage are preferable to orogastric lavage. Because camphor-containing solutions are so rapidly absorbed, the benefit of gastrointestinal decontamination is expected to rapidly diminish as the time following ingestion increases. Emetic agents should not be administered because camphor-induced seizures can occur rapidly prior to the onset of emesis, raising the risk of pulmonary aspiration. Although not of proven efficacy, administration of activated charcoal, 1 g/kg, is also reasonable because it is considered safe. There is no antidote for camphor. Most patients survive with supportive care. Although the management of camphor-induced seizures is not well

studied, patients should be treated with benzodiazepines. Repeat doses of benzodiazepines may be needed to control seizures. If benzodiazepines fail to control seizures, other sedative-hypnotic agents, including phenobarbital, pentobarbital, and propofol, should be administered. Case reports suggest that most patients who develop life-threatening camphor toxicity develop symptoms within a few hours postexposure. Based on this, an observation period of at least 2â€“4 hours following a potentially toxic ingestion of camphor is reasonable.

In case reports, hemodialysis with a lipid dialysate and either hemoperfusion using an Amberlite resin or charcoal hemoperfusion successfully removed camphor.[3,21,39,40,44] Neither isolated lipid hemodialysis nor lipid dialysis in combination with hemoperfusion is routinely recommended or widely available.

Naphthalene

History and Epidemiology

Historically, naphthalene toxicity has resulted from its use as an antihelminthic and an antiseptic.[61] Toilet-bowl and diaper-pail deodorizers containing naphthalene have also caused toxicity.[10,75] Naphthalene is the single most abundant component of coal tar and is a component of petroleum. Occupational exposures to naphthalene may occur during the manufacture of dyes, synthetic resins, celluloid, solvents, and fuels.

Most unintentional exposures to naphthalene-containing moth repellents occur in children and do not cause life-threatening toxicity. According to Toxic Exposure Surveillance System (TESS) data from the AAPCC, between 1998 and 2003 there were approximately 9000 exposures to naphthalene, no deaths, and 15 cases of â€œmajor toxicityâ€• (see Chap. 130 for complete references).

Pharmacology, Pharmacokinetics, and Toxicokinetics

Naphthalene ($C_{10}H_8$), an aromatic bicyclic hydrocarbon, is a white, flaky crystalline solid with a noxious odor. Synonyms include white tar and tar camphor. Naphthalene toxicity is reported following ingestion, dermal application, and inhalation.[12,14,16,56,70] Although the absorption of naphthalene is not well studied, highly lipid-soluble compounds may increase both oral and dermal absorption.

Naphthalene is slowly metabolized in the liver to Î±- and Î²-naphthol and to Î±- and Î²-naphtholoquinone.[53] These hepatic metabolites, primarily Î±-naphthol, but not the parent compound,[53,74] cause the oxidant stress responsible for naphthalene-induced hemolysis and methemoglobinemia. As with most xenobiotics, the toxic amount of naphthalene reported in the medical literature is highly variable. As little as one naphthalene mothball has resulted in toxicity, including hemolysis in an infant.[20,75] Workplace standards include the OSHA PEL and ACGIH TLV, which are 50 mg/m^3 (10 ppm), and the ACGIH STEL, which is 75 mg/m^3 (15 ppm).

Pathophysiology

To understand naphthalene-induced hemolysis and methemoglobinemia, it is important to understand how oxidant stress affects erythrocytes and the normal mechanisms erythrocytes use to prevent and reverse the effects of oxidant stress.

Oxidant stressors can cause methemoglobinemia and/or hemolysis. When oxidant stress causes an iron atom from any of the 4 globin chains of hemoglobin to be oxidized from the ferrous state (Fe^{2+}) to the ferric state (Fe^{3+}) state, methemoglobin is formed (Chap. 122). When oxidant stress causes hemoglobin denaturation, the heme groups and the globin chains dissociate and precipitate in the erythrocyte, forming Heinz bodies. An erythrocyte with denatured hemoglobin is more susceptible to hemolysis and to removal by the

reticuloendothelial system (Chap. 24).

Hemolysis and methemoglobinemia can occur independently of each other or simultaneously in patients with either normal or deficient glucose-6-phosphate dehydrogenase activity.[20 , 32 , 70 , 75]

Theoretically, patients with glucose-6-phosphate dehydrogenase deficiency are at increased risk for both hemolysis and methemoglobinemia following oxidant stress. In practice, however, patients with glucose-6-phosphate deficiency are at much greater risk of xenobiotic-induced hemolysis than of xenobiotic-induced methemoglobinemia.

Patients with known glucose-6-phosphate dehydrogenase (G6PD) deficiency are at increased risk for hemolysis because they have decreased glutathione stores.[74 ,87] Glucose-6-phosphate deficiency affects all races but is most prevalent in Africans, African Americans, and patients of Mediterranean and Asian descent. The gene that codes for G6PD is X-linked; consequently, males are affected more often than females.

Infants are also at increased risk of methemoglobinemia because fetal hemoglobin is more susceptible to the formation of methemoglobin and also because nicotinamide adenine dinucleotide (NADH) methemoglobin reductase activity is decreased, impairing the reduction of methemoglobin to hemoglobin.[35]

Clinical Manifestations

Both acute and chronic exposures to naphthalene result in similar toxicity.[10 , 74] Ingestion and inhalational exposures to naphthalene

commonly cause headache, nausea, vomiting, diarrhea, abdominal pain, fever, and altered mental status.[10 , 43 , 48] Dermal exposure results in dermatitis.[23]

Hemolysis or methemoglobinemia usually becomes clinically evident, as early as 24â€“48 hours postexposure, but more typically on the

third day postexposure because of the time necessary for the metabolism of naphthalene.[14] Anemia secondary to hemolysis often does not reach its nadir until 3â€“5 days postexposure.

Signs and symptoms of hemolysis and methemoglobinemia are nonspecific and include tachycardia, tachypnea, shortness of breath, generalized weakness, decreased exercise tolerance, and altered mental status. Methemoglobinemia may produce cyanosis, whereas hemolysis may produce pallor and jaundice (Chap. 122). Renal failure as a complication of naphthalene-induced hemolysis and hemoglobinuria is reported. Naphthalene or its metabolites cross the placenta.[4] Naphthalene pica during pregnancy causes both maternal and fetal toxicity. Children born to mothers who were experiencing naphthalene toxicity at the time of delivery have developed hemolytic anemia believed to be related to the maternal naphthalene exposure.[74]

Diagnostic Testing

No specific diagnostic testing is indicated, although both naphthalene and its metabolites can be identified in blood and urine. Identification of 1-naphthol and 2-naphthol in the urine can confirm exposure to naphthalene;[49] qualitative or quantitative testing for naphthalene or its metabolites is rarely clinically indicated when managing a case of an acute overdose.

The presentation of naphthalene-induced hemolysis is similar to that of hemolysis from other causes. Reticulocytosis occurs as a response to restore a normal hemoglobin concentration. Hyperbilirubinemia from hemolysis is characterized by an elevation of the indirect bilirubin (unconjugated bilirubin) and a relatively normal direct fraction. Serum haptoglobin is usually low because the haptoglobinâ€“ hemoglobin complex is cleared by the kidneys. Both the direct and indirect Coombs tests are negative in naphthalene-induced hemolytic anemia. Lactate dehydrogenase is elevated because it is released from hemolyzed red blood cells. Gross or microscopic hemoglobinuria is

confirmed by a urine dipstick that reacts strongly positive for hemoglobin with a paucity of red blood cells on microscopic examination of the urine sediment. This should be differentiated from myoglobinemia by measuring the serum creatine phosphokinase, which will be elevated in patients with rhabdomyolysis and myoglobinuria.

Examination of a peripheral blood smear can reveal evidence of hemolysis before a patient develops clinical or laboratory evidence of anemia. The peripheral smear may reveal red blood cell (RBC) fragmentation, anisocytosis, microspherocytosis, reticulocytosis, nucleated RBCs, and Heinz body formation (Chap. 24). Peripheral smear abnormalities and anemia may occur within the first 24 hours following ingestion.[10 , 58 , 74 , 75] Testing for G6PD activity is not routinely recommended during an acute episode of hemolysis. Reticulocytes have higher G6PD activity than do older RBCs. If G6PD activity is measured during an episode of hemolysis when many of the older RBCs have already been destroyed, the G6PD activity may be falsely normal. It is best to delay testing for G6PD activity for a few months following an episode of hemolysis. Family members of patients with life-threatening G6PD deficiency should also be tested.

Naphthalene-induced methemoglobinemia is similar in presentation to methemoglobinemia from other xenobiotics. The percentage of methemoglobin can rapidly be determined using a cooximeter (Chap. 122).

Management

Most patients with an unintentional exposure to all or part of one naphthalene-containing mothball or do not require medical evaluation. Patients who should be evaluated in a healthcare facility following an acute ingestion include those who recently ingested more than one naphthalene-containing mothball equivalent, those with signs or symptoms of toxicity, especially hemolysis and/or methemoglobinemia, those with known or suspected G6PD deficiency,

all intentional ingestions, and those patients with large inhalational exposures, especially after exposure occurs in an occupational setting.

Gastrointestinal decontamination is not well studied in patients who have ingested naphthalene. Most patients with unintentional exposures do not require gastrointestinal decontamination. Emesis may be useful following ingestion of multiple naphthalene-containing mothballs in children, provided it can be administered within 30â€“60 minutes postingestion. Administration of activated charcoal, 1 g/kg, although not of proven efficacy, is also reasonable because it is considered safe. Repeat doses of activated charcoal 0.5 g/kg and/or whole-bowel irrigation with polyethylene glycol electrolyte lavage solution would only be indicated for patients with large ingestions of naphthalene who are expected to have significant ongoing absorption of naphthalene within the gastrointestinal tract.

Diagnostic testing within the first 24â€“48 hours postexposure may detect the onset of methemoglobinemia and/or hemolysis before a patient becomes symptomatic. Most low-risk patients who are asymptomatic within the first 24â€“48 hours postexposure and who have no laboratory evidence of hemolysis or methemoglobinemia can be managed as outpatients if reevaluation within 24 hours can be arranged. Patients who are discharged should be instructed to return if they become symptomatic. High-risk patients, patients with laboratory evidence of hemolysis and/or methemoglobinemia and patients who cannot reliably be managed as outpatients should be admitted.

Patients with life-threatening hemolysis and anemia should be transfused with packed red blood cells. However, most patients with functioning bone marrow are able to compensate for the hemolysis by increasing reticulocytosis and will not require a transfusion. Patients with symptomatic methemoglobinemia should receive methylene blue, 1â€“2 mg/kg (0.1â€“0.2 mL/kg of a 1% solution) intravenously. Repeat doses may be necessary (see Antidotes in Depth: Methylene Blue).

Paradichlorobenzene

History and Epidemiology

Paradichlorobenzene is widely used as a deodorizer, disinfectant, repellent, fumigant, insecticide, fungicide, and industrial solvent. Today, paradichlorobenzene is the most common component of moth repellents. Exposure to paradichlorobenzene in the United States is extremely common. A 1995 study suggested that 2,5-dichlorophenol, a metabolite of paradichlorobenzene, was detectable in the urine in 98% of the US population.[31]

Most unintentional exposures to paradichlorobenzene-containing moth repellents occur in children and do not cause toxicity. According to the TESS data by the AAPCC, there have been no deaths and

no reports of major toxicity from paradichlorobenzene between 1998 and 2003.

Pharmacology, Pharmacokinetics, Toxicokinetics, and Pathophysiology

Paradichlorobenzene ($C_6 H_4 Cl_2$) is a colorless solid with a noxious odor. It is available as pure white crystals, as a solid in combination with other chemicals, or as a liquid dissolved in volatile solvents or oil. The mechanism for the effects, pharmacology, and toxicokinetics of paradichlorobenzene have not been studied. Although rare, paradichlorobenzene toxicity has been reported following ingestion and inhalation.[31, 45] Workplace standards include the OSHA PEL and ACGIH TLV, which are 450 mg/m^3 (75 ppm), and the ACGIH STEL, which is 675 mg/m^3 (110 ppm).

Clinical Manifestations

Inhalation of paradichlorobenzene may cause nausea and vomiting, headache, and mucous membrane irritation.[13,31]

Only a single case report links acute ingestion of a moth repellent, purportedly containing paradichlorobenzene with hemolysis. The demothing agent itself was not confirmed to be paradichlorobenzene.[26]

Case reports associate chronic exposure to paradichlorobenzene with weight loss, ataxia, pulmonary granulomatosis, dyspnea, hepatotoxicity, anemia, and fixed drug eruptions.[9,13,18,45,46,65,72]

Diagnostic Testing

Both paradichlorobenzene and its metabolite, 2,5-dichlorophenol, can be identified in blood and urine following exposure. Identification of 2,5-dichlorophenol can confirm exposure to paradichlorobenzene. Quantifying the amount of paradichlorobenzene in the urine of workers may be useful for monitoring occupational exposures.[19] Qualitative or quantitative testing for paradichlorobenzene or its metabolites is not generally indicated when managing a patient with an acute overdose.

Management

Referral to a Healthcare Facility

Most unintentional exposures to paradichlorobenzene do not cause life-threatening toxicity. Thus most asymptomatic patients with unintentional exposures can be managed as outpatients. Patients who should be evaluated in a healthcare facility include those with clinical signs or symptoms, suicidal patients, and patients who have sustained a large exposure.

Water solubility (g/L)

1.2
0.03
0.08
Buoyancy in water
Floats
Sinks
Sinks
Buoyancy in water saturated with table salt
Floats
Floats
Sinks
Radiopacity
Radiolucent
Faintly radiopaque
Densely radiopaque
Melting point
350.6Â°F (177Â°C)
176Â°F (80Â°C)
127.4Â°F (53Â°C)
Placement in covered test tube in 140Â°F (60Â°C) water bath
Does not melt
Does not melt
Melts
Boiling point
399.2Â°F (204Â°C)
424.4Â°F (218Â°C)
345.2Â°F (174Â°C)
Addition of chloroform
Untested
Blue color
No reaction
Place on copper wire in a flame
Untested
Flame is yellow-orange

Initially flame is yellow-orange then bright green			
Solubility in turpentine			
Untested			
Fast			
Slow			
Characteristic	Camphor	Naphthalene	Paradichlorobenzene

TABLE 99-1. Moth Repellents: Laboratory Differentiation [42, 52, 74]

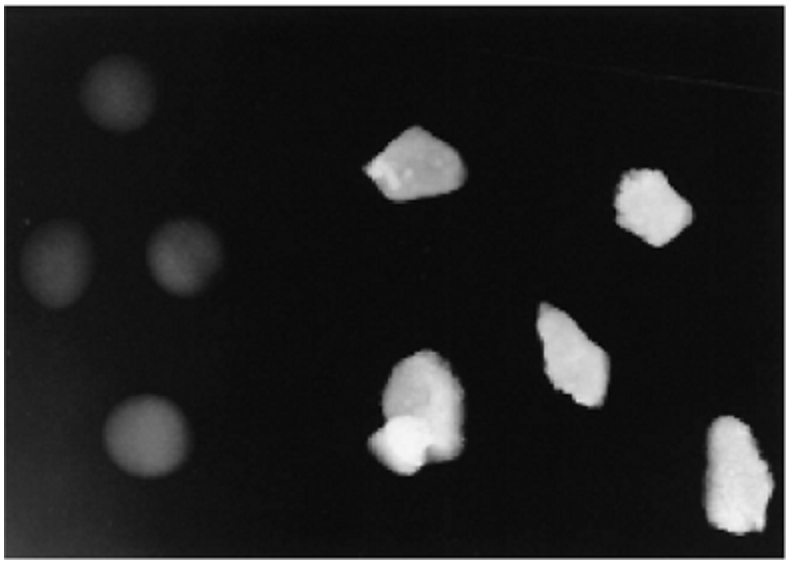

Figure 99-1. Radiograph of mothballs. Paradichlorobenzene (on the right) is densely radiopaque, whereas naphthalene (on the left) is faintly radiopaque.

Gastrointestinal Decontamination

Gastrointestinal decontamination has not been studied in patients who ingest paradichlorobenzene. Most patients with unintentional exposures do not require gastrointestinal decontamination. Administration of activated charcoal, 1 g/kg, although not studied, is

reasonable for patients with large, intentional ingestions.

Moth Repellent Recognition

Healthcare providers occasionally must determine whether a mothball is made of naphthalene, paradichlorobenzene, or camphor. When the container is unavailable, as is often the case, mothballs are difficult to distinguish based on appearance, odor, texture, or size. Most mothballs are white, crystalline, and have a noxious

odor.[73] Camphor moth repellents are more oily than both naphthalene and paradichlorobenzene mothballs. If controls are available, moth repellents can often be differentiated based on their odor and texture.[1] Although most new paradichlorobenzene moth repellents are slightly larger than most new naphthalene moth repellents, all moth repellents shrink over time when exposed to air, making size an unreliable differentiating characteristic. Identifying a moth repellent as paradichlorobenzene can often result in outpatient management, saving both money and undue worry. The tests described in Table 99-1 and shown in Figure 99-1 might allow rapid identification of the component of an unknown moth repellent. When performing these tests it is most helpful to have camphor, naphthalene, and paradichlorobenzene controls available for comparison.

Summary

Historically, the most common components of moth repellents are camphor, naphthalene, and paradichlorobenzene. In the United States, paradichlorobenzene has largely replaced both camphor and naphthalene. If an unknown moth repellent can be identified as paradichlorobenzene, limited toxicity is expected following an acute exposure. It is important for clinicians to understand how to use simple tests to identify the component of an unknown mothball. Because life-threatening camphor and naphthalene toxicity are still reported, it is important for clinicians to understand how to manage

patients exposed to both of these xenobiotics.

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Chapter 100
Caustics

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Rama B. Rao

A 20-year-old man ingested a cup of liquid drain opener (100% sodium hydroxide) in an attempted suicide. He presented to the emergency department (ED) 4 hours later complaining of oropharyngeal, chest, and abdominal pain. His vital signs were: blood pressure, 130/80 mm Hg; pulse 100 beats/min; respiratory rate, 22 breaths/min; and temperature, 99Â°F (37.2Â°C). His lips, tongue, and oral cavity were erythematous and swollen with evidence of significant epithelial sloughing (Fig. 100-1). He was drooling, but had no stridor and his lungs were clear. His heart was regular in rhythm without murmurs or gallops. Bowel sounds were present and his abdomen was soft with mild epigastric tenderness. His stool was negative for occult blood. The patient's extremities were warm and well perfused, and his neurologic examination was unremarkable.

Two large-bore intravenous lines were inserted and 0.9% sodium chloride was infused at 250 mL/h. Blood was sent for serum

electrolytes, complete blood count, platelet count, coagulation profile, type and cross-match, and arterial blood gas analysis. Chest and abdominal radiographs were unremarkable. A fiberoptic inspection of the oro- and nasopharynx revealed laryngeal and cricopharyngeal burns, prompting nasotracheal intubation with an intubating bronchoscope. The arterial blood gas analysis revealed: pH, 7.30; PCO_2, 30 mm Hg; and PO_2, 88 mm Hg. Subsequent upper gastrointestinal endoscopy performed revealed a grade IIa noncircumferential burn of the midesophagus, a grade IIb circumferential burn of the distal esophagus, and ulcerations penetrating the mucosal surface of the gastric antrum (Fig. 100-2). Over the next few hours his vital signs remained unchanged, as did the rest of his physical examination.

The patient was started on IV steroids (methylprednisolone 40 mg every 8 hours) and IV antibiotics (piperacillin/tazobactam 3.375 g every 6 hours and vancomycin 1 g every 12 hours) and was transferred from the ED to the intensive care unit. Following intensive medical care for 1 week, and surgical release of oral cavity contractures, he was extubated and able to tolerate clear liquids by mouth within 2 weeks. He was discharged with both medical and psychiatric followup care after several weeks in the hospital.

History and Epidemiology

Caustics cause both clinical and histologic damage on contact with tissue surfaces. Table 100-1 lists common caustics and the commercial products that contain them. They are available, many for home use, in both solid and liquid forms, with variations in viscosity, concentration of solution, and pH.

As early as 1927, regulatory legislation in the United States governing the packaging of lye- and acid-containing products mandated that warning labels be placed on products containing these xenobiotics. In response to the recognition that caustic

exposures were more frequent in children, in 1970 the Federal Hazardous Substances Act and Poison Prevention Packaging Act was passed stating that all caustic agents with a concentration >10% must be placed in child-resistant containers. By 1973, the household concentration for child-resistant packaging was lowered to 2%. In addition, the subsequent development of poison prevention education has led to a dramatic decrease in the incidence of unintentional caustic injuries in children in the United States. The positive impact of both regulatory legislation and education is evident when observing the decrease of exposures in the United States compared to the number of exposures in developing nations that lack these policies.

Usually, children are unintentionally exposed to household products. Adults may be exposed to household or industrial products that result in either occupational exposure or are used in suicide attempts.

Although less frequent, intentional exposures by adults are invariably more significant. One study noted that although children comprised 39% of admissions for caustic ingestions, adults comprised 81% of patients requiring treatment.[45] The severity of a caustic injury may not be immediately evident in patients who present shortly after exposure. Predicting which patients will require immediate interventions to prevent morbidity and mortality requires multiple clinical and laboratory parameters. This chapter reviews the pathophysiology and approach to patients with potentially serious exposures.

Pathophysiology

A caustic is a xenobiotic that causes both functional and histologic damage on contact with tissue surfaces. Although there are many ways to categorize caustics, they are most typically classified as acids or alkalis. An acid is a proton donator[78] and causes significant injury, generally at a pH below 3. An alkali is a proton

acceptor[78] and causes significant injury, generally at a pH above 11. The extent of injury is determined by duration of contact; ability of the substance to penetrate tissues; volume, pH, and concentration; the presence or absence of food in the stomach; and a property known as titratable acid or alkaline reserve (TAR). TAR quantifies the amount of neutralizing xenobiotic needed to bring the pH of a

caustic to that of physiologic tissues. Neutralization of caustics takes place at the expense of the tissues, resulting in the release of thermal energy, producing burns. Generally, as the TAR of caustics increases, so does their ability to produce tissue damage.[6,11,30,43,48,93] Some xenobiotics, such as zinc chloride and phenol, have a high TAR and are capable of producing severe burns even though they possess a near-physiologic pH. Chapter 12 contains a more detailed discussion of the chemistry of acids and bases.

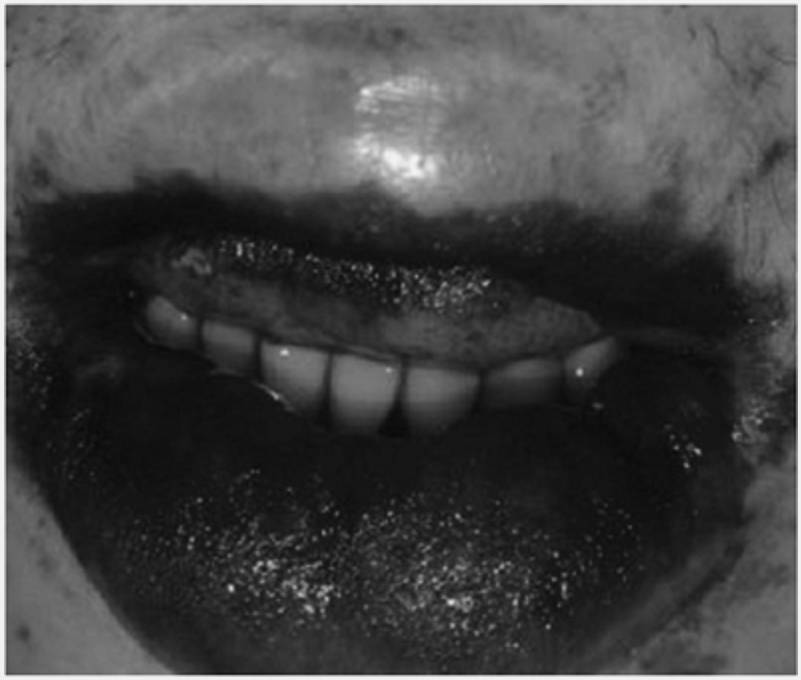

Figure 100-1. Photograph demonstrating burns to the lips and tongue of a 20-year-old man following ingestion of 100% sodium hydroxide.

Alkalis

Following exposure to an alkaline xenobiotic, dissociated hydroxide (OH^-) ions penetrate tissue surfaces producing what is histologically described as liquefactive necrosis. This process includes protein dissolution, collagen destruction, fat saponification, cell membrane emulsification, transmural thrombosis, and cell death.[6,43] Animal studies following alkali exposure to the eye[47] demonstrate rapid formation of corneal epithelial defects with eventual deep penetration that may lead to perforation. Similarly, animal studies of the esophagus demonstrate that erythema and edema of the mucosa occur within seconds followed by an inflammatory reaction extending to the submucosa and muscular layers. The alkali, such as sodium hydroxide (â€œliquid lyeâ€•), then continues to penetrate until the OH^- concentration is sufficiently neutralized by the tissues.[6,61,65,114]

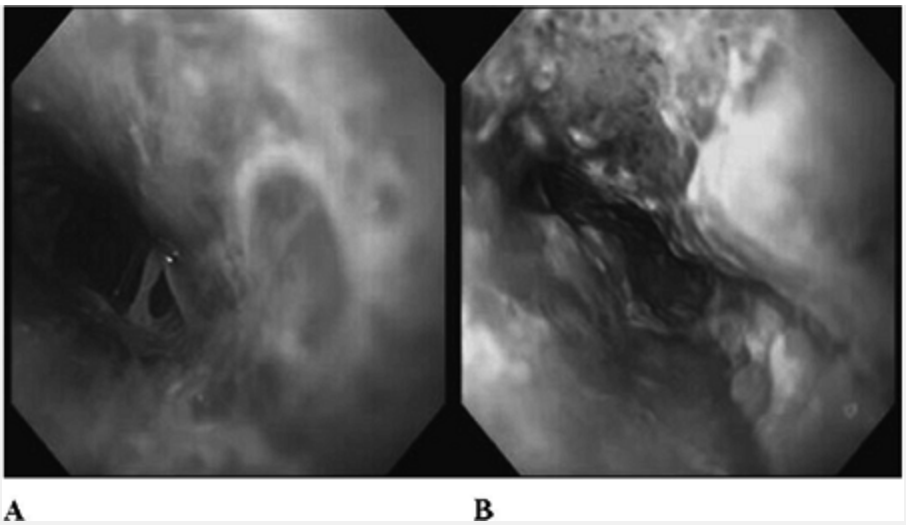

Figure 100-2. Endoscopy images of a 20-year-old man following ingestion of 100% sodium hydroxide. A. Grade IIa noncircumferential burn of the midesophagus B. Grade IIb circumferential burn of the distal esophagus.

TABLE 100-1. Sources of Common Caustics

Chemical	Applications
Acetic acid	Permanent wave neutralizers, photographic stop bath
Ammonia (ammonium hydroxide)	Toilet bowl cleaners, metal cleaners and polishes, hair dyes and tints, antirust products, jewelry cleaners, floor strippers, glass cleaners, wax removers

Benzalkonium chloride	Detergents
Boric acid	Roach powders, water softeners, germicide
Formaldehyde, formic acid	Deodorizing tablets, plastic menders, fumigant, embalming agent
Hydrochloric acid (muriatic acid)	Metal and toilet bowl cleaners
Hydrofluoric acid	Antirust products, glass etching, microchip etching
Iodine	Antiseptics
Mercuric chloride ($HgCl_2$)	Preservative
Methylethyl ketone peroxide	Industrial synthetic agent
Oxalic acid	Disinfectants, household bleach, metal polish, antirust products, furniture refinisher
Phenol (creosol, creosote)	Antiseptics, preservatives

Phosphoric acid	Toilet bowl cleaners
Phosphorus	Matches, fireworks, rodenticides, methamphetamine synthesis
Potassium permanganate	Illicit abortifacient, antiseptic solution
Selenious acid	Gun bluing agent
Sodium hydroxide	Detergents, Clinitest tablets, paint removers, drain cleaners and openers, oven cleaners
Sodium borates, carbonates, phosphates, and silicates	Detergents, electric dishwasher preparations, water softeners
Sodium hypochlorite	Bleaches, cleansers
Sulfuric acid	Automobile batteries, drain cleaners
Zinc chloride	Soldering flux

Although federal regulations have lowered the maximal available household concentration of many caustics, there are two products of industrial strength that seem to be readily available and therefore warrant special mention: ammonium hydroxide and

sodium hypochlorite. Ammonia (ammonium hydroxide) products are weak basesâ€”partially dissociated in waterâ€”that can cause significant esophageal burns, depending on the concentration and volume ingested.[45,105,112,114] Household ammonium hydroxide ranges in concentration from 3â€“10%. Strictures have formed in patients who ingested 28% solutions.[87] Sodium hypochlorite (bleach) is the major component in most industrial and household bleach preparations. Large case series and reports have found that grades II and III injuries occur only in patients with large-volume ingestions of concentrated products[24] and that most other patients do well with supportive care.[17,45,111] A series of 393 patients with household bleach ingestions demonstrated no stricture formation,[64] and

a canine model found that although vomiting was a common effect of bleach, no esophageal lesions were noted, and perforation only occurred following prolonged contact.

Historically, ingestion of button batteries has been considered a unique caustic exposure. Composed of metal salts and a variety of alkaline xenobiotics, such as sodium and potassium hydroxide, leakage of battery contents was a legitimate concern. In recent years, however, new techniques used in the production of button batteries that effectively prevent leakage of battery contents within the gastrointestinal tract have shifted the concern following their ingestion from caustic to foreign-body exposure. For a more in depth review of the management of button battery ingestion, the reader is referred to the literature and the previous editions of this text.

Household detergents, such as laundry powders and dishwasher detergents, contain silicates, carbonates, and phosphates, and have the potential to induce caustic burns and strictures even when ingested unintentionally.[18,112] Airway compromise also can occur,[18,27,71] but the majority of exposures result in only minor toxicity.

Cationic detergents include quinolinium compounds, pyridinium compounds, and quaternary ammonium agents. These are frequently found in products for industrial use, as well as household fabric softeners. A concentration >7.5% can cause severe burns.[69] These xenobiotics bind well to activated charcoal;[69] however, because no large series has been evaluated with this therapy, all patients with symptoms or signs of caustic injury, intentional ingestions, or exposures to concentrations >7.5% should be evaluated endoscopically and activated charcoal should be avoided.[69]

Acids

In contrast to alkaline exposures following exposure to an acid, hydrogen (H^+) ions desiccate epithelial cells, producing an eschar and resulting in what is histologically referred to as coagulation necrosis. This process leads to edema, erythema, mucosal sloughing, ulceration, and necrosis of tissues. Dissociated anions of the acid (Cl^-, SO_4^{2-}, PO_4^{3-}) also act as reducing agents further injuring tissue.

Ophthalmic exposure to acids results in coagulative necrosis that tends to prevent further penetration into deeper layers of the eye.

In most series, following an acid ingestion, both the gastric and esophageal mucosa are equally affected.[25,54,128] On occasion, the esophagus may be spared damage while severe injury is noted in the stomach.[21,40,45,112] (See ILCAUSTICS1 in the Image Library at http://www.goldfrankstoxicology.com). This tends to be a rarer finding than concomitant injury to both stomach and esophagus, and is probably related to the rapid transit time of liquid acids through the upper gastrointestinal tract. Skip lesions from acid ingestions may be a function of viscosity and contact time.[45] Additionally, acid-induced pylorospasm may lead to gastric outlet obstruction, antral pooling, and

perforation.[16,21,24,25,40,54,62,63,74,85,110,111,124,127] A cat model of the effects of sulfuric acid on the esophagus revealed a coagulative necrosis of the mucosa with whitish discoloration of the tissues and underlying smooth muscle spasm.[6] Other animal models demonstrate esophageal motility dysfunction and shortening.[108,109]

Chapters 92 and 101 contain a more detailed discussion of mercury and hydrofluoric acid, respectively, each a uniquely caustic compound, and the management specific to their exposure.

Classification and Progression of Caustic Injury

Esophageal burns, secondary to both alkali and acid exposures, are classified based on endoscopic visualization that employs a grading system similar to that used with burns of the skin. Grade I burns are generally described as hyperemia or edema of the mucosa without evidence of ulcer formation.[20,60,127] Grade II burns include submucosal lesions, ulcerations, and exudates. Some authors further divide grade II lesions into grade IIa, noncircumferential lesions, and grade IIb, near-circumferential injuries.[17] Grade III burns are defined as deep ulcers and necrosis into the periesophageal tissues.[33,37,44,60]

Human case reports, postmortem studies, histologic inspection of surgical specimens and experimental animal models reveal a consistent pattern of injury and repair following caustic injury.[1,31,38,72,80,102] As wound healing of gastrointestinal tract tissue occurs, neovascularization and fibroblast proliferation take place, laying down new collagen and replacing the damaged tissue with granulation tissue. A similar pattern of repair occurs following caustic injuries of the eye.

Burns of the esophagus may persist for up to 8 weeks as remodeling takes place, and may be followed by esophageal

shortening.[122] If the initial injury penetrates deeply enough, there is progressive narrowing of the esophageal lumen. The dense scar formation presents clinically as a stricture.[22,43] Strictures can evolve over a period of weeks to months, leading to dysphagia and significant nutritional deficits.[98,103,122] Grade I burns carry no risk of stricture formation.[20,60,127] Grade II circumferential burns lead to stricture formation in approximately 75% of cases. Grade III burns invariably progress to stricture formation and are also at a high risk of perforation.[4,45,80]

Clinical Presentation

The gastrointestinal tract, respiratory tract, eyes, and skin of a patient can be sites of caustic injury. Caustics may produce severe pain on contact with any of these tissues. By far, the majority of long-term morbidity and mortality from caustic exposure results from oral ingestion.

In general, patients who have ingested alkaline or acid agents have similar initial presentations. Depending on the type, amount, and formulation (solid vs. liquid) of the substance, ingestion may lead to the development of severe pain of the lips, mouth, throat, chest, or abdomen. Oropharyngeal edema and burns may lead to drooling and rapid airway compromise. Symptoms of esophageal involvement include dysphagia and odynophagia, whereas epigastric pain and hematemesis may be symptoms of gastric involvement.

Respiratory tract damage may occur through direct inhalation or aspiration of vomitus leading to the clinical manifestations of hoarseness, stridor, and respiratory distress. Injury may result in epiglottitis, laryngeal edema and ulceration, pneumonitis, and impaired gas exchange. Patients may also be tachypneic or hyperpneic as a compensatory response to the metabolic acidosis generated by elevated lactate from necrotic tissue or hemodynamic compromise.

Predictors of Injury

Many attempts have been made to define a method for clinical identification of patients with grade II or III esophageal injuries as

these injuries typically progress to severe complications. Various studies, all involving alkaline xenobiotics, examine the predictive value of stridor, oropharyngeal burns, drooling, vomiting, and abdominal pain. A retrospective study of 378 children admitted for a caustic injury found that signs or symptoms could not be used to predict significant esophageal injury.[33] However, one prospective study of 79 children evaluated for vomiting, drooling, and stridor found that a combination of two or more of these signs was a predictor of significant esophageal injury as visualized on endoscopy.[20] Studies of the presence or absence of oropharyngeal burns identified on examination as a predictor of distal esophagogastric injury have repeatedly found this finding to be poorly predictive.[2,12,20,33,37,95,118] In one study there was a 37.5% incidence of esophageal lesions in the absence of oropharyngeal lesions, and 22.2% of these were second- and third-degree burns.[95] A prospective study of alkali ingestions by both adults and children found that stridor was 100% specific for significant esophageal injury, but was based on only three patients with this sign.[37]

Based on the findings above, endoscopy, a standard diagnostic tool used in the management of caustic ingestions, should be performed in all patients with intentional ingestions. Endoscopy should also be performed in any patient with an unintentional ingestion in the presence of stridor, and in any patient with one or more of the following findings: pain, vomiting, and drooling.[20] Children with unintentional caustic ingestions who remain completely asymptomatic and tolerate liquids after a few hours of observation probably require no further medical care.

The abdominal examination is likewise an unreliable indicator of the severity of injury. The presence of abdominal pain suggests tissue injury, but the absence of pain or findings on abdominal examination do not preclude life-threatening gastrointestinal damage.[28,54,98,105,126] Esophageal perforations result in mediastinitis and are commonly associated with fever, dyspnea, chest pain and subcutaneous emphysema of the neck and chest. Abdominal peritoneal signs indicate viscus perforation.

In addition to the direct effects that occur with tissue contact, acids are systemically absorbed, resulting in damage to the spleen, liver, biliary tract, pancreas, and kidneys, as well as producing a metabolic acidosis, hemolysis, and, ultimately, death.[50,122]

Significant complications can occur at various stages of wound recovery. Most importantly, these include airway compromise, hemodynamic instability secondary to hemorrhage from vascular erosion or septic shock, and perforations of the gastrointestinal tract with the development of mediastinitis or peritonitis, and other overwhelming infections from bacteria residing in the oropharynx. A patient who survives acute injury with an acid or an alkali may also subsequently develop stricture formation, gastric atony, decreased acid secretion, pseudodiverticula, and gastric outlet obstruction.[13,36,62,110,127]

Other complications reported include motility abnormalities of the pharynx and esophagus,[23] formation of aorto- and tracheoesophageal fistulas, delayed massive hemorrhage from erosion into a great vessel, and pulmonary thrombosis.[10,45,60,86,105,107]

Those patients surviving a few weeks after a grade II or III injury may subsequently present with dysphagia and vomiting from stricture formation. One study suggested that involvement of the entire length of the esophagus, as well as hematemesis and increased serum lactic dehydrogenase, are useful indicators for the

development of strictures.[88] Strictures may also present with esophageal motility disorders caused by impaired smooth muscle reactivity.[117] The early assessment and long-term prognosis may be better defined by manometric studies of the esophagus which provide precise information on the severity of the initial injury and aid in long-term prognosis.[35]

Although the risk of carcinoma after caustic ingestions is inadequately studied, three patients developed squamous cell cancer of the stomach following acid ingestion[26] and 15 patients developed squamous cell cancer of the esophagus following lye ingestion many years after their initial injuries.[57] Long-term survivors of moderate and severe injury of the esophagus have a risk of esophageal carcinoma that is 1000 times higher than that of the general population and appears to present with a latency of up to 40 years.[5]

Diagnostic Testing

Laboratory

All patients with presumed caustic exposure should have an evaluation of pH, blood type and cross-match, hemoglobin, coagulation parameters, electrolytes, and urinalysis. Elevated prothrombin time (PT) and partial thromboplastin times,[126] as well as an arterial pH lower than 7.22,[14] are associated with severe caustic injury.

Absorption of nonionized acid from the stomach mucosa may result in acidemia. Following ingestion of hydrochloric acid, hydrogen and chloride ions (both of which are accounted for in the measurement of the anion gap) dissociate in the serum resulting in a hyperchloremic normal anion gap metabolic acidosis. Other acids, such as sulfuric acid, result in an elevated anion gap metabolic acidosis because the anionâ€”sulfate (SO_4^{2-})â€”is indirectly

measured in the calculation of the anion gap. Although alkalis are not absorbed systemically, necrosis of tissue may result in a metabolic acidosis with an elevated lactate.

A gastric pH >7.30 correlated retrospectively with severe alkaline injury. The prospective usefulness of this information is limited, as obtaining gastric secretions without direct visualization is dangerous. One prospective study in children also found an increase in uric acid and decreases in phosphate and alkaline phosphatase concentrations to be useful in predicting the presence of esophageal injuries.[90]

Radiology

Chest and abdominal radiographs are used in the initial stages of management to detect gross signs of esophageal or gastric perforation. Signs of alimentary tract perforation that may be seen on plain radiographs include pneumomediastinum, pneumoperitoneum, and pleural effusion. However, these studies have a limited sensitivity, and an absence of findings does not preclude perforation.[126] Free intraperitoneal air is best seen on an upright chest radiograph. Occasionally, free air may only be visible on the lateral view.[125] In patients too ill to obtain an upright chest radiograph, an abdominal radiograph obtained with the patient in a left-side down position may reveal free intraperitoneal air adjacent to the liver. CT is considerably more sensitive than radiography for detecting viscus perforation and should be obtained in patients with potentially serious caustic ingestions as soon as is feasible.[29,120]

A contrast esophagram is useful for defining the extent of esophageal injury (Fig. 100-3). Late after the ingestion, it can detect stricture formation. In patients for whom there is a high suspicion

for esophageal perforation and in whom adequate visualization of

the upper gastrointestinal tract by endoscopy is not possible (grade IIb circumferential burns or grade III burns), an enteric contrast study (esophagram and upper GI series) can be obtained 24 hours after the ingestion.[97,129] Extravasation of contrast outside of the gastrointestinal tract is diagnostic of perforation.[127] Water-soluble contrast should be used when perforation is suspected as it is less irritating to mediastinal and peritoneal tissues if extravasated.[31] However, barium contrast agents are more radiopaque than water-soluble agents and offer greater radiographic detail. Consequently, some authors recommend barium swallow if the water-soluble contrast study is nondiagnostic but demonstrates no leak.[41,68,113] In addition, if there is risk of aspiration, barium is preferred because water-soluble contrast material can cause a severe chemical pneumonitis. Significant necrosis with impending perforation may be suspected on enteric contrast studies when there is esophageal dilation, displacement of the pleural reflection, and widening of the pleuroesophageal line.[72] Enteric contrast studies may fail to detect perforation, and therefore must be interpreted within the context of the patient's clinical status.[10,19,42,54,72]

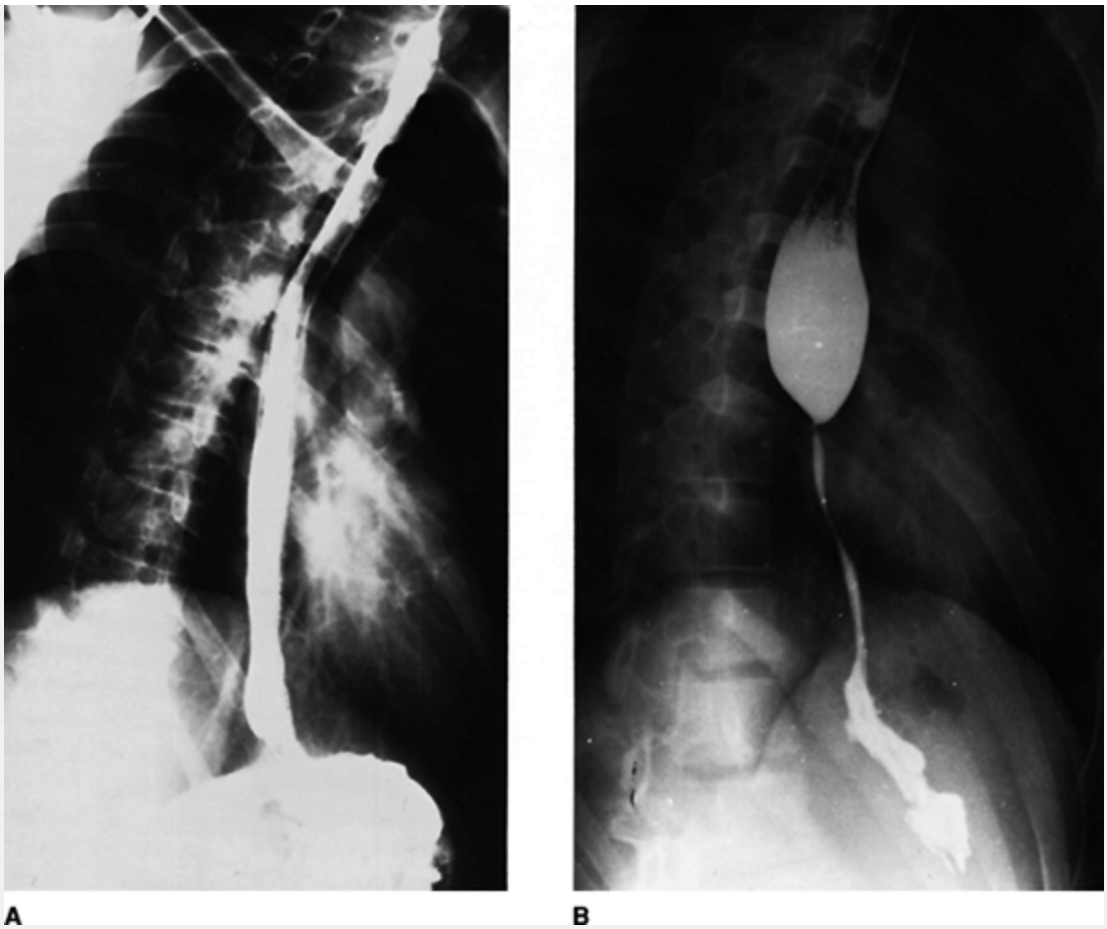

Figure 100-3. A. Barium swallow several days after ingestion of liquid lye shows the esophagus to be atonic. There is poor coating of the esophagus, suggesting edema and intramural penetration. Note that the initial evaluation immediately following a caustic ingestion to assess the extent of injury is esophagoscopy, rather than a contrast esophagram. B. Four months later, a repeat barium esophagram shows a severe stricture below the middle third of the esophagus. The barium barely passes the stricture, and the remainder of the esophagus is pencil thin. *(Courtesy of Emil J. Balthazar, MD, Professor of Radiology, New York University.)*

Although promising, a role for CT in caustic ingestions has not been formally investigated. CT has great sensitivity at detecting extraluminal air in the mediastinum and peritoneal cavity as a sign of perforation. In addition, CT can visualize the esophagus and stomach distal to severe caustic burns that cannot be safely seen using endoscopy or an esophagram. CT may therefore replace enteric contrast radiography for detection of perforation in the acute stage (within 24 hours) of a caustic ingestion. Other imaging modalities have been proposed. One study suggested a role for a technetium 99m-labeled sucralfate swallow for assessing esophageal injury after ingestion of caustic substances.[81] In another study, esophageal ultrasonography was helpful in determining the depth of injury.[84]

Another use of radiographic imaging is to noninvasively follow the patient after initial evaluation and stabilization. For example, contrast radiography is routinely used in the weeks or months following a caustic ingestion to detect esophageal narrowing representing stricture formation.[72,115] Chest CT may also be useful to determine the response of strictures to dilation procedures.[63]

Endoscopy

Endoscopy should be performed within 12 hours and generally not later than 24 hours postingestion. Numerous case series demonstrate that the procedure is safe during this period. Early endoscopy serves multiple purposes in that it allows patients with minimal

or no evidence of gastrointestinal injury to be discharged. It also offers a rapid means of obtaining diagnostic and prognostic information while shortening the period of time that patients forego nutritional support, permitting more precise treatment regimens.[17,22,24,28,43,45,67,79,105,106,119,123,127] The use of

endoscopic assessment from the 2nd or 3rd day postingestion is discouraged and should be avoided between 5 days and 2 weeks postingestion as it is at this time that wound strength is least and the risk of perforation is greatest.

The choice of rigid versus flexible endoscopy is dependent on the comfort and experience of the endoscopist. The flexible endoscope has a smaller diameter but may require gentle insufflation of air to achieve and enhance visualization. A prospective evaluation of the role of fiberoptic endoscopy in the management of caustic ingestions recommended the following guidelines: (a) direct visualization of the esophagus prior to advancing the instrument, (b) minimal insufflation of air, (c) passage into the stomach unless there is a severe (particularly circumferential) esophageal burn, and (d) avoidance of retroversion or retroflexion of the instrument within the esophagus. Provided that the patient is hemodynamically stable and endoscopy is indicated, every attempt should be made to visualize the esophagus, stomach and duodenum after a caustic ingestion.

The absence of burns in the esophagus does not imply that severe necrosis and ulcerations do not exist in the stomach[79,112,118,127] and duodenum. In the case of termination of endoscopy because of grade IIb or grade III esophageal burns, barium studies,[97] CT, or consideration of surgical exploration should be undertaken to visualize remaining structures.

Endoscopy permits limited evaluation of gastrointestinal injury. For example, the endoscopist is only able to appreciate the mucosal surface of tissues, and not the serosal side. This is especially evident in stomach ulcerations, which may appear black and necrotic from a true burn through the layers of the stomach, or from the effect of stomach acid on the blood exposed from a shallow lesion. Recent studies suggest that the use of endosonography during endoscopy may improve assessment of injury depth.[7,59] Often, though, only direct visualization of serosal

and mucosal tissues with laparoscopy or laparotomy allows for definitive evaluation.

Most cases of perforation clearly linked to endoscopy have occurred when the endoscope was advanced through an esophagus with severe circumferential lesionsâ€”a violation of current endoscopic standards.[119] In addition, perforations are also more likely to occur when rigid instruments are used in children or in uncooperative patients. The use of the flexible endoscope has decreased the risk of endoscopic evaluation.[97] Some authors advocate the presence of a surgeon during endoscopy to assist in the assessment for potential surgical intervention.[105]

Management

Acute Management

As in the case of any patient presenting with a toxicologic emergency, initial stabilization should always begin with basic decontamination of the patient and observation of universal precautions by the examiner. Airway inspection and protection should be followed by basic resuscitation principles. Examination of the oropharynx for signs of injury, drooling, and vomitus, as well as careful auscultation of the neck and chest for stridor, may reveal signs of airway edema that should prompt airway protection. Careful and constant attention to signs and symptoms of respiratory distress and airway edema, such as stridor and change in voice, are mandatory and should prompt intubation as airway edema may rapidly progress over minutes to hours.

If airway involvement is significant enough to warrant intubation, it is best to mobilize a team of the most skilled physicians early in case of unforeseen complications. A delay in prophylactic airway protection may make subsequent attempts at intubation or bag-valve-mask ventilation difficult or impossible. Direct visual

inspection of the vocal cords with a fiberoptic laryngoscope may also reveal signs of impending airway compromise. Patients necessitating intubation are best served by direct visualization of the airway either via direct laryngoscopy or fiberoptic endoscopy as perforation of edematous tissues of the pharynx and larynx is a grave complication that may occur during blind nasotracheal intubation attempts. Paralytic agents for induction of intubation should be avoided as airway edema and bleeding may distort the ability to successfully ventilate via bag-valve-mask.

Nonsurgical airway placement is recommended whenever possible as both cricothyrotomy and tracheostomy will interfere with the surgical field if esophageal repair is required.[126] Some patients with significant ingestions, however, may require emergent surgical airway intervention. The decision to perform the technique of a surgical airway is dependent on the status of the patient, the ability to orotracheally or nasotracheally intubate via a fiberoptic endoscope, and the comfort of the physician performing the procedure.

Following control of the airway, large-bore intravenous access should be secured and volume resuscitation initiated. Although unstudied, most clinicians agree that patients with signs of caustic-induced airway edema benefit from dexamethasone 10 mg IV in adults and 0.6 mg/kg up to a total dose of 10 mg in children. Both acid and alkali ingestions cause â€œthird spacingâ€• of intravascular fluid to the interstitial space, which can result in hypotension. Empiric rehydration with clinical assessment of central venous pressures and neck vein distension should be used to guide individual fluid requirements.

Serial physical examinations and constant monitoring of heart rate, respiratory rate, blood pressure, and urine output may provide information on the severity of the exposure and the progression in clinical status.

Decontamination, Dilution, and Neutralization

Decontamination should begin with careful, copious irrigation of the patient's skin and eyes when indicated to remove any residual caustic agent and to prevent contamination of other patients and staff.

Gastrointestinal decontamination is usually limited in the patient with a caustic ingestion. Induced emesis is contraindicated, as it may cause reintroduction of the caustic to the upper gastrointestinal tract and airway. Activated charcoal is also contraindicated, as it will interfere with tissue evaluation by endoscopy and preclude a subsequent management plan. Additionally, most caustics are not adsorbed to activated charcoal.

Gastric emptying via cautious placement of a narrow nasogastric tube with gentle suction may be attempted to remove the remaining acid in the stomach in patients with large intentional ingestions of acid who present within 30 minutes.[93] Although this technique has never been studied and carries the risk of perforation, the outcome for these patients is often grave and options for treatment are limited. Therefore, preventing absorption of some portion

of the ingested acid may have potential benefit in reducing systemic toxicity. Although the procedure has the potential to induce injury, a risk-to-benefit analysis favors gastric emptying following a presumed lethal ingestion.

In contrast, gastric emptying should be avoided with alkaline and unknown caustic ingestions as blind passage of a nasogastric tube carries the risk of perforation of damaged tissues, a risk that outweighs the benefit.

Exceptions to the general rules of gastrointestinal decontamination

of caustic agents exist in the management of zinc chloride ($ZnCl_2$) and mercuric chloride ($HgCl_2$). Both are caustics with severe systemic toxicity.[15,75,76,94] Ingestion of these xenobiotics causes life-threatening illness from cationic metal exposure. The local caustic effects, though of great concern, are less consequential than the manifestations of systemic absorption. For this reason, aggressive decontamination with gentle nasogastric tube aspiration and administration of activated charcoal serve as primary gestures in the initial management of patients with these ingestions. Additionally, there are some in vitro data to suggest adequate charcoal adsorption of Hg^{2+}.[3] The local effects of these xenobiotics can be managed supportively and directly assessed after systemic absorption has been prevented or treated.

The use of dilutional therapy has been examined using in vitro, ex vivo, and in vivo models in an attempt to assess its efficacy in caustic ingestions. An early in vitro model demonstrated a dramatic increase in temperature when either water or milk was added to crystal Drano.[104] Another in vitro model found less consequential increases in temperature despite large volumes of diluent. Results of both studies suggested that dilutional therapy was of limited benefit.[73] Dilutional therapy was also attended by an increase in temperature in an ex vivo study of harvested rat esophagi that examined the histopathologic effects of saline dilution after an alkali injury. Additionally, the usefulness of dilution appeared to be inversely related to the length of time from exposure, with minimal efficacy noted in as little as 30 minutes.[50,51] In contrast, an in vivo canine model of alkaline injury demonstrated that water dilution did not cause an increase in either temperature or intraluminal pressures.[53]

The extrapolation of these variable results to humans with caustic ingestions is limited, and suggests that histologic damage can only be attenuated by milk or water when administered within the first seconds to minutes following ingestion.[6,50,51,52,53,65,114] For solid, as opposed to liquid, substances (eg, crystal lye), there may be

some value for delayed dilutional therapy, as tissue contact time is increased with solid agents and their concentration is usually 100% over a small surface area. Milk may be the best agent to attenuate the heat generated by a caustic.[112]

Caution should be used in advising patients or family members about the use of dilutional agents. A child who refuses to swallow or take oral liquids should never be forced to do so. In general, dilutional therapy should be limited to patients within the first few minutes after ingestion who have no airway compromise, who are not complaining of significant pharyngeal, chest, or abdominal pain, who are not vomiting and who are alert. Dilutional therapy should be avoided in patients with nausea, drooling, stridor, or abdominal distension as it may stimulate vomiting and result in reintroduction of the caustic into the upper gastrointestinal tract.[104]

Attempts at neutralization of caustics should likewise be avoided. This technique has the potential to worsen tissue damage by forming gas and generating an exothermic reaction. In vitro and ex vivo models demonstrate that neutralization of caustics generates heat, requires a large volume to attain physiologic pH, and may have limited usefulness in preventing histologic damage after the first several minutes of caustic exposure.[49,74,104] In one in vivo canine model, orange juice was used to neutralize sodium hydroxide-induced gastric injury and demonstrated no change in temperature or intraluminal pressure.[53] Despite this study, neutralization is not recommended at this time as there are no other data demonstrating that clinical outcome is improved.

Surgical Management

The decision to perform surgery in patients with caustic ingestions is obvious in the presence of either endoscopic or diagnostic imaging evidence of perforation,[126] severe abdominal rigidity, or persistent hypotension. Hypotension is a grave finding and often

indicates perforation or significant blood loss.

Many patients will not have an obvious indication for surgical intervention despite impending perforation, necrosis, sepsis, or delayed hemorrhage. Although more challenging to diagnose, all of these sequelae are potentially avoidable if surgery is performed early[89] as morbidity and mortality increase in patients whose surgery is delayed.[28,54,56,101,105] For this reason, some surgeons advocate surgery for all patients with grades II and III esophageal burns identified on endoscopy.[28,79] This aggressive approach allows for direct inspection of serosal surfaces and an opportunity for early surgical repair.

Multiple studies have attempted to codify the signs and symptoms necessary or sufficient to rapidly identify patients who would benefit from surgery, but who lack clear clinical indications. Several retrospective and prospective series of caustic ingestions found that patients with large ingestions (>150 mL), shock, acidemia, or coagulation disorders had severe findings on surgical exploration. These studies also reinforce that the abdominal examination was frequently unreliable in predicting the need for surgery.[105,126,128] It should be noted, again, that patients with severe acid injuries may lack abdominal pain, abdominal tenderness, and have positive findings on diagnostic imaging.[25,54,128] One author used a stepwise approach of bronchoscopy, endoscopy, and abdominal ultrasonography to provide additional information regarding extent of injury prior to surgery. Respiratory distress, ascites, pleural fluid, and a serum pH below 7.2 were used as indications for surgery.[126] A history of a large-volume caustic ingestion (between 40 and 200 mL) should also prompt consideration of early surgical intervention as delay is associated with increased mortality.[25,54,126]

Surgical intervention may include laparotomy for tissue visualization, resection, and repair of perforations. Laparoscopy may also be used, although it may not allow inspection of the

posterior aspect of the stomach.

Subacute Management

Grade I Esophageal Injuries

The extent of tissue injury dictates the subsequent management and disposition of patients with caustic ingestions. Patients with isolated grade I injuries of the esophagus do not develop strictures and are not at increased risk of carcinoma. Their diet can be resumed as tolerated. No further therapy is required. These patients can be discharged from the hospital as long as they are able to eat and drink and their psychiatric status is stable.

Grade IIa Esophageal Injuries

If endoscopy reveals grade IIa lesions of the esophagus and sparing of the stomach, a soft diet

can be resumed as tolerated, or a nasogastric tube can be passed under direct visualization. If oral intake is contraindicated because of the risk of perforation, feeding via gastrostomy, jejunostomy, or total parenteral nutrition should be instituted as rapidly as possible. Providing interim enteral support is imperative as metabolic demands are increased in any patient with a significant burn.

Grades IIb and III Esophageal Injuries

Patients with grades IIb and III lesions must be followed for the complications of perforation, infection, and stricture development. There is some evidence that grade III burns, in particular, will progress to stricture formation regardless of therapy.[4,45,80,119] Additionally, patients with grade III burns are also at high risk for other complications, including fistula formation, infection, and

perforation with associated mediastinitis and peritonitis. The use of corticosteroids in the management of these burns may mask infection and make the friable, necrotic esophageal tissue more prone to perforation.[92] For these reasons, steroid therapy is not recommended for grade III esophageal burns. When required in these patients for other indications such as caustic-induced airway inflammation, steroids should be administered in conjunction with antibiotics.

Strictures form as a result of the natural process by which the body repairs injured tissue through the production of collagen with resultant scar formation. Strictures are a debilitating complication of both acid and alkaline ingestions that can evolve over a period of weeks or months. A variety of management strategies have been used in an attempt to prevent strictures and esophageal obstruction. Currently, controversy exists regarding the use of steroid therapy in the management of grade IIb circumferential esophageal burns. Steroid therapy is theorized to arrest the process of inflammatory repair and potentially prevent stricture formation. A meta-analysis of studies completed from 1956â€“1991, with a total of 361 patients, evaluated the efficacy of corticosteroid therapy and found that in patients with grade II and grade III esophageal burns, strictures formed in 19% of the corticosteroid-treated group and in 41% of the untreated group.[55] The usefulness of the results of this study, however, are limited as no distinction was made between grade II and grade III burns. Another meta-analysis of studies from 1991â€“2003, with a total of 211 patients, was unable to find a benefit in treating patients with steroids with grade II and grade III esophageal burns.[92] However, no distinction was made between grade IIa and grade IIb lesions. In addition, a multitude of case series also failed to clearly differentiate between grades IIa, IIb, and III lesions, making clinical application of their results difficult.[4,19,80,83,105,119]

Two prospective studies attempted to evaluate the efficacy of steroid therapy for caustic injuries to the esophagus. The first

spanned an 18-year period during which a total of 60 children with caustic esophageal injury were randomized to corticosteroid therapy plus antibiotics or no corticosteroid therapy. In this study, circumferential burns (grades IIb and III) were distinguished from those that were not circumferential (grades I and IIa). The incidence of stricture was comparable for the treated and untreated groups.[3] This study is limited in that no distinction was made between grades IIb and III circumferential burns, and it lacked the power to find a 30% difference. The second prospective study spanned a 3-year period during which a total of 104 patients with grades IIa, IIb, or III lesions were treated with corticosteroids plus antibiotics or no corticosteroid therapy. In this study, although no distinction was made between grades IIa, IIb, or III burns, there was no evidence that corticosteroid treatment could prevent the development of strictures. Additionally, it was observed that patients treated with corticosteroids had a higher incidence of esophageal and antipyloric stenosis.[58]

Adequate human data demonstrating the efficacy of corticosteroids with or without antibiotics in the treatment of grade IIb circumferential lesions have yet to be generated. Although both prospective studies discussed above failed to demonstrate a benefit of corticosteroid treatment, it is imperative that the clinician understands that neither study clearly differentiates between grades IIb and III lesions. Because of the inherent risks involved in this therapy, and the paucity of data supporting their use, steroid therapy in the management of grade IIb esophageal burns can no longer be routinely recommended at this time.

No major outcome studies have investigated the use of antibiotics alone as prophylactic treatment for stricture prevention, but most clinicians would agree that it is probably best to reserve antibiotics for an identified source of infection.

In both animal models[100] and in human case series,[46,82,99] intraluminal stents and nasogastric tubes[82,123] made of silicone

rubber tubing can successfully maintain the patency of the esophageal lumen. For nutritional support, the stents are usually attached to a feeding tube secured in the nasopharynx through which the patient can receive feedings without interfering with esophageal repair. These tubes are left in place for 3 weeks.[99,100] and are often used with concomitant corticosteroid and antibiotic therapy. In animal models, the use of a stent for 3 weeks is superior in maintaining esophageal patency when compared to corticosteroids and antibiotics alone.[100]

Potential disadvantages of esophageal stents include mechanical trauma at the site and increased reflux, both of which may inhibit healing.[109] A feline model of esophageal exposure to sodium hydroxide used stents but reported deaths from aspiration and mediastinitis.[100] One series of 251 humans exposed to caustics who were managed with silicone rubber stents found that the procedure was successful in preventing stricture formation.[9]

Additionally, multiple xenobiotics have been studied in various animal models in an attempt to identify agents that either inhibit synthesis or stimulate breakdown of collagen and thereby prevent stricture formation. Î²-Amino propionitrile (BAPN), penicillamine, *N*-acetylcysteine (NAC), halofuginone, vitamin E, and colchicine are some of these agents.[116] BAPN was examined in a canine model in conjunction with dilation, and there was some suggestion that it was useful.[70] Both penicillamine and NAC were of some benefit in preventing strictures in rats and rabbits.[34,66,116] Halofuginone, a specific inhibitor of collagen type I synthesis, and vitamin E, a known antioxidant, significantly reduced esophageal stricture[91] and collagen synthesis in rats,[39] respectively. In addition, epidermal growth factor and interferon-Î³ also decreased collagen synthesis and stenosis following sodium hydroxide burns in rats.[8] Colchicine, which decreases collagen synthesis, was found to delay wound healing and was associated with stricture formation in rabbits with sodium hydroxide-induced esophageal burns. As none of these xenobiotics have been adequately studied

in humans, they cannot currently be recommended in the routine management of caustic ingestions.

Currently, in patients with endoscopically identified grade IIb lesions, esophageal stents may be considered for the prevention of esophageal strictures but steroids should not be routinely used.

Chronic Treatment of Strictures

Commonly, the management of esophageal strictures includes early endoscopic dilation for which a variety of types of dilators

are available. Contrast CT can be used to determine maximal esophageal wall thickness, which can then be used to predict response,[63] as well as the number of sessions required to achieve adequate dilation. Multiple dilations are often necessary. In one study, patients with a maximal esophageal wall thickness of 9 mm or greater required more than 7 sessions to achieve adequate dilation. This was significantly higher than in patients with a lesser maximal wall thickness.[63] Measurement of maximal wall thickness may be also be useful in determining long-term followup, type of nutritional support, and the potential need for surgical repair as an alternative to dilations. It may also provide an indication for those who should undergo dilations under fluoroscopy to limit the risk of perforation.

The risk of perforation from esophageal dilation is decreased if the initial procedure is delayed until at least 4 weeks postingestion, when healing, remodeling, and potential stricture formation in the esophagus have taken place. Several series report perforation secondary to esophageal dilation.[45,60,63,96,119] Following perforation, patients may complain of dyspnea or chest pain with associated subcutaneous emphysema or pneumomediastinum. Diagnostic imaging may identify the perforation and provide information for emergent surgical repair if the diagnosis is unclear.

Patients with stricture formation require long-term endoscopic followup for the presence of neoplastic changes of the esophagus that may occur with a delay of several decades.[5]

Management of Ophthalmic Exposures

Ophthalmic exposures frequently occur from splash injuries, and, more recently, from the alkaline byproducts of sodium azide released in automobile air bag deployment and rupture.[121] The mainstay of therapy for these patients is immediate irrigation of the eye for a minimum of 15 minutes with 0.9% sodium chloride, lactated Ringer solution, or tap water, if it is the only agent immediately available. Several liters of irrigation fluid are recommended. The normal pH of ophthalmic secretions is close to 7.40. This can be tested colorimetrically by using a urine dipstick, which can test a range of pH from 5 to 9 using a color chart.[77] Litmus paper can be used in the same fashion. Another option is Nitrazine paper, which changes color from yellow to dark blue at a pH above 6.5,[32] and which may be useful in acid exposures. These different test strips can be applied to the ophthalmic secretions to test the baseline pH, and followed with intermittent evaluations after 15 minutes to determine the adequacy of irrigation. If these xenobiotics are not readily available, irrigation should not be delayed, as the depth of penetration of the caustic agent will determine outcome. Anterior chamber irrigation may be required; if required, it is performed emergently by an ophthalmologist. A thorough eye examination should be completed and followup should be arranged. Chapter 20 contains a more detailed description of the evaluation and management of toxicologic emergencies of the eye.

Summary

Assessing the severity of injuries in patients with caustic exposures can be clinically challenging. For all patients with

caustic exposures, the primary consideration is basic decontamination of the patient, as well as adherence to universal precautions by healthcare professionals, in an effort to prevent further exposures. For patients with ingestions, this must be immediately followed by airway assessment and stabilization and consideration of multiple bedside, laboratory, and diagnostic imaging factors to decide how best to inspect the tissues of the gastrointestinal tract. Ideally, early in the course of management, gastroenterologists and surgeons are involved in the care of the patient, so that any surgical intervention deemed necessary can be performed promptly. Exposures to the skin and eyes require rapid decontamination with simple irrigants such as 0.9% sodium chloride solution.

Household and industrial exposures to caustic agents constitute a potentially life-threatening global health concern. Public health efforts, such as the successful implementation of child-proofing caustic substance containers and limiting the concentration of caustic agents in household items in the United States should be encouraged in developing nations as well.

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Chapter 101
Hydrofluoric Acid and Fluorides

Mark Su

A 32-year-old migrant worker was asked to clean graffiti off a building. After cleaning a single facade of a building with hydrofluoric acid solution on a sponge, he noticed intense pain to his right (dominant) hand. He presented to the emergency department 6 hours later. He complained of severe hand pain but had a normal physical examination. A calcium gluconate slurry was made and placed in a sterile surgical glove that the patient wore on his right hand. The patient's pain temporarily resolved but recurred after 20 minutes. An additional calcium gluconate slurry was made and the same therapy was applied with the same result. The patient was admitted to the hospital for pain control with opioids. Over the next 12 hours, the skin of the affected hand appeared raised, dusky, and pale on the palmar surface. The hand surgery service transferred the patient to the regional burn center. At the burn center, debridement of the abnormal-appearing tissue was performed. The patient was discharged after several days in the hospital and was lost to followup.

History and Epidemiology

Hydrofluoric acid (HF) has been known for centuries for its ability to dissolve silica. The Nuremberg artist Schwanhard is given credit for the first attempt (in 1670) to use HF vapors to etch glass.[40] Since then, HF has developed multiple uses in addition to glass etching, such as brick cleaning, etching microchips in the semiconductor industry, electroplating, leather tanning, rust removal, and the cleaning of porcelain.[22,40] During the past 3 years, the American Association of Poison Control Centers (AAPCC) has reported more than 2000 exposures to HF and several deaths. Hand exposures are by far the most common presentation. Exposures to HF are often unintentional and they can be an occupationally related hazard. The actual number of work-related poisonings from HF appears difficult to quantitate because of limitations in ICD (*International Classification of Diseases*) medical coding and lack of notification of regional poison centers by worksites.[7]

Hydrofluoric acid is also the most common cause of fluoride poisoning, although other forms of fluoride, including sodium fluoride (NaF) and ammonium bifluoride (NH_4HF_2), may also produce significant toxicity. Historically, sodium fluoride has been used as an insecticide, rodenticide, antihelminthic agent in swine, and a delousing powder on poultry and cattle. Ammonium bifluoride is mainly used in industrial inorganic chemistry, especially in the processing of alloys and in glass etching. Other sodium salts are widely used in, for example, the steel industry, drinking water, toothpaste additives, electroplating, lumber treatment, and the glass and enamel industries.

The widespread use of HF and fluoride-containing compounds has resulted in significant toxicity. In 1988, an oil refinery in Texas released a cloud of hydrogen fluoride gas that resulted in 36 people requiring hospital treatment.[40] The petroleum industry has been plagued by similar HF incidents since then. NaF was

responsible for the poisoning of 263 people and 47 fatalities when it was mistaken for powdered milk and unintentionally combined with scrambled eggs.[50] These and other forms of fluoride salts can be converted to HF in vivo after ingestion. Consequently, many inorganic fluoride compounds can result in significant fluoride toxicity, especially when large exposures occur.

Chemistry

Hydrofluoric acid has unique properties that can cause life-threatening complications following seemingly trivial exposure. Anhydrous HF is highly concentrated (>70%) and used almost exclusively for industrial purposes. The aqueous form of HF, which generally ranges in concentrations from 3â€“40%, is commonly used in both industrial and household products.

Hydrofluoric acid is synthesized as the product of gaseous sulfuric acid and calcium fluoride, which is subsequently cooled to a liquid.[51] The pK_a of aqueous HF is 3.5; consequently, it is classified as a weak acid. As such, it is approximately 1000 times less dissociated than equimolar hydrochloric acid.

NaF is commonly synthesized by the reaction of sodium hydroxide (NaOH) with HF, with subsequent purification by recrystallization. Compared to other fluoride salts that are relatively water insoluble, such as potassium fluoroborate and potassium hexafluorophosphate, NaF is highly soluble and readily dissociates.[2]

To synthesize NH_4HF_2 ammonium fluoride (NH_4F) is first formed by the reaction of ammonium hydroxide (NH_4OH) and HF. Ammonium fluoride is then converted to bifluoride by dehydrating an aqueous solution.

Pathophysiology

Exposures to HF occur via dermal, ocular, inhalation, and oral

routes with one reported case of toxicity from an HF enema.[15] A permeability coefficient of 1.4 Ã— 10^{24} cm/sec allows HF to penetrate

deeply into tissues prior to dissociating into hydrogen ions and highly electronegative fluoride ions.[28] These fluoride ions avidly bind to extracellular and intracellular stores of calcium and magnesium, ultimately leading to cellular dysfunction and cell death.[8,49,58] The alteration in local calcium homeostasis probably causes neuroexcitation and accounts for the development of neuropathic pain.

There are several theories regarding the fate of calcium and fluoride ions in tissues. Formation of insoluble calcium fluoride (CaF_2) is proposed as the etiology for both the precipitous fall in serum calcium concentration and the severe pain associated with tissue toxicity. In vitro evidence suggests that fluorapatite is formed in the presence of phosphate and hydroxyapatite. This may be a more likely pathway for deposition of the fluoride ion.[8]

In the anhydrous form, the high concentration of hydrogen ions in HF also produce a corrosive burn similar to that caused by strong acids.

A final mechanism for fluoride toxicity includes in vitro evidence for the interference of many enzyme systems by binding with magnesium and manganese. The minimal lethal dose in humans is approximated to be 1 mg/kg of fluoride.[40]

Clinical Manifestations

Local Effects

Skin

The extent of tissue injury in dermal exposures is determined by

the volume, concentration, and contact time with the tissues. Dermal exposures to HF typically involve low concentrations of the agent. Following dermal exposure, it is usually recognized that the higher the concentration of HF, the more rapid the onset of excruciating pain at the site of contact.[26,51,83] Concentrations of greater than 50% cause immediate pain with visible tissue damage.[78] Household rust-removal products have concentrations ranging between 6 and 12%. Consequently, exposure to these products often result in a delay of several hours before patients develop pain.[26,79,87,88] The initial site of injury may also appear relatively benign, despite significant subjective complaints of pain. Over time, the tissue may become hyperemic, with subsequent blanching and coagulative necrosis as calcium precipitates.[67] (See ILHFHAND in the Image Library at http://www.goldfrankstoxicology.com) Ulcerations may form at a rate dependent on the concentration and duration of contact.[22,41,52] If more than 20% of the body surface area is burned with high-concentration HF, life-threatening systemic toxicity should be expected.[16,64,66,78,83] Small body surface area exposures to low concentrations typically do not result in life-threatening systemic toxicity, although fatalities have resulted with dermal exposures to concentrated (anhydrous) HF covering only 2.5% body surface.[83]

Pulmonary

Patients with inhalational exposures can present with a variety of signs and symptoms depending on the HF concentration and exposure time. Thirteen oil refinery workers exposed to a low-concentration HF mist experienced minor upper respiratory tract irritation.[47] Alternatively, in a mass inhalational exposure to HF, throat burning and shortness of breath were among the more common chief complaints.[91] Some of these patients had altered pulmonary function tests and hypoxemia, and 16% developed hypocalcemia. Stridor, wheezing, rhonchi, and erythema and

ulcers of the upper respiratory tract were described. Eye pain was also noted, reinforcing that ophthalmic injury can accompany inhalational or dermal exposures.[47,56,73,91]

Gastrointestinal

Intentional ingestion of concentrated HF (or other fluoride-containing compounds such as NaF) causes significant gastritis yet often spares the remainder of the gastrointestinal tract. Patients promptly develop vomiting and abdominal pain. Although systemic absorption is rapid and almost invariably fatal, there is at least one report of a patient with an ingestion of a low concentration of HF who suffered multiple episodes of ventricular fibrillation and was successfully resuscitated.[81] Following HF ingestion patients may present with an altered mental status, airway compromise, and dysrhythmias.[10,50,53,81]

Ophthalmic

Hydrofluoric acid appears to result in more extensive injury to the eye than most other acids.[59] Ophthalmic exposures from liquid splashes or hydrogen fluoride gas denude the corneal and conjunctival epithelium, and lead to stromal corneal edema, conjunctival ischemia, sloughing, and chemosis.[40] Fluoride ions can penetrate deeply to affect the anterior chamber structures.[40] The effects are usually noted within one day.[40] Other possible findings include corneal revascularization, recurrent epithelial erosions, and, sometimes, keratoconjunctivitis sicca (dry eye) developing as a long-term complication.[4,59,74]

Systemic Effects

Significant systemic toxicity can occur via any route because of the ability of HF to penetrate tissues. Potential for systemic toxicity is an important consideration in the management of these

patients as they should be rapidly decontaminated and treated.[9,13,27,77,78,84,85] As these examples describe, fatal exposures to HF share the similar features of hypocalcemia, hypomagnesemia, and, in many cases, hyperkalemia as preterminal events.[2,10,19,27,46,51,53,60,61,83] In some circumstances, the hypocalcemia severely disrupts the coagulation cascade, resulting in coagulopathy on postmortem examination.[53,62,63]

Fatalities from HF may occur as a result of either sudden-onset myocardial conduction failure or ventricular fibrillation. Although the evidence regarding the mechanism of myocardial irritability is inconclusive, electrolyte disturbances that lead to ventricular dysrhythmias and fibrillation are thought to be the primary cause of death in patients with severe systemic fluoride poisoning.[16,64,78,83,94] Some postmortem cases reveal significant structural myocardial injury.[62] However, these findings are inconsistently encountered in humans and in animal cardiac arrest models that fail to demonstrate any histologic abnormalities of the myocardium.[21,57]

Most theories regarding myocardial irritability relate to the hypocalcemia causing an efflux of potassium ions into the extracellular space.[21,49,62] The subsequent hyperkalemia may alter the automaticity and resting potential of the heart, leading to fatal dysrhythmias.[61] Dogs treated with quinidine, a potassium efflux blocker, are protected from lethal doses of intravenous sodium fluoride.[21] Likewise, the antidysrhythmic agent amiodarone, which also possesses potassium efflux blockade properties, has demonstrable efficacy both in vitro and in vivo.[18,82] However, efficacy in humans has not been studied or documented. Furthermore, the mechanism of toxicity may be much more complicated.[96] A child with systemic fluoride toxicity, who was appropriately repleted with calcium, and who had normal electrolytes still experienced nonfatal ventricular fibrillation.[9,96] Perhaps this is because serum potassium, calcium,

and magnesium concentrations only partly represent tissue concentrations.[8,9,21,60,61] Furthermore, HF may directly impair myocardial function. Rabbits exposed to topical HF over 2% of their total body surface area developed focal necrosis of myocardial fibers, as well as significant elevations in cardiac enzymes that persisted for almost 5 days after injury.[95]

Assessing Severity of Clinical Exposures

Historical and clinical features of an exposure will determine which HF exposures are life-threatening. All oral ingestions and inhalational exposures should be considered potentially fatal, as well as burns of the face and neck, regardless of HF concentration. Inhalational exposure should be assumed for all patients with skin burns of greater than 5% body surface area, exposure to HF concentrations greater than 50%, and head and neck burns.[39] Patients presenting with altered mental status are critically ill and necessitate rapid therapy.

Hydrofluoric acid concentrations of greater than 20% have potential for significant toxicity in a patient even if only a small surface area has been exposed. As a general rule, patients who experience severe pain within minutes of contact are most likely exposed to a very high concentration of HF and their condition can rapidly deteriorate. An otherwise well-appearing patient may have a precipitous demise without any clinical manifestations of hypocalcemia.

Diagnostic Testing

Diagnostic testing for systemic fluoride poisoning is currently based on monitoring of serum electrolytes. Ionized calcium should be serially monitored along with magnesium and potassium.[27]

Additional information may be obtained from a venous or arterial blood gas analysis. As systemic toxicity progresses, there is potential for development of metabolic acidosis.[8] Serum fluoride concentrations may be assessed but the results will not be returned in a clinically relevant timeframe. Although a serum fluoride concentration of 0.3 mg/dL has been reported as a fatal, one patient survived with a serum fluoride concentration of 1.4 mg/dL.[83,96]

Electrocardiographic findings of both hypocalcemia (prolonged QTc interval duration) and hyperkalemia (peaked T waves), in both human case reports and in dog studies, may be reliable indicators of toxicity.[2,13,27,35,63,83] In fact, ECG findings of peaked T waves from hyperkalemia have preceded the onset of ventricular dysrhythmias, thus potentially serving as a marker of severe fluoride toxicity.[9,60] The ECG is therefore an important screening tool for systemic fluoride toxicity and may also be used to monitor therapeutic efficacy.

Management

General

For all types of exposures, the mainstay of management is to prevent or limit systemic absorption, assess for systemic toxicity, and rapidly correct any electrolyte imbalances. Intravenous access should be obtained. An ECG should be examined for signs of hypocalcemia, hypomagnesemia, and hyperkalemia. The patient should be placed on continuous cardiac monitoring, and have a rapid assessment of serum electrolyte concentrations. A Foley catheter should be placed as needed to follow urine output.

Rapid airway assessment and protection should occur early in patients with inhalation or ingestion, respiratory distress, ingestion with vomiting, or burns significant enough to cause a

change in mental status or voice.

For patients with less-significant dermal exposures, recent studies have focused on alternatives to irrigation with water or saline as topical decontamination techniques. One group advocates the use of the compound Hexafluorine for dermal and ocular decontamination of HF splashes.[54,80] Despite anecdotal supportive data, in a controlled and blinded experimental study Hexafluorine treatment was less effective than irrigation with water followed by the application of topical calcium.[34] In a followup animal study, water irrigation was as effective as Hexafluorine in preventing systemic toxicity from HF.[36] At this time, until further objective data are available, it is premature to recommend the routine use of Hexafluorine for initial decontamination of HF exposures. Topical iodine ointment was studied for HF-induced burns in guinea pigs.[92] Iodine has demonstrated protective effects against burns from various alkylating agents, including mustard gas, and is hypothesized to inhibit apoptosis.[92] Because experience with iodine treatment of human HF burns is lacking at this time, it cannot be recommended. To prevent absorption from dermal exposures, irrigation with copious amounts of water should be done. The most important therapy for skin exposures is rapid removal of clothing and irrigation of the affected area with copious amounts of water or saline, whichever is more readily available.[1,44,48,52]

One report describes a woman who was dying from severe HF toxicity who was treated by amputation of the affected limb, and survived. Although not routinely recommended, this may be an alternative measure for patients who are inadequately responding to all other therapeutic modalities.[12,43]

Dermal Toxicity

Several therapeutic options have been studied and described in animal models for treatment of topical HF burns. Unfortunately,

many study designs use histologic or subjective wound inspection as outcome parameters,[14,69] some with unblinded inspection.[11,24,43,44] These animal models do not address the parameters of pain reduction, cosmesis, and functionality that are clinically important.

Topical calcium gel should be applied to the affected area. This is prepared by mixing 3.5 g of calcium gluconate powder in 150 mL of sterile water-soluble lubricant, or 25 mL of 10% calcium gluconate in 75 mL of sterile water-soluble lubricant.[1,14,39] If calcium gluconate is unavailable, calcium chloride or calcium carbonate can be used in a similar formulation.[17] Topical therapy for both severe and nonâ€“life-threatening exposures scavenges fluoride ions. An animal study examining the efficacy and mechanism of topical calcium gel therapy found that the fluoride ion concentration of the calcium gel was significantly higher than nonâ€“calcium-containing gel controls. Although a limited study, these animals also had a decrease in urinary fluoride ion concentration as compared to controls, suggesting less overall absorption of the HF into the tissues.[44] Quaternary ammonium compounds, such as topical benzalkonium chloride, have also been advocated in the treatment of HF burns and can be used when available;[52] however, calcium-containing gels appear to be more efficacious. Delivery of calcium transcutaneously may be enhanced by various means. In a rodent study of HF burns, iontophoretic (facilitated transport using an electromotive force) delivery of calcium

appeared to increase calcium concentrations in vitro and improve pathologic changes in vivo.[93] Significant limitations to this study are time to administration of therapy and feasibility in patients with complex burns.[75] Human data are lacking. Dimethyl sulfoxide (DMSO) mixed with topical calcium salts may also facilitate the transport of calcium ions through the skin to penetrate deeply into the tissues. It also is able to act as a scavenger of free radicals,

thus limiting inflammation and ongoing injury.[30] Although one group of authors recently advocated the combined use of DMSO and calcium,[30] concerns remain over reported adverse effects of DMSO.[40] There is currently inadequate data to support the use of DMSO in the treatment of HF burns.

Four therapies have had variable success in human exposures: the application of calcium via topical, intradermal, intravenous, and intraarterial routes. After irrigation, a gel solution of calcium carbonate or gluconate can be mixed directly into a sterile surgical glove and then placed on the patient's hand for 30 minutes. Two case series report limited success with this therapy.[1,17] Some patients describe prompt and dramatic relief of pain. Alternatively or simultaneously, analgesics can be administered orally or intravenously as needed, but preferably not to the point of sedation, because local pain response will guide therapy. Digital blocks with subcutaneous lidocaine or bupivacaine can be used for patients presenting 12â€“24 hours after the injury from a low concentration of HF and no systemic signs of toxicity.[23]

If topical gel therapy fails within the first few minutes of application, consideration should be given to intradermal therapy with calcium gluconate, because the benefit in pain control often occurs immediately. This treatment may have limited usefulness, however, in small spaces, such as fingertips. Histologic studies in animal models demonstrate that 10% calcium chloride solution can be damaging to the tissues and should be avoided.[23,29] The preferable method is to approach the wound from a distal point of injury and inject intradermally no more than 0.5 mL/cm^2 of 5% calcium gluconate. Although one author recommends a palmar fasciotomy whenever this method of treatment is used,[1] this practice is not currently recommended unless a compartment syndrome is present. The potential for iatrogenic injury exceeds potential benefit. The limits of intradermal injection include the potential to increase soft-tissue damage without adequate relief, infection, and inadequate space to safely inject without causing a

compartment syndrome. Effective pain relief is especially problematic for nail involvement, leading some authors to suggest removal of the nail. This approach has some advantages in accessing the affected area; however, it is a painful procedure that is often cosmetically undesirable and the outcome is not always significantly improved. If considering local injection of calcium salts, distensible areas of the body such as the arm or thigh are acceptable, but injection into the digits should be avoided.

If the wound is large or on a section of the fingerpad or an area that is not amenable to intradermal injections, consideration should be given to the use of intraarterial calcium gluconate. This procedure delivers calcium directly to the affected tissue from a proximal artery. Placement should be ipsilateral and proximal to the affected area, usually in the radial or brachial artery. The method of obtaining access is somewhat debated. Because of the potential to damage the endothelial lining of the artery, and because extravasation can have potentially devastating consequences, angiographic confirmation or direct visualization of the vessel was formerly recommended. This practice is still prudent if cannulation of the artery is expected to be difficult because of prior surgery or if an anatomic deformity is suspected. If the arterial line is carefully placed in a single attempt, and a good confirmatory arterial tracing is obtained, the infusion can be started. The recommended protocol consists of 10 mL of 10% calcium gluconate added to either 40 mL of D_5W (dextrose 5% in water) or 0.9% sodium chloride solution infused continuously over 4 hours.[1,42,70,79,87,88] This results in a 2% calcium gluconate solution. An animal model examined the effect of undiluted 10% calcium gluconate intraaortically. Although the model did not involve exposure to HF, there was significant tissue injury in the vessel wall as compared to a 2% calcium gluconate solution.[23] Calcium chloride has also been used successfully, although the potential for vessel injury and extravasation are significant and there is no defined benefit over calcium gluconate.[86,97] The

complications associated with the use of intraarterial calcium infusion in several case series were relatively benign, and include radial artery spasm, hematoma, inflammation at the puncture site, and a fall in serum magnesium.[79,87] After the infusion is initiated, patients typically experience significant pain relief. Patients requiring an arterial line for treatment should be admitted to the hospital, as the majority will require more than one treatment, and some patients may require as many as five separate infusions of calcium gluconate. Although wounds may require dÃ©bridement,[1] some suggest that following intraarterial calcium infusion, tissue can be salvaged that initially would not have been considered viable.[88] There have been no reported cases of clinically significant hypercalcemia following infusion as the total dose infused is quite low, although serum calcium concentrations were not always routinely recorded.

Administration of magnesium salts is an alternative or adjunctive therapy to the administration of calcium for dermal HF burns. Magnesium hydroxide and magnesium gluconate gel used in rabbit models show some histologic evidence of efficacy in dermal HF burns.[14] Two other animal models of intravenous magnesium for the management of dermal HF burns also suggest efficacy in terms of wound healing.[20,90] In theory, magnesium appears to be an excellent antidote for fluoride poisoning because magnesium fluoride is more soluble than calcium fluoride and magnesium is readily excreted by the kidneys.[90] However, these magnesium models are limited and both topical and intravenous magnesium therapy are insufficiently evaluated in humans.

Another reported therapy for localized HF poisoning is an intravenous Bier block technique that uses 25 mL of 2.5% calcium gluconate. In one case, the effects lasted 5 hours and there were no adverse events.[33] In two other cases of patients exposed to HF, a 6% calcium gluconate solution administered using this procedure resulted in rapid and complete analgesia and minimal tissue necrosis.[76] Although the intravenous Bier block technique is not

reported as being used in a substantial number of patients, it may be particularly useful when intraarterial infusion is problematic.[76] Further data are required before this therapy is routinely recommended.

All patients with digital exposures should be observed over 4â€“6 hours, as the pain is likely to recur and reapplication of the gel or an alternative therapy may be necessary. Even if successful pain control is achieved, the patient will require specialized followup and wound care.

Inhalational Toxicity

Patients with symptomatic inhalational injuries can be treated with nebulized calcium gluconate. A report of patients exposed to a low concentration of HF and treated with 4 mL of a 2.5% nebulized

calcium gluconate solution demonstrated a subjective decrease in irritation with no adverse effects.[47] Another report demonstrated a good outcome following nebulization of a 5% calcium gluconate solution in a patient with an inhalational exposure.[45] Because nebulized calcium gluconate appears to be a relatively benign therapy, it should be given to all patients with symptomatic inhalational exposures to any concentration of HF because of the possibility of systemic toxicity.[25]

Ingestions

In patients with intentional ingestions of HF, gastrointestinal decontamination poses a dilemma. Induction of emesis is also potentially harmful. Although placement of a nasogastric tube to perform gastric lavage in these patients is clearly associated with risks to the patient, insertion of a nasogastric tube may be beneficial if safely done and in a timely manner. Consequently, gastric emptying via a nasogastric tube should be considered

because these exposures are almost universally fatal.[2,10,53,63] Healthcare providers should exercise extreme caution during this procedure because dermal or inhalational exposures can occur in the absence of appropriate protection. Because aqueous HF is a weak acid, the risk of perforation by passage of a small nasogastric tube may be lower than the risk of death from systemic absorption.[2,53] In the acidic environment of the stomach, more of the weak acid solution remains unionized, thus penetrating the gastric mucosa and causing rapid systemic poisoning. Moreover, activated charcoal is unlikely to adsorb the relatively small fluoride ions.

If an oral exposure occurs, a solution of calcium or magnesium salt should be delivered to the stomach as soon as possible to prevent HF penetration and to provide an alternative source of cations for the damaging electronegative fluoride ions.

When comparing the efficacy of calcium to magnesium salts, calcium may be better than magnesium in reducing the bioavailability of fluoride as described in a murine model.[32] Magnesium citrate (in a standard cathartic dose; see Antidotes in Depthâ€"Calcium), magnesium sulfate, or any of the calcium solutions can be administered orally to prevent absorption. Although intuitive, evidence for the benefit of oral calcium or magnesium salts is limited. In a mouse model of oral HF toxicity, administration of calcium- or magnesium-containing solutions did not change average survival time.[31] The study results, however, were limited because the calcium and magnesium salts were premixed together with the HF during administration, thus being an atypical model of HF ingestion. In a more recent study, the survival rate of mice poisoned with NaF was significantly greater when treated with high doses of oral $CaCl_2$ or $MgSO_4$.[38]

Ophthalmic Toxicity

Patients with ophthalmic exposures should have each eye irrigated

with 1 L of 0.9% sodium chloride solution, lactated Ringer solution, or water.[59] Although there are limited data, repetitive or prolonged irrigation appears to worsen outcome.[59] A complete ophthalmic examination should be performed after the patient is deemed stable, and an ophthalmology consultation should be obtained. One case report demonstrated a good outcome following ocular HF exposure with the use of 1% calcium gluconate eyedrops.[4] Although two recent reviews also recommend the use of 1% calcium gluconate for this purpose,[25,30] calcium salts tend to be irritating to the eye and this therapy has not been adequately studied; consequently, routine use is not indicated at this time. There is no role for gel therapy or intraocular injection in these patients, again, because most calcium and magnesium salts are potentially toxic to ocular tissues and may actually worsen outcome.[3,59]

Systemic

If there is a clinical suspicion of severe toxicity, the immediate intravenous administration of calcium and magnesium salts is recommended. In general, calcium gluconate is preferred over calcium chloride because of the risks associated with extravasation (see Antidotes in Depth: Calcium). Patients can require several grams of calcium to treat severe HF toxicity.[27,81] Intravenous magnesium can be administered to adults as 20 mL of a 20% solution (4 g) over 20 minutes. An approach that uses intravenous calcium or magnesium, and local calcium or magnesium gels to limit absorption may protect against life-threatening hypocalcemia and hyperkalemia. An animal model of hydrogen fluoride toxicity found that maintaining a normal acidâ€“base balance was protective against HF toxicity.[72] Furthermore, in a study of patients receiving enflurane anesthesia, urine alkalinization improved the excretion of fluoride.[71] Thus, it may be beneficial to correct any significant acidemia with hydration and IV sodium bicarbonate.

Treatment with large quantities of calcium and magnesium has not generally resulted in significant hypercalcemia or hypermagnesemia.[25] Several explanations are proposed. First, total-body calcium and magnesium stores are severely decreased so that large doses are required for adequate repletion. Also, most patients who are exposed to HF, are young and healthy, with intact renal function.[25] Administration of calcium also results in antidiuretic hormone antagonism on renal tubular reabsorption resulting in polyuria which facilitates the urinary excretion of calcium and magnesium.[25]

Standard treatment for systemic fluoride toxicity includes administration of calcium salts and sodium bicarbonate, which may also antagonize hyperkalemia.

Because most of the fluoride ions are eliminated renally,[5,37,44,77] hemodialysis may be considered in patients with severe HF poisoning if renal function is compromised. There are several reported cases of successful clearance of fluoride ions via hemodialysis with one case also using continuous venovenous hemodialysis.[5,6] Because the reported clearance rate did not differ significantly from normally functioning kidneys, it is unclear whether hemodialysis alters outcome in patients with normal renal function.

Although the use of quinidine is protective in dogs,[62] it has not been studied or used in humans, and at this time cannot be routinely recommended.

Summary

Hydrofluoric acid and fluoride salts are extremely potent cellular toxins. Hydrofluoric acid exposure typically results in isolated local tissue damage but may also result in severe systemic toxicity and death especially in large exposures. Fluoride salts cause systemic toxicity only when ingested. Development of fluoride toxicity is

dependent on many variables including form, concentration, route(s) of exposure, and immediacy and completeness of decontamination, as well as premorbid health conditions. Treatment consists of immediate decontamination, protection of staff, rapid administration of agents to detoxify fluoride ions, enhancement of

elimination of fluoride ions, and, rarely, extracorporeal removal. It is imperative for physicians to be aware of the potentially deceptive nature of the fluoride toxin, as well as the possible therapeutic modalities used to treat these patients.

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Antidotes in Depth

Calcium

Mary Ann Howland

Calcium is essential in maintaining the normal function of the heart, vascular smooth muscle, skeletal system, and nervous system. It is vital in enzymatic reactions, in neurohormonal transmission, and in the maintenance of cellular integrity.[28,45] The endocrine system maintains calcium homeostasis. Approximately half of the total serum calcium is ionized and active, and the remainder is bound to albumin. Hypercalcemia raises the threshold for nerve and muscle excitation, resulting in muscle weakness, lethargy, and coma.[28] Hypocalcemia can result in tetany and seizures (Chap. 17).[28]

Calcium Channel Blockers

Calcium enters cells in numerous ways; of these, only the voltage-dependent L-type channels in cardiac and smooth muscles are inhibited by calcium channel blockers (CCBs) available in the United States.[4,62] Because CCBs do not alter either receptor-operated channels or the release of calcium from intracellular

stores,[66] in overdose with CCBs, the serum calcium concentration remains normal. Calcium channel blocker overdoses (Chap. 58) may result in hypotension, myocardial depression, bradycardia, sinus arrest, atrioventricular (AV) block, shock, pulmonary edema, altered mental status, nausea, vomiting, constipation, metabolic acidosis with hyperglycemia, and seizures.[51]

Intravenous administration of calcium to dogs poisoned with verapamil or diltiazem improves cardiac output secondary to an increase in inotropy.[4,26] Heart rate and cardiac conduction are affected minimally, if at all, until much larger doses of calcium are given.[22,26,58] Case reports and reviews of the literature suggest similar findings in humans.[1,2,12,21,30,41,54,55,64]

Calcium should be administered to symptomatic patients with CCB overdoses. Unfortunately, the sickest patients respond inadequately, and other measures are often required. The dose of calcium needed to treat patients with CCB overdose is unknown. In animal experiments, there appears to be a dose-related improvement.[12,26] The customary approach is to administer an initial intravenous dose of 3 g of calcium gluconate (30 mL of 10% calcium gluconate) or 1 g of calcium chloride (10 mL of 10% calcium chloride) in adults.[51] Based on recent case reports, this dose may need to be repeated every several minutes, as needed. The hypothesis is that sufficient calcium needs to be present to compete with the CCB for binding to the L-type calcium channel. One author used a total of 10 g of calcium gluconate as 1 g boluses over 12 minutes after diltiazem-induced asystole and another 2.5 g of calcium gluconate minutes later for a second asystolic event, for a total of 12.5 g of calcium gluconate over 28 minutes in an adult. The corrected serum calcium concentration was 3.36 mmol/L (normal: 2.2â€“2.6 mmol/L) about 1 hour after administration of the calcium gluconate.[32] Several authors have successfully treated patients with a total of 18â€“30 g of calcium gluconate either by intermittent bolus dose or infusion without adverse effects.[12,40]

However, if calcium is administered to a patient with cardioactive steroid toxicity, it could prove quite harmful.[25,70] In the event of concurrent overdose with both a cardioactive steroid and a calcium channel blocker, the early use of digoxin-specific antibody fragments should enable the subsequent safe use of calcium.

Therapy in children is based on even more limited data. The current pediatric guidelines of the American Heart Association[24] suggest an initial dose of 20 mg/kg of 10% calcium chloride (0.2 mL/kg) up to the adult dose infused over 5â€“10 minutes, followed by infusions of 20â€“50 mg/kg/h if a beneficial effect is observed. They suggest calcium chloride based on one study that compared the chloride to the gluconate salt in critically ill children.[11] However, in patients in cardiac arrest, this dose can be given by slow intravenous push over 10â€“20 seconds.[24] This dose should be repeated as necessary. Extrapolating from adult data, repeating the dose every several minutes is warranted, depending on the life-threatening nature of the ingestion. Calcium chloride can be irritating to tissues if extravasated, leading to necrosis and the need for skin grafting.[37] Consequently, calcium gluconate may be preferable. A starting dose in children should be about 60 mg/kg of 10% calcium gluconate (0.6 mL/kg) titrating to the adult dose if needed. To avoid hypercalcemia, serum calcium concentration should be monitored when more than 2 doses are administered.

Ethylene Glycol

Ethylene glycol poisoning (Chap. 103) results in the generation of oxalic acid, which complexes with calcium and subsequently precipitates in the kidneys, brain, and elsewhere, resulting in hypocalcemia.[1,31,50,62,65] After exposure to ethylene glycol, serum calcium should always be monitored. Signs of hypocalcemia include prolongation of the QTc interval on the electrocardiogram (ECG), the presence of Chvostek and Trousseau signs, and tetany. Intravenous calcium should be administered in the customary

doses (as above) to patients with these findings, accompanied by frequent monitoring of serum calcium.

Hydrofluoric Acid and Fluoride and Bifluoride Salts

Soluble salts of fluoride and bifluoride (eg, sodium, potassium, and ammonium) have all of the toxicity associated with hydrofluoric acid and should be managed accordingly. Any body contact with hydrofluoric acid (Chap. 101) can result in severe burns and death, depending on concentration and duration of exposure. The pathophysiologic derangements noted result from (a) release of free hydrogen ions; (b) complexation of fluoride with calcium and magnesium to form insoluble salts, which cause cellular necrosis; (c) liberation of potassium ions; and (d) cellular dehydration.[7,8,13,20,42,44,46,67] Following hydrofluoric acid exposure, the gluconate salt of calcium is used topically and subcutaneously to manage minor to moderate cutaneous burns, intravenously to treat systemic hypocalcemia, and intraarterially to manage significant

burns.[1,7,8,13,14 and 15,18,20,23,42,44,47,52,57,59,61,67,68 and 69,73] Experimental studies demonstrate that when concentrated hydrofluoric acid burns are immediately flushed with water and then covered with 2.5% calcium gluconate gel or topical dimethyl sulfoxide (DMSO)/10% calcium gluconate plus subcutaneous 10% calcium gluconate, there is a significant reduction in burn size.[8,67] A randomized clinical trial comparing the DMSO/calcium gluconate combination to calcium gluconate alone is currently underway in Australia.[27] Although a DMSO preparation is not commercially available, a 2.5% calcium gluconate topical gel is marketed. In the event that the commercial preparation is inaccessible, a topical calcium gel can be prepared from calcium carbonate tablets or calcium gluconate powder or solution, and a water-soluble jelly

such as K-Y Jelly (mix 3.5 g calcium gluconate powder or 25 mL of calcium gluconate 10% solution or 10 g of calcium carbonate tablets with 5 ounces of K-Y Jelly). An experimental study in rats demonstrated that iontophoretic delivery of calcium chloride appeared to enhance the delivery of calcium and to reduce the burn area significantly if applied within 30 minutes and may be a promising modality in the future.[58,72]

The chloride salt is also acceptable for topical therapy. Calcium chloride should never be injected if subcutaneously extravasated, it can result in severe tissue necrosis.

Deaths from hypocalcemia secondary to skin, gastrointestinal, and inhalational hydrofluoric acid toxicity are documented in the literature.[14,23] In severe hydrofluoric acid exposures, aggressive administration of intravenous calcium using a Bier block technique (10 mL of 10% calcium gluconate plus heparin 5000 units in a total volume of 40 mL) or intraarterial calcium (10 mL of 10% calcium gluconate in 50 mL of 0.9% sodium chloride solution over 4 hours) may be required, along with frequent serum calcium determinations to titrate the dose.[27] One patient who was massively exposed to hydrofluoric acid required a total of 267 mEq of calcium over 24 hours.[23] An ingestion of 30 mL of 70% hydrofluoric acid theoretically generates 660 mEq of fluoride.

To facilitate the availability of the maximum amount of calcium, simultaneous administration of IV, oral, and nebulized 2.5% calcium gluconate should also be given, if there are no contraindications. To prepare nebulized calcium gluconate, mix 1.5 mL of 10% calcium gluconate solution with 4.5 mL of sterile water or saline to make a 2.5% solution. For moderate to severe burns (generally from hydrofluoric acid concentrations >10%) of the fingers and hands, an intraarterial calcium infusion may be more effective than local (or IV) therapy, although it is more invasive[52,61,68,69] and more hazardous.[61] One group successfully used 10 mL of 10% calcium gluconate solution mixed in 40â€“50

mL of 5% dextrose infused intraarterially over 4 hours followed by subsequent 40-mL infusions after 4 hours when pain persisted.[68] Serum calcium and serum magnesium concentrations should be carefully monitored in all severely poisoned patients.[61,68]

Phosphates

Inappropriate use of oral and rectal phosphates (eg, laxatives) can result in hypocalcemia, hyperphosphatemia, and hyperkalemia, as well as significant morbidity and mortality.[3] Intravenous calcium may be needed for life-threatening hypocalcemia. The administration of calcium in the presence of hyperphosphatemia risks precipitation of calcium phosphate throughout the body. Hemodialysis and other therapies should be considered.

Hypermagnesemia

Hypermagnesemia causes both direct and indirect depression of skeletal muscle, resulting in neuromuscular blockade, loss of reflexes, and profound muscular paralysis (Chap. 17).[28] Excess magnesium also causes widening of the PR interval and QRS complex on the ECG, and depression of the sinoatrial (SA) node, leading to a bradycardic cardiac arrest. Intravenous calcium serves as a physiologic antagonist to these effects of magnesium (see Table A27-1).

Hyperkalemia

Hyperkalemia causes significant myocardial depression. Electrocardiographic changes are well defined: the height of the T wave increases and lengthening of the PR interval and QRS complex occur; ultimately, a sine wave pattern leading to cardiac arrest may occur (Chap. 5).[28] Calcium makes the membrane threshold potential less negative so that a larger stimulus is required to depolarize the cell. This stabilization antagonizes the

hyperexcitability caused by modest hyperkalemia. However, when severe hyperkalemia exists, voltage-gated sodium channels are inactivated and cannot be depolarized, regardless of the strength of the impulse. Calcium may transform the voltage sensor of the sodium channel from inactive to closed, thus allowing the sodium channel to be opened with depolarization.[29] If hyperkalemia is secondary to the toxic effects of cardioactive steroids on the Na^+-K^+-adenosine triphosphatase (ATPase) pump, intravenous calcium can potentially exacerbate an already excessive intracellular calcium concentration, making IV calcium potentially harmful.

Î²-Adrenergic Antagonists

In vitro studies suggest that the negative inotropic action of propranolol (Chap. 59) and analogs is related to interference with both the forward and reverse transport of calcium in the sarcoplasmic reticulum and to inhibition of microsomal and mitochondrial calcium uptake.[19,38,44] In a canine model of propranolol poisoning, the administration of a bolus of calcium chloride followed by a continuous infusion improved mean arterial pressure, maximal left ventricular pressure change over time, and peripheral vascular resistance, but had no effect on bradycardia or QRS prolongation.[39] Several case reports attest to the beneficial effects of calcium in Î²-adrenergic antagonist overdose.[10,33,53,60] Because distinguishing an overdose of a calcium channel blocker from a Î²-adrenergic antagonist is difficult and often the two are taken simultaneously, as long as no contraindications exist, a trial of intravenous calcium seems reasonable.

Black Widow Spider Envenomation

Envenomation by the black widow spider (*Latrodectus spp*) (Chap. 115) leads to local and systemic symptoms. Most commonly, severe abdominal or back pain begins within several hours of envenomation.[16] The venom exerts its effects by opening sodium

channels leading to calcium influx; the release of synaptic transmitters, including norepinephrine and acetylcholine, are believed to be involved.[56] Intravenous calcium, along with analgesics,

benzodiazepines, and muscle relaxants, is used to successfully relieve the pain and muscle spasms.[16,34] Rarely, antivenom may be indicated. Animal studies suggest that the venom induces changes in the permeability of calcium that may be overcome by increasing the extracellular concentration of calcium.[35,49] One prospective study noted improvement in 6 of 13 patients treated with calcium gluconate.[34] However, a large retrospective study of 163 patients casts doubt on the effectiveness of calcium.[16] Very few patients in the study had received adequate pain relief from calcium, and all but one patient also required opioids.[16] Most research suggests that there is no longer a role for calcium in the management of black widow spider envenomation (see Chap. 115).

TABLE A27-1. Calcium Salts for Intravenous Use

	Calcium Gluconate (Ca^{2+} Gluconate)	Calcium Chloride ($CaCl_2$)
10% Solution	10 mL = 1 g of Ca^{2+} gluconate	10 mL = 1 g of $CaCl_2$
	1 mL = 0.45 mEq elemental Ca^{2+}	1 mL = 1.36 mEq elemental Ca^{2+}
Adult dose	3 g (30 mL of 10% Ca gluconate)	1 g (10 mL of 10% $CaCl_2$)

	Repeat every several minutes as necessary	Repeat every several minutes as necessary
Pediatric dose (not to exceed the adult dose)	60 mg/kg (0.6 mL/kg) of Ca^{2+} gluconate 10% infused by slow intravenous bolus over 10â€“20 seconds in cardiac arrest or over 5â€“10 minutes in a well-perfused patient	20 mg/kg (0.2 mL/kg) infused by slow intravenous push over 10â€“20 seconds in cardiac arrest or over 5â€“10 minutes in a hemodynamically stable patient
	Repeat every several minutes as necessary	Repeat every several minutes as necessary

Safety Issues and Calcium Preparations

Severe hypercalcemia is defined by a serum calcium concentration greater than 3.5 mmol/L (14.0 mg/dL) in a patient with a normal albumin concentration. The adverse effects of hypercalcemia (independent of the rate of administration) include nausea, vomiting, constipation, hypertension if intravascular volume is maintained, polyuria, polydipsia, cognitive difficulties, hyporeflexia, coma, and enhanced sensitivity to cardioactive steroids.[5] Significant hypercalcemia may lead to myocardial

depression. The symptoms exhibited depend on the patient's age, rate of increase in the serum calcium, and duration of the hypercalcemia.[5]

A variety of calcium salts are available for parenteral administration. The two most commonly used are calcium chloride and calcium gluconate (Table A27-1). Neither salt should be mixed with sodium bicarbonate because calcium carbonate, a precipitate, is formed. Calcium chloride is an acidifying salt and is extremely irritating to tissue. It should never be given intramuscularly, subcutaneously, or perivascularly.[28,45] Calcium gluconate is less irritating, but care should also be taken to avoid extravasation. The best reason for choosing calcium gluconate in almost all clinical situations is that the tissue risk is far less. Equivalent doses of calcium chloride and calcium gluconate produce similar serum ionized calcium measurements, with peaks occurring within 30 seconds and accompanied as measured by hemodynamic values.[43] These measurements support the idea that simple dissociation of calcium from gluconate is responsible for releasing calcium, rather than hepatic metabolism. Earlier evidence suggesting that infusions of intravenous calcium chloride produce slightly larger increases in ionic calcium than do infusions of calcium gluconate has been challenged.[43,71] Intravenous calcium must be administered slowly, at a rate not exceeding 0.7â€“1.8 mEq/min or one 10-mL vial of calcium chloride over 10 minutes in adults. More rapid administration may lead to vasodilation, hypotension, bradycardia, dysrhythmias, syncope, and cardiac arrest.[6,17,36,45,63]

In cases of extreme life-threatening hypocalcemia or for a patient in extremis, a slow IV push may be required.

Summary

Intravenous calcium is an effective antidote for the hypocalcemia induced by ethylene glycol and hydrofluoric acid. It serves as a

physiologic antagonist to the cardiac and/or neurologic effects of hypermagnesemia and hyperkalemia and counteracts the effects of calcium channel blocker overdoses. It may have some benefit in the treatment of Î²-adrenergic receptor antagonist overdoses. The efficacy of calcium in the management of patients with black widow spider envenomation is of limited value. Great care must be taken to avoid extravasation. Calcium chloride, in particular, can cause tissue necrosis. Equivalent doses of calcium gluconate and calcium chloride deliver equal amounts of ionic or active calcium. Electrocardiographic monitoring and frequent serum calcium determinations are required to prevent iatrogenic toxicity. Although most clinical experience involves intravenous use, advances in intraarterial, topical, and inhalational calcium therapy offer unique potential advantages in certain circumstances.

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Chapter 102 Hydrocarbons

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An 18-month-old girl was found by her mother immediately after ingesting â€œa mouthfulâ€• of clear oil from a decorative oil lamp. The child coughed and gagged, and within a few minutes began vomiting fluid that smelled similar to the oil that remained in the lamp. Within 90 minutes of the ingestion, the child had 3 episodes of vomiting, and her respirations were increasingly sonorous. The mother called the poison center, and the child was referred to the nearest emergency department (ED).

In the ED, the child was tachypneic and agitated. Vital signs were: blood pressure, 110/50 mmHg; pulse, 110â€“160 beats/min; respiration, 60 breaths/min; and she was afebrile. Pulse oximetry was 82% on room air. The mucous membranes were moist, and no oropharyngeal lesions were noted. Nasal flaring was present. Tachypnea and chest retractions were noted, although the breath sounds were clear and equal. The heart was rapid and regular. Bowel sounds were decreased, but the abdomen was soft. She was awake,

agitated, and moved all extremities equally. The skin was dry, with capillary refill of less than 2 seconds. Supplemental oxygen by nasal cannula raised the oxygen saturation to 94%. Chest radiograph showed right middle and lower lobe infiltrates.

The child was given intravenous methylprednisolone and ceftriaxone in the ED and was transferred to a pediatric intensive care unit (PICU). A nasogastric tube was placed and attached to suction, and additional thin, oily liquid was removed from the patient's stomach. Despite poison center recommendations to hold antibiotics and corticosteroids, these were continued in the PICU. Overnight she was able to maintain her oxygen saturation at greater than 90% with supplemental oxygen. The child never required assisted ventilation. After 24 hours in the PICU, her respirations improved, such that she was transferred to a general pediatric ward, still on supplemental oxygen. Her status continued to improve and she was discharged home on the third day.

Follow up was obtained at 2 months, at which time crackles were auscultated over her lower lung fields. Chest radiography revealed pneumatoceles in both lower lobes.

Spawned during the industrial revolution, organic chemistry evolved out of advances in coal tar technology. The discovery of aniline dye led to bulk distillation of coal tar to recover crude naphtha and aromatic hydrocarbons such as benzene. Additional coal tar distillation products included light oil, creosote oil, anthracene oil, road tar, and pitch. Eventually, petroleum replaced coal tar as the primary source of fossil fuel, naphtha, aromatic solvents, and other organic compounds. Besides fuels, the heterogeneous petroleum distillate compounds are used as solvents, lubricating oils, chemical feedstocks, and as chemical intermediates. There are numerous consumer and household applications of petroleum distillates as paint thinners, furniture polish, lamp oils, and lubricants (Table 102-1).

Although *hydrocarbons* represent chemically diverse substances, they are related primarily by the ways in which they are used. Most hydrocarbons in everyday use, such as gasoline, kerosene, and fuel

oils, are variable mixtures obtained as distillation fractions. This complicates the assessment of their toxicity. As a result, in discussing hydrocarbon toxicology, generalities are often used to discuss the behavior of these complex mixtures. This chapter highlights the toxicology of individual hydrocarbons when they are commercially available in purified form, or when individual compounds present unique toxicologic issues.

Chemistry

A *hydrocarbon* is an organic compound made up primarily of carbon and hydrogen atoms, typically ranging in length from 1â€“60 carbon atoms. This definition includes products derived from plants (pine oil, vegetable oil), animal fats (cod liver oil), natural gas, petroleum, and coal tar. There are two basic types of hydrocarbon molecules, *aliphatic* (straight or branched chains) and *cyclic* (closed ring), each with its own subclasses. The aliphatic compounds include the *paraffins* (*alkanes* , with a generic formula $C_n H_{2n+2}$); the *olefins* (*alkenes* have 1 double bond and *alkadienes* have 2 double bonds); *acetylenes* (generic formula $C_n H_{2nâ€“2}$ with a triple bond); and the *acyclic terpenes* (polymers of isoprene, $C_5 H_8$). Some aliphatic compounds have branches in which the subchain also contains carbon atomsâ€”both the chain and branches are essentially straight.

Solvents are a heterogenous class of chemicals used to dissolve and to provide a vehicle for delivery of other chemicals. The most common industrial solvent is water. The common solvents most familiar to toxicologists are the *organic solvents* (containing 1 or more carbon atom), and most of these are hydrocarbons. Most are liquids under the conditions in which they are used. Specifically named solvents (Stoddard solvent, white naphtha, ligroin) represent mixtures of hydrocarbons emanating from a common distillation fraction.

Saturated hydrocarbons contain carbon atoms only in their most reduced state, with each carbon bound to either hydrogen or to another carbon. No double or triple bonds are present. Conversely,

unsaturated compounds are those with hydrogens removed, and double or triple bonds are present.

Adhesives (glues)
Mothballs
Baby oil
Motor oils
Car waxes
Naphtha
Cod liver oil
Paint removers
Contact cement
Paint thinners
Furniture polishes
Paraffin
Furniture refinishers
Paste waxes
Gasoline
Petroleum jelly
Home heating fuel
Pine oils
Kerosene
Plastic cement
Kitchen waxes
Solvents
Lacquers
Stain removers
Laxatives
Sterno fuel
Lighter fluids
Stoddard solvent
Liquid solder
Turpentine
Liquid steel

Typewriter correction fluids
Mineral oil
Varnish removers
Mineral seal oil
Wax
Mineral spirits

TABLE 102-1. Household Products Containing Hydrocarbons

The cyclic hydrocarbons include the *alicyclics* (3 or more carbon atoms in a ring structure, with properties similar to those of aliphatics), *aromatics* , and *cyclic terpenes.* The alicyclics are further divided into the *cycloparaffins* (*naphthenes*) such as cyclohexane, and the *cycloolefins* (2 or more double bonds) such as cyclopentadiene.

Aliphatics
Gasoline
4â€“10
Motor vehicle fuel
86â€“410 (30â€“210)
30
Naphtha
8â€“12
Charcoal lighter fluid
212â€“392 (100â€“200)
29
Kerosene
5â€“15
Heating fuel
392â€“572 (200â€“300)
35
Turpentine
C_{10} H_{16}
Paint thinner

311 (155)
33
Mineral spirits
9â€“12
Paint and varnish thinner
230â€“392 (110â€“200)
30â€“35
Mineral seal oil
13â€“17
Furniture polish
572â€“932 (300â€“500)
30â€“35
Heavy fuel oil
20â€“45
Heating oil
617â€“1004 (325â€“540)
>450
Aromatics
Benzene
C_6H_6
Solvent, reagent, gasoline additive
176 (80)
31
Toluene
C_7H_8
Solvent, spray paint solvent
231.8 (+++)
28
Xylene
C_8H_{10}
Solvent, paint thinner, reagent
291.2 (144) (*o*), 282.2 (139) (*m*), 280.4 (138) (*p*)
28
Halogenated

Methylene chloride
CH_2Cl_2
Solvent, paint stripper, propellant
104 (40)
27
Carbon tetrachloride
CCl_4
Solvent, propellant, refrigerant
170.6 (77)
30
Trichloroethylene
$HClC = CCl_2$
Degreaser, spot remover
188.6 (87)
27
Tetrachloroethylene
$Cl_2C = CCl_2$
Dry cleaning solvent, chemical intermediate
249.8 (121)
28

[a] Direct values for kinematic viscosity in Saybolt seconds universal (SSU) were not available for the following compounds: naphtha, xylene, methylene chloride, carbon tetrachloride, trichloroethylene, perchloroethylene, and toluene. SSU was calculated by converting from available measurements in centipoise viscosity and/or centistokes viscosity using the following conversions: the value in centistokes is estimated by dividing centipoise by density at 68Â°F (20Â°C); SSU is approximated from centistokes using $y = 3.2533x + 26.08$ ($R^2 = 0.9998$). Centipoise viscosity for naphtha was estimated from the value for butylbenzene. Centipoise viscosity for xylene is the average of *o*- , *m*- , and *p*- xlylene.

Compound	Carbon Atoms/Formula	Common Uses	Boiling Point Â°F (Â°C)	Viscosity (SSU)[a]

TABLE 102-2. Physical Properties of Common Hydrocarbons

The aromatic hydrocarbons are divided into the *benzene* group (1 ring), *naphthalene* group (2 rings), and the *anthracene* group (3 rings). *Polycyclic aromatic hydrocarbons* (polynuclear aromatic hydrocarbons) have multifused benzenelike rings. Aromatic organic compounds may also be *heterocyclic* (eg, where oxygen or nitrogen substitutes for carbon in the ring). Structurally, these molecules are flat, with reactive electron clouds above and below the ring.

The *cyclic terpenes* are the principal components of a variety of plant-derived essential oils, often providing color, odor, and flavor. *Limonene* in lemon oil, *menthol* in mint oil, *pinene* in turpentine, and *camphor* are all terpenes (Chap. 42).[140]

The physical properties of hydrocarbons vary by the number of carbon atoms and molecular structure (Table 102-2). Unsubstituted, aliphatic hydrocarbons containing up to 4 carbons are gaseous at room temperature, 5â€“19 carbon molecules are liquid, and longer-chain molecules tend to be tars or solids. Branching of chains tends to destabilize intermolecular forces, such that less energy is required to separate the molecules. The result is that, for a given molecular size, highly branched molecules have lower boiling points, and tend to be more volatile.[137]

As discussed previously, most commercial hydrocarbon products are variable mixtures of individual hydrocarbon compounds. An illustrative example of a *mixture* is gasoline. Gasoline is a mixture of alkanes, alkenes, naphthenes and aromatic hydrocarbons, predominantly 5â€“10 carbon molecules in size.[209] Natural gasoline is separated from

crude oil in a common distillation fraction. However, most commercially available gasolines are actually blends of up to 8 component fractions from refinery processors. More than 1500 individual compounds may be present in commercial grades, but most analytical methods are only able to isolate 150â€“180 compounds from gasolines. Notably, *n* -hexane is present at up to 6%, and benzene is present between 1 and 6%, depending on the grade and the place of origin of the product. In addition, a number of additives may go into the final formulation: alkyl leads, ethylene dichloride, and ethylene dibromide in leaded gasoline, and oxygenates like methyl *t* -butyl ether (MTBE), as well as methanol and ethanol.

Organic halides contain 1 or more halogen atoms (fluorine, chlorine, bromine, iodine) usually substituted for a hydrogen atom in the parent structure. Examples include chloroform, trichloroethylene (TCE), and the freons.

Oxygenated hydrocarbons demonstrate toxicity specific to the oxidation state of the carbon, as well as to the atoms adjacent to it (the â€œRâ€• groups). The *alcohols* are widely used as solvents in

industry and in household products. Their toxicity is discussed in Chaps. 75 and 103 . *Ethers* contain an oxygen bound on either side by a carbon atom. Acute toxicity from ethers tends to mirror that of the corresponding alcohols. *Aldehydes* and *ketones* contain a single carbon-oxygen double bond (C=O)â€”the former at a terminal carbon, the latter somewhere in the middle. Organic *acids* , *esters* , *amides* , and *acyl halides* represent more oxidized states of carbon; human toxicity is agent specific.

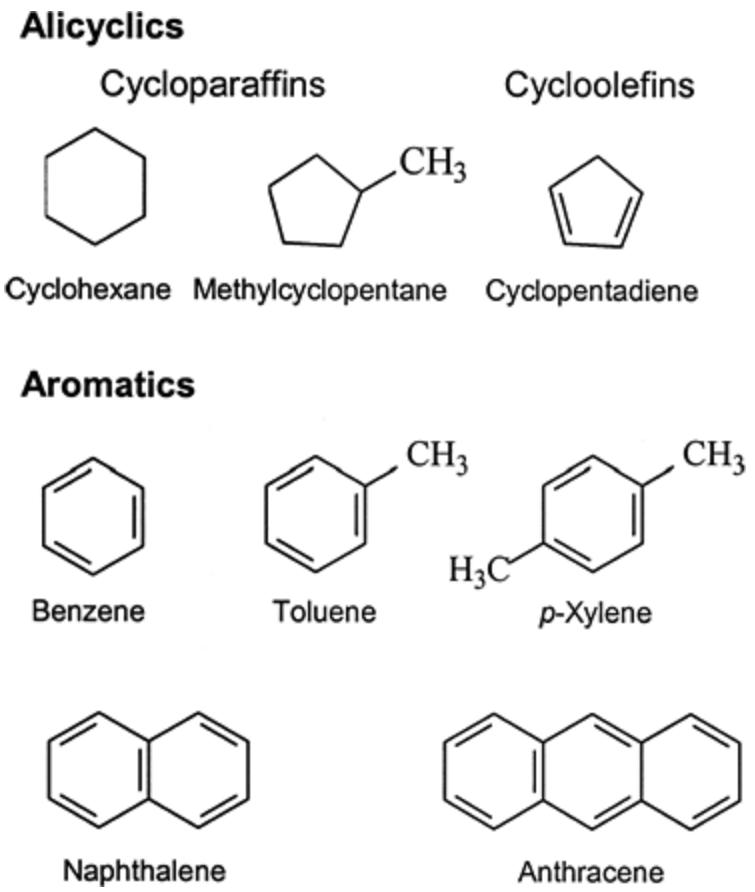

Figure 102-1. Basic hydrocarbon structures.

Phenols consist of benzene rings with an attached hydroxyl (alcohol) group. The parent compound, phenol, has only one hydroxyl group attached to benzene. The toxicity of phenol can be dramatically altered by addition of other functional groups to the benzene ring (Chap. 98). Cresols, catechols, and salicylate are examples of substituted phenols.

A variety of amines, amides, nitroso and nitro compounds, as well as phosphates, sulfites, and sulfates are used commercially and in industry. The addition of these functional groups to hydrocarbons dramatically alters the toxicity of the compound.

Figure 102-1 presents the chemical structures of some of the more commonly encountered hydrocarbons.

History and Epidemiology

The process of obtaining hydrocarbons from coal involves distillation of bituminous (soft) coal to remove *coal gas* , which can then be separated into a variety of natural gases. A large amount of distillate residue from the heating process remains as *coal tar* , which can be separated into kerosene and a variety of other hydrocarbon mixtures. The principal commercial source of hydrocarbons today involves distillation of crude oil. Petroleum is heated to fixed temperatures in a large-scale distillation procedure, allowing separation of hydrocarbons into distillation fractions by vapor (boiling) point. Because of the relationship between boiling point and molecular weight, this process roughly divides substances into like-sized mixtures. The most-volatile fractions come off early as gas, and are used primarily for heating. The least-volatile fractions (larger than about 10 carbons) are used chiefly for fuel and/or lubricants, paraffins, petroleum jelly, and asphalt. The remaining volatile hydrocarbon fractions (C_5 to C_{10}) form the fractions most commonly used as solvents.

Longer alkanes are often submitted to an industrial process known as *cracking* , in which they are superheated in a chamber, where catalytic pyrolysis converts them into shorter-chain alkanes and alkenes. Refineries then typically employ processes such as *catalytic isomerization* , to increase the amount of branching in the hydrocarbon chain (which increases the â€œoctaneâ€• of the fuel), and *catalytic reforming* , which converts alkanes and cycloalkanes into aromatic compounds.[137]

Essential oils (or volatile oils) are typically fragrant hydrocarbon plant extracts. Examples include menthol, eucalyptus oil, clove oil, sassafras oil, and pennyroyal oil, among others. These oils have been used from antiquity for a variety of medicinal reasons, and are enjoying resurgence with recent popularity of herbal supplements (Chap. 43). Mineral oil, castor oil, and glycerine are commonly used as laxatives. Hydrocarbon-based ointments, petroleum jelly, and camphor are used topically on skin and mucous membranes. Phenol and substituted

phenols are common medical disinfectants (Chap. 98). Diethyl ether and halogenated hydrocarbon compounds, like chloroform, were among the first general anesthetics, used more than 150 years ago.[125, 168] Cyclopropane and TCE have been widely used as general anesthetics.[125]

Occupations at risk for solvent exposure include petrochemical workers, plastics and rubber workers, printers, laboratory workers, painters, and hazardous waste workers. But exposures are ubiquitous in many occupations, and even in everyday life. In fact, the Occupational Safety and Health Administration estimates that nearly 238,000 American workers are exposed annually to significant concentrations of benzene alone.[95] The epidemiology of hydrocarbon exposure and hydrocarbon-related illness is particularly difficult to analyze. Because a common property of organic solvents is their high volatility, inhalational exposure occurs frequently and their high lipid solubility allows for dermal absorption.[83] Most exposures do not involve ingestionâ€”they may range from pumping your own gasoline to painting the spare bedroom, to applying or removing fingernail polish. Tables 102-1 and 102-2 list frequently encountered hydrocarbon-containing compounds.

In the years 1999â€“2003, a yearly average of 59,370 human exposures to hydrocarbon were reported to poison centers that contribute to the Toxic Exposures Surveillance System (TESS) database of the American Association of Poison Control Centers (AAPCC). These exposures accounted for 2.6% of the total human exposures reported, and resulted, on average, in 13 deaths per year. The incidence of both exposures and deaths has not changed appreciably in this database since the first AAPCC report in 1983. Over the 5-year period 1999â€“2003, 36â€“39% of exposures were unintentional exposures in children younger than 6 years of age. Although exposures in children appear to be declining compared to prior years of TESS data, this may be an artifact of the way that cases are coded in the database. Within the TESS database, many thousands of hydrocarbon exposures are not listed as such, but are ascribed to

â€œchemicals, pesticides, personal care products, cleaning substances, paints, automotive products,â€• and the like (see Chap. 130 for references). Certainly, these numbers dramatically underestimate North American exposures. More concerning is a

trend toward increased intentional abuse of volatile solvents by young people in our country (Chap. 79).

Three populations appear to be at risk for hydrocarbon-related illness: children with unintentional exposuresâ€”often ingestions; workers with occupational exposuresâ€”often dermal and inhalational; and adolescents/young adults who intentionally abuse solvents through inhalation.

Pharmacology

The acute toxicity of inhaled hydrocarbon vapor manifests principally through depression of consciousness. The acute central nervous system (CNS) toxicity of solvent vapors from occupational overexposure or recreational abuse, parallels the pharmacology of an inhaled general anesthetic.[176] The concentration of a volatile anesthetic that will produce loss of nociception in 50% of patients is defined as the minimum alveolar concentration (MAC) required to induce anesthesia. Inhaled solvent vapor will similarly produce unconsciousness in 50% of subjects when the partial pressure in the lung reaches its median effective dose (ED_{50}). Essentially all patients will be anesthetized when the partial pressure is raised 30% above the MAC (MAC Ã— 1.3). The doseâ€“response curves suggest that essentially no individual will be rendered unconscious by an inhaled dose 30% below the MAC. However, acute impairment of cognitive and motor function may occur at much lower exposures.[24]

Industrial exposure to lipid-soluble solvents, such as aromatic, aliphatic, or chlorinated hydrocarbons, are more likely to cause both acute and chronic CNS effects than will industrial exposure to water-soluble hydrocarbons like alcohols, ketones, and esters.[120] The

property of an inhaled anesthetic that correlates most closely with its ability to extinguish nociception is its lipid solubility.[84] The Meyer-Overton hypothesis, proposed more than 100 years ago, implies that an anesthetic agent dissolves into some crucial lipid compartment of the CNS causing inhibition of neuronal transmission.[125] Nonspecific inhibition of neuronal transmission through membrane or membrane protein conformational changes may occur.[166, 174]

At least some hydrocarbons may have specific cellular sites of action within the CNS.[16] Volatile anesthetics, for example, can affect ligand-gated ion channels. They interact with acetylcholine receptors to increase neurotransmitter binding[66] and to potentiate nicotinic blockade.[30] Anesthetics stimulate Î³-aminobutyric acid type A ($GABA_A$) activity,[118, 134] as do toluene and trichloroethane (TCA);[22] and anesthetics may inhibit GABA catabolism.[46] Some agents stimulate glutamate release.[92] Toluene, on the other hand, inhibits neurotransmission at glutamate *N*-methyl-D-aspartate receptors. Toluene and TCE enhance glycine receptor function. Prolonged exposure to toluene can perturb dopaminergic transmission.[22] General anesthetic effects are modulated by adenosine[171] and by $Î±_2$ agonism.[169] This line of mechanistic research suggests that the Meyer-Overton hypothesis may be too simplistic to explain the differences in pharmacologic profiles observed with this wide class of individual chemicals.

Toxicokinetics

Human toxicokinetic data are lacking for most hydrocarbons, and much of our understanding of the kinetics of this large family of chemicals comes from animal studies. Hydrocarbons are variably absorbed through ingestion, inhalation, or dermal routes of exposure, depending on their structure and chemical properties. Partition coefficients, in particular, are useful predictors of the rate and extent of the absorption and distribution of hydrocarbons into tissues as the higher the value the greater the potential for redistribution. A partition

coefficient for a given chemical is the ratio of concentrations achieved between two different media at equilibrium. The blood-to-air and tissue-to-air or tissue-to-blood coefficients directly relate to the pulmonary uptake and distribution of hydrocarbons. The tissue-to-blood partition coefficient is commonly determined by dividing the tissue-to-air coefficient by the blood-to-air coefficient.[70 , 150] Table 102-3 lists the partition coefficients for commonly encountered hydrocarbons. Where human data is limited, rat data is presented in the table as human and rat data often correlate.[150]

Inhalation is a major route of exposure for most volatile hydrocarbons. The absorbed dose is determined by the air concentration, duration of exposure, minute ventilation, and the blood-to-air partition coefficient. Most hydrocarbons cross the alveolus through passive diffusion. The driving force for passive diffusion across the alveolus is the difference in vapor concentration between the alveolus and the blood. Hydrocarbons that are highly soluble in blood and tissues are readily absorbed through inhalation, and blood concentrations rise rapidly following inhalation exposure. Although aromatic hydrocarbons are generally well absorbed through inhalation, for aliphatic hydrocarbons, absorption through inhalation varies by molecular weight: Aliphatic hydrocarbons with between 5 and 16 carbons are readily absorbed, whereas those with more than 16 carbons are not as readily absorbed.[3]

Absorption of aliphatic hydrocarbons through ingestion is inversely related to molecular weight, ranging from complete absorption at lower molecular weights, to approximately 60% for 14C hydrocarbons, 5% for 28C hydrocarbons, and essentially no absorption for aliphatic hydrocarbons with >32 carbons.[3] Oral absorption of aromatic hydrocarbons with between 5 and 9 carbons ranges from 80â€“97%. Oral absorption data for aromatic hydrocarbons with more than 9 carbons are limited.

While the skin is a common area of contact with solvents, for most hydrocarbons the dose received from dermal exposure is a small

fraction of the dose received through other routes, such as inhalation. The skin is composed of both hydrophilic (proteinaceous portion of cells) and lipophilic (cell membranes) regions. While many hydrocarbons can remove lipids from the stratum corneum, permeability is not simply a result of lipid removal; permeability is also increased with hydration of the skin. When compounds have near equality in the water-to-lipid partition coefficient, their rate of skin absorption is increased. Solvents that contain both hydrophobic and hydrophilic moieties (eg, glycol ethers, dimethylformamide, dimethylsulfoxide) are particularly well absorbed.[120] Other factors, in addition to the partition coefficient and permeability constant, that determine penetration across the skin include the thickness of the skin layer, the difference in concentration of the solvent on both sides of the epithelium, the diffusion constant, and skin integrity (ie, normal vs. cut or abraded).

The dose received via skin absorption will also depend on the surface area of the skin exposed and the duration of contact. Although highly volatile compounds may have a short duration of skin contact because of evaporation, skin absorption can also occur from contact with hydrocarbon vapor. In studies with human volunteers exposed to varying concentrations of hydrocarbon vapors, the dermal dose accounted for only 0.1â€“2% of the inhalation

dose. With massive exposure (eg, whole-body immersion), dermal absorption may contribute significantly to toxicity.[83] Significant dermal absorption with resultant toxicity has been described with carbon tetrachloride,[99] tetrachloroethylene,[83] and phenol.[117]

Aliphatics

n -Hexane

2.29[a]

159[a]

11 min

99 min

10â€“20% exhaled; liver metabolism by CYP
2â€“Hexanol, 2, 5-hexa-nedione, Î³-valerolactone
Paraffin/tar
Not absorbed or metabolized
Aromatics
Benzene
8.19
499[a]
8 h
90 h
12% exhaled; liver metabolism to phenol
Phenol, catechol, hydroquinone, and conjugates
Toluene
18.0[a]
1021[a]
4â€“5 h
15â€“72 h
Extensive liver extraction and metabolism
80% metabolized to benzyl alchol; 70% renally excreted as hippuric acid
o -Xylene
34.9
1877[a]
30â€“60 min
20â€“30 h
Liver CYP oxidation
Toluic acid, methyl hippuric acid
Halogenated
Methylene chloride
8.94
120[a]
Apparent tÂ½ of COHb 13 h
40 min
92% exhaled unchanged. Low doses metabolized; high doses exhaled.

Two liver metabolic pathways
(a) CYP 2E1 to CO and CO_2
(b) Glutathione transferase to CO_2 , formaldehyde, formic acid

Carbon tetrachloride
2.73
359[a]
84â€“91 min[a]
91â€“496 min[a]
Liver CYP, some lung exhalation (dose-dependent)
Trichloromethyl radical, trichloromethyl peroxy radical, phosgene
TCE
8.11
554[a]
3 h
30 h
Liver CYPâ€”epoxide intermediate; trichloroethanol is glucuronidated and excreted
Chloral hydrate, trichloroethanol, trichloroacetic acid
1,1,1- Trichloroethane
2.53
263[a]
44 min
53 h
91% exhaled; liver CYP
Trichloroacetic acid, trichloroethanol
Tetrachloroethylene
10.3
1638[a]
160 min
33 h
80% exhaled; liver CYP
Trichloroacetic acid, trichloroethanol
[a] Fat/blood partition coefficient is obtained by dividing the fat/air

coefficient by the blood/air coefficient. As determined in rat models. All coefficients are determined at 98.6Â°F (37Â°C).

Partition Coefficients				tÂ ½	
Blood/Air	Fat/Air	Î±	Î²	Elimination	Relevant Metabolites

TABLE 102-3. Kinetic Parameters of Select Hydrocarbons

Once absorbed into the central compartment, hydrocarbons are distributed to target and storage organs based on their tissue-to-blood partition coefficients, and on the rate of perfusion of the tissue with blood. During the onset of systemic exposure, hydrocarbons accumulate in tissues, such as fat, that have coefficients between tissue and blood that are >1 (eg, for toluene, the fat-to-blood partition coefficient is 60). Table 102-3 lists the distribution half-lives of selected hydrocarbons.

Hydrocarbons can be eliminated from the body unchanged, for example, through expired air, or can be metabolized to more polar compounds, which are then excreted through urine or bile. Table 102-3 lists the blood elimination half-lives (for first-order elimination processes) and metabolites of selected hydrocarbons. Some hydrocarbons are metabolized to toxic compounds (eg, methylene chloride, carbon tetrachloride, *n* -hexane, methyl-*n* -butyl ketone). The specific toxicities of these metabolites are discussed under Special Cases below.

Pathophysiology

Pulmonary

For years, the medical literature held stage for debate over the

pathogenesis of lung injury after hydrocarbon exposure. Early investigators debated whether pulmonary toxicity was caused by gastrointestinal absorption of hydrocarbons with subsequent pulmonary toxicity, or by direct aspiration into pulmonary parenchyma.[28, 54, 58, 71, 94, 115, 155, 158, 206] The rat and baboon models made it clear that hydrocarbons are absorbed in the gastrointestinal tract and can be recovered from lung and many other tissues.[14, 122] Based on the amounts absorbed in these animal studies, however, the volume of ingested hydrocarbon needed to cause pulmonary toxicity would be enormous. A number of other animal models (dogs, monkeys, and baboons) employing gastric instillation of hydrocarbon demonstrated lack of pulmonary toxicity when aspiration did not occur.[56, 94, 215, 220] It is currently held that aspiration is the main route of injury from ingested hydrocarbons.

The mechanism of pulmonary injury, however, is not completely understood. Intratracheal instillation of 0.2 mL/kg of kerosene causes physiologic abnormalities in lung mechanics (decreased compliance and total lung capacity) and pathologic changes such as interstitial inflammation, polymorphonuclear exudates, intraalveolar edema and hemorrhage, hyperemia, bronchial and bronchiolar necrosis, and vascular thrombosis.[71, 72, 81, 89, 163, 164] These changes most likely reflect both direct toxicity to pulmonary tissue and disruption of the lipid surfactant layer.[75, 173, 213]

Several factors are associated with pulmonary toxicity after hydrocarbon ingestion. These include specific physical properties of the hydrocarbon ingested (Table 102-2), the volume ingested, and the occurrence of vomiting. The properties of *viscosity*, *surface tension*, and *volatility* of a particular hydrocarbon are the main determinants of its aspiration potential (Table 102-2).[73, 94]

Viscosity is the measurement of a fluid's resistance to flow. *Kinematic viscosity* is the absolute viscosity divided by the fluid's

density, usually expressed in stokes or in centistokes (mm^2/sec). One

method of quantifying viscosity is by the rate of flow through a calibrated orifice. This is measured in Saybolt Seconds Universal (SSU). At a given temperature, viscosity values can be converted from International System of Units (SI) units of kinematic viscosity (eg, the stoke or the centistoke) to SSU by dividing by the density of the compound. Substances with low viscosities (SSU <60; eg, turpentine, gasoline, naphtha) are associated with a higher tendency for aspiration in animal models. The US Consumer Products Safety Commission has issued a rule requiring child-resistant packaging for products that contain 10% or more hydrocarbon by weight and that have a viscosity <100 SSU.[198]

Surface tension is a cohesive force generated by attractionâ€"Van der Waals forcesâ€"between molecules.[148] This influences adherence of a liquid compound along a surface (â€œits inability to creepâ€•), and is measured using a modified Wilhelmy balance.[94] The lower the surface tension, the higher the aspiration risk.[73 , 94]

Volatility is the tendency for a liquid to become a gas. Hydrocarbons with high volatility tend to vaporize, displace oxygen, and lead to transient hypoxia.

It is not clear which of the physical properties of the hydrocarbon is most important in predicting toxicity. Several studies have examined the risk of pulmonary toxicity relative to the amount of hydrocarbon ingested, with or without vomiting. Some have found an association between the volume ingested and risk for pulmonary toxicity, whereas others have not.[21 , 26 , 49] Similar discrepancies hold for presence of vomiting.[21 , 26 , 38 , 144 , 145] Moreover, the validity of these studies has been questioned because of retrospective methodology and poor response rates regarding the volume ingested. Only one prospective study addressed these issues: the Co-Operative Kerosene Poisoning Study (COKP). Forty-six hospitals participated in this series of 760 cases. Of these, 54% of patients had clear estimates of the amount of kerosene ingested: 29% were reported to have ingested >30 mL; 35% ingested were reported to have 10â€“30 mL; and 35% were reported

to have ingested <10 mL. No association was found between amount of kerosene ingested and the age of the patient. In patients who ingested more than 30 mL, there was a 52% chance of developing pulmonary complications.[151] Those patients who ingested this amount were found to have a higher chance of developing central nervous system complications than did those who ingested less than 30 mL. Regarding spontaneous vomiting, the cooperative study was able to provide data on only 273 of the 760 patients. There was a 54% incidence of pulmonary toxicity when vomiting occurred, and 39% when there was no history of vomiting.[151] Although these features may be useful for predicting the possibility of hydrocarbon-induced pulmonary toxicity, none of these parameters is 100% predictive. Serious poisoning may be less likely with hydrocarbons that have higher viscosity and higher surface tension, such as mineral oil. However, severe hydrocarbon pneumonitis also is associated with â€œlow-riskâ€• hydrocarbons.[162] Furthermore, it is suggested that patients are severely injured with low-volume (<5 mL) ingestions, as well as in ingestions without a history of coughing, gagging, or vomiting.[9]

Intravenous (IV) and subcutaneous injection of hydrocarbons are reported.[160, 170, 200] Severe hydrocarbon pneumonitis may occur following intravenous exposure. Animal experiments show that intravascular hydrocarbons injure the first capillary bed encountered.[28] Intravenous injection causes pulmonary toxicity, and portal vein injection leads to direct hepatic injury.[28, 54, 94, 158, 216, 220] The clinical course after IV hydrocarbon injection mirrors that of aspiration injury.

Cardiac

Exposure to hydrocarbons by any route may cause cardiotoxicity. Halogenated hydrocarbons and benzene are most frequently implicated, although toluene and gasoline may also induce dysrhythmias.[19] A canine model demonstrated ventricular premature

beats and/or ventricular fibrillation after inhalation of trichloroethane followed by intravenous injection of epinephrine.[157] Dysrhythmia-induced sudden death, termed the â€œsudden sniffing death syndrome,â€• is well-described after inhalation of chlorinated hydrocarbons, but also for aromatic compounds.[110] Classically, sudden death in the setting of hydrocarbon exposure follows an episode of sudden exertion.[20, 67, 156] Tachydysrhythmias, cardiomegaly, and myocardial infarction are uncommonly reported after exposure by ingestion.[97, 179] A retrospective followup cohort of exposed methylene chloride workers did not find evidence of excess long-term cardiac disease.[146]

Central Nervous System

The specific mechanism of CNS depression from hydrocarbon toxicity is unclear. It is enticing to propose that specific channel inactivation or stimulation of inhibitory channels is responsible (see Pharmacology above). However, to date, no unifying theory or evidentiary support for specific receptor binding explains the acute CNS impairment that occurs with either volatile anesthetic or other hydrocarbon inhalation. In cases of hydrocarbon aspiration, hypoxia from pulmonary damage may contribute to the CNS depression.[122, 217]

The CNS toxicity of chronic toluene abuse is well-described, and illustrates the ability of some hydrocarbons to produce pathologic changes in the CNS. Prolonged, moderate-to-heavy exposure to hydrocarbons, as occurs in volatile solvent abuse (Chap. 79), can lead to irreversible CNS damage. The primary pathologic process is white matter degeneration (*leukoencephalopathy*). Autopsy studies of the brains of chronic toluene abusers show profound atrophy and mottling of the white matter, as though the lipid-based myelin were dissolved away. These pathologic features correlate with the clinical syndrome of a â€œwhite matter dementia.â€• [61, 69] Microscopic examination shows a consistent pattern of myelin and oligodendrocyte loss with relative preservation of axons.[109] Animal studies of toluene poisoning

have also revealed biochemical changes including diminished norepinephrine and dopamine concentrations and alterations in various neurotransmitter levels.[165]

Peripheral Nervous System

Peripheral neuropathy is well described following occupational exposure to *n* -hexane or methyl-*n* -butyl ketone (MnBK).[27] Methyl ethyl ketone (MEK) may exacerbate this neurotoxicity, probably by interfering with metabolic pathways of *n* -hexane and MnBK.[8 , 161] This axonopathy results from a metabolic intermediateâ€”2,5-hexanedioneâ€”common to both hexane and MnBK. The mechanism by which this intermediate causes peripheral neuropathy may relate to decreased phosphorylation of neurofilament proteins, with disruption of the axonal cytoskeleton (see Special Cases below). Other organic solvents, such as carbon disulfide, acrylamide, and ethylene oxide, may cause a similar peripheral axonopathy.[77]

Cranial and peripheral neuropathies are reported after acute and chronic exposure to trichloroethylene (TCE).[36 , 100 , 114 , 187] Pathologically, TCE appears to induce a myelinopathy.[62 , 77]

Hepatic

Chlorinated hydrocarbons (Table 102-2) are particularly hepatotoxic. In most cases, this occurs via phase I activation to a reactive intermediate (Chap. 13). In the case of carbon tetrachloride, this intermediate is the trichloromethyl radical. This toxic metabolite forms covalent bonds with hepatic macromolecules, and may initiate lipid peroxidation.[29] Hepatic injury, manifested as aminotransferase elevation and hepatomegaly, is usually reversible, except in massive overexposures (see Special Cases below). Hepatotoxicity in animals has been ranked for common hydrocarbons as follows: carbon tetrachloride >> benzene, trichloroethylene > pentane.[214]

Dermal

Most hydrocarbon solvents cause nonspecific irritation of the skin and mucous membranes. Repeated, prolonged contact can dry and crack the skin. The mechanism of dermal injury appears to be defatting of the lipid layer of the stratum corneum. Up to 9% of workers may develop eczematous lesions from dermal contact.[221] Limonene and turpentine contain sensitizers, that rarely can result in contact allergy (Chap. 29).

Immunologic

Hydrocarbons disturb the integrity of membrane lipid bilayers, causing swelling and increased permeability to protons and other ions. This alters the structural and functional integrity of the membrane. Changes in the lipid composition of the membrane occur, and membrane lipopolysaccharides and proteins are disturbed.[174] Resultant toxicity may directly destroy capillary endothelium.[28] Additionally, there appears to be derangement of basement membranes, and this is postulated to underlie both alveolar and glomerular toxicity of hydrocarbons.[181] Immune mechanisms may account for basement membrane dysfunction in chronic exposures. Hydrocarbon exposure is suggested as a possible cause of Goodpasture syndrome (immune dysfunction causing both pulmonary damage and glomerulonephritis),[25] although the association is not widely accepted. Measurable changes in immune function occur after hydrocarbon exposure,[17] but our knowledge of any clinical implications is incomplete.

Clinical Manifestations

Pulmonary

Most patients who develop pulmonary toxicity after hydrocarbon ingestion have an episode of coughing, gagging, and choking. This

occurs shortly after ingestion, usually within 30 minutes, and is presumptive evidence of aspiration.[123] Absence of tachypnea on initial evaluation has an 80% negative predictive value for aspiration pneumonitis.[207] More severely affected patients may rapidly develop progressive pulmonary toxicity over the subsequent hours to days. Pulmonary toxicity manifests as crackles, rhonchi, bronchospasm, tachypnea, hypoxia, hemoptysis, acute lung injury (hemorrhagic or nonhemorrhagic), or signs of respiratory distress.[194] Cyanosis develops in approximately 2â€“3% of patients.[129] This may be caused by simple asphyxiant effects from volatilized hydrocarbons, ventilationâ€“perfusion mismatch, or, rarely, by methemoglobinemia (aniline, nitrobenzene, nitrite-containing hydrocarbons). Clinical findings often worsen over several days but typically resolve within 5â€“7 days. Death is rare (<2%), and is typically a consequence of severe progressive respiratory insult marked by hypoxia, ventilationâ€“perfusion mismatch, and barotrauma.[20, 59, 91, 128, 177, 205, 224]

Radiographic evidence of pneumonitis develops in 40â€“88% of admitted patients.[18, 21, 26, 58, 115, 145, 155] Findings can develop as early as 15 minutes or as late as 24 hours after exposure (Fig. 102-2).[49, 68, 89, 102, 151, 201] Ninety percent of patients who develop radiographic abnormalities develop evidence by 4 hours postingestion.[49] The majority of patients who have respiratory signs and symptoms beyond the initial history of gagging, choking, and coughing develop radiographic pneumonitis.[9] Clinical signs of pneumonia (eg, crackles, rhonchi) are evident in 40â€“50% of patients.[58] A small percentage (<5%) are completely asymptomatic after a period of observation, but have radiographic findings.[9] Chest radiographs performed immediately on initial presentation are not useful in predicting infiltrates in either symptomatic or asymptomatic patients.[207]

Specific radiologic findings include perihilar densities, bronchovascular markings, bibasilar infiltrates, and pneumonic consolidation.[18, 74] Right-sided involvement occurs in 75% of cases and bilateral

involvement in approximately 50%. Upper lobe involvement is uncommon.[18 , 32 , 89] Pleural effusions develop in 3% of cases,[126] with one third appearing within 24 hours. Pneumothorax, pneumomediastinum, and pneumatoceles are uncommonly reported.[15 , 23 , 40 , 101 , 116] Initial radiographs after ingestion may reveal two liquid densities in the stomach, known as the â€œdouble-bubbleâ€• sign.[50] This represents an airâ€“fluid (hydrocarbon or water) and a hydrocarbonâ€“water interface, as the hydrocarbon is not miscible with gastric fluids (primarily water) and may have a specific gravity less than that of water.

Radiographic changes often progress over several days, typically reaching a maximum at 5â€“7 days with resolution over several weeks. Radiographic resolution does not correlate with clinical improvement, which usually lags behind by several days to weeks.[71] Long-term followup in patients with hydrocarbon pneumonitis is limited.[32 , 68 , 82 , 155 , 190] Frequent respiratory tract infections are described in individuals after hydrocarbon pneumonitis, but studies addressing this are poorly controlled.[68 , 156 , 194] As with other pneumonic infiltrates, delayed formation of pneumatoceles may occur.[23 , 101 , 116] Bronchiectasis and pulmonary fibrosis are reported, but appear to be uncommon.[78 , 127 , 155] In one study, 82% of patients examined 8â€“14 years after hydrocarbon-induced pneumonitis had asymptomatic minor pulmonary function abnormalities.[82] The abnormalities were consistent with small-airway obstruction and loss of elastic recoil. The authors hypothesized that this group may be predisposed to chronic obstructive pulmonary disease.

Cardiac

The most worrisome cardiotoxicity associated with hydrocarbon exposure is that of myocardial sensitization and dysrhythmias.[19 , 157] This phenomenon is well described for halogenated hydrocarbons and less so for aromatic compounds. Sudden death can occur after

exposure to high concentrations of volatile inhalants or inhaled anesthetics, apparently resulting from tachydysrhythmias. Atrial fibrillation, ventricular fibrillation, and sudden cardiac death are reported.[79, 143, 156] Myocardial depression occurs by an unclear mechanism.[10] The mechanism of dysrhythmia induction appears to be endogenous catecholamine mediated extrasystoles occurring in the setting of altered repolarization, manifested by QTc interval prolongation.[20, 67, 110, 156, 157]

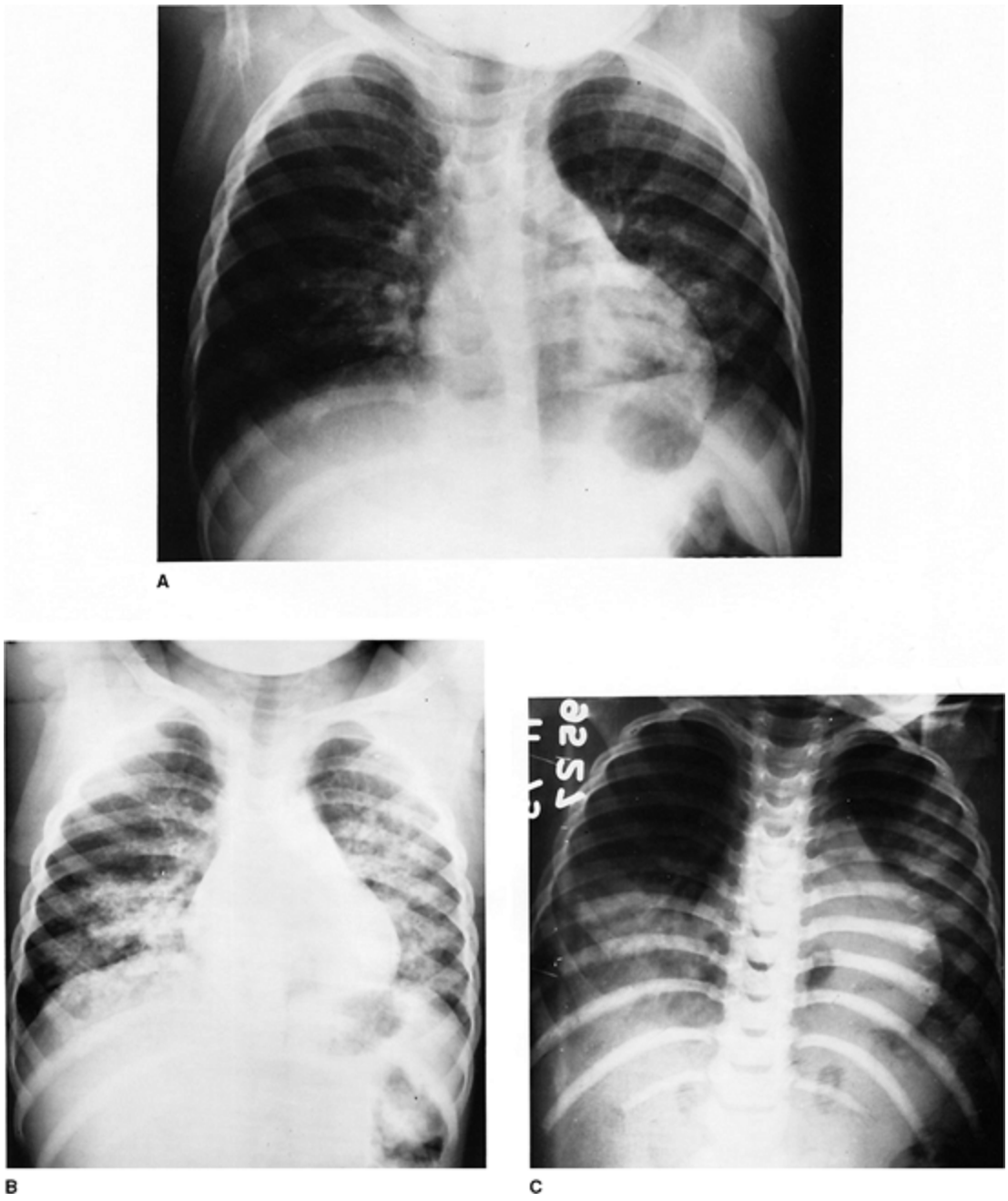

Figure 102-2. Three sequential radiographs of a young girl with severe hydrocarbon aspiration pneumonitis. A. Initial: Patchy densities appear in basilar areas of both lung fields with increased interstitial markings and peribronchial thickening. B. Day 2: More extensive diffuse alveolar infiltrates are apparent. C. Day 6: Dense consolidation and atelectasis are evident in the right lower lobe. *(Courtesy of Nancy Genieser, MD, Professor of Radiology, New York University.)*

Central Nervous System

Transient CNS excitation may occur initially after acute hydrocarbon inhalation or ingestion.[110] More commonly, CNS depression or general anesthesia occurs, and may be profound.[58] Coma and seizures are reported in 1â€“3% of cases.[115 , 145 , 155 , 223] Chronic occupational exposure or volatile substance use may lead to a chronic neurobehavioral syndrome; the painter's syndrome, most completely described after chronic toluene overexposure. The clinical features include ataxia, spasticity, dysarthria, and dementia, consistent with a leukoencephalopathic syndrome.[64] The severity and reversibility of this syndrome depends on the intensity and duration of toluene exposure.[165] Infrequent exposure may produce no clinical neurologic signs, whereas heavy (eg, daily) use can lead to significant neurologic impairment after as little as 1 year, but more commonly after 2â€“4 years of use. The specific cognitive and neuropsychological findings in toluene-induced dementia are termed a â€œwhite matter dementia.â€•[61 , 64 , 69]

Initial findings include behavioral changes, impaired sense of smell, impaired concentration, and mild unsteadiness of hand movements and gait. Further exposure leads to slurred speech, head tremor, poor vision, deafness, stiff-legged and staggering gait, and dementia. Physical findings can include nystagmus, ataxia, tremor, spasticity with hyperreflexia and abnormal Babinski reflexes, deafness, impaired vision, and a broad-based, staggering gait. An abnormal brainstem auditory-evoked response appears to be a sensitive indicator of toluene-induced CNS damage. Electroencephalograms can show mild, diffuse slowing. Computed tomography in severe cases shows mild-to-moderate cerebellar and cortical atrophy. MRI findings are consistent with white matter disease. Most cases show significant clinical

improvement after 6 months of abstinence, although with moderate to severe abuse, improvement may be incomplete.[165] Chronic toluene use is addictive and can produce withdrawal.

In the occupational setting, the extent of the exposure is rarely as substantial as during volatile substance misuse. Given the significantly lower exposures, the findings among workers overexposed to solvents (ie, exposure above permissible exposure limits) are often subclinical, and detected primarily through neurobehavioral testing. In rare cases, however, a worker may be acutely overexposed to solvent concentrations that can produce central nervous system depression. Repeated symptomatic overexposures over long periods of time have the potential to lead to a chronic encephalopathy as evident from the experience with solvent abusers.[61]

Peripheral Nervous System

Peripheral neuropathy may occur after exposure to *n* -hexane, MnBK, and possibly to toluene.[27 , 88 , 105 , 186] The axonopathy typically begins in the distal extremities and progresses proximally (a classic â€œdying-backâ€• neuropathy), and should be considered in the assessment and differential diagnosis of the patient with Guillain-BarrÃ© syndrome (GBS) although sensory finding are present with MnBK and absent with GBS.[175] The longest axons appear to be affected initially, so that the patient manifests a â€œlength-dependent polyneuropathy.â€• With discontinuation of exposure many of the effects reverse over weeks to months.[90 , 105 , 152 , 222] However, the phenomenon of â€œcoastingâ€• may occur, in which neuropathy progresses for a time (weeks to months) after discontinuation of the toxic insult.[175] A reversible peripheral neuropathy occurring in 40% of chronic toluene abusers is manifested by severe motor weakness, without sensory deficits or areflexia.[186] It is unclear whether the toluene in these early series may have been contaminated by *n* -hexane or MnBK.[8 , 176]

Trichloroethylene is associated with trigeminal neuralgia.[36 , 43 , 60 ,

[114] Trigeminal nerve damage was documented by evoked potentials follows 15 minutes of TCE inhalation.[114] Some evidence suggests that decomposition products or impurities in TCE may be responsible for cranial neuropathy.[43, 60]

Gastrointestinal

Hydrocarbons are irritants to the gastrointestinal mucous membranes. Nausea and vomiting are common after ingestion. As discussed earlier, vomiting may be associated with increased risk of pulmonary toxicity.[26, 144, 145, 162] Hematemesis can occur, and was reported in 5% of cases in one study.[144] Gastrointestinal ulcerations are found in animal studies.[14, 106]

Hepatic

Hepatic injury may occur after exposure to halogenated hydrocarbons, particularly carbon tetrachloride. Carbon tetrachloride can produce fatal centrilobular necrosis by inhalational, oral ingestion, or dermal exposure.[131] Vinyl chloride is a known liver carcinogen. Trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane are considered less hepatotoxic than vinyl chloride.[131, 192] Hepatotoxicity rarely follows ingestion of petroleum distillates.[98] Jaundice, right upper quadrant pain, and encephalopathy may occur. Aminotransferase elevation typically resolves with cessation of exposure, except in extreme poisoning.

Renal

Halogenated hydrocarbons such as chloroform, carbon tetrachloride, ethylene dichloride, tetrachloroethane, and 1,1,1-trichloroethane are also nephrotoxic. Acute renal failure and distal renal tubular acidosis occur in some painters and volatile-substance abusers.[104] Toluene may cause a renal tubular acidosis-like syndrome (see Toulene below). Human studies of nephrotoxicity are confounded by other exposures,

and the findings in many animal studies conflict.[2]

Hematologic

Hemolysis has been sporadically reported to occur after hydrocarbon ingestion.[1, 7, 184] One retrospective study of 12 patients showed hemolysis in 3 individuals and disseminated intravascular coagulation in another.[7] Although 1 patient required transfusion, hemolysis is usually mild and does not require red blood cell transfusion (see discussion of benzene and its effects on the bone marrow under Benzene below).

Dermatologic

Contact dermatitis and blistering may progress to partial- and even full-thickness burns.[85] Severity is proportional to duration of exposure. Hydrocarbons are irritating to skin. Acute, prolonged exposure can cause dermatitis and even full-thickness dermal damage.[85] Chronic dermal exposure to kerosene or diesel fuel can cause oil folliculitis.[51, 199] A specific skin lesion called *chloracne* is associated with exposure to chlorinated aromatic hydrocarbons with highly specific stereochemistry (eg, dioxins, polychlorobiphenyls).

Soft-tissue injection of hydrocarbon is locally toxic, leading to necrosis. Secondary cellulitis, abscess formation, and fasciitis can occur. Infectious complications are treated by meticulous wound

care, with surgical dÃ©bridement as necessary. A particularly destructive injury involves high-pressure injection-gun injury. These injuries typically involve the extremities, with high-pressure injection of grease or paint into the fascial planes and tendon sheaths. Emergent surgical debridement is necessary in most of these cases.[63, 139]

Hydrocarbons with Specific and Unique

Toxicity

n -Hexane

Hexane is a 6-carbon simple aliphatic hydrocarbon. It is a constituent of some brake-cleaning fluids, rubber cement, glues, spray paints, coatings, and silicones. Outbreaks of *n* -hexaneâ€“related neurotoxicity have occurred in printing plants, sandal shops, furniture factories, and automotive repair shops.[44] Human exposure occurs primarily by inhalation. Both *n* -hexane and MnBK are well-known peripheral neurotoxins that cause a classic â€œdying-backâ€• peripheral polyneuropathy, beginning in a â€œstocking-gloveâ€• distribution (see Fig. 102-3).[27 , 45] Neurotoxicity does not appear to be directly caused by the parent compounds, but results from a common metabolic intermediateâ€”2,5-hexanedione. Toxicity appears related to the ability of this intermediate to form a ringed pyrrole structure, which causes decreased phosphorylation of neurofilament proteins, disrupting the axonal cytoskeleton.[77] Similar 5- and 7-carbon species do not induce similar neurotoxicity, except those that are direct precursor intermediates in the metabolic pathway producing 2,5-hexanedione.[77 , 188]

Methylene Chloride

Methylene chloride is commonly encountered in paint removers, as well as in cleaning and degreasing agents and in aerosol propellants. Like other halogenated hydrocarbons, it can rapidly induce general anesthesia by inhalation or ingestion. Unlike other hydrocarbon agents, methylene chloride and similar halomethanes (eg, methylene dibromide) are metabolized by liver P450 mixed-function oxidase to carbon monoxide. Significant, delayed, and prolonged carboxyhemoglobinemia can occur (Table 102-3 and Chap. 120).[4 , 153 , 154 , 180 , 183]

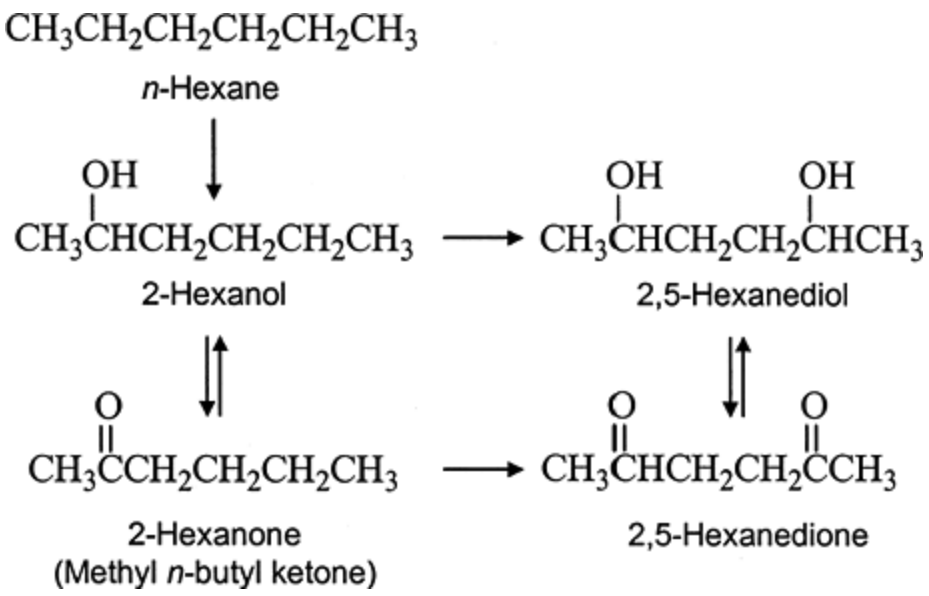

Figure 102-3. The metabolism of both organic solvents *n* -hexane and methyl *n* -butyl ketone produce the same neurotoxic metabolite, 2,5-hexanedione.

Carbon Tetrachloride

Carbon tetrachloride (CCl_4) although not actually a hydrocarbon, has been used as an industrial solvent and reagent. Its use in the United States has declined dramatically since recognition of its toxicity caused the Environmental Protection Agency to restrict its commercial use.[3] Absorption occurs by all routes, including dermal. It is an irritant to skin and mucous membranes, and is a potent gastric irritant when ingested. As with other halogenated hydrocarbons, aspiration can result in pneumonitis, and systemic absorption may result in ventricular dysrhythmias.[57]

More unique to CCl_4 exposures are hepatotoxicity and nephrotoxicity. Both occur more commonly with repetitive exposure (eg, occupational exposures).[47 , 99 , 191] Toxicity follows phase I dehalogenation of the parent compound, which produces free radicals, causes lipid peroxidation and the production of protein adducts.[29] Localization of specific phase I hepatic enzymes in the centrilobular area of the liver

results in regionalized (zone 3) centrilobular injury after CCl_4 exposure (Chap. 26). Hepatotoxicity is typically manifested as reversible aminotransferase elevation with or without hepatomegaly. Cirrhosis is reported in both animal models and in humans with prolonged overexposures. Nephrotoxicity is less-well studied, but may result from a similar mechanism.[33] The proximal convoluted tubule and the loop of Henle appear to be specifically targeted.[65] Carbon tetrachloride is a suspected human carcinogen.[3]

Benzene

Benzene is hematotoxic and associated with acute hemolysis, or the delayed development of aplastic anemia and acute myelogenous leukemia.[5 , 76 , 111 , 130 , 149] Other aromatic hydrocarbons that are reported to cause similar hematologic effects most likely are contaminated with benzene. An excess risk has not been demonstrated in groups with long-term exposure to toluene, xylene, or other aromatic hydrocarbons.[13 , 53 , 159 , 202 , 212] Other hematologic malignancies also may be linked to benzene, including chronic myelocytic leukemia, myelodysplastic syndromes, and lymphoma.[193] Chromosomal changes are believed to provide a marker for carcinogenicity.[197] Because of the carcinogenic risk, most benzene-based solvents have been unilaterally removed from the US market, and the Occupational Safety and Health Administration (OSHA) has limited the permissible worker exposure level to 1 ppm.[95]

Toluene

Toluene has essentially replaced benzene as the primary organic solvent in many commercial products. Many oil paints and stains contain primarily toluene as solvent. As such, it is readily available and readily abused as an inhalant. The CNS sequelae of chronic solvent inhalation are most frequently related to chronic toluene exposure.

Chronic toluene abuse can cause a syndrome that resembles transient distal renal tubular acidosis (RTA).[189 , 203] Although the mechanism is incompletely understood, the acidosis results in great part from the urinary excretion of hippuric acid (Table 102-3).[42 , 103] Renal potassium loss may be severe and can result in symptomatic hypokalemia.[103] Clinical findings are a hyperchloremic metabolic acidosis, hypokalemia, and aciduria. There is typically an associated transient renal azotemia, as well as proteinuria and an active urine sediment.[186 , 203] Some have reported a proximal RTA, or the Fanconi syndrome.[138 , 203] A metabolic acidosis resulting from the

metabolism of toluene to benzyl alcohol through alcohol dehydrogenase to benzoic acid may be an adequate explanation for the serum and urine acidâ€“base disturbances.

Pine Oil and Terpenes

Pine oil is an active ingredient in many household cleaning products. It is a mixture of unsaturated hydrocarbons comprised of terpenes, camphenes, and pinenes. The major components are terpenes, which are found in plants and flowers. Wood distillates are products derived from pine trees and include pine oil and turpentine. Patients who ingest pine oil often emit a strong pine odor. Wood distillates are readily absorbed from the gastrointestinal tract and ingestion may cause CNS and pulmonary toxicity without aspiration.

The clinical features of pine oil ingestion can include central nervous system depression, respiratory failure, and gastrointestinal dysfunction and are rarely fatal.[108 , 210] Aspiration pneumonitis remains the primary clinical concern. Acute toxicity is similar to that of petroleum distillate ingestion, and management is similar. Rare reported complications of wood distillate ingestion include turpentine-associated thrombocytopenic purpura, acute renal failure, and hemorrhagic cystitis.[112 , 204]

Tar and Asphalt Injury

Tar and asphalt injuries are common occupational hazards among construction workers. Asphalt workers are at risk for toxic gas exposure of hydrogen sulfide, carbon monoxide, propane, methane, and volatilized hydrocarbons.[93] In addition, cutaneous exposure to these hot hydrocarbon mixtures can cause severe burns. The material quickly hardens and is very difficult to remove. Immediate cooling with cold water is important to limit further thermal injury. Complete removal is essential to ensure proper burn management and to limit infectious complications. Attempts to mechanically remove hardened tar or asphalt often cause further damage. Dissolving the material with mineral oil, petroleum jelly, or antibacterial ointments (Neosporin, Polysporin) have met with variable success. Surface-acting agents combined with an ointment (De-Solv-it, Tween-80, Polysorbate 80) are more effective.[55 , 185 , 196]

Diagnostic Testing

Laboratory and ancillary testing for hydrocarbon toxicity should be guided by available information regarding the specific agent, the route of exposure, and the best attempt at quantifying the exposure. Inhalation or ingestion of hydrocarbons associated with pulmonary aspiration are most likely to result in pulmonary toxicity. The use of pulse oximetry and arterial blood gas testing in this group of patients is warranted when clinically indicated. Early radiography is indicated in patients who are severely symptomatic; however, radiographs performed immediately after hydrocarbon ingestion demonstrate a low predictive value for the occurrence of aspiration pneumonitis. In the asymptomatic patient, early radiography is not cost-effective. Patients observed for 6 hours after an ingestion, who demonstrate no abnormal pulmonary findings, have adequate oxygenation, are not tachypneic, and have a normal chest radiograph after the 6-hour observation period, have a good medical prognosis with very low risk of subsequent deterioration.[9 , 207]

The choice of specific diagnostic laboratory tests to assess organ system toxicity or function following exposure to a hydrocarbon depends on the type, dose, and route of exposure, and on the assessment of the patient's clinical condition. Useful clinical tests may include pulse oximetry, an electroencephalogram, or EEG.[147] Laboratory tests include serum or urine electrolytes, arterial blood gas, complete blood counts, and creatine phosphokinase. If a hydrocarbon has specific target organ toxicities (eg, benzene/bone marrow, carbon tetrachloride/liver, or *n* -hexane/peripheral nervous system), evaluation and monitoring of target organ system function is indicated.

Specific diagnostic testing for hydrocarbon poisoning can include (a) bioassays for the specific hydrocarbon or its metabolites in blood, breath, or urine, or (b) assessment of toxicity or function of the hydrocarbon's target organ. Bioassays for a hydrocarbon are seldom necessary for diagnosis or management of hydrocarbon poisoning in the emergency setting. Exceptions include testing to assist in differential diagnosis (eg, testing for carbon tetrachloride in a comatose patient with unexplained hepatic and renal toxicity or a carboxyhemoglobin determination in a paint stripper with chest pain), testing for worker compensation purposes (eg, testing for urinary trichloroethanol and trichloroacetic acid in a worker exposed to trichloroethylene with unexplained bouts of dizziness), or for forensic purposes (eg, sudden death in a huffer).

When deciding whether to obtain a bioassay for a hydrocarbon, the clinician should determine (a) what is the most informative biologic sample (blood, urine, breath) and how should it be collected, handled, and stored? (b) What are the kinetics of the hydrocarbon and the timing of exposure, and how should the results be interpreted in light of these kinetics? (c) What ranges of concentrations are associated with toxicity? Most hydrocarbon bioassays are performed by only a few, specialized clinical laboratories. The analytic toxicologist can often assist the clinician in determining the appropriate choice and timing of a bioassay. Table 102-3 provides useful information on the

elimination kinetics of selected hydrocarbons and on their common metabolites.

Chronic overexposures to hydrocarbons, as occur with volatile substance use, can result in persistent damage to the central nervous system. Damage can be detected and quantified using neuroimaging methods such as magnetic resonance imaging (MRI) or positron emission tomography (PET). Major MRI findings in patients with chronic toluene abuse include atrophy, white matter T2 hyperintensity, and T2 hypointensity involving the basal ganglia and thalamus.[39] Neurobehavioral testing can be used to detect subtle central nervous system effects following chronic occupational overexposures.

Management

Hydrocarbons are a diverse family of compounds with a wide spectrum of toxicities. Moreover, many exposures deal with mixtures of hydrocarbons rather than with individual agents. As such, identification of the specific type, route, and amount of hydrocarbon exposure is essential to effective management.

Decontamination is one of the cardinal principles of toxicology, with priority that is second only to stabilization of the cardiopulmonary status. Safe decontamination can avoid further absorption of toxicant(s), and avoids secondary casualties in those attempting to provide care. Protection of rescuers with appropriate personal protective equipment and rescue protocols is paramount, especially in situations where the victim has lost consciousness. The principle of removing the patient from the exposure (eg, vapor

or gaseous hydrocarbon) or the exposure from the patient (eg, hydrocarbon liquid on skin or clothing), while protecting the rescuer, implies that personal protective equipment be considered at each level of the healthcare delivery system.

Contraindications

- Occurrence of spontaneous vomiting
- Asymptomatic intially and at initial medical evaluation

Indications

- A hydrocarbon with inherent systemic toxicity (CHAMP)
  - C: camphor
  - H: halogenated hydrocarbons
  - A: aromatic hydrocarbons
  - M: hydrocarbons containing metals
  - P: hydrocarbons containing pesticides

TABLE 102-4. Gastric Emptying for Hydrocarbon Ingestion

Exposed clothing should be removed and safely discarded as further absorption or inhalation of hydrocarbons from grossly contaminated clothing can worsen systemic toxicity.[182] Decontamination of the skin should have a high priority in massive hydrocarbon exposures, particularly those exposures involving highly toxic hydrocarbons (Table 102-4). Water may be ineffective in decontaminating most hydrocarbons, but early decontamination with soap and water may be adequate. The caregiver should remain aware that certain hydrocarbons are highly flammable and pose a fire risk to hospital staff (Chap. 125).

Despite decades of vigorous debate, the role of gastric decontamination after hydrocarbon ingestion remains controversial.[19 , 54 , 132 , 133 , 218 , 220] Many clinical studies have addressed the efficacy of gastric lavage versus ipecac-induced emesis to prevent pulmonary toxicity.[9 , 21 , 38 , 49 , 141 , 142 , 144 , 145 , 151] Results of these studies are equivocal, but the studies were predominantly retrospective and nonrandomized. It is likely that patients manifesting greater toxicity underwent gastric emptying more frequently, and that this biased early studies against a demonstrable benefit from gastric

emptying. Moreover, patients with spontaneous vomiting were frequently included in the gastric emptying group.[49] This may have further biased these studies, as vomiting appears to increase risk of pneumonitis.[49 , 151]

Two studies prospectively randomized patients who underwent gastric lavage. Neither study had uniform indications for gastric lavage. One study, the COKP trial, was only able to randomize patients at 7 of 46 hospitals. In the subset of randomized gastric lavage patients, 44% had pulmonary complications versus 47% of those who were not lavaged. The other study reported pulmonary complications in 47% of the lavaged group, versus 61% of controls. Available studies do not offer a definitive answer to the debate over gastric emptying after hydrocarbon ingestion, although many authors have offered opinions.[11 , 12 , 71 , 119 , 132 , 133 , 211]

If there are no contraindications, gastric emptying is potentially useful when the hydrocarbon has inherent severe toxicity or the hydrocarbon is used to solubilize a potent xenobiotic or is coingested with a more potent xenobiotic (Table 102-4). Patients who have no symptoms at home or upon initial medical evaluation may not need gastric emptying.[9 , 121] For patients who do require gastric emptying gastric lavage is the superior method.[141 , 142 , 151] If gastric lavage is performed, a small nasogastric tube (18-French, not a large-bore tube) should be employed. If there is no gag reflex, an endotracheal tube should be placed prior to lavage (Chap. 8). In summary, gastric emptying is probably indicated after massive (eg, intentional, suicidal) ingestions, or after ingestion of severely toxic hydrocarbons, such as those denoted in the mnemonic CHAMP (Table 102-4).

Activated charcoal (AC) has limited ability to decrease gastrointestinal absorption of hydrocarbons and may distend the stomach and predispose patients to vomiting and aspiration.[112 , 135 , 208] As discussed earlier, gastrointestinal absorption plays a small role in hydrocarbon toxicity. The use of AC may be justified in patients with mixed overdoses, but its role in isolated hydrocarbon ingestions

appears limited. The use of cathartics and promotility agents for hydrocarbon ingestions is also of limited importance in current management.

The use of olive oil or mineral oil was previously suggested as management for hydrocarbon ingestions.[21, 68, 223] Although these hydrocarbon oils have very high viscosities and low aspiration potential, they show no benefit in animal models,[135] can cause hydrocarbon pneumonitis and lipoid pneumonia themselves, and are therefore not indicated.[52]

Antibiotics are frequently administered in the setting of hydrocarbon pneumonitis to treat possible bacterial superinfection.[49, 94, 101, 144, 151, 201] In experimental models superinfection occurs as rapidly as 7 hours after aspiration.[94] Using radiolabeled *Staphylococcus aureus*, hydrocarbon-injured lungs were shown to have a decreased ability to clear bacteria by 4 hours after insult.[35]

Despite this, animal models, including guinea pigs, dogs, and baboons, did not demonstrate any efficacy of prophylactic antibiotics.[31, 178, 216] One study showed that administered antibiotic altered bacterial lung flora to predominantly Gram-negative organisms, compared to Gram-positive lung cultures in the controls.[31] These studies led to decreased use of prophylactic antibiotics, so that clinical evidence of infection dictated therapy for most clinicians.[58] This approach, however, is not without limitations. Abnormal lung auscultation, fever, leukocytosis, and abnormal radiographic findings are the initial manifestations of both bacterial pneumonia and hydrocarbon pneumonitis. Abnormal temperatures are reported to occur in 50â€“90% of patients with hydrocarbon toxicity.[21, 38, 49, 71, 115, 144, 145] An elevated temperature is often initially noted, with the temperature reaching maximum at 8â€“12 hours, then declining over several days.[49, 145] Leukocytosis is frequently reported, present in up to 60% of patients who aspirate hydrocarbons.[115, 144, 145, 155]

Antibiotic administration may be justified in severely poisoned patients. Ideally, sputum cultures should direct antibiotic use. These,

however, are often delayed and are not useful in critically ill patients. Most authorities do not recommend prophylactic antibiotics. Most recommend close observation of temperature and blood leukocyte count, as delayed elevation (24 hours after presentation) of temperature and/or leukocytes may signal bacterial superinfection. No human studies are available to support either approach, and this issue remains controversial.

Corticosteroids, like antibiotics, have been prophylactically administered in the setting of hydrocarbon pulmonary toxicity.[41, 78, 127, 151] The rationale for their use is prevention and limitation of the inflammatory response in the lungs after hydrocarbon injury. Animal models do not show any benefit of corticosteroid administration.[6, 31, 178, 219] In one study, corticosteroids increased the risk for bacterial superinfection with or without concomitant antibiotics.[31, 172] Furthermore, two controlled human trials failed to show a benefit from corticosteroid administration.[86, 124] It is clear that corticosteroid use does not improve the acute course of hydrocarbon pulmonary toxicity, but some authors purport improved

outcome with delayed corticosteroid therapy (5â€“10 days after onset of acute respiratory distress syndrome).[101, 107] None of the experimental or human studies, however, address long-term effects such as pulmonary fibrosis, chronic obstructive pulmonary disease, or bronchiectasis. The incidence of long-term effects is poorly studied, but they appear to be relatively uncommon. Coupled with the possible increased risk of bacterial superinfection, corticosteroid administration in this setting is not recommended.

Patients with severe hydrocarbon toxicity pose unique problems for management. Respiratory distress requiring mechanical ventilation in this setting may be associated with a large ventilationâ€“perfusion mismatch. The use of positive end-expiratory pressure (PEEP) in this setting is often beneficial.[162, 224] However, very high levels of PEEP may be required with subsequent increased risk of barotrauma.[162, 224] High-frequency jet ventilation (HFJV), using very high respiratory

rates (220â€“260) with small tidal volumes, has helped to decrease the need for PEEP.[37 , 162 , 224] Patients who continue to have severe ventilationâ€“perfusion mismatch despite PEEP and HFJV have benefitted from extracorporeal membrane oxygenation (ECMO).[87 , 96 , 224] ECMO appears to be a useful option in severe pulmonary toxicity after other treatments have failed.

As discussed, the toxic mechanism for hydrocarbon-induced pulmonary damage may in part be a result of detrimental effects on surfactant.[75] Several commercial surfactant preparations are available and are useful for other disease conditions associated with inadequate surfactant function. One animal model did not show benefit, whereas another showed increased survival and improved pulmonary function after exogenous surfactant.[173 , 213] No studies are currently available to suggest the clinical effectiveness in humans. Further study is warranted prior to use in hydrocarbon aspiration pneumonitis.

Cyanosis is uncommon after hydrocarbon toxicity. Although this is most often caused by severe hypoxia, methemoglobinemia associated with hydrocarbon exposure is reported.[48 , 113] The potential for methemoglobinemia should be investigated in patients who remain cyanotic following normalization of arterial oxygenation.

Hypotension in severe hydrocarbon toxicity raises additional concerns. The etiology of hypotension in this setting is often compromise of cardiac output because of high levels of PEEP. Hydrocarbons do not have significant direct cardiovascular effects, and decreasing the PEEP may improve hemodynamics. The use of Î²-adrenergic catecholamines (eg, dopamine, epinephrine, isoproterenol, norepinephrine) should be avoided if possible, as certain hydrocarbons predispose to dysrhythmias.[20 , 67 , 156 , 157]

Management of dysrhythmias associated with hydrocarbon toxicity should be include consideration of electrolyte and acidâ€“base abnormalities (eg, hypokalemia and acidosis from toluene), hypoxemia, hypotension, and hypothermia. Ventricular fibrillation poses a specific concern, as common resuscitation algorithms

recommend epinephrine administration to treat this rhythm. If it is ascertained that the dysrhythmia emanates from myocardial sensitization by a hydrocarbon solvent, catecholamines should be avoided. In this setting, lidocaine has been used successfully, as has Î²-adrenergic antagonism.[136]

Hyperbaric oxygen (HBO) was studied in a rat model of severe kerosene-induced pneumonitis.[167] HBO at 4 ATA showed some benefit in 24-hour survival rates. No followup studies have been performed. Patients with carbon tetrachloride poisoning, however, may benefit from hyperbaric oxygen (see Antidotes in Depth: Hyperbaric Oxygen).[34 , 195]

In the past, hospital admission was routinely recommended for patients who had ingested hydrocarbons, because of concern over possible delayed symptom onset and progression of toxicity.[38 , 49 , 80] Several reports documented patients with relatively asymptomatic presentations who rapidly decompensated with respiratory compromise.[9 , 80 , 121] However, progressive symptoms after hydrocarbon ingestion are rare.[9 , 121] In a retrospective study of 950 patients, only 14 (1.5%) had progression of pulmonary toxicity.[9] Of these 14, 7 had persistence of symptoms for less than 24 hours. Eight hundred patients were asymptomatic on initial evaluation with normal chest radiographs, remained asymptomatic after 6â€“8 hours of observation, and had a normal repeat radiograph. No patient in this group of 800 had progressive symptoms, and all were discharged without clinical deterioration. Seventy-one of the 950 patients had initial respiratory symptoms but were asymptomatic at initial medical evaluation. Of the 71 patients, 36 had radiographic evidence of pneumonitis. Among these 36 patients, 2 (6%) developed progression of pulmonary symptoms during their 6-hour observation period. Of the 35 who had a normal radiograph, 2 (6%) developed pulmonary symptoms and radiographic pneumonitis during the 6-hour observation period. The 4 patients who were hospitalized for progression of symptoms became asymptomatic over the next 24 hours and had no complications.

A separate poison center-based study evaluated 120 asymptomatic patients for an 18-hour telephone followup period.[121] Sixty-two patients had initial pulmonary symptoms that quickly resolved. One of the 62 patients (1.6%) developed progressive pulmonary toxicity. This patient was hospitalized and had resolution of symptoms within 24 hours without complications.

It is clear that the vast majority of patients exposed to a hydrocarbon do not need hospitalization.[9,121] A number of investigators have suggested protocols for determining which patients can be safely discharged.[9,12,106,119,121] None of these protocols has been prospectively validated. However, rational guidelines for hospitalization can be recommended. Those patients who have clinical evidence of toxicity, and most individuals with intentional ingestions, should be hospitalized. Patients who do not have any initial symptoms, have normal chest radiographs obtained at least 6 hours after ingestion, and who do not develop symptoms during the 6-hour observation period can be safely discharged. Care should be individualized for patients who are asymptomatic but who have radiographic evidence of hydrocarbon pneumonitis, and for patients who have initial respiratory symptoms but quickly become asymptomatic during medical evaluation. Reliable patients may be considered for possible discharge with next-day followup.

Summary

Hydrocarbons are a diverse group of xenobiotics that can cause toxicity by inhalation, ingestion, or dermal absorption. Most hydrocarbons occur as mixtures of several to many chemicals. Ubiquitous use of hydrocarbons in our society means that exposures are extremely common. Populations at particular risk for toxicity include children who ingest hydrocarbon compounds, workers who are occupationally exposed by inhalation or dermal absorption, and youths who intentionally inhale volatile hydrocarbons.

Toxicity is largely determined by the route of exposure, and is xenobiotic specific. Aspiration pneumonitis is the primary concern after hydrocarbon ingestion. Many hydrocarbons are poorly absorbed

from the gastrointestinal tract and unlikely to produce systemic poisoning. Acute systemic toxicity is unlikely to occur in the absence of CNS effects such as excitation or sedation. Most hydrocarbons are capable of producing profound CNS depression, even general anesthesia if absorbed systemically.

Specific hydrocarbons may demonstrate specific organ toxicity: the halogenated hydrocarbons are cardiotoxic, hepatotoxic, and nephrotoxic. Most are also acutely toxic to the CNS and some are also peripheral neurotoxins. Diagnosis is predominantly clinical. Diagnostic studies are rarely specific, and hydrocarbon-specific studies are seldom helpful in the acute setting. Skin decontamination is important in massive dermal exposures. Gastrointestinal decontamination, as well as the use of prophylactic antibiotics or corticosteroids, remain controversial. Management is largely supportive, and no specific antidotes are available.

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Chapter 103
Toxic Alcohols

Sage W. Wiener

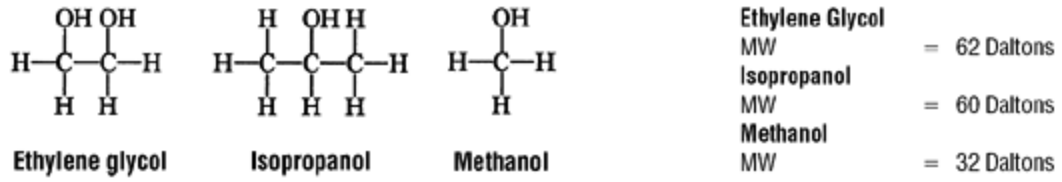


Figure. No Caption Available.

A 56-year-old man was brought to the hospital by ambulance after being of â€œantifreezeâ€• was also brought. The patient had a history of diabe rosiglitazone. He had appeared normal when he was last seen, several ho that he had been upset after losing his job. Upon initial evaluation, the p but withdrew to pain. There was no sign of trauma. Initial vital signs wer 68 beats/min; respirations, 18 breaths/min; and temperature 98.4Â°F (3(saturation of 100% on room air, and rapid bedside glucose was 114 mg/d and reactive to light, and a funduscopic examination was normal. A gag were moist, the lungs were clear to percussion and auscultation, and a c sounds were present, the bladder was not distended, the skin was warm a clubbing, cyanosis, or edema of the extremities. The neurologic examinatio

consciousness, but was otherwise without focal findings.

An intravenous line was established with 0.9% NaCl solution, and the pat Empiric thiamine and naloxone were administered with no response. A sc arterial blood gas revealed a metabolic acidosis with respiratory compensa 94 mm Hg. The blood lactate concentration was 0.7 mEq/L. Serum electr mEq/L; CL^- , 108 mEq/L; HCO_3^- , 16 mEq/L; Ca^{2+} , 8.8 mEq/L. Other si mg/dL; creatinine, 1.2 mg/dL; glucose 116 mg/dL; ethanol 0 mg/dL; urir osmolality, 421 mOsm/kg. Acetaminophen and salicylates were undetectab mEq/L and the calculated osmolarity was 292 mOsm/L, giving an osmol ga with a Woods lamp and did not fluoresce; the sediment did not contain a

The patient was treated with fomepizole (15 mg/kg IV, followed by 10 mg IV every 6 hours), folate (50 mg IV every 6 hours), and pyridoxine (50 m the medical intensive care unit (ICU), and nephrology consultation reques dialyzed for 4 hours. Initial toxic alcohol levels had not been requested, b recovered and sent for analysis. In the serum, ethylene glycol and isopro methanol was 95 mg/dL. Fomepizole and folate were continued after hem was 119 mg/dL. The patient was dialyzed again, with a subsequent metha (about 48 hours after presentation), his mental status had gradually retur increased to 15 mg/kg every 12 hours. After a third course of hemodialys therapy was discontinued except for folate. The patient was transferred to evaluation. The can brought with the patient by the family contained au

Chemistry

Alcohols are hydrocarbons that contain a *hydroxyl* (-OH) group. The term alcohols other than ethanol, that is, those alcohols not intended for inges all alcohols are toxic, causing inebriation and end-organ effects, such as l The most common toxic alcohols encountered clinically are methanol and glycol contains 2 hydroxyl groups; molecules with this characteristic are

termed *diols* (also known as *glycols* because these molecules generally ha alcohols include isopropanol (or isopropyl alcohol or 2-propanol), benzyl glycol (1,3-propanediol). *Primary* alcohols, such as methanol and ethanol, the molecule (the *terminal* carbon), whereas *secondary* alcohols, such as

bound to nonterminal carbons.

Glycol ethers are glycols with a hydrocarbon chain bound to one or more structure R_1 O-CH_2 -CH_2 -O-R_2 or R_1 O-CH_2 -CH_2 -CH_2 -OR_2). Poisoning resemble toxic alcohol poisoning. Glycol ethers commonly encountered inc known as 2-butoxyethanol, ethylene glycol monobutyl ether, or butyl cell methoxyethanol), and diethylene glycol (2,2â€²-dihydroxydiethyl ether). T uses, and are found in household and automotive products, such as hydr cleaner, paints, lacquers, and fog machine liquid. Use of the E-series gly has dramatically declined over the past few decades, as they have been ethers (derivatives of propylene glycol).[7 , 25] However, butoxyethanol is s equivalents with the necessary physical properties.[25] Polyethylene glycol (polymer of ethylene glycol with the structure H(OCH_2 CH_2)$_n$ OH. High mo soluble in water, but not absorbed by the gastrointestinal tract when inge osmotic laxative. Different chain lengths have different physical properties texturizer in many medicinal and food products.

History and Epidemiology

Methanol was a component of the embalming fluid used in ancient Egypt. 1661 by distillation of boxwood, calling it *spirit of box.* The molecular cor Dumas and Peligot, who coined the term *methylene* from the Greek roots production began in 1923, and today most methanol is used for the synt containing consumer products that are commonly encountered include mo solid cooking fuel for camping and chafing dishes (eg, Sterno cans), phot antifreeze (â€œdry gasâ€•). Methanol is also used as a solvent by itself, alcohol. Most reported cases of methanol poisoning in the United States in products by individuals, with more than 60% caused by ingestion of wind review.[23] However, there have been sporadic epidemics of mass methano tainted fermented beverages.[8 , 70] These epidemics are a continuing prob

Ethylene glycol was first synthesized in 1859 by Charles Wurtz, and first during World War II, when its precursor, ethylene oxide, became readily as an engine coolant (antifreeze used in car radiators, as opposed to anti contains methanol).

Isopropanol is primarily available as rubbing alcohol. Typical household p
also a solvent used in many household, cosmetic, and topical pharmaceut
ubiquitous, inexpensive, and its common name contains the word alcohol,
common toxic alcohol exposure reported to poison centers in the United
substitute.

Most glycol ether poisoning is in the industrial setting because these prod
ethers were also responsible for many poisoning epidemics in the 20th c
for the more benign medication diluent propylene glycol, has repeatedly r
largely in children from ingestion of contaminated elixirs. The first such e
in the United States, while subsequent epidemics in India, Nigeria, Bangl
contaminated acetaminophen (Chap. 2).[38 , 85 , 103 , 118 , 133]

Toxicokinetics and Toxicodynamics

Alcohols are readily absorbed after ingestion,[36 , 42] but are not complete
gastric alcohol dehydrogenase, and because of first-pass metabolism by th
absorbed in significant amounts by inhalation, poisoning by this route is
methanol fumes from industrial processes for up to 6 hours, in concentra
and Health Administration [OSHA] permissible exposure limit) there was
formate.[77] However, cases of inhalational poisoning have been reported v
a drug of abuse (â€œhuffingâ€•) and with massive exposures of rescue v
overturned rail car filled with methanol.[3 , 37 , 83 , 128] Ethylene glycol and
are not reported to cause poisoning by inhalation. Most alcohols have so
isopropanol, methanol, and the glycol ethers are able to penetrate the sk
[, 79 , 129] Most reported cases of toxic alcohol poisoning by this route inv
greater surface-area-to-volume ratio in these patients), and likely also i
glycol ethers have high percutaneous absorption, and it appears that absc
water.[66 , 76]

Once absorbed, alcohols are rapidly distributed to total body water (Table
small oral dose of methanol on an empty stomach, the measured volume
distribution half-life of about 8 minutes.[42] Although peak concentrations c
investigation, anecdotal experience suggests that peak concentrations may
ingestions.

Without intervention, toxic alcohols are eliminated primarily through succ dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), each of whic to the reduction of NAD^+ (oxidized form of nicotinamide adenine dinucleot nicotinamide adenine dinucleotide) and H^+ (hydrogen ion). Methanol is r acid (Fig. 103-1). Ethylene glycol has two hydroxyl groups that are seria in turn, glycoaldehyde, glycolic acid, glyoxylic acid, and finally oxalic acid

This metabolism, like ethanol metabolism by the same enzymes, is zero-or about 10 mg/dL/h.[21 , 61 , 90] This rate is apparently unchanged in chronic

Benzyl alcohol
$C_6 H_6 OH$
?
Benzoic acid, hippuric acid
+
â€“
+
Neonatal â€œgasping syndromeâ€•
Bacteriostatic preservatives
Ethanol[a]
$CH_3 CH_2 OH$
Zero-order kinetics 15â€“20 mg/dL/h
Acetaldehyde, acetic acid
+
+
+
Intoxication
Solvents, beverages, colognes
Ethylene glycol
$CH_2 OHCH_2 OH$
8.5 h
Oxalic acid, glycolic acid
+ +
â€“
+

Renal failure, hypocalcemia, calcium oxalate crystals in urine
Antifreeze (95%), solvents, deicers, airconditioning units
Glycol ethers
$HOCH_2$ CH_2 OR
Varies
Varies
+
â€“
+
Similar to ethylene glycol
Solvents, industrial coatings
Isopropanol
CH_3 $CHOHCH_3$
2.5â€“3.5 h
Acetone
â€“
+
+ +
Hemorrhagic tracheobronchitis
Rubbing alcohol, solvents, lacquer
Methanol
CH_3 OH
Zero-order kinetics 8.5 mg/dL/h
Formaldehyde, formic acid
+ +
â€“
+
Blindness, pale edematous optic disc
Antifreeze, solvents, gasohol denaturant
Propylene glycol
CH_2 $OHCHOHCH_3$
2â€“5 h
Lactic acid, pyruvic acid
+

â€“

+

Lactic acidosis

Solvents, deicers

+ = Presence and degree of symptoms; â€“ absence of symptoms.

[a] Only in the case of alcoholic ketoacidosis is there a high anion gap me

Substance	Formula	Half-life	Metabolites	High Anion Gap Acidosis	Ketosis	Dep

TABLE 103-1. Toxic Alcohols: Characteristics, Signs, and Symptom

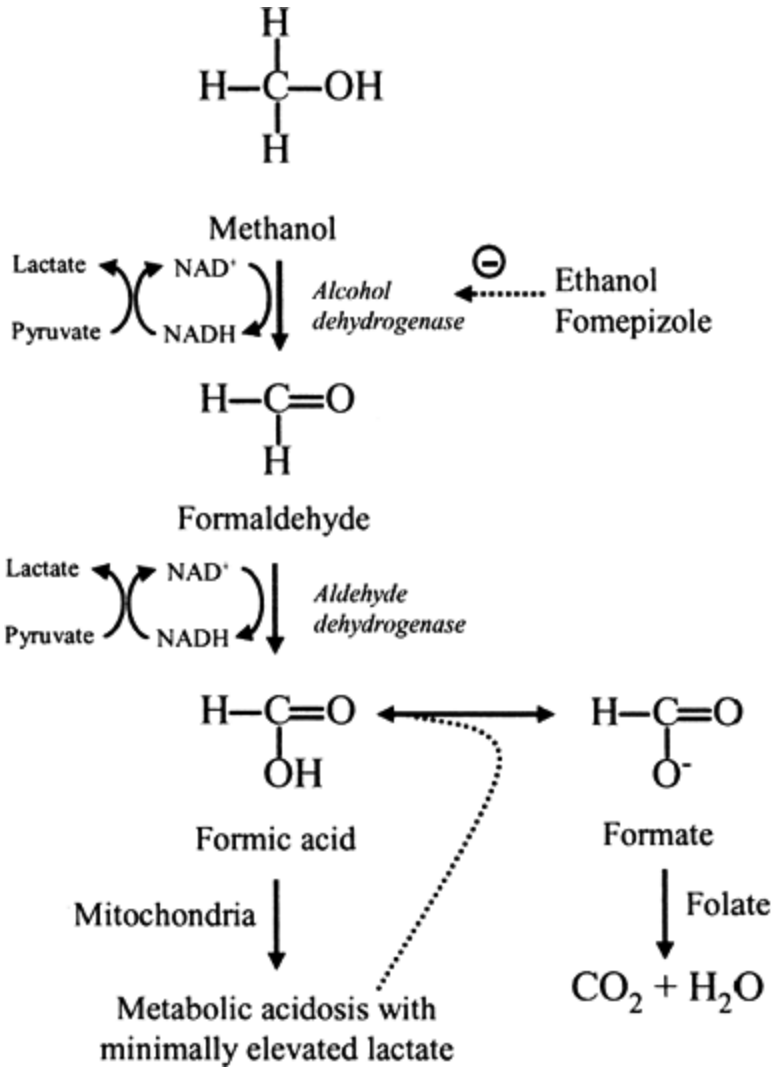


Figure 103-1. Major pathways of methanol metabolism. Metabolic acidos equilibrium to favor the more toxic formic acid.

Alternate minor metabolic pathways, such as catalase, exist for methanol ingestion, the formate metabolite is bound by tetrahydrofolate and then formyltetrahydrofolate dehydrogenase to carbon dioxide and water. Ethyle and glycine using thiamine and pyridoxine as cofactors. Because of the lo normally minor metabolic pathways are attractive targets for potential th

Methanol and ethylene glycol may also be eliminated from the body as u function is normal, ethylene glycol is slowly cleared by the kidneys, with [19 , 123] Methanol does not have significant renal elimination, and is cleare

glycol as a vapor in expired air (half-life 30â€“54 hours).[13 , 106]

Clinical Manifestations and Pathophysiolog

Central Nervous System Effects

All alcohols may cause inebriation, depending on the dose (Table 103-2) higher-molecular-weight alcohols are more intoxicating than lower-mole

alcohols (eg, isopropanol â‰ˆ ethylene glycol > ethanol > methanol).[13] inebriation does not exclude toxic alcohol ingestion, particularly if the pa quantities of ethanol and is tolerant of its CNS effects. This is intuitively of 25â€“50 mg/dL are potentially associated with toxicity, although in mo car with a serum ethanol concentration of up to 93 mg/dL (equivalent to as measured by breathalyzer).

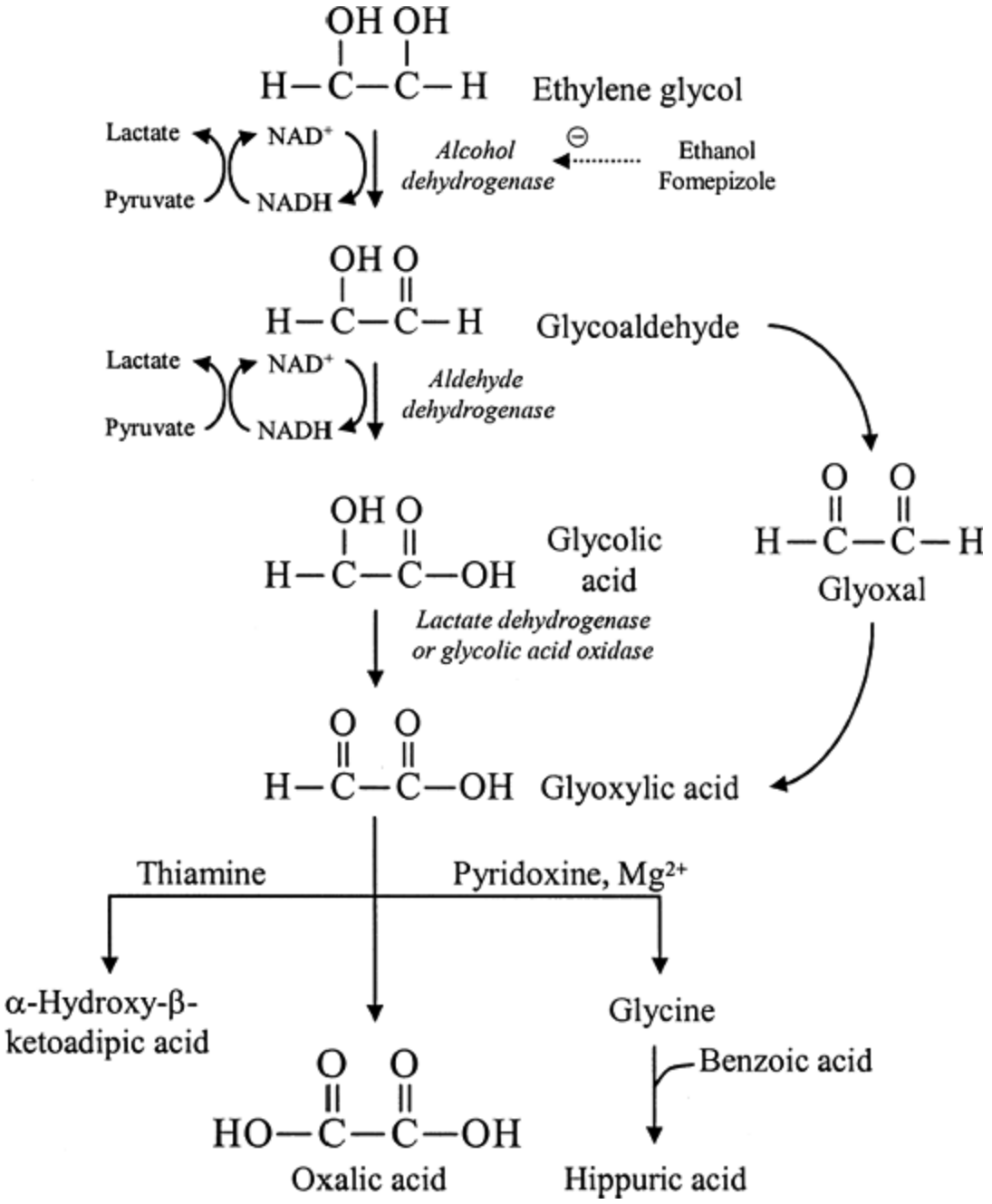


Figure 103-2. Pathways of ethylene glycol metabolism. Thiamine and py metabolites.

Cardiovascular
Tachycardia
Tachycardia

Tachycardia
Hypertension/hypotension
Hypotension
Hypotension
Dysrhythmias
Myocarditis
Myocardial depression

Central nervous
Ataxia
Areflexia
CNS depression
Meningoencephalitis
Ataxia
Convulsions
Convulsions
CNS depression
Dizziness
CNS depression
Dizziness
Headache
Intoxication
Headache
Hypothermia
Myoclonus
Intoxication
Intoxication
Cranial nerve abnormalities
Muscle weakness
Hypothermia

Gastrointestinal
Nausea, vomiting
Abdominal pain, cramping

Gastritis
Hematemesis
Nausea, vomiting
Abdominal pain
Anorexia
Gastritis
Nausea, vomiting
Pancreatitis
Ophthalmic
Ophthalmoplegia
Nystagmus

â€œSnow fieldsâ€•
Blurred vision
Hyperemic optic discs
Mydriasis
Papilledema, blindness
Pulmonary
Hyperventilation, tachypnea, pneumonitis
Respiratory depression
Odor of acetone
Respiratory depression
Hemorrhagic tracheobronchitis
Respiratory depression
Renal
Crystalluria
Renal insufficiency
Renal tubular acidosis
Rhabdomyolysis

Other

Hemolytic anemia

Organ System	Ethylene Glycol	Isopropanol	Methanol

TABLE 103-2. Signs and Symptoms of Toxic Alcohol Exposures

The CNS manifestations of toxic alcohol poisoning are incompletely unders alcohol inebriation is similar to ethanol inebriation, in which case effects GABAergic tone (both directly and through inhibition of presynaptic Î³-am receptors) and inhibition of the *N* -methyl-D-aspartate (NMDA) glutamate CNS effects of other alcohols are clinically similar, there is no direct evid same.

Metabolic Acidosis

Metabolic acidosis with an elevated anion gap is a hallmark of toxic alcoh metabolism of these alcohols to toxic organic acids. The acids have no ra elimination (unlike acetic acid from ethanol metabolism, which can enter t accumulate. In methanol poisoning, formate is responsible for the acidosi in ethylene glycol poisoning, glycolic acid is the primary acid responsible making a minor contribution. Among the toxic alcohols,

isopropanol is unique in that it is not metabolized to an acid metabolite b Acetone is a ketone, not an aldehyde, and therefore cannot be further me isopropanol has no organic acid metabolite and does not cause metabolic is the defining characteristic of isopropanol poisoning.

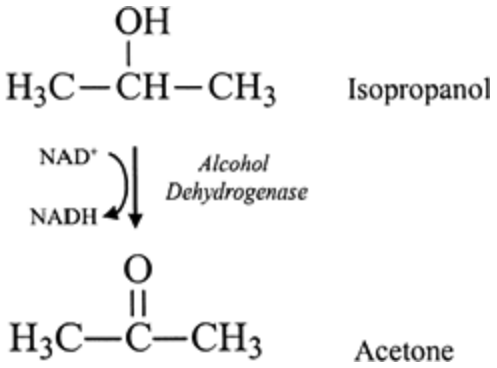


Figure 103-3. Isopropanol metabolism.

Specific End-Organ Effects

Additional end-organ effects depend on which alcohol is involved. Methan blurry or hazy vision or defects in color vision, to â€œsnowfield visionâ€ On physical examination, central scotoma may be present on visual field the optic disc, and papilledema are described as characteristic findings.[8] methanol is a mitochondrial toxin, inhibiting cytochrome oxidase (much li oxidative phosphorylation.[31 , 98 , 99] Although it is unclear why this resul are relatively spared, retinal pigmented epithelial cells and optic nerve ce [86 , 126 , 127]

Interestingly, neurons in the basal ganglia appear to be similarly suscepti lesions (particularly putamen and, less commonly, caudate nucleus) char computerized tomography or magnetic resonance imaging after methanol lesions of this type are nonspecific and can occur in other disease states monoxide exposure), they may occur in the absence of hypotension and suggesting a direct toxic mechanism. Rarely, injury to other tissues may pancreatitis are reported after methanol poisoning.[52 , 73] For unclear reas incidence of pancreatitis (50%).[52] Myoglobinuria and resultant acute renal severe methanol poisoning.[46]

The most prominent end-organ effect of ethylene glycol is nephrotoxicity. complex with calcium to precipitate as crystals in the renal tubules, leadi addition, the intermediate products of ethylene glycol metabolism are direc mechanism yet to be described, causing acute tubular necrosis and there [, 112] Furthermore, although oxalic acid has long been recognized as a tox not cause glomerular injury;[67] thus the presence of necrotic lesions to th some pathology specimens provides indirect evidence that oxalic acid is r nephrotoxicity of ethylene glycol.[35]

Ethylene glycol can occasionally affect other organ systems. In severe po present in sufficient amounts to cause hypocalcemia by precipitation with of the QTc interval on the electrocardiogram and dysrhythmias.[120] Precipi brain has also been found on autopsy after severe ethylene glycol poison multiple cranial nerve abnormalities that occasionally develop,[124] althoug

causation. A leukemoid reaction may also occur in the setting of severe mechanism remains unclear.[96]

Hemorrhagic gastritis has been reported in association with isopropyl alcc assumed to be caused by a local irritant effect, one reported case of he isopropanol exposure suggests that this is not the only mechanism, and, i effect.[29]

Diagnostic Testing

Toxic Alcohol Concentrations

Actual serum methanol, ethylene glycol, and isopropanol concentrations ar when toxic alcohol poisoning is suspected shortly after exposure. Howeve commonly measured by gas chromatography with or without mass-spect are not available in most hospital laboratories on a 24-hour basis, if avail these are only available as â€œsend-outâ€• tests, so results arrive too Enzymatic assays for methanol, formic acid, ethylene glycol, and glycolic and these may lead to more readily available clinical tests, but a comme veterinary use only. A group in Finland described a point-of-care breath t transform infrared (FT-IR) analyzer similar to the â€œbreathalyzersâ€• u Although analyzers like this are used to check for methanol as a combust approved for medical use in the United States. Once approved, they woul analysis because they are easy to use and provide a rapid result. They a concentrations, a feature that would be very helpful during hemodialysis be used to detect ethylene glycol because of its low volatility.

Patients presenting late after ingestion may already have metabolized all and thus may have low or no measurable toxic alcohol concentrations. An more helpful in late cases of ethylene glycol ingestion. Some authors hav glycolic acid in addition to testing for the parent compound when ethylen Similarly, a formic acid concentration may be valuable when a patient pr Clearly, a low or undetectable toxic alcohol concentration must be interpre other clinical data, such as the presence of acidosis and end-organ toxicit concentrations as potentially valuable additions.

Samples must be handled correctly for accurate toxic alcohol results. Par
methanol and isopropanol, concentrations may be falsely low if the sampl

are not airtight. This loss of volatile alcohol commonly results in low cor
done as â€œadd-onâ€• tests to samples already opened for electrolyte

Other alcohols, such as benzyl alcohol and propylene glycol, as well as th
assessed by gas chromatography. Thus, these xenobiotics present a muc
methanol and ethylene glycol. Enzymatic assays for methanol or ethylene
alcohol and propylene glycol, although false-positive ethylene glycol tests
Consequently, a high index of suspicion is critical to making the diagnosis
of history, specific toxic alcohol testing should be performed.

Once alcohol concentrations are obtained, their interpretation represents
Traditionally, a methanol or ethylene glycol level greater than 25 mg/dL l
evidence supporting this as a threshold is often questioned. In a case se
the 1950s, a methanol level of 52 mg/dL was the lowest associated with
origin of the 25 mg/dL threshold, incorporating a 50% reduction as a ma
the 52-mg/dL concentration presented 24 hours after his initial ingestion,
poisoned than suggested by his serum concentration at that point. In fact
poisoning involve late presenters with metabolic acidosis.[74] The only repo
presenting early with only an elevated methanol concentration (45.6 mg/d
acidosis or end-organ toxicity.[12 , 74] However, until better data is availabl
mg/dL as a threshold for treatment.

Because of the problems with obtaining and interpreting actual serum co
have been used to assess the patient with suspected toxic alcohol poisor
should include serum electrolytes (including calcium), blood urea nitroge
serum osmolality, and a serum ethanol concentration. An arterial blood g
also helpful in the initial evaluation of ill-appearing patients.

Anion Gap and Osmol Gap

For a full discussion of the anion gap concept, see Chap. 17 . As discusse
of toxic alcohol poisoning. In fact, the possibility of methanol or ethylene
when patients present with an anion gap acidosis of unknown etiology, fr

Unless other clinical information suggests otherwise, it is important to e ketoacidosis in these patients (the most common causes of anion gap ac This is because of the extensive evaluation and expensive, potentially inva individual would be committed. However, elevated lactate concentrations m methanol and ethylene glycol poisoning.

The unmeasured anions in toxic alcohol poisoning are the dissociated org The acidosis takes time to develop, sometimes as long as 24 hours for m gap elevation early after reported toxic alcohol ingestion does not exclude the body, the development of acidosis will not begin to occur until the rat below a number that varies by alcohol.

A potential early surrogate marker of toxic alcohol poisoning is an elevat 17). However, it is important to recognize that osmol gap elevation is n alcohol poisoning. Because a baseline osmol gap is generally not available osmol gap ranges from -14 to +10, so-called normal osmol gaps cannot example, in a patient with a baseline osmol gap of -10, a gap of +5 repr mg/dL, or an ethylene glycol concentration of 93 mg/dL, concentrations a moderately elevated osmol gap (+10 to +20) is not necessarily diagnos many other disorders, such as alcoholic ketoacidosis and lactate-associate However, a markedly elevated osmol gap (>50) is difficult to explain by

Further complicating matters, the anion gap and osmol gap have a recipr because soon after ingestion, the alcohols present in the serum raise the gap, because metabolism to the organic acid anion has not yet occurred. organic acid anions, the anion gap, rises while the osmol gap falls, becau particles that have already been accounted for in the calculated osmolarity theory patients who present early after ingestion may have a high osmol who present later may have the reverse.[59 , 60] Figure 103-4 depicts a m process.

Ethanol Concentration

A serum ethanol concentration is an important part of the assessment of poisoning. As discussed in Chap. 17 , the ethanol concentration is necess addition, because ethanol is the

preferred substrate of alcohol dehydrogenase (4:1 over methanol, and 8: concentration would be protective if coingested with a toxic alcohol. In fa mg/dL virtually preclude toxic alcohols as the cause of an unknown anion presence of such a concentration should have prevented metabolism to th ingested several hours after significant amounts of a toxic alcohol.[56]

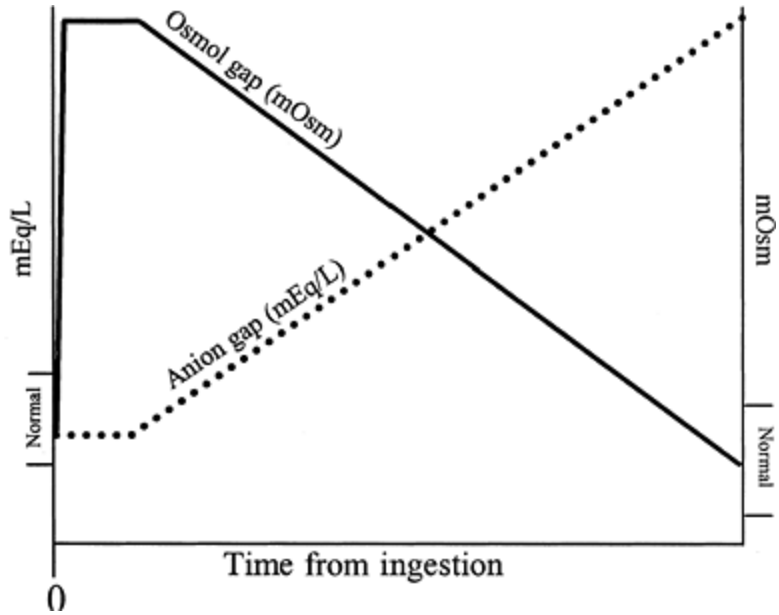


Figure 103-4. The reciprocal relationship of anion gap and osmol gap ov shortly after an ingestion may have a normal anion gap, whereas patients normal osmol gap.

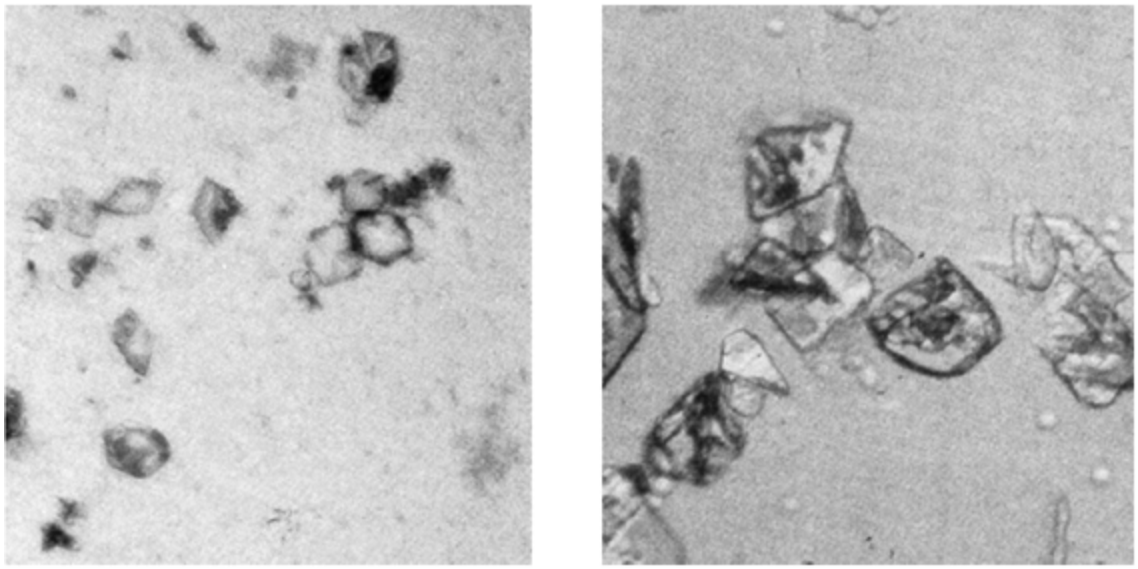


Figure 103-5. Calcium oxalate crystals (dehydrate forms) under low (A) of a patient following the ingestion of ethylene glycol.

Lactate

Both methanol and ethylene glycol can result in elevated lactate concent Formate, as an inhibitor of oxidative phosphorylation, can lead to anaero elevation. Additionally, metabolism of all alcohols results in an increased production of lactate from pyruvate. Furthermore, hypotension and organ also result in elevated lactate concentrations. Lactate production by these concentrations less than 5 mmol/L.

In ethylene glycol poisoning, the glycolate metabolite may also cause a measured by some analyzers, particularly those that analyze whole-blood implicated include ABL 625, Beckman LX 20, Chiron 865, Bayer (formerly Hitachi 911 analyzers, but not the Vitros 950.[93, 111, 138] The artifact res lactate oxidase enzyme used in these machines,[93, 111, 138] although dire anode has also been suggested as a possible mechanism.[121] The presence used to diagnose ethylene glycol poisoning in hospitals where multiple lac and without sensitivity to glycolate.[121]

Other Diagnostics

The urine may provide information in the assessment of the patient with Calcium oxalate monohydrate (spindle-shaped) and dihydrate (envelope-sh urine sediment is examined by microscopy, although this finding is neithe one series, calcium oxalate crystals were present in the urine of only 63% ethylene glycol ingestion.[14]

Some brands of antifreeze contain fluorescein to facilitate the detection of is ingested and the urine is examined with a Woods lamp within the first fluorescence.[137] False-positive fluorescence may result from examining th because of the inherent fluorescence of these materials, so if this test is be poured onto a piece of white gauze or paper. Recent work suggests th children had urinary fluorescence in one study.[18]

The evaluation of patients with known or suspected ethylene glycol poisor concentration and a creatinine concentration. Patients with methanol poisc assessment of liver enzymes and serum lipase and/or amylase concentrat associated hepatitis and pancreatitis.

Management

As always, immediate resuscitation of critically ill patients starts with ma circulation. Because alcohols may cause respiratory depression and coma are commonly necessary for patients with severe poisoning. Alcohol-indu often lead to hypotension, and many patients will require fluid resuscitat Gastrointestinal decontamination is rarely, if ever, indicated for toxic alcc and limited binding to activated charcoal. However, placement of a nasog contents is probably worthwhile

in intubated patients, as absorption may sometimes be delayed after a la

Alcohol Dehydrogenase Inhibition

The most important part of the initial management of patients with know (after initial resuscitation) is blockade of ADH. This allows for the establis

arrangement for hemodialysis while preventing the formation of toxic me
blockade may itself serve as definitive therapy.

Teleologically, ADH exists for the purpose of metabolizing ethanol, so it is
higher affinity for ethanol than for other alcohols. In fact ADH has an affi
vitro than its affinity for methanol, and 67 times greater than its affinity
[109] Thus significant concentrations of ethanol prevent metabolism of othe
is the traditional method of ADH inhibition and still the only option in son
administered through a central venous catheter and titrated to maintain a
Antidotes in Depth: Ethanol). Complications of the infusion, although un
respiratory depression (with supratherapeutic concentrations), flushing,
and gastritis, as well as inebriation, so patients getting intravenous ethan
unit. Orally administered ethanol is also effective, and may be considered
unavailable, particularly in rural areas where there may be a significant d

Fomepizole is a more recently developed competitive antagonist of ADH t
reliably inhibits ADH when administered as an intravenous bolus every 12
be monitored as with an ethanol infusion.[13, 14] It does not cause inebria
effects, so it does not require intensive care unit monitoring.[4, 5, 13, 14]
preferred method of ADH blockade, despite being significantly more expen
intensive care unit (ICU) monitoring and laboratory costs probably compen
fomepizole, unless the patient requires intensive monitoring anyway based
fomepizole is 15 mg/kg intravenously as an initial loading dose followed b
hours of therapy, fomepizole induces its own metabolism, so the dose mus
hours.

Indications for ethanol or fomepizole therapy may be based on the history
a believable history of methanol or ethylene glycol ingestion should be t
because, as discussed above, early symptoms and laboratory markers (ot
absent. In addition, any patient with an anion gap acidosis without anoth
osmol gap should also be treated. Once concentrations are available, ther
concentration is below 25 mg/dL, although as discussed above, this numb
than on data.

Hemodialysis

The definitive therapy for patients poisoned by toxic alcohols is hemodial and their toxic metabolites from the blood, and can correct the acidâ€“ba hemodialysis have become more controversial with the advent of fomepiz with its low incidence of adverse effects. Ethylene glycol can generally be once ADH is blocked and the glomerular filtration rate (GFR) is normal, ar an invasive procedure like hemodialysis are not warranted, except for a patients with end-organ toxicity or severe acidosis have significant amoun addressed by ADH blockade, and acidosis is associated with poor prognos failure will not eliminate the parent compound once ADH is blocked, excep of methanol. Therefore, there is a consensus that metabolic acidosis, sign and seizures), and renal failure are indications for hemodialysis. A â€œtox osmol gap are more relative indications for hemodialysis, and decisions mu physician for the specific clinical scenario, taking into account the availab advocated using toxic metabolite concentrations (if available) as additiona case series, an elevated formate concentration appears to be a better pr clinically important toxicity.[105] Similarly, glycolic acid concentrations are concentrations of death and renal failure.[112] However, although clearance substantial,[64 , 65 , 72] the overall clearance in one case series did not ap endogenous concentrations in patients also treated with folate and bicarb quality in this series.[140]

The American Academy of Clinical Toxicology (AACT) practice guidelines a methanol concentration for hemodialysis in the absence of acidosis, renal clinical status.[4] The AACT guidelines for ethylene glycol actually advise a alone, without any of these clinical indications.[5] Clearly, there is still insu concentrations of alcohols or their metabolites where dialysis is absolutely a subjective one based on the overall clinical scenario.[57] However, until m concentration of 25 mg/dL remains a reasonable indication for hemodialys mg/dL in the absence of alcohol dehydrogenase blockade or abnormal ren reasonable indication.

Although hemodialysis effectively clears isopropanol and acetone from the this purpose. Because isopropanol does not cause a metabolic acidosis an organ effects, the risks of hemodialysis likely outweigh the benefits.

Many patients will require multiple courses of hemodialysis to clear the to

nephrologists to estimate the dialysis time required.[54] Pharmacokinetically and will decrease the toxic alcohol concentration by half in about 2Â½ ho blockade should be continued during and after hemodialysis until a subse xenobiotic is confirmed to be nontoxic. Ethanol infusion rates must be inc therapeutic serum concentration as the ethanol is cleared (see Antidotes redosed every 4 hours during hemodialysis to maintain therapeutic serum

Adjunctive Therapy

There are several therapeutic adjuncts to ADH blockade with or (especial considered for these patients. One difference that has been invoked to ex methanol in some species is the relative abundance of hepatic folate store Folate and leucovorin enhance the clearance of formate in animal models metabolism of ethylene glycol to ketoadipate, and pyridoxine enhances its to hippuric acid). Although all of these modalities offer theoretical advanta change outcome in humans. However, there is one human case report sh folinic acid therapy.[63] Additionally, some authors have suggested that an clearance by hemodialysis was because it was dwarfed by the effectivenes study group and the control group.[72] Because of the safety of vitamin su outweighs the risk of therapy (see Antidotes in Depth: Thiamine Hydroch and Leucovorin [Folinic Acid]).

Formate (dissociated formic acid), is much less toxic than the undissociat undissociated formic acid has a much higher affinity for cytochrome oxida target site for toxicity.[81] In addition, the undissociated form is better able Alkalinization with a bicarbonate infusion shifts the equilibrium to favor th accordance with the Henderson-Hasselbalch equation. This also enhances f trapping.[65] Uncontrolled case series data have shown that patients treate expected outcomes after severe methanol poisoning,[97] but the results are ADH blockade and hemodialysis.[13 , 62 , 91] Additionally, the severity of th poisoning is a good predictor of severe neurologic effects such as coma a not been proven to prevent these effects. However, in the absence of co (eg, hypokalemia, volume overload), alkalinization should be used in the poisoning and a significant acidosis. A blood pH greater than 7.20 is a r

also be considered for patients with ethylene glycol poisoning and signifi

Other Alcohols

Propylene Glycol

Propylene glycol is commonly used as an alternative to ethylene glycol It is also used as a diluent for many pharmaceuticals (such as phenytoin successively metabolized by ADH and ALDH to lactate, lactic acidosis resu result in extremely high lactic acid levelsâ€”levels that would be incompat disease process. In other disease states associated with lactate accumulat reflection of underlying anaerobic metabolism, a marker of severe illness pathophysiology. Lactic acidosis from propylene glycol is surprisingly well more sinister than itself, and it is rapidly cleared by oxidation to pyruvat carbohydrate metabolism. (Chapter 53 further discusses propylene glycol

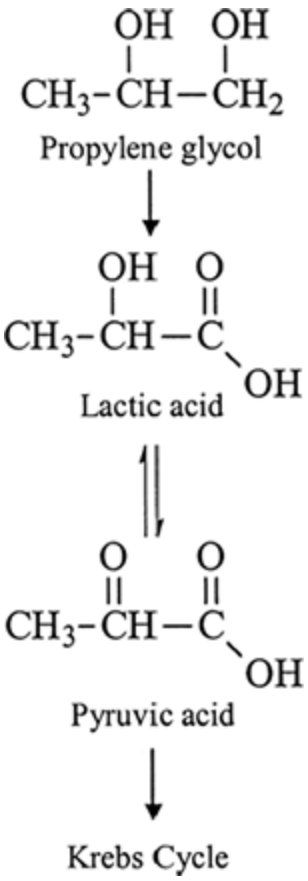
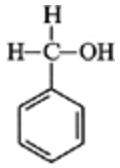


Figure 103-6. Propylene glycol metabolism to lactic acid. Under normal pyruvate which, following decarboxylation, enters the Krebs cycle.

Benzyl Alcohol



Benzyl alcohol

Benzyl alcohol used as a preservative for intravenous solutions. It is no it was responsible for â€œneonatal gasping syndrome,â€• involving mu acidosis, and death from its metabolism to benzoic acid and hippuric acid benzyl alcohol.)

Glycol Ethers

Diethylene Glycol

Diethylene glycol's toxicity in humans was first recognized in 1937 after manifestations typically begin with abdominal pain, nausea, and vomiting acidosis, acute renal failure, and progressive mental status depression ov poisoning in children is also manifested by liver failure, respiratory failu optic neuritis, and paresthesias.[10 , 103 , 122] Two cases of adults with

intentional diethylene glycol ingestions resulted in peripheral neuropathy peripheral demyelination and axonal degeneration at autopsy.[28] Despite the only reported patient to have nerve conduction studies performed af evidence of an axonopathy.[53] The patient developed total quadriplegia, th course of several months.[53]

It is unclear whether toxicity is caused by the diethylene glycol parent co

the ether linkage is stable in the body; ethylene glycol was not detectabl glycol poisoning,[53] nor could it be detected in a rat model of diethylene hydroxyethoxyacetic acid was an identified metabolite.[136] It is also uncle hydroxyethoxyacetic acid occurs in humans, or whether this metabolism aldehyde dehydrogenase. In rats, fomepizole blocks this metabolism.[136] I minimal toxicity after diethylene glycol ingestion when treated with fome suffered severe toxic effects despite early fomepizole therapy.[115]

Based on the limited currently available evidence, it is reasonable to initi hemodialysis, in patients who present early after diethylene glycol ingesti ingestion are likely to need hemodialysis for renal failure.

Butoxyethanol

Most cases of butoxyethanol poisoning involve adults with intentional ing Unintentional exposures in children to household glass cleaners containing adverse effects.[25, 132] Cases of butoxyethanol poisoning are likely to con physical properties as an amphiphilic solvent with a low evaporation rate replacement in industry has not yet been found.[72] The disposition of buto entirely clear, but Figure 103-7 summarizes what is known. It does not occurs in humans, but this remains controversial.

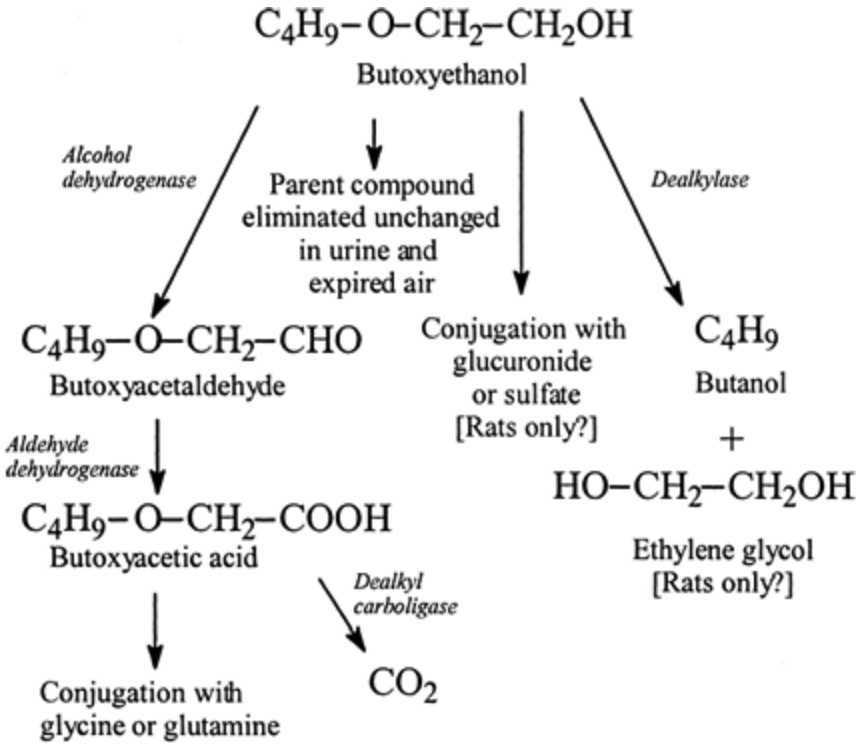


Figure 103-7. Elimination of butoxyethanol. It is still not certain whethe formation occur in humans.[39]

Clinical manifestations of acute butoxyethanol toxicity may include menta hyperchloremic metabolic acidosis, acute renal failure, hemolysis, nonhem injury, and mild elevation of the aminotransferases.[6, 16, 41, 47, 87, 11 cause adverse effects. Although butoxyethanol does not increase cancer ra hemangiosarcomas in male mice and forestomach tumors in female mice. Protection Agency has said that it could not yet determine whether butox effects on fetal development are also unclear.[33, 40, 80, 95]

Partly because its metabolism and mechanism of toxicity are incompletely acute butoxyethanol poisoning is still controversial. Good outcomes have alone,[87] and after ethanol and bicarbonate therapy with hemodialysis.[47] did not appear to hasten butoxyethanol elimination and persistent neurol alcohol dehydrogenase inhibition with ethanol or fomepizole is a reasonal considered in patients with severe acidosis.

Ethylene Glycol Monomethyl Ether

Ethylene glycol monomethyl ether poisoning should be increasingly rare ir substantial toxicity has greatly limited its use. For example, in Sweden, it in 1993 to 19 tons per year in 1997.[68] In the United States, production ha past 20 years.[135] After exposure, 86% of ethylene glycol monomethyl etl and excreted in the urine.[44 , 68] Ethanol and pyrazole completely block th that this metabolism involves alcohol dehydrogenase.[94 , 116] Clinical man with only 3 cases reported. One man developed hemorrhagic gastritis and ultimately proved fatal.[141] Two men recovered after developing confusion metabolic acidosis, tachycardia, tachypnea, and renal failure in one case. ethylene glycol monomethyl ether metabolism, acute toxicity should be t blockade, although there are not yet human outcome data to support the

Chronic hematologic effects, typically after inhalation or dermal exposure resulting in anemia, leucopenia, or pancytopenia in severe cases.[135] Repr azoospermia in men[134] and increased frequency of spontaneous abortions occurred in animal models of ethylene glycol monomethyl ether exposure, known exposure (eg, workers in the semiconductor industry).[135] Obviously important element of clinical management for these patients.

Summary

Toxic alcohol poisoning is complex and may result in consequential toxicit inebriation, and subsequent toxicity results from metabolism to organic a and end-organ effects. The time required

for this metabolism results in a delay before toxicity clinically manifests available, the serum anion gap and osmol gap may help with decision mal history is concerning. Therapy consists of ADH antagonism with fomepizole therapy with bicarbonate, folate or folinic acid, pyridoxine, and thiamine. because it removes the alcohol and the toxic metabolites while correcting abnormalities. However, hemodialysis may have a more limited role in th poisoning, because of the safety and efficacy of fomepizole.

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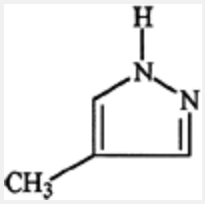
Antidotes in Depth

Fomepizole

Mary Ann Howland



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Fomepizole is a competitive inhibitor of alcohol dehydrogenase (ADH) that prevents the formation of toxic metabolites from ethylene glycol and methanol. It may also have a role in halting

the disulfiramâ€“ethanol reaction, and in limiting the toxicity from a variety of xenobiotics that rely on alcohol dehydrogenase for metabolism to toxic metabolites. In addition, as both an inducer and an inhibitor of certain cytochrome P450 (CYP) isoenzymes, the presence of fomepizole may lead to drug interactions.

History

In 1963, Theorell and associates described the inhibiting effect of pyrazole on the horse ADH-NAD^+ (nicotinamide adenine dinucleotide) enzymeâ€“coenzyme system.[71] They noted that pyrazole appeared to block ADH by complexation, and that the administration of pyrazole to animals poisoned with methanol and ethylene glycol improved survival.[72] However, pyrazole also inhibited other liver enzymes, including catalase and the microsomal ethanol-oxidizing system.[50] Additional adverse effects of pyrazole administration resulted in bone marrow, liver, and renal toxicity, and these effects increased in the presence of ethanol and methanol.[61] These factors led to the search for less-toxic compounds with comparable mechanisms of action.

In 1969, Li and Theorell found that both pyrazole and 4-methylpyrazole (fomepizole) inhibited ADH in human liver preparations.[49] Studies in rodents found that fomepizole was relatively nontoxic regardless of the presence or absence of ethanol.[10] Subsequent studies of fomepizole in monkeys and humans poisoned with methanol and ethylene glycol demonstrated both the inhibitory effect and relative safety of fomepizole.[15,16,61]

Pharmacology

Fomepizole has a molecular weight of 82 daltons and a pKa of 2.91 at low concentrations and a pKa of 3.0 at high concentrations. The freebase is used in the United States, whereas the salts are used in Europe. The freebase is chemically equivalent to the chloride

and sulfate salts at physiologic pH.[20]

Values for K_m (Michaelis-Menten dissociation constant) have been estimated for the toxic alcohols, along with the value for K_I (dissociation of enzyme-inhibitor complex inhibition constant) with fomepizole. The smaller the K_m, the higher the affinity of the substrate (alcohol) for the enzyme, and the lower the concentration of the substrate that is needed to half saturate the enzyme. Studies in monkey and human livers demonstrate that fomepizole is a competitive inhibitor of alcohol dehydrogenase.[53,68] In monkey liver, fomepizole demonstrated very similar K_Is for both ethanol and methanol at 7.5 and 9.1 Âµmol, respectively.[53] In this same model, the K_m was 3.2 for ethanol and 20.1 Âµmol for methanol, demonstrating a 6 times higher affinity of ethanol for alcohol dehydrogenase than methanol.[53] The affinity was 15 times higher when human liver was used.[67] Studies in monkeys demonstrate that a fomepizole concentration of 9â€“10 Âµmol/L (0.74â€“0.8 Âµg/mL) is needed to inhibit the metabolism of methanol to formate.[10,61] In human liver, the level needed to achieve inhibition is about 0.9â€“1 Âµmol/L.[49,67] The most recent trial that used intravenous fomepizole attempted to maintain a serum fomepizole concentration above 10 Âµmol/L. Current dosing calls for a serum fomepizole concentration of 100â€“300 Âµmol/L to insure a margin of safety.[1]

The CYP2E1 isozyme oxidizes ethanol and a number of other xenobiotics to toxic metabolites, including acetaminophen, carbon tetrachloride, nitrosamines, and benzene. Fomepizole, like ethanol and isoniazid, has dual effects on this isozyme. Fomepizole induces this isozyme in rat liver and kidney, but not in the lung, through a posttranscriptional mechanism not involving increased mRNA. However, when fomepizole is present, the isoenzyme is inhibited. It is not until after fomepizole is eliminated, that the consequences of induction are manifest.[13,76,77] In hepatocyte culture, fomepizole stabilizes and maintains the induced metabolic activity of the

isoenzyme for about 1 week.[78]

Pharmacokinetics

The volume of distribution of fomepizole is about 0.6â€“1 L/kg; it is metabolized to 4-carboxpyrazole, an inactive metabolite that accounts for 80â€“85% of the administered dose.[58] In healthy human volunteers, oral doses of fomepizole were rapidly absorbed and demonstrated saturation and nonlinear kinetics.[37] The K_m (concentration at which the maximum elimination rate is 50%) was estimated to be 75 Âµmol/L.[37,56] First-order kinetics were exhibited at concentrations below the K_m, whereas zero-order elimination occurred at concentrations 100â€“200% of the K_m.[37] Thus elimination of fomepizole at doses of 10 mg/kg, 20 mg/kg, 50 mg/kg, and 100 mg/kg was 3.66, 5.05, 10.3, and 14.9 Âµmol/L/h, respectively.[37] Classical Michaelis-Menten kinetics would predict that the elimination rate should be the same at the two higher doses, but this is not the case. The authors speculate that multiple metabolic pathways with different affinities exist and predominate at different fomepizole concentrations. At a dose of 20 mg/kg, the half-life of fomepizole calculated from the linear portion of the curve was 5.2 hours and occurred when serum concentrations were less than 100 Âµmol/L. Peak concentrations after oral administration were achieved within 2 hours and were 132, 326, 759, and 1425 Âµmol/L following 10, 20, 50, and 100 mg/kg doses, respectively. Every increase of 10 mg/kg in the oral dose of fomepizole raised the serum concentration

130â€“160 Âµmol/L.[37] The renal clearance was low (0.016 mL/min/kg), and only 3% of the administered dose was excreted unchanged in the urine.[37]

In a pharmacokinetic study in healthy volunteers, oral administration produced similar serum concentrations to IV fomepizole.[55] The pharmacokinetics of intravenous fomepizole

were studied in 14 patients being treated for ethylene glycol toxicity.[45] A mean peak concentration of 342 Âµmol/L (200â€“400 Âµmol/L) was achieved following a loading dose of 15 mg/kg (183 Âµmol/kg).[58,69] A significant weakness of the study affecting toxicokinetic data is that the effect of simultaneous plasma ethanol concentrations was not analyzed. The lowest fomepizole plasma concentration of 105 Âµmol/L was present at 8 hours after the loading dose. The rate of elimination was determined to be zero order at 16 Âµmol/L/h as compared with a first-order elimination half-life of 3 hours during hemodialysis. Other authors have reported similar fomepizole clearances (12.99 Âµmol/L/h).[17] A recent pharmacokinetic analysis in patients poisoned with methanol or ethylene glycol demonstrated a mean peak fomepizole concentration of 19 Âµg/mL (226 Âµmol/L), an apparent half-life of 14.5 hours (in presence of methanol or ethylene glycol), and an apparent half-life of 40 hours in the presence of ethanol along with methanol or ethylene glycol. In the sole death, hepatic tissue contained 12 Âµg/g of fomepizole, even when the plasma concentration was <1 Âµg/mL (12 Âµmol/L).[75]

The plasma clearance of fomepizole during hemodialysis was 230 mL/min. Previous analysis using determinations of dialysis fluid revealed an extraction ratio of approximately 75% and a dialysance of 117 mL/min, which was very similar to a simultaneous ethylene glycol determination.[26] The dialysance of fomepizole was similar to urea in a pig model and suggests no significant protein binding of fomepizole.[38]

The pharmacokinetic interactions between fomepizole and ethanol were studied in a double-blind crossover design in healthy human volunteers.[42] Fomepizole was given orally in doses of 10, 15, and 20 mg/kg 1 hour prior to oral ethanol at 0.5â€“0.7 g/kg as a 20% solution in orange juice. Fomepizole decreased the elimination rate of ethanol by approximately 40%, from 12â€“16 mg/dL/h to about 7â€–9.5 mg/dL/h. When intravenous fomepizole was administered at 5 mg/kg over 30 minutes and ethanol was administered orally

at doses to achieve a concentration of 50â€“150 mg/dL for 6 hours beginning at the end of the fomepizole infusion, the elimination of fomepizole was decreased by approximately 50%.[42] This decrease occurred without a change in the amount or fraction of unchanged fomepizole appearing in the urine. The authors suggested that the ethanol probably inhibited the metabolism of fomepizole to 4-carboxypyrazole by the cytochrome P450 system. A single low dose of fomepizole given to humans had a maximal effect on ethanol metabolism at 1.5â€“2 hours.[9] Thus ethanol and fomepizole mutually inhibit the elimination of each other, prolonging their respective plasma concentrations. Methanol also decreases the elimination of fomepizole by approximately 25% in the monkey.[61]

Methanol

In Vitro and Animal Studies

Studies using human livers demonstrate the inhibitory effect of fomepizole on alcohol dehydrogenase.[67] Studies in monkeys, the animal species that most closely resembles humans in metabolizing methanol, also clearly demonstrate the inhibitory effect of fomepizole in preventing the accumulation of formate.[8,61,62]

Human Experience

The largest fomepizole case series to date involved 11 patients who were given IV fomepizole in the approved US dosing regimen.[16] Following administration, formate concentrations in all patients fell and the arterial pH increased.[16] Case reports demonstrate similar findings.[17,28,32]

Effect of Fomepizole on Methanol and

Formate Concentrations

Methanol exhibits dose-dependent kinetics.[41] At low doses (0.08 g/kg), which achieve serum concentrations of about 10 mg/dL, methanol elimination is first order, with a half-life of about 2.5â€“3 hours.[45,48] In concentrations of about 100â€“200 mg/dL, methanol exhibits zero-order kinetics and is eliminated at about 8.5â€–9 mg/dL/h in untreated humans[41] and 4.4â€–7 mg/dL/h in untreated monkeys.[24,64] When monkeys were given 3 g/kg of methanol with resultant serum concentrations of about 500 mg/dL, the elimination of methanol exhibited apparent first-order kinetics. This alteration is likely caused by the greater contribution of other first-order pathways, such as pulmonary and urinary elimination, which may account for a greater fraction of the total body clearance under these circumstances.[41] Once fomepizole is administered, the elimination of methanol becomes first order in humans, and the half-life of methanol is about 54 hours.[16] When the metabolism of methanol to formate by alcohol dehydrogenase is blocked, formate is eliminated with a half-life dependent on dose and the uncertain effect of folate and bicarbonate therapies. When formate was administered to monkeys in the absence of methanol, formate half-life was 30â€“50 minutes.[21] In monkeys given methanol followed by fomepizole, the formate levels decreased by more than 80% in 2 hours.[8] A recent analysis of formate concentrations in 6 patients with methanol poisoning treated with fomepizole, folate, and sodium bicarbonate revealed a formate half-life of 235 Â± 83 minutes.[46]

Ethylene Glycol

In Vitro and Animal Studies

Monkeys given 3 g/kg of ethylene glycol intraperitoneally, recovered without treatment, whereas those given 4 g/kg died without therapy. All those given 4 g/kg of ethylene glycol with

fomepizole survived.[21]

Human Experience

The first 3 patients treated with oral fomepizole improved clinically and tolerated the therapy.[4] Subsequent case reports and case series using fomepizole orally or IV, with or without hemodialysis, have also demonstrated effectiveness of fomepizole in preventing glycolate accumulation.[5,11,15,31,34,44,63,69]

Effect of Fomepizole on Ethylene Glycol and Glycolate Concentrations in Humans

Renal function is essential in the elimination of ethylene glycol. With normal renal function, the half-life of ethylene glycol is about 8.6 hours.[69] Based on pooled human data, the half-life of ethylene glycol after alcohol dehydrogenase is blocked by fomepizole is about 14â€“17 hours in those patients with normal renal function, and about 49 hours in patients with impaired renal function.[4,31,69] Based on a limited number of determinations, the renal clearance

of ethylene glycol averaged 31.5 mL/min during the first 2 days; the corresponding creatinine clearance was 112 mL/min, and estimated total-body clearance during fomepizole therapy was 57 mL/min.[5] These calculations suggest that the renal clearance of ethylene glycol accounted for only 55% of estimated total body clearance. In a study where neither renal function was defined nor the amount of glycolate (MW = 76 daltons) excreted unchanged by the kidneys described, glycolate had a mean half-life of 10 Â± 8 hours in patients treated with fomepizole before hemodialysis, and a mean half-life of less than 3 hours during hemodialysis.[63]

Safety and Adverse Effects

Retinol dehydrogenase, which is responsible for converting retinol to retinal in the eye, is an isozyme of ADH. As such, it was essential to study whether fomepizole would inhibit this enzyme and subsequently produce retinal damage.[61] Studies in several animal species demonstrate that fomepizole is relatively nontoxic, with no demonstrable signs of ophthalmic toxicity.[8] Two of the largest case series, and 2 recent case reports confirm the lack of retinal toxicity with fomepizole and demonstrate the reversibility of methanol-induced visual toxicity when patients are treated with fomepizole and hemodialysis before permanent ophthalmic toxicity developed.[15,16,25,70]

The LD_{50} (median lethal dose for 50% of test subjects) of fomepizole in mice and rats is 3.8 mmol/kg after IV administration, and 7.9 mmol/kg following oral administration.[52] An oral placebo-controlled, double-blind, single-dose, randomized, sequential, ascending-dose study was performed in healthy volunteers to determine fomepizole tolerance at 10â€“100 mg/kg.[41] There were no adverse effects in the 10 and 20 mg/kg groups, whereas at 50 mg/kg, 3 of 4 subjects experienced slight to moderate nausea and dizziness within 2.5 hours of fomepizole administration. All subjects reported comparable symptoms at 100 mg/kg, which lasted for 30 hours in 1 individual without vital sign or laboratory abnormalities noted. The most common adverse effects of the use of fomepizole reported by the manufacturer (in a total of 76 patients and 63 volunteers) were headache 12%, nausea 11%, and dizziness 7%. Other less commonly observed adverse effects include phlebitis, rash, fever, and eosinophilia. Similarly, divided daily doses of fomepizole up to 20 mg/kg for 5 days have been administered without any demonstrable toxicity.[60] The most common laboratory abnormality after fomepizole administration is a transient elevation of aminotransferase levels, which was reported in 6 of 15 healthy volunteers.[40] In the 2

largest case series of patients treated with fomepizole for toxic alcohol poisoning, there were no adverse events classified as â€œdefinitelyâ€• or â€œprobablyâ€• related to fomepizole.[15,16] Fomepizole is not approved for use in children, but has been used successfully in children who have ingested ethylene glycol and methanol.[6,12,18,22,23,33,75]

Fomepizole is pregnancy category C and thus should be utilized appropriately as indicated.

Disulfiram and Other Xenobiotics

Fomepizole successfully terminated the adverse reactions resulting from the use of disulfiram administered to volunteers pretreated with a small dose of ethanol and those reactions occurring in a chronic alcoholic surreptitiously given disulfiram by his wife.[51] Pretreatment with oral fomepizole was also successful in preventing the facial flushing and tachycardia typically associated with ethanol administration in ethanol-sensitive Japanese subjects.[35,36]

Limited animal studies and a few case reports suggest that fomepizole may be effective in limiting the toxicity secondary to diethylene glycol, triethylene glycol and 1,3-difluoro-2-propanol.[11,27,73] The role of fomepizole in overdoses secondary to 2-butoxyethanol (ethylene glycol monobutyl ether, butyl cellosolve) is unclear, but fomepizole may be useful if administered within several hours of ingestion and before rapid metabolism of butoxyethanol to butoxyacetic acid occurs.[57] Isopropanol is probably metabolized at least in part by alcohol dehydrogenase, but fomepizole therapy is not indicated, as this intervention would prolong the metabolism of isopropanol to acetone.[1]

Comparison to Ethanol

Ethanol has been used for many years to inhibit the metabolism of methanol and ethylene glycol to their respective toxic metabolites. Although very inexpensive, ethanol has many disadvantages, compared to fomepizole. Ethanol causes central nervous system depression that is at least additive to that of the methanol or ethylene glycol; dosing difficulties occur as a result of the rapid and often unpredictable rate of ethanol metabolism, and prolonged ethanol administration causes tolerance to ethanol to develop; an intravenous formulation of ethanol is not readily available; the serum concentrations of ethanol must be closely monitored; a 5 or 10% intravenous preparation of ethanol is hyperosmolar;[79] and there is a great potential for hyponatremia and hypoglycemia or other ethanol-related adverse effects, such as pancreatitis and hepatitis. In contrast to all of these problems associated with ethanol administration, fomepizole has the advantage of being a very potent inhibitor of alcohol dehydrogenase without producing central nervous system (CNS) depression. Fomepizole dosing is much easier without a need for serum concentration monitoring, thus allowing for every-12-hour dosing except during hemodialysis, when dosing should occur every 4 hours. Limited adverse effects of fomepizole include local reactions at the site of infusion when concentrations exceeding 25 mg/mL are employed, nausea, dizziness, anxiety, headache, rash, transiently elevated aminotransferases, and eosinophilia.

Fomepizole is preferred to ethanol for all of the above reasons. Ethanol should only be used when fomepizole is not readily available. Hospitals should be encouraged to stock fomepizole.

Dosing

The loading dose of fomepizole is 15 mg/kg IV, followed in 12 hours by 10 mg/kg every 12 hours for 4 doses. If therapy is necessary beyond 48 hours, the dose is then increased to 15 mg/kg every 12 hours, for as long as necessary. This increase is

recommended because fomepizole stimulates its own metabolism. Patients undergoing hemodialysis require additional doses of fomepizole to replace the amount removed during hemodialysis.

The manufacturer recommends dosing fomepizole every 4 hours during hemodialysis. Fomepizole should be administered at the beginning of hemodialysis if the last dose was more than 6 hours earlier. At the completion of hemodialysis, administer the next scheduled dose if more than 3 hours has transpired on one-half of the dose if 1â€“3 hours has passed.

The fomepizole dose must be diluted in 100 mL of 0.9% sodium chloride solution or D_5W (dextrose 5% in water) prior to IV administration, and then infused over 30 minutes to avoid venous irritation

and phlebosclerosis. Once diluted, fomepizole remains stable for 24 hours when stored in the refrigerator or at room temperature.[1]

Fomepizole therapy should be continued until the methanol or ethylene glycol is no longer present in sufficient concentrations to produce toxicity. Although these concentrations are not precisely known, 25â€“50 mg/dL of either ethylene glycol or methanol is a conservative estimate that can be lowered in the presence of acidâ€“base disturbances.[1,2 and 3]

The threshold concentrations for hemodialysis of methanol or ethylene glycol can be based on measurements when analyses can be done in a timely fashion. The duration of fomepizole therapy in the absence of hemodialysis can be estimated based on the assumption of half-life of the toxic alcohol when blocked with fomepizole. The half-life of methanol is approximately 54 hours in the presence of fomepizole.[11] The half-life of ethylene glycol in the presence of fomepizole is approximately 14â€“17 hours in patients with normal renal function, and 49 hours in patients with impaired renal function.[4,34,69]

Availability

Fomepizole is marketed as Antizol injection by Orphan Medical in a tray pack containing 4 vials (1.5 mL vials of 1 g/mL). Temperatures of <77Â°F (25Â°C) cause the contents of the fomepizole vials to solidify. Warming reliquifies the product without adversely affecting its potency.

Summary

Fomepizole is a potent competitive inhibitor of alcohol dehydrogenase that is useful in inhibiting the metabolism of methanol, ethylene glycol, and other xenobiotics that use alcohol dehydrogenase in the formation of toxic metabolites. Once alcohol dehydrogenase is blocked, the decision to use hemodialysis depends on how much damage has occurred to the organs of elimination, and how well the body can eliminate both the parent compound and the toxic metabolites formed prior to fomepizole administration. Fomepizole appears to be safe and, although it has been used successfully orally, only an intravenous dosing regimen is approved and available. Although the price of fomepizole is higher than ethanol, its many advantages over ethanol, including the ability to often deliver care ouside the ICU, make fomepizole the preferable antidote. Hospitals should be encouraged to stock fomepizole.

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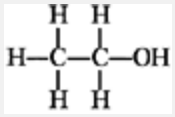
Antidotes in Depth

Ethanol

Mary Ann Howland



Ethanol

Ethanol is used therapeutically as a competitive substrate to xenobiotics metabolized by alcohol dehydrogenase, thus limiting the metabolism of those xenobiotics to toxic metabolites. Methanol

and ethylene glycol[7] are the two most lethal xenobiotics when metabolized by this pathway. Other xenobiotics whose metabolism may be inhibited by the presence of ethanol include short-chain polyethylene glycols, such as di- and triethylene glycol,[42] and monofluoroacetate and fluoroacetamide. Ethanol also affects the cytochrome P450 enzyme system, especially 2E1, for which it has biphasic properties as an inhibitor/inducer similar to fomepizole and isoniazid. Only the competitive relationships of ethanol with potentially toxic xenobiotics are used to therapeutic advantage, while the effect on the cytochrome P450 system often leads to unwanted drug interactions and pharmacokinetic tolerance after several days of administration.

Affinity for Alcohol Dehydrogenase

The dose of ethanol necessary to achieve competitive inhibition depends on the relative concentrations of the toxic alcohols and their affinity for the enzyme. An affinity constant, K_m, is used to express the degree of affinity: the lower the K_m value, the stronger the affinity. A summary of in vitro experiments using human liver demonstrated a K_m of 30 mM for ethylene glycol, 7 mM for methanol, and 0.45 mM for ethanol.[22,33,34] This means that the affinity of ethanol for alcohol dehydrogenase is 67 times that of ethylene glycol and 15.5 times that of methanol. Studies in methanol-poisoned monkeys revealed that when ethanol was administered at a molar ethanol-to-methanol (E/M) ratio of 1:4, the metabolism of methanol was reduced by 70%; at a 1:1 E/M ratio, metabolism was reduced by >90%.[24] In these experiments, the dose of methanol was kept constant at about 1 g/kg (31 mmol/kg), whereas the dose of ethanol was varied. Although the methanol serum concentration was not measured, a calculation using this dose and a volume of distribution of 0.6 L/kg would predict a serum concentration of about 166 mg/dL. Even in molar ratios as high as 8:1, methanol did not inhibit ethanol metabolism. When ethylene glycol and methanol are administered together,

ethylene glycol did not inhibit methanol metabolism.[24] Smaller amounts of ethanol are required to block the metabolism of ethylene glycol, compared to the amount of ethanol required to block the metabolism of methanol, as the affinity of ethylene glycol for alcohol dehydrogenase is even less than that of methanol.[16,22,33,34,36,40] Most authors[1,16,40] recommend either a serum ethanol concentration of 100 mg/dL, or at least a 1:4 molar ratio of ethanol to methanol or ethylene glycol, whichever is greater. One hundred mg/dL (~22 mmol/L) ethanol protects against 88 mmol/L (286 mg/dL) of methanol or 88 mmol/L (546 mg/dL) of ethylene glycol. Inhibiting the metabolism of methanol and ethylene glycol, impedes the formation of toxic metabolites and prevents the development of metabolic acidosis.[9,12,15,40] After this toxic metabolic pathway is blocked with ethanol, renal, pulmonary, and extracorporeal routes of toxic alcohol removal become the sole mechanisms for elimination.

Case reports attest to the efficacy of ethanol in preventing the sequelae of methanol and ethylene glycol poisoning when administered in a timely fashion after the toxic alcohol ingestion and before the accumulation of the toxic metabolites.[4,6,18,39,44] In the presence of sufficient blocking concentrations of ethanol, the half-life of ethylene glycol in 2 patients with normal kidney function was 17.5 hours, which was comparable to 17 hours in a case series of patients receiving fomepizole alone with normal kidney function.[4,31,38] A half-life of 46.5 hours for methanol was reported in a patient with methanol poisoning who had received a sufficient quantity of ethanol. Again, this half-life for methanol in the presence of ethanol was quite similar to the 54 hours reported in a case series of methanol poisoned patients treated only with fomepizole.[2,18]

Pharmacokinetics and Dosing

Ethanol can be given either enterally or intravenously (Tables A29-

1 and A29-2). Concentrations of 20â€“30% orally and 5â€“10% IV are well tolerated. Intravenous administration has the advantage of complete absorption,[20] avoidance of gastrointestinal symptoms, and ability to be administered to an unconscious or uncooperative patient. The disadvantages of IV ethanol include difficulty in obtaining and preparing an intravenous ethanol solution, the hyperosmolarity of a 5% ethanol solution (about 950 mOsm/L), the possibility of osmotic dehydration, hyponatremia, and venous irritation. Ethanol administered enterally is rapidly absorbed and achieves peak concentrations in about 1â€“1.5 hours.[5,11,23,41] The amount of ethanol absorbed after oral administration is variably dependent on a number of factors, such as fasting, nutritional status, accelerated gastric emptying, female gender, genetics, chronic alcoholism, lean body mass, and increasing age, as well as the presence of certain H_2 antihistamine receptor antagonists.[3,6,11,19,21,43,45] Sufficient concentrations are generally achieved when 0.8 g/kg of ethanol is given orally over 20 minutes.[3,5,6,11,21,41]

Regardless of route, the objective is to rapidly achieve and maintain a level of at least 100 mg/dL of ethanol, which is adequate for enzyme inhibition in most cases. Inhibition is best achieved by administering a loading dose of ethanol, followed by a maintenance dose. The volume of distribution for ethanol is approximately

0.6 L/kg.[46] The loading dose of ethanol is obtained by the following formula:

$$\begin{aligned}\text{Loading dose} &= C_p \times Vd \\ &= 1\ \text{g/L (100 mg/dL)} \times 0.6\ \text{L/kg} \\ &= 0.6\ \text{g/kg}\end{aligned}$$

C_p = plasma concentration which for this agent is comparable to the serum concentration

TABLE A29-1. Intravenous Administration of 10% Ethanol

Loading Dose[c]	Volume (mL)[b] (given over 1 hour as tolerated)					
	10 kg	15 kg	30 kg	50 kg	70 kg	100 kg
0.8 g/kg of 10% ethanol (infused over 1 hour as tolerated)	80	120	240	400	560	800
Maintenance Dose[a]	Infusion Rate[b] (mL/h for various weights)[d]					
	10 kg	15 kg	30 kg	50 kg	70 kg	100 kg
Normal						
80 mg/kg/h	8	12	24	40	56	80
110 mg/kg/h	11	16	33	55	77	110
130 mg/kg/h	13	19	39	65	91	130
Chronic Alcoholic						

150	mg/kg/h	â€”	â€”	â€”	75	105	150
During Hemodialysis							
250	mg/kg/h	25	38	75	125	175	250
300	mg/kg/h	30	45	90	150	210	300
350	mg/kg/h	35	53	105	175	245	350

[a]Infusion to be started immediately following the loading dose. Concentrations above 10% are not recommended for IV administration. The dose schedule is based on the premise that the patient initially has a zero ethanol level. The aim of therapy is to maintain a serum ethanol level of 100â€“150 mg/dL, but constant monitoring of the ethanol level is required because of wide variations in endogenous metabolic capacity. Ethanol will be removed by hemodialysis, and the infusion rate of ethanol must be increased during hemodialysis. Prolonged ethanol administration may lead to hypoglycemia.
[b]For a 5% concentration, multiply the amount by 2.
[c]A 10% V/V concentration yields approximately 100 mg/mL. [d]Rounded to the nearest mL.
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For a 70-kg person, the loading dose would be 42 g (70 kg Ã— 0.6 g/kg) of ethanol, or 420 mL of 10% V/V (volume-to-volume) ethanol. However, an 0.8-g/kg or 8-mL/kg loading dose of a 10%

ethanol solution is recommended in order to provide a margin of safety because of the inconsistencies in bioavailability and the ongoing metabolism that occurs during administration.[20,35] The IV loading dose should be administered over 20â€“60 minutes, as tolerated by the patient. The 10% ethanol concentration is preferable to the 5% concentration in order to limit the volume of fluid administered. It is also preferred over the more concentrated solutions in order to limit local venous irritation and avoid postinfusion phlebitis. Because of the free water content and significant hypertonicity of the 10% solution, the patient should be closely observed for the development of hyponatremia.

To maintain an ethanol concentration of 100 mg/dL, enough ethanol has to be administered to replace the ethanol that is undergoing elimination (66â€“130 mg/kg/h). The average hourly dose for a 70-kg person is 4.6 g, but higher doses are required in chronic alcoholics (100â€–154 mg/kg/h) or others who may have induced enzymes, and in those undergoing hemodialysis (250â€–350 mg/kg/h; Chap. 10.[8,16,26,31,32]

Because ethanol elimination varies in each individual, frequent serum ethanol determinations should be made to ensure adequate dosing while also monitoring blood glucose and fluid and electrolyte status. Also, any increase in the anion gap or decrease in bicarbonate concentration implies that the ethanol dose is inadequate to achieve blockade of alcohol dehydrogenase and the ethanol dosing should be increased.

Problems encountered with the administration of ethanol include further risk of central nervous system depression[10,27,30] or ethanol-related toxicities, such as hepatitis and pancreatitis, hypoglycemia, dehydration, and fluctuating serum concentrations, and potential drug interactions resulting in disulfiramlike reactions.[47]

Availability

A more practical problem often involves finding or preparing the ethanol to be given. Hospital pharmacies and emergency departments should stock ethanol for such a purpose, but frequently do not. Commercial preparations of 5% ethanol in 5% dextrose are available for IV administration. Alternatively, sterile ethanol USP (absolute ethanol) can be added to 5% dextrose to make a solution of approximately 10% ethanol concentration; 55 mL (not 50 mL) of absolute ethanol is then added to 500 mL of 5% dextrose to produce a total end volume of 555 mL (10% = 10 mL in 100 mL, in this case, 55 mL in 555 mL or 55/555). If oral administration is chosen, it is important to remember that the â€œproofâ€• number on the label is double the concentration; that is, â€œ100-proofâ€• ethanol is 50% ethanol. If there will be any delay in obtaining ethanol for intravenous use, oral therapy with ethanol should be initiated immediately.

Comparison to Fomepizole

Although ethanol has been used as an antidote for toxic alcohols for many years in adults and children[37] and has the advantages

of easy access and low cost, fomepizole is a very potent inhibitor of alcohol dehydrogenase with many favorable attributes.[13,14,17,25,28,29] Fomepizole does not produce central nervous system (CNS) depression, is easier to dose, and does not require serum concentration monitoring. Although the price of fomepizole is higher than ethanol, its many advantages over ethanol make fomepizole the preferable antidote. Hospitals should be encouraged to stock fomepizole.(see Antidote in Depth: Fomepizole and Chap. 103).

TABLE A29-2. Oral Administration of 20% Ethanol

Loading Dose[c]	Volume (mL)					
	10 kg	15 kg	30 kg	50 kg	70 kg	100 kg
0.8 g/kg of 20% ethanol, diluted in juice. May be administered orally or via nasogastric tube	40	60	120	200	280	400
Maintenance Dose[a]	mL/h for various weights[c,d]					
	10 kg	15 kg	30 kg	50 kg	70 kg	100 kg
Normal						
80 mg/kg/h	4	6	12	20	28	40
110 mg/kg/h	6	8	17	27	39	55
130 mg/kg/h	7	10	20	33	46	66
Chronic Alcoholic						
150 mg/kg/h	8	11	22	38	53	75

During Hemodialysis						
250 mg/kg/h	13	19	38	63	88	125
300 mg/kg/h	15	23	46	75	105	150
350 mg/kg/h	18	26	53	88	123	175

[a]Concentrations above 30% (60 proof) are not recommended for oral administration. The dose schedule is based on the premise that the patient initially has a zero ethanol level. The aim of therapy is to maintain a serum ethanol level of 100â€“150 mg/dL, but constant monitoring of the ethanol level is required because of wide variations in endogenous metabolic capacity. Ethanol will be removed by hemodialysis, and the dose of ethanol must be increased during hemodialysis. Prolonged ethanol administration may lead to hypoglycemia.
[b]A 20% V/V concentration yields approximately 200 mg/mL.
[c]Rounded to the nearest mL.
[d]For a 30% concentration, multiply the amount by 0.66.
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Summary

When administered appropriately, ethanol is an excellent first step in preventing further metabolism of methanol and ethylene glycol. The disadvantages of ethanol compared to fomepizole are making

ethanol an outmoded antidote. However, neither fomepizole nor ethanol affect the toxic metabolites that are already present in the body. Once alcohol dehydrogenase is blocked, the decision whether to use hemodialysis depends on how much end-organ damage has occurred, how well the body can eliminate the parent compound without the benefit of hemodialysis, and how much toxic metabolite is already present. With the use of either ethanol or fomepizole, the increase in hospital length of stay in an ICU or on a medical floor may be substantial, particularly for methanol-poisoned patients without the benefit of hemodialysis.

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Chapter 104

Pesticides: An Overview with a Focus on Principles and Rodenticides

Neal E. Flomenbaum

A 35-year-old Hispanic man with a past psychiatric history was brought to the emergency department after claiming to have ingested an unidentified rodenticide called â€œTres Pasitos.â€• His vital signs were: blood pressure 120/70 mm Hg; pulse 45 beats/min; respiratory rate 28 breaths/min; and temperature 97.8Â°F (36.6Â°C). The patient was lethargic, diaphoretic, incontinent of urine and stool, and had no evidence of trauma or seizure. The patient had prominent fasciculations of his face and extremities, 3-mm pupils, and profuse oropharyngeal secretions requiring frequent suctioning. His pulmonary examination revealed scattered rales, and his abdomen had hyperactive bowel sounds. His neurologic examination was significant for symmetric decrease in muscle strength and garbled speech, but he was fully oriented. The patient immediately received atropine, 2 mg IV, which elevated his heart rate and decreased his oropharyngeal secretions. Over the first 30 minutes,

the patient required 10 mg of atropine to achieve and maintain a normal level of consciousness, and subsequently a continuous infusion of IV atropine was initiated at 4 mg/h. Pralidoxime IV at 500 mg/h was started simultaneously. The patient was admitted to the critical care unit and was fully recovered by 36 hours. An initial red blood cell cholinesterase level was reported as slightly decreased (3414 U/L; normal 5300â€“10,000 U/L).[66]

Introduction to Pesticides, Rodenticides and Herbicides: Definition, Regulation, and Epidemiology

Pesticides are substances or mixtures of substances intended to prevent, destroy, repel, or mitigate any pest and any substances or mixture intended for use as a plant regulator, defoliant, or desiccant.[29] â€œPestsâ€• are insects, fungi, herbs, rodents, and worms. Beginning with the 2000 annual report, the American Association of Poison Control Centers, Toxic Exposure Surveillance System (AAPCC-TESS) has listed 5 subcategories of pesticides: fungicides (nonmedicinal), herbicides, insecticides, repellents, and rodenticides. Other types of pesticides not specifically listed by TESS include desiccants, defoliants, and nematocides.

The total number of yearly pesticide exposures reported by TESS has risen steadily to a current level of almost 100,000 annual exposures, as has the number of exposures involving children younger than 6 years of age, who continue to represent more than 50% of the total. The annual number of deaths reported to TESS that are attributed to all pesticides each year remains less than 50 (Chap. 130).

Since 1947, the production, use, and distribution of all pesticides in the United States has been regulated by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and its subsequent amendments in 1972, 1975, and 1978. The Environmental Protection Agency (EPA) was given the authority to administer and enforce FIFRA regulations in 1970.

Currently under FIFRA all pesticides must be registered with the EPA and are classified for either general use or restricted use by licensed or certified applicators. The EPA and the FDA together establish pesticide tolerance levels for agricultural products and foods. Under the 1978 amendment, FIFRA allows individual states to regulate and enforce pesticide regulations and some states have now established even more stringent requirements and lower acceptable levels than the EPA. The EPA, however, maintains the authority to act when states are unable or unwilling to do so. The EPA also regulates pesticides under several other Acts: The Federal Environmental Pesticide Control Act, the Resource Conservation Recovery Act of 1972 (RCRA), the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA, also called the â€œsuperfundâ€• Act), the Toxic Substance Control Act (TSCA), the Clean Water Act and the Safe Drinking Water Act.[98]

I Danger
0â€“50
0â€“200
0â€“0.05
Corrosive: corneal opacity not reversible within 21 d
Corrosive
II Warning
50â€“500
200â€“2000
0.05â€“0.5
Corneal opacity reversible within 8â€“21 d; irritation persisting for 7 d
Severe irritation at 72 h
III Caution
500â€“5000
2000â€–20,000
0.5â€–5.0
Corneal opacity; irritation reversible within 7 d
Moderate irritation at 72 h
IV None
>5000

	>20,000				
	>5.0				
	Irritation cleared within 24 h				
	Mild or slight irritation at 72 h				

Category and Signal Word	Oral LD_{50} (mg/kg)	Dermal LD_{50} (mg/kg)	Inhalation LC_{50} (mg/L)	Eye Irritation	Skin Irritation

TABLE 104-1. EPA Toxicity Classifications

According to FIFRA, both the pesticide and its manufacturer must be registered with the EPA. The pesticide must be sold exactly as formulated, registered, and labeled. Failure to comply with these regulations can result in civil and criminal penalties, product recalls, product seizures, or banning a product from future sales.[98] Of more immediate concern however, is the authority granted by FIFRA to protect the health of the population. When evidence indicates that a pesticide may be a significant health hazard, one or more of the following actions may be taken: permissible workplace exposure limits may be issued, a product may be removed from sale, or its registration may be canceled, restrictions on use or application of a product may be ordered and tolerance levels for pesticide residue on food stuffs or water contamination may be set.[98] Since 1978, demonstration of efficacy of a pesticide may be waived, unless the product affects public health. The Food Quality Protection Act of 1996 requires that EPA establish tolerances based in part on the higher vulnerability of children to pesticide residues, and on the aggregate exposures from residues from all sources and from all agents with the same mechanism of toxicity.[80]

Table 104-1 summarizes the EPA's toxicity classifications and the significance of oral median lethal dose for 50% of test subjects (LD_{50}) is discussed under rodenticides below. The remainder of this chapter deals

with the clinical problems posed by rodenticide poisoning. Some of the oldest and most toxic rodenticides are discussed individually in Chap. 104 , 105 , 106 , 107 and 108 whereas others are discussed in Chaps. 85 (Arsenic) and 96 (Thallium). Chap. 109 and Chap. 110 discuss insecticides. Chap. 111 discusses herbicides and Chap. 112 discusses fumigants.

Epidemiology: Rodenticides

Reported rodenticide exposures in the United States are most commonly associated with young children. About 20,000 rodenticide exposures are reported annually to AAPCC-TESS and over 85% involve children younger than 6 years of age (Chap. 130). Remarkably, despite the very large number of exposures, no more than 5 deaths are reported each year from rodenticide poisoning. Beginning with the 2001 report, TESS added three types of rodenticides to the specific rodenticide categories that are tracked: bromethalin, cholecalciferol, and zinc phosphide. TESS continues to track Î±-naphthyl thiourea (ANTU), warfarin and â€œsuperwarfarinsâ€• (or long-acting types of anticoagulants), barium carbonate, monofluoroacetate, strychnine, Vacor, â€œother,â€• and â€œunknown,â€• but since 2001, cyanide, which was previously listed both as a rodenticide and as a â€œchemical,â€• has been listed only as a chemical.

Of the 20 deaths caused by rodenticides reported by AAPCC-TESS between 1999 and 2003, long-acting anticoagulants accounted for 9, strychnine 5, and zinc phosphide 1; the combination of â€œotherâ€• and â€œunknownâ€• rodenticides accounted for a total of 5 deaths. However, in considering the human toll of rodenticide exposures, it is important to note that the TESS database does not specifically list as a rodenticide exposure any encounter with a pesticide that is used as a rodenticide, but not marketed or officially labeled as a rodenticide.

The case at the beginning of this chapter is an example of an insecticide used as a rodenticide and is one of a series of 35 such cases referred to the New York City Poison Control Center between 1994 and 1997; all of

the cases involved an insecticide illegally imported and sold as Tres Pasitos rodenticide primarily within the Dominican community in New York City.[66] The active ingredient of Tres Pasitos is aldicarb, a carbamate cholinesterase inhibitor. Used legally in some parts of the United States as an insecticide, aldicarb is not registered for use as a rodenticide but is sold covertly for such use in local shops.

Although children constitute the largest group of patients exposed to rodenticides, suicidal persons, potential homicide victims, pest control operators, and intoxicated, psychiatric, and impaired older adult persons are also at substantial risk of intentional or unintentional rodenticide exposures. The large number of unintentional ingestions of rodenticides placed in food containers or dishes, with or without added bait such as peanut butter, illustrates the danger of marketing toxic substances in such dishes or transferring toxic substances to other containers. Additional epidemiologic data on pesticides, herbicides, fumigants, and specific rodenticides are found in the corresponding chapters.

The Definition and Classification of Rodenticides

A rodenticide is any product commercially marketed to kill rodents, mice, squirrels, gophers and other small animals. Rodenticides are a heterogeneous group of chemicals bearing little or no relationship to one another, apart from their current or historic use as rodenticides. The â€œperfect rodenticide,â€• one that effectively kills rodents but is not toxic to humans or nonrodent pets, has yet to be discovered or synthesized. Instead, a wide variety of less-than-perfect rodenticides are commercially available differing from one another in chemical composition, mechanism for killing rodents, and toxicity to humans.[38, 54, 55, 65, 75] Purportedly â€œeffective and harmlessâ€• products are periodically introduced, only to be subsequently withdrawn when the true human toxicities become known. Some of

these products may remain in basements, on hardware store shelves, or

in use by professional pest control operators long after they are officially withdrawn from sale.

Rodenticides have been classified in several different ways: (a) as inorganic and organic compounds; (b) by animal selectivity; (c) by nature and onset of symptoms; and (d) according to their LD_{50} in rats.[5] Classification by LD_{50} is emphasized in this chapter and used to organize all of the consequential rodenticides in Table 104-2 .

Inorganic and Organic Compounds

Inorganic compounds include the salts of arsenic (Chap. 85), thallium (Chap. 96), phosphorus (Chap. 107), barium (Chap. 105), and zinc phosphide (Chap. 112). Organic compounds include sodium fluoroacetate (Chap. 106), ANTU, warfarin (Chap. 57), red squill (Chap. 114), strychnine (Chap. 108), norbormide, and Vacor.[5]

Animal Selectivity

The cardioactive steroid red squill was promoted as a safe rodenticide because humans and other animals presumably would vomit the highly emetogenic poison prior to experiencing any cardiotoxic effects; rats do not vomit and therefore would be expected to experience the cardiotoxic effects of red squill. Norbormide, an irreversible smooth-muscle constrictor, causes widespread ischemic necrosis and death in rats, but does not appear to affect other animals or humans because it acts on a specific norbormide receptor found only in the smooth muscle of rats. ANTU, a relatively selective rodenticide, is a derivative of phenylthiourea without the bitter taste characteristic of the thiourea. ANTU causes pulmonary edema in rats that have not developed tolerance to it. ANTU, however, is only relatively selective: although rats are more sensitive to it than other animals, large doses (>4 g/kg) can also be lethal to primates.

All of the rodenticides classified as inorganic, and organic rodenticides such as strychnine and sodium fluoroacetate, are nonselective and of

extreme concern when ingested by humans and domestic animals. Use of this entire group of rodenticides is restricted to commercial pest control operators and government agencies.

Nature and Onset of Symptoms

Although a rodenticide classification system based purely on the nature and onset of symptoms seems very appealing, such a system may be unreliable, may create a false sense of security, and may result in inappropriate management and/or inadequate followup. Many different rodenticides cause neurologic and/or gastrointestinal signs and symptoms, whereas characteristic or pathognomonic signs such as â€œrisus sardonicusâ€• from strychnine, or alopecia from thallium, may not be recognized, do not always occur consistently (especially after ingesting small amounts), or, as in the case of thallium-induced alopecia, will not occur until days after an acute ingestion. Classifying rodenticides by the time of onset of symptoms may similarly lump together within a late-onset group some of the least toxic (regular warfarin type, cholecalciferol) and most toxic, (long-acting warfarin type, thallium) rodenticides.

LD_{50} in Rats

Probably the most clinically useful way of classifying rodenticides at present is by toxicity based on LD_{50} data in rats. With a few noteworthy exceptions, the relative degree of toxicity per kilogram and the characteristic adverse effects generally hold among different mammals, allowing the healthcare provider the opportunity to consider a combination of historical and characteristic physical evidence to diagnose or exclude various rodenticides and to decide on an optimal management plan. The limitations of this classification system, however, must be understood to use it appropriately: (a) in rare cases, the LD_{50} may vary unpredictably among species (eg, Vacor); and (b) repeated ingestions of less toxic rodenticides (eg, short-acting anticoagulants, cholecalciferol) may, in fact, make them highly toxic (Table 104-2).

Highly Toxic Rodenticides (Signal Word: â€œDangerâ€•)

According to FIFRA highly toxic rodenticides are those substances with a single-dose LD_{50} of less than 50 mg/kg body weight. The label â€œDangerâ€• is the strongest warning issued by the Consumer Product Safety Commission for a potential toxic hazard. Lower hazard levels are denoted by â€œWarningâ€• and â€œCautionâ€• (Table 104-1). The highly toxic â€œDangerâ€• group includes thallium (Chap. 96), sodium monofluoroacetate (SMFA, compound 1080) and fluoroacetamide (compound 1081) (Chap. 106), strychnine (Chap. 108), zinc phosphide (Chap. 112), elemental phosphorus (Chap. 107), arsenic (Chap. 85), barium carbonate[51 , 62 , 78 , 87 , 93 , 94 , 106] (Chap. 105) and Vacor (*N* -3-pyridylmethyl-*N* â€²-*p* -nitrophenyl-urea) (see Table 104-2 and previous editions of this text for an extensive discussion of Vacor).

Moderately Toxic Rodenticides (Signal Word: â€œWarningâ€•)

Moderately toxic rodenticides, those with an LD_{50} of 50â€“500 mg/kg body weight, include the â€œselectiveâ€• rodenticide ANTU and cholecalciferol (vitamin D_3), one of the newest and increasingly popular rodenticides.

Î±-Naphthyl-Thiourea (ANTU)

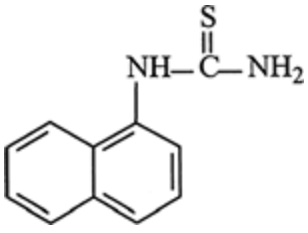

Figure. No Caption Available.

ANTU kills rats by causing acute lung injury and pleural effusion, probably because of damage to the lung capillaries resulting in increased permeability.[11, 86] Young rats and rats exposed initially to small, nonlethal doses are relatively resistant to the lethal effects of ANTU, possibly by developing pulmonary cell hyperplasia.[9] The heart appears to be unaffected by ANTU.[11, 86] There are no well-documented cases or series of human ANTU exposures from which human toxicity can be accurately determined. In several older series of combined ANTU plus chloralose ingestions, it appears that the respiratory symptoms were more severe from the combination than from chloralose alone, suggesting pulmonary effects of ANTU in humans. Of the 14 patients poisoned by the

P.1472

P.1473

P.1474

combination, 11 required intubation because of tracheobronchial hypersecretion.[33, 38] Recommended treatment for ANTU ingestions is administration of activated charcoal (AC).[65] Supportive and symptomatic care should be provided as there is no known antidote.

Toxin Name	Physical Characteristics	Toxic Mechanism	Estimated Fatal Dose	Diagnostic Presenting Signs and Symptoms	Onset	Antidote and/or Treatment*
Indandiones						
Pindone (Pival)	Moldy, acrid odor, fluffy yellow powder, concentrations 0.005–2.5%	Anticoagulation via interference with clotting factors II, VII, IX, X; death from hemorrhage	?	Chronic ingestion possibly produces cardiac and neurologic symptoms as well as bleeding with elevated INR	Delayed several days	Vitamin K_1, fresh frozen plasma (FFP) as indicated Activated factor VII
Pivalyn	0.5%					
Diphacinone	0.005–2.0%					
Chlorophacinone	0.005–2.5%					
Valone	0.005–2.5%					

[a] The LD_{50} values used in this table are derived from data on acute oral ingestions of the commercial product by rats. In some cases the commercial product contains a very small percentage of active ingredient. The signal words that appear on labels of registered products may differ from the signal word assigned to the acute oral LD_{50} test because the label may also reflect another study (acute dermal or inhalational LD_{50}) requiring a more severe signal word. See Table 104–1 for the Consumer Product Safety Commission definitions and use of signal words as indicators of potential hazard of toxicity. Peacock D, Biologist, Registrations Division Office of Pesticide Programs, EPA, Washington, DC.

*Gastrointestinal decontamination should be provided as appropriate (Chap. 8); only unique or controversial aspects are discussed in this table.

TABLE 104-2. Management of Specific Rodenticide Ingestions

Cholecalciferol

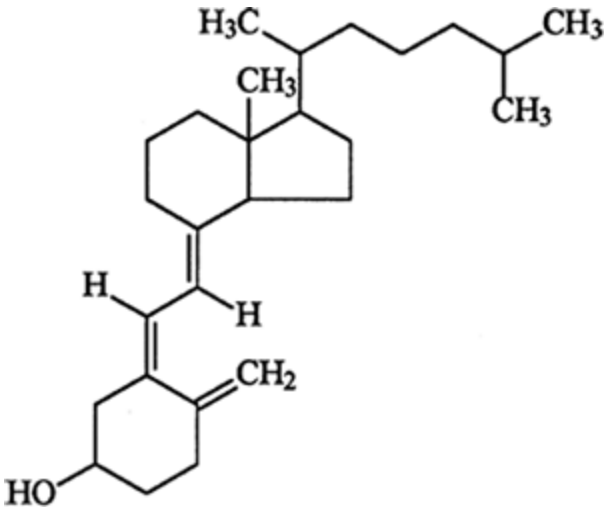

Figure. No Caption Available.

Cholecalciferol (vitamin D_3) was first registered and marketed in the United States in 1984. It is now used by professional pest control operators as Quintox, and by the general public as Rampage. Cholecalciferol mobilizes calcium from the bones of rodents and rabbits and in toxic doses produces hypercalcemia, osteomalacia, and metastatic calcification of the cardiovascular system, kidneys, stomach, and lungs; death typically occurs in 2â€“5 days.[58 , 59 and 60] Although all animals are susceptible to the effects of cholecalciferol, rats and mice succumb to much lower doses than do larger animals such as cats and dogs.[59 â€“60] Cholecalciferol appears to be an effective rodenticide either when a large amount is consumed in one meal or when smaller amounts are consumed over a 2â€“3-day period.[59 , 60 , 83] Because death is not immediate and the cholecalciferol does not impart unusual characteristics to the bait, the bait shyness that occurs with zinc phosphide, ANTU, strychnine, and other rodenticides does not occur with cholecalciferol.[58 , 59 and 60] The closely related vitamin D_2 (or ergocalciferol) has been used as a rodenticide in Europe and Canada since 1978, without the development of resistance reported to date.[58 , 59 and 60]

Although rats manifest the signs of severe acute hypercalcemia, including lethargy and ultimately death from myocardial infarction in 2â€“5 days,[83] no serious human toxicity or death from the rodenticide form of

cholecalciferol are reported to date. It is important to note that all of the advice for managing human ingestions of cholecalciferol rodenticide is based on experience with treating therapeutic forms of vitamin D poisoning and hypercalcemia. One case of cholecalciferol poisoning in an industrial setting may be particularly relevant because, as in the case of a child who might repeatedly ingest small amounts of rodenticide, the exposure described was to small doses over a 32-day period and resulted in prolonged hypercalcemia.[43]

Although calciferol levels are not readily available, a normal serum calcium level obtained 48 hours after an acute ingestion almost certainly excludes any significant toxicity. Immediate intervention after a large acute ingestion may include gastric emptying by emesis or orogastric lavage, followed by gastric decontamination with AC and possibly sorbitol Repetitive dosing of AC has been recommended, but data are insufficient to confirm usefulness of either approach.

Treatment for moderate to severe degrees of hypercalcemia (greater than 11.5 mg/dL) includes IV fluid therapy with 0.9% sodium chloride solution if the patient is hypovolemic and can tolerate a fluid load. Potassium and magnesium levels should be monitored and maintained. Furosemide should be administered.

Low-Toxicity Rodenticides (Signal Word: â€œCautionâ€•)

The remaining rodenticides, with one exception, are of low toxicity (LD_{50}, 500â€“5000 mg/kg). This category includes red squill (*Urginea maritima*)[89, 102] (Chap. 114), norbormide, bromethalin, and the anticoagulants (Chap. 57). The â€œwarfarin-typeâ€• anticoagulant rodenticides and the long-acting â€œsuperwarfarinâ€• forms are responsible annually for more than 80% of the reported exposures and approximately 50% of the deaths attributed to rodenticides. Norbormide and bromethalin are discussed below.

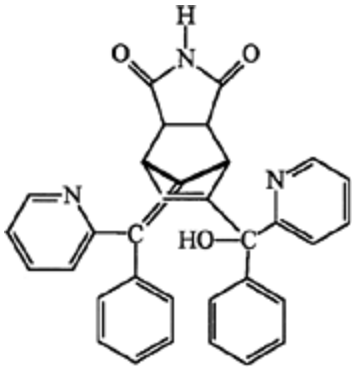

Figure. No Caption Available.

Norbormide

Norbormide, an irreversible smooth-muscle constrictor, appears to be specific for rats and has no known human toxicity. Rats die as a result of intense generalized vasoconstriction, resulting in tissue anoxia.[65] In vitro, norbormide promotes calcium entry into smooth muscle cells, inducing a myogenic contraction, selective for the small vessels in rats, whereas in the arteries of other mammals (and in the rat aorta), norbormide behaves like a calcium channel blocker.[12] Following exposure it is sufficient to achieve gastric decontamination with AC.

Bromethalin

The commercial product formulation of bromethalin, is considered to be of low toxicity defined above. Bromethalin was registered with the EPA in 1982, became available in 1986, and is currently available commercially in the United States primarily in the form of green pellets mixed with cornmeal (which gives it a fresh corn odor) and denatonium benzoate Bitrex. Bromethalin is marketed under trade names such as Assault or Vengeance.

From the time that bromethalin first became available, concern was expressed about its potential toxicity.[58] However, the first possible

bromethalin-induced case of human toxicity was not reported until 1996,[15] perhaps because as late as 1997, bromethalin had been registered in only 6 states and in 2 of these states, California and New York, bromethalin first became available in 1996. Since 2001, TESS has been reporting between 333 and 581 annual exposures, including 275 to 461 in children younger than 6 years old. The outcome of the exposures have been noted as â€œmoderateâ€• or less (most frequently â€œnoneâ€•) in all cases, with no deaths reported to date.

Bromethalin is considered to be a highly effective, single-feeding rodenticide with a mode of action reportedly involving the uncoupling of oxidative phosphorylation in the mitochondria, resulting in decreased adenosine triphosphate (ATP) production, increased fluid accumulation, and consequent increased pressure on nerve axons interrupting nerve impulse conduction.[59]

The pathologic changes resulting from a 1.5-mg/kg oral dose of bromethalin administered to cats, included spongy changes, hypertrophied fibrous astrocytes, and hypertrophied oligodendrocytes in the white matter of the cerebrum, cerebellum, brainstem, spinal cord, and optic nerve.[26, 28] Prior to sacrifice of the animal, the clinical manifestations of bromethalin poisoning in these cats included ataxia, focal motor seizures, decerebrate posture, decreased proprioception, and depressed level of consciousness. Dogs given oral doses of 6.25 mg/kg of bromethalin developed hyperexcitability, tremors, seizures, depression, and death within 15â€“63 hours of exposure.[27] Death in animals is also usually preceded by paralysis and loss of tactile sensation.[103, 104]

Because there is no known antidote for bromethalin, symptomatic and supportive care should be provided.

Dangerous Old, New, and Unusual Rodenticides: The Worldwide Problem

The confusion caused by other types of pesticides inappropriately used as rodenticides is compounded occasionally when a dangerous rodenticide

favored in one part of the world is introduced and used in a different area, or when a highly toxic, previously abandoned rodenticide is â€œrediscovered.â€• All 3 types of problems are being increasingly reported. Accessibility to the products and global travel may explain part of the problem.

Tetramethylene Disulfotetramine (Tetramine, TETS, TEM)

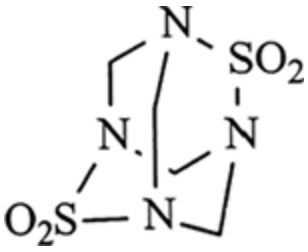

Figure. No Caption Available.

During the past decade, several reports have appeared in the medical literature describing the toxicity of the illegal Chinese rodenticide tetramine.[8 , 22] First patented as a rodenticide in the United States in 1953, tetramine was eventually banned in China in 1984.[8] This quick-acting, single-dose poison nevertheless, is still produced in many parts of China and is occasionally responsible for unintentional or deliberate poisonings. In September 2002, a deliberate adulteration of restaurant food with tetramine by a competing restaurant owner poisoned 300 people and caused 42 deaths, all in schoolchildren. In that same year, the first known case of tetramine poisoning in the United States resulted from a 15-month-old infant playing with the white powder brought back from China by her parents and applied to a kitchen corner;[8] the child developed convulsive status epilepticus that was refractory to lorazepam, phenobarbital, and pyridoxine. The child required intubation and was left with multiple neurologic deficits including persistent absence seizures, possible cortical blindness, multiple epileptogenic foci months later, and developmental delay 1 year later.

Tetramine is an indirect acting Î³-amino butyric acid (GABA) antagonist similar in some respects to picrotoxin with an LD_{50} of 0.1â€“0.3mg/kg.[32] Tetramine is more lethal than the World Health Organization's (WHO) most toxic registered pesticide, sodium fluoroacetate. Tetramine is also suggested to be 100 times more toxic (on a g/kg basis)[8] to humans than potassium cyanide.[8] As little as 5â€“10 mg/kg of tetramine may be lethal.[22] Because of its high stability in water, tetramine is a relatively persistent environmental contaminant that theoretically could cause secondary poisonings.[22]

In addition to its most common manifestation of toxicity, which is refractory seizures, tetramine also causes coma and possibly coronary ischemia. Symptoms are said to begin from 30 minutes to 13 hours after exposure and fatality may occur within 3 hours of onset. A variety of methods have been used to treat tetramine poisoning in China, including AC hemoperfusion and hemodialysis, but none have proven to be uniformly successful

and there are no proven antidotes for tetramine. Management includes the standard approach to gastrointestinal decontamination with AC and the standard approach to seizures with benzodiazepines, and with effective airway protection.

Î±-Chloralose (Glucochloral, Chloralosane)

Î±-Chloralose is a crystalline powder (usually colored pink or blue) that is formed by the condensation of glucose with trichloroacetaldehyde (chloral). Î±-Chloralose is a central nervous system depressant, still used as a veterinary anesthetic. Its effects in humans include sedation, anesthesia, spontaneous myoclonic movements, and generalized convulsions.[33 , 48] Most human exposures are nonfatal and most current reports appear to emanate from France and Europe. Management in this case is also supportive, with the use of airway protection and the administration of AC.

Salmonella -Based Rodenticides

Salmonella enteritides , a human pathogen, is an active ingredient in rodenticides still produced and used in Central America and Asia. Biorat, currently available in several countries, is made by coating rice grains with a combination of *S. enteritides* and warfarin. The strain of *Salmonella* â€”phage type 6aâ€”found in Biorat is similar to the strain of *Salmonella* that was in Ratin, a rodenticide used in Europe until the 1960s, which caused human illness and deaths.[71] In 1954 and 1967, the WHO recommended not using *Salmonella* -based rodenticides because of their threat to human health. Since 1980, *S. enteritides* has been responsible for a global pandemic of foodborne illness associated with eggs and poultry.[71] In addition to inadvertent exposures, *Salmonella* -based rodenticides have been used intentionally to cause human illness.

Managing the Patient Exposed to an Unknown Rodenticide

For the patient exposed to an unknown rodenticide, the approach is more complicated than for a patient who ingests a known common commercial rodenticide such as warfarin or cholecalciferol. First, as always, adequate breathing and circulation must be assured, as the patient is briefly examined. If the patient is initially stable, the next priority is to make every effort to fully identify the type and quantity of rodenticide ingested

If the rodenticide and its package material are not brought with the patient, someone should be sent to get them because identifying a harmless rodenticide ingestion early on is more cost-effective and less traumatic to the patient than treating for an unknown ingestion. If the rodenticide container is labeled, and the information is telephoned back to the health care provider, care should be taken to obtain the full name, not just the brand name. The names are frequently used interchangeably by manufacturers. For example, until 1986, there was a line of rodenticides all carrying the â€œPied Piperâ€• name on a variety of very different products: Pied Piper for Rats and Mice contained ANTU and

warfarin; whereas Pied Piper Kwik-Kill Mouse Seed contained strychnine; and Pied Piper Rodenticide contained red squill. Many manufacturers still use similar names for dissimilar poisons.

Although full identification of the rodenticide is important, a careful physical examination should be performed in any case, searching for toxic signs that indicate specific rodenticides:

- Gastrointestinal symptomatology, paresthesias, and the late onset of hair loss are characteristic of thallium (Chap. 96).[10 , 23 , 24 , 39 , 44 , 56 , 64 , 67 , 74]
- Irritability or â€œapprehensionâ€• followed by seizures, coma, and death from respiratory failure or ventricular tachycardia and fibrillation are produced by SMFA, fluoroacetamide[17 , 18 , 19 , 20 , 36 , 70 , 77 , 84 , 96 , 99] (Chap. 106) and tetramine.
- Central nervous system stimulation, opisthotonos, prolonged recurrent motor seizures, and medullary paralysis followed by death suggest strychnine poisoning (Chap. 108).[6 , 14 , 30 , 41 , 46 , 50 , 53 , 68 , 69 , 72 , 76 , 85 , 91 , 97 , 101 , 105]
- Hypotension, vomitus with a rotten or â€œfishyâ€• odor, cardiopulmonary collapse, coma, renal damage, and leukopenia suggest various metal phosphide poisonings (Chap. 112).[1 , 2 , 4 , 16 , 21 , 35]
- Oral and skin burns, luminescent â€œsmokingâ€• vomitus, and stools with a garlic odor, and gastrointestinal and biliary damage characterize yellow phosphorus poisoning (Chap. 107).[25 , 57 , 79 , 88 , 95 , 100]
- Dysphagia, muscle cramps, seizures, hematemesis, and bloody diarrhea followed by cardiovascular collapse suggest arsenic (Chap. 85).[49 , 92]
- The combination of striking hyperglycemia with or without ketoacidosis, and severe postural hypotension, autonomic and

peripheral neuropathies, ileus, and esophageal or GI perforation characterize Vacor poisoning (see Goldfrank's Toxicologic Emergencies, 7th ed., Chap. 90).[3 , 31 , 34 , 37 , 40 , 42 , 45 , 47 , 52 , 61 , 63 , 81 , 82 , 90]

- Muscle tremors, myoclonic jerks with flexion of major muscle groups, and unresponsiveness may be the human manifestations of bromethalin poisoning (Chap. 104).
- Dyspnea, crackles, acute lung injury, pleural effusions, and hypothermia are seen with massive ingestions of ANTU (Chap. 104).
- Nausea, vomiting, diarrhea, and abdominal pain will probably be the only effects of ingesting red squill, but when those effects are combined with signs of ventricular irritability (premature ventricular contractions and ventricular fibrillation), then this potent emetic and cardioactive steroid is certainly identified (Chap. 114).[73 , 89 , 102]
- Signs or symptoms of a bleeding disorder and abnormal coagulation or international normalized ratio (INR), or low levels of coagulation factors, point to either a large acute ingestion of a superwarfarin rodenticide, such as brodifacoum, or repeated (chronic) ingestion of a regular warfarin-type rodenticide (Chap. 57).[13]
- Finally, evidence of hypercalcemia following (massive or chronic) rodenticide ingestion suggests cholecalciferol (vitamin D_3).

If a toxic syndrome is identified, aggressive management, including the use of specific antidotes, may be necessary (see Table 104-2). Immediately following an ingestion and prior to the development of signs and symptoms of toxicity, there is no rodenticide currently in use for which orogastric lavage followed by AC, and possibly an intestinal evacuant cathartic, is contraindicated, although they may be unnecessary. After the patient is symptomatic however, orogastric lavage, AC, and catharsis must be individualized according to the specific toxin and the patient's clinical condition.

If every effort to identify the rodenticide fails, the following diagnostic

evaluation may be indicated: A complete blood cell count (CBC) or hemoglobin (Hgb)/hematocrit (Hct) determination and

INR will help diagnose and manage repetitive ingestions of the older warfarin-type rodenticide, chronic ingestions of the newer superwarfarin anticoagulant rodenticides, and a large single ingestion of a superwarfari a few days after ingestion. Following acute ingestions, the CBC and INR will not be useful until 48 hours later. Repetitive ingestions of the otherwise harmless older warfarins is an important consideration for children who have pica, and for institutionalized, emotionally disturbed adults who may nibble grainlike rodenticides repeatedly. Serum glucose, potassium, and bicarbonate determinations will identify hyperglycemia and ketoacidosis caused by Vacor, and an elevated serum calcium concentration suggests cholecalciferol (vitamin D_3) ingestion. Liver enzymes, BUN, and creatinine are useful baseline determinations for rodenticides that cause hepatic or renal damage, respectively (eg, zinc phosphide, yellow phosphorus, cholecalciferol). A serum sample and 50 mL of urine should be obtained and sent to the toxicology laboratory with the request to hold it for possible heavy metals screening, especially if the patient is vomiting. Finally, if indicated by history or symptomatology, additional specimens may be collected for specific rodenticide determinations (eg, thallium, strychnine); a digoxin level may offer a clue to Red Squill ingestion. Chest and abdominal radiographs ma be useful because of the radiopaque nature of some of the uncommonly used rodenticides (Chap. 6).

If there is any doubt about either the nature of the rodenticide or the reliability of the patient (or parents) after the diagnostic evaluation, the patient should be admitted for observation. No matter what type of rodenticide was ingested, a determination should be made regarding whether the ingestion was unintentional, a suicide gesture or attempt, or a manifestation of abuse or neglect.[7] A psychiatric assessment is, of course, indicated for any possible suicide attempt.

Summary

As developed and underdeveloped parts of the world continue to experiment with and use a variety of exotic and very toxic or lethal rodenticides, it will be even more important to be able to discriminate between expected sequela of known or suspected rodenticides and unexpected sequela from other pesticides or xenobiotics used inappropriately as rodenticides. The key to managing the patient who ingested a rodenticide is to identify the rodenticide, the quantity ingested, its potential toxicity, and any available specific antidote. Toxic ingestions should be excluded or treated immediately; conversely, patients with the most common acute anticoagulant, bromethalin or cholecalciferol exposures should not be overtreated.

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Chapter 105
Barium

Andrew Dawson

Barium (Ba)

Atomic number	=	56
Atomic weight	=	137.33
Normal concentrations Serum	=	< 0.2 mg/L

A 34-year-old woman was brought to the emergency department by her husband after she stated that she unintentionally ingested his hair care product. Her complaints included abdominal pain, diarrhea, palpitations, and weakness. Initial vital signs were: blood pressure 140/90 mm Hg; pulse 100 beats/min; respiratory rate 16 breaths/min; and rectal temperature 98.6Â°F (37Â°C). Oxygen saturation by pulse oximetry was 96% on room air. Physical examination was only remarkable for diffuse and symmetrical muscle weakness. An ECG demonstrated sinus tachycardia with U waves and intermittent runs of ventricular tachycardia. An arterial blood gas was obtained while the patient

was breathing room air, and showed: pH, 7.34; PCO_2, 46 mm Hg; PO_2, 90 mm Hg.

The patient was attached to continuous ECG monitor, given 100% oxygen via a nonrebreather mask, and an intravenous bolus of lidocaine (100 mg) was administered. Her dysrhythmia transiently improved, but recurred. Subsequently, electrolytes were notable for sodium, 138 mEq/L; potassium, 2.4 mEq/L; chloride, 95 mEq/L; bicarbonate, 20 mEq/L; glucose, 110 mg/dL; BUN, 18 mg/dL; and creatinine, 1.2 mg/dL.

The patient was given potassium chloride (40 mEq) by mouth and an intravenous infusion of 10 mEq/h was started. Her serum potassium and ECG were checked hourly. After the first hour, during which a total of 50 mEq of potassium chloride was administered, her serum potassium rose to 2.8 mEq/L, and she continued to have some ectopy on her ECG. A total of 180 mEq/L of potassium chloride was administered (with combined oral and IV therapy) over 10 hours before her ECG returned to normal and her weakness resolved. She was observed for another 24 hours, and before being transferred to the psychiatry service for further evaluation of her behavior and rationale for ingestion of this xenobiotic. At that time her serum potassium was 3.8 mEq/L and she was asymptomatic.

Chemistry

Barium is a soft metallic element with an atomic weight of 137.327 that is located at number 56 in the periodic table (between Cesium and Lanthanum). The metal oxidizes easily when exposed to water or alcohol and has a melting point of 1341Â°F (727Â°C) and a boiling point of 3398Â°F (1870Â°C). Elemental barium is not found in nature; it normally occurs as an oxide, dioxide, sulphate (barite), or carbonate (witherite). It was first isolated by Sir Humphry Davy in 1808. Chemically, barium resembles calcium more than any other element. Although some salts occur naturally,

most salts used for commercial purposes are produced from the more commonly found carbonate or oxides. Barium salts may be either water-soluble or insoluble. The solubility of all barium salts increases as pH is lowered. The soluble salts: acetate, chloride, hydroxide, oxide, nitrate, and (poly)sulfide, are the most commonly associated with toxicity (Table 105-1). Barium (poly)sulfide may also produce toxicity through the formation of hydrogen sulfide when it combines with the acid normally present in the stomach. Insoluble salts such as the arsenate, chromate, fluoride, oxalate, and sulfate are rarely associated with toxicity. However, the solubility of barium carbonate is low at a normal pH, but increases significantly when the pH is lowered. Additionally, in gastric acid, barium conversion to the highly soluble barium chloride occurs.

History and Epidemiology

Barium poisoning is rare, with less than 100 exposures reported annually to the Toxic Exposure Surveillance System (TESS) database (Chap. 130). Toxicity has been reported for most forms of barium, although it is most commonly reported following the intentional ingestion of soluble salts found in rodenticides,[8] insecticides, or depilatories.[9] Toxicity has also followed occupational exposure to barium salts by ingestion or inhalation. An explosion of the propellant barium styphnate caused extensive burns and trauma in a 50-year-old man who also developed significant barium toxicity within 2 hours of exposure which persisted for at least 4 days.[12] Barium carbonate has an appearance that is similar to that of flour and has been responsible for most unintentional barium poisonings. Despite the fact that barium sulfate is insoluble,

rare cases of unintentional toxicity have been reported during radiographic procedures and include complications associated with oral[18] and rectal administration.[11,16,20] Toxicity and death

occurred when soluble barium salts unintentionally contaminated contrast solution[2] and flour.[7]

TABLE 105-1. Available Barium Salts

Barium Salt	Solubility*	Common Uses
Acetate	58.8	Textile dyes
Carbonate	0.02 Solubility increases markedly in an acid pH. Also conversion to barium chloride	Rodenticide, welding fluxes, pigments, glass, ceramics, pyrotechnics, electronic devices, welding rods, ferrite magnet materials, optical glass, manufacture of caustic soda and other barium salts
Chloride	375 (26Â°C)	Textile dyes, barium salts, pigments, boiler detergents, in purifying sugar, as mordant in dyeing and printing textiles, as water softener, in manufacture of caustic soda and chlorine, polymers, stabilizers

Fluoride	1.2 (25Â°C)	Welding fluxes
Nitrate	87	Optical glass, ceramic glazes, pyrotechnics (green light), fireworks, explosives, antiseptic preparation
Oxide	34.8	In glass, ceramics, refining oils and sugar, as an additive in petroleum products and also as materials of plastics, pharmaceuticals, polymers, glass and enamel industries.
Styphenate		Propellent used in manufacture of explosive detonators
Sulfate	0.002	Radiopaque contrast media, manufacture of white pigments, paper making
Sulfide	0.9	Depilatories, manufacture of fluorescent tubes

*In g/L at 68Â°F (20Â°C); where the solubility was not measured at 68Â°F (20Â°C), the temperature (Â°C) used is shown in parentheses.

Toxicokinetics

Toxicity can occur from ingestion of as little as 200 mg of barium salt, although oral lethal doses are reported to range from 1 to 30 g barium salt. In ambient air, inhaled concentrations greater than 250 mg/m^3 are considered dangerous.

Following ingestion, 5â€“10% of soluble barium salts are absorbed,[15] with the rate of absorption dependent on the degree of water solubility of the salt. The time to peak plasma concentrations is 2 hours.[13]

Toxicokinetics are characterized by a rapid redistribution phase, followed by a slow decrease of plasma barium levels with a reported half-life ranging between 18 hours and 3.6 days.[13,21] Renal elimination of the absorbed dose accounts for 10â€“28% of total barium excretion, with the feces being the predominant route of elimination.

Deaths are most commonly reported following ingestion, but have also occurred from inhalation, intraperitoneal exposure, vaginal exposure, or by extravasation.[14] Death from an ingestion of barium chloride was associated with the following barium levels at autopsy: blood, 9.9 mg/L; bile, 8.8 mg/L; urine, 6.3 mg/L; and gastric contents, 10 gm/L.[14]

Pathophysiology

Clinical Manifestations

At a cellular level, barium induces hypokalemia by two synergistic mechanisms. Barium is a competitive blocker of the potassium rectifier channel, which is responsible for the efflux of intracellular potassium out of the cell. It may also directly increase cell

membrane permeability to sodium. This causes a secondary increase $Na^{+}â€“K^{+}$ pump electrogenesis, leading to a shift of extracellular potassium into the cell.

Intracellular trapping of potassium leads to depolarization and paralysis.[15] Additionally, the inhibition of potassium channels increases vascular resistance and reduces blood flow[3,5] and is the likely mechanism for hypertension and lactic acidosis.

Although severe hypokalemia is a major contributor to paralysis, some authors have found that muscle weakness is better correlated with barium concentration than with potassium concentration.[19,22] This suggests a possible direct effect of barium on either skeletal muscle or neuromuscular transmission.

Abdominal pain, nausea, vomiting, and diarrhea commonly occur within 1 hour of ingestion. Esophageal injury[1] and hemorrhagic gastritis are also reported.[14] Severe hypokalemia is the cardinal feature of barium toxicity and can occur within 2 hours following oral or parenteral exposure. Hypokalemia may be exacerbated by blood transfusions, suggesting that fresh red blood cells provide a new reservoir for K^{+} sequestration.[12] Progressive hypokalemia is associated with severe ventricular dysrhythmias, hypertension, profound flaccid muscle weakness, and respiratory failure.

Other less commonly reported effects include lactic acidosis, hypophosphatemia, and rhabdomyolysis.[13] Altered level of consciousness and seizures[5] and basal ganglia manifestations are reported.[10] It is unclear whether these later findings are a result of direct toxicity or secondary to tissue ischemia.

Diagnostic Studies

Barium can be measured by a variety of techniques. Mass spectrometry can quantitate barium in blood and urine. Graphite furnace atomic absorption spectrometry (GF-AAS) has also been used.[15] Serum barium levels are not readily available, but values

greater than 0.2 mg/L are considered abnormal.[4]

Following acute exposures, patients should have serum electrolytes (particularly potassium and phosphate) measured hourly while performing continuous ECG monitoring. Creatine phosphokinase (CPK), acidâ€“base status, and renal function should also be measured. A plain abdominal radiograph may show barium, but the sensitivity and specificity of radiography has never been determined for barium poisoning.[15]

Differential Diagnosis

Other causes of acute hypokalemia (Chap. 17) associated with paralysis, such as periodic hypokalemic paralysis, toluene toxicity, and diuretic use, should be considered if there is no history or laboratory confirmation of barium exposure. Likewise, toxicological etiologies for flaccid paralysis such as hypermagnesemia, botulism, and the administration of neuromuscular blockers should also be considered.

Management

Patients should be admitted to a monitored bed with full respiratory support readily available. Patients who are asymptomatic at 6 hours with normal potassium concentrations can be discharged.

Decontamination

Activated charcoal (AC) is unlikely to be effective. Orogastric lavage should be considered in patients who present early after ingestion, but is unlikely to provide extra benefit in patients who are already symptomatic or who have had spontaneous emesis. Oral sodium sulfate administration may prevent absorption by precipitating unabsorbed barium ions to insoluble, nontoxic barium

sulfate. Oral magnesium sulfate has also been used with success.[17] The oral dose of magnesium sulfate is 250 mg/kg for children and 30 g for adults. Intravenous magnesium sulfate or sodium sulfate is not advised, because it may lead to renal failure as a result of precipitation of barium in the renal tubules.[19,24]

Patients in respiratory failure should receive assisted ventilation. Aggressive correction of hypokalemia is important to minimize the risk or to treat cardiac dysrhythmias. Large doses of potassium replacement (400 mEq in 24 hours) are reported to be required to correct serum potassium, but may still not improve muscle strength (Chap. 17).[15] As hypokalemia is a result of intracellular sequestration of potassium, potassium supplementation increases the total body potassium load. In this situation, rebound hyperkalemia may occur when barium is eliminated, especially in the setting of a patient with impaired renal function, and the necessity of observation should be anticipated.

Enhancement of Elimination

Correction of hypokalemia alone may not reverse weakness and would not be expected to completely restore the resting membrane potential. In this setting, hemodialysis can be considered. Hemodialysis for the management of severe barium toxity has been reported in three cases.[21,23] Additionally, in a case report, continuous venovenous hemo(dia)filtration (CVVHDF) tripled the measured barium elimination, reduced serum barium half-life by a factor of 3, stabilized serum potassium levels, and rapidly improved motor strength, with complete neurological recovery within 24 hours.[15] Either method of enhanced elimination should be considered in any severely symptomatic patient who does not respond to correction of hypokalemia.

Summary

Although poisoning by barium salts is rare, these salts are widely used in industry and therefore represents a substantial risk for human exposure. The ingestion of barium salts is typically followed by a rapid onset of symptoms and can result in life-threatening toxicity. In addition to good supportive care the mainstay of treatment is rapid correction of hypokalemia.

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Chapter 106

Sodium Monofluoroacetate and Fluoroacetamide

Fermin Barrueto

A previously healthy 23-year-old woman arrived at the emergency department (ED) after drinking a â€œshotâ€• of liquid in a bottle marked â€œSMFA solution (1%).â€• She was actively vomiting and complaining of abdominal pain. She was taking no prescription medications, had no allergies, and denied ingesting any non prescription medications or using any illicit drugs. After 30 minutes of evaluation, she had a single generalized tonic-clonic seizure.

Her vital signs were: blood pressure 95/50 mm Hg; pulse 136 beats/min; respiratory rate 28 breaths/min; temperature 100.1Â°F (37.98Â°C); and pulse oximetry 95% on room air. There was no drooling or stridor. Head and neck examination revealed no burns on the face or within the oropharynx. Her lungs were clear to auscultation, and cardiovascular examination revealed tachycardia with delayed capillary refill of 4 seconds. The abdominal examination was benign, and the neurologic examination done

before the seizure revealed an agitated but alert and oriented woman with no focal deficits.

Laboratory analysis of a blood sample drawn before her seizure occurred revealed a hematocrit of 36.4%, a hemoglobin of 11 g/dL, a white blood cell count of 12,100/mm^3, and a platelet count of 275,000/mm^3. The electrolyte analysis revealed: sodium, 143 mEq/L; chloride, 101 mEq/L; potassium, 3.0 mEq/L; bicarbonate, 18 mEq/L; blood urea nitrogen, 49 mg/dL; creatinine, 2.9 mg/dL; glucose, 105 mg/dL; and calcium, 8.0 mg/dL, and an anion gap of 24. Arterial blood gas analysis revealed a pH of 7.30; PCO_2 of 25 mm Hg: and PO_2 of 75 mm Hg. Serum lactate concentration was 6.2 mmol/L. ECG revealed sinus tachycardia with occasional premature ventricular contractions and a prolonged QTc interval of 501 milliseconds. Chest radiograph was normal.

After the seizure resolved spontaneously, the patient was given 2 mg of lorazepam intravenously. She became hypotensive, with a blood pressure of 75/40 mm Hg despite a 2-L bolus of 0.9% sodium chloride. The patient was intubated and a norepinephrine infusion was started. Twelve hours after arrival in the ED and 24 hours from the estimated time of ingestion, the patient experienced cardiac arrest and died despite maximal supportive care.

History and Epidemiology

Sodium monofluoroacetate (SMFA) is synthesized by plants such as gifblaar (*Dichapetalum cymosum*), native to Brazil, Australia, and South and West Africa.[10] The highest concentration of the compound is reportedly in the seeds of a South African plant, *Dichapetalum braunii*, at a concentration of 8.0 mg/g.[10] The compound was developed by the Denver Research Station in the 1940s as a means of controlling rodent populations. When SMFA (CAS No. 62-74-8) was developed, it was assigned the compound number 1080, which was registered as its trade name.

Fluoroacetamide, a similar pesticide, is known as Compound 1081. Use of either was banned in the United States in 1972, except in the form of collars intended to protect sheep and cattle from coyotes. These collars, imbedded with SMFA, are placed around the neck of the livestock, which is the typical point of attack for coyotes. It is an effective poison against most mammals and some amphibians.[20]

Currently, SMFA is used extensively in New Zealand and Australia to control the possum population and other animal species considered pests that have no natural predators. During 2004 the New Zealand National Poisons Center received 91 inquiries regarding SMFA, of which only one concerned possible human exposure (personal communication).

Pharmacokinetics and Toxicodynamics

Sodium monofluoroacetate is an odorless and tasteless white powder with the consistency of flour. When it is dissolved in water, it is said to have a vinegar-like taste. Sodium monofluoroacetate and fluoroacetamide (CAS No. 640-19-7) are well absorbed orally, and poisoning has also occurred from inhalation.[9,10,11] Detailed toxicokinetic data are lacking in humans, but in sheep, up to 33% can be excreted unchanged in the urine over 48 hours. Glucuronide and glutathione conjugates have also been isolated.[9] Substantial defluorination is not thought to occur in vivo. The plasma half-life is estimated to be 6.6â€“13.3 hours in sheep.[9] Sodium monofluoroacetate has an LD_{50} of 0.06 mg/kg in dogs; the extrapolated LD_{50} in humans is 2â€“5 mg/kg.

Pathophysiology

Sodium monofluoroacetate, a structural analog of acetic acid (Figure 106-1), is an irreversible inhibitor of the tricarboxylic acid

cycle within the mitochondria (Figure 13-3). Monofluoroacetic acid enters the mitochondria when it is converted to monofluoroacetyl-coenzyme A (CoA) by acetate thiokinase. Once inside the mitochondria, citrate synthase joins the monofluoroacetyl-CoA complex with oxaloacetate to form fluorocitrate. Fluorocitrate then covalently binds aconitase, preventing the enzyme from any further interaction in the tricarboxylic acid cycle.[14] Thus fluorocitrate acts as a â€œsuicide-inhibitorâ€• of aconitase, producing a biochemical dead end. The subsequent increase in citrate, which chelates divalent cations, causes hypocalcemia. This sequence was well demonstrated in an animal model in which citrate was administered intrathecally, resulting in seizures that were attenuated with calcium administration.[12]

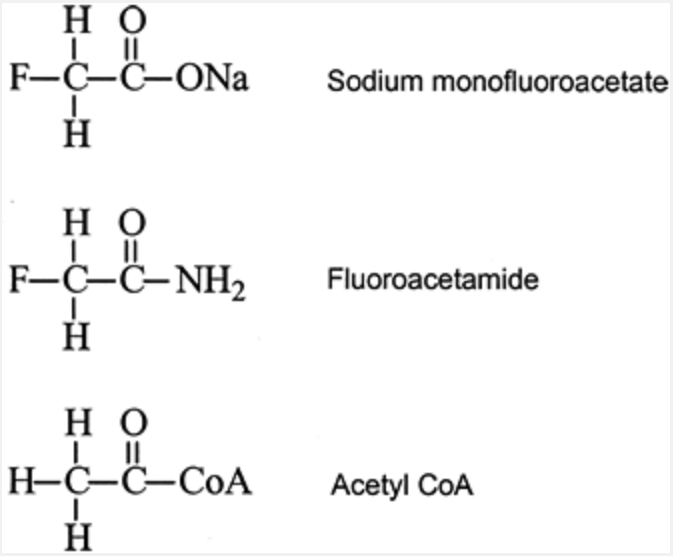

Figure 106-1. Structural similarities among acetyl-CoA, sodium monofluoroacetate, and fluoroacetamide.

Suicide inhibition of aconitase impairs energy production, leading to metabolic acidosis with an elevated lactate concentration. Additionally, other tricarboxylic acid cycle intermediates increase

in concentration, contributing to the toxicity. Fluoride toxicity, from enzymatic defluorination of sodium monofluoroacetate and fluoracetamide, does not occur substantially in vivo and is of minor significance.

Clinical Manifestations

The majority of the clinical experience with SMFA is associated with intentional self-poisoning; fluoroacetamide poisoning is presumed to have a similar presentation.[1,2,13,22] Most patients will develop symptoms within 3â€“6 hours from the time of exposure. In the largest case series, 38 Taiwanese patients ingested SMFA; 7 died.[6] The most common symptoms of exposure recorded at the time of ED presentation were nausea and vomiting (74%), diarrhea (29%), agitation (29%), and abdominal pain (26%).[6] The mean time to presentation to the hospital was 10.9 Â± 5.7 hours for those who died and 3.4 Â± 0.6 hours for the survivors. All deaths occurred within 72 hours of admission to the hospital. The presence of respiratory distress and/or seizures was statistically a poor prognostic indicator of death. All 7 patients who died had systolic blood pressures less than 90 mm Hg on presentation to the ED, compared with 16% of the survivors.[6] One published case report describes the survival of an unresponsive patient with episodic hypertension after SMFA exposure.[19]

The physiologic effects of impaired energy production were described in two patients: one survivor and one fatality.[7] Invasive hemodynamic monitoring revealed persistent low systemic vascular resistance and increased cardiac output, despite adequate fluid resuscitation.[7]

In summary, the common clinical presentation of SMFA exposure is the presence of nausea, vomiting, agitation, abdominal pain, and diarrhea. Signs and symptoms associated with severe poisoning are seizures, respiratory distress, and hypotension. Neurologic sequelae such as cerebellar dysfunction may be permanent.[23]

Diagnostic Testing

The presence of SMFA and fluoroacetamide can be confirmed with gas chromatography-mass spectrometry and thin-layer chromatography.[3,5,15] Simultaneous analysis for rodenticides that can induce seizure, for example, fluoroacetamide and â€œtetramine,â€• has been performed by gas chromatography in China, where exposure to these xenobiotics is more probable.[4,25] An elevated serum citrate concentration has been proposed as a useful marker for exposure to SMFA. However, none of these studies can be performed in a clinically relevant time period. A combination of history, signs, symptoms, and common laboratory tests can assist with the diagnosis.

A complete blood cell count may reveal leukocytosis. Electrolyte abnormalities include hypokalemia and hypocalcemia. Creatinine, liver enzymes, and bilirubin level may also be elevated. Hypokalemia, an anion gap metabolic acidosis, and an elevated creatinine level[8] are associated with severe poisoning but are very nonspecific.[6] An electrocardiogram is valuable in the diagnosis of SMFA exposure: a prolonged QTc interval, atrial fibrillation with a rapid ventricular response, ventricular tachycardia, and other dysrhythmias may be present. An initial computed tomography scan of the brain may be normal, but subsequent scans may reveal brain atrophy if the patient survives the exposure.[23]

Treatment

Initial decontamination should include removal of clothes and cleansing of skin with soap and water. Because there is no antidote for SMFA or fluoroacetamide poisoning, orogastric lavage should be considered for exposed patients who present to the ED prior to significant emesis. Appropriate patients should receive activated charcoal (AC), however, there is a study in rats that showed colestipol was more effective in binding SMFA than AC.[16]

Although there are no human data to support this, the use of colestipol, if available, should also be considered in life-threatening cases.

In animal models, the ethanol and glycerol monoacetate (monacetin) are thought to be antidotes, acting as acetate donors for ultimate incorporation into the tricarboxylic acid cycle.[23] Both of the xenobiotics are converted to acetyl-CoA and compete for binding of citrate synthase with monofluoroacetyl-CoA. This may prevent the â€œsuicide-inhibitionâ€• of aconitase, subsequent increase in citrate, and the formation of the toxic metabolite fluorocitrate.[23]

Ethanol has been used in human cases, although the appropriate dose is unknown.[6,7,18] A reasonable therapeutic dose that is considered safe is the amount of ethanol required to obtain and sustain an ethanol serum concentration of 100 mg/dL as must be achieved in the treatment of ethylene glycol or methanol poisoning (Antidotes in

Depth: Ethanol). In smaller mammals, the dose is estimated to be 1.5â€“8.0 mL/kg of 50% ethanol administered orally. One patient who ingested 240 mg, which is typically a lethal dose of SMFA, mixed the SMFA with a Taiwanese wine (30% ethanol) and survived.[6] Although not sufficiently investigated, it is possible that the ethanol effectively decreased or delayed the full toxic effect of the SMFA.

In a mouse model,[17] use of a combination of calcium salts, sodium succinate, and Î±-ketoglutarate resulted in improved survival. The rationale of using these antidotes is to provide tricarboxylic acid cycle intermediates that are distal to the inhibition by the toxin of aconitase in an attempt to improve energy production. Of particular note, these antidotes were not effective unless calcium was co-administered, emphasizing the importance of replenishing electrolytes, particularly the divalent cations that are chelated by

citrate.[22]

If a patient develops hypotension and shock, rapid administration of intravenous fluids should be followed by a vasopressor, such as norepinephrine. Supportive care, correction of electrolyte abnormalities (calcium and potassium), ethanol infusion and monitoring for dysrhythmias and seizures are the mainstays of treatment.

Summary

Sodium monofluoroacetate and fluoroacetamide are potent pesticides that inhibit the tricarboxylic acid cycle disrupting cellular energy production. Patients who are exposed to SMFA typically present with nausea, vomiting, agitation, and abdominal pain which may be followed by hypotension, respiratory distress, shock, seizures, and death. Hypokalemia, hypocalcemia, metabolic acidosis, and elevation of serum creatinine also occur. Treatment of SMFA and fluoroacetamide poisoning involves replenishing electrolytes, correcting hypotension with intravenous fluids and vasopressors if necessary, monitoring for dysrhythmias, and treatment of seizures. Ethanol, although not a perfect antidote, is typically available and can be administered rapidly and safely. The efficacy of other experimental antidotes is unknown.

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Chapter 107
Phosphorus

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Michele Burns Ewald

Phosphorus (P)		
Atomic number	=	15
Atomic weight	=	30.97
Normal concentrations Serum	=	3â€“4.5 mg/dL (1â€“1.4 mmol/L)

A 3-year-old girl was brought to the emergency department by her parents immediately after she was found eating rat bait containing Stearns' Electric Brand Paste, which contains 2.5% elemental phosphorus. Initially, the girl was unconscious and her vital signs were: blood pressure 50/30 mm Hg; pulse 160 beats/min; respirations 44 breaths/min; and temperature 98.6Â°F (37.0Â°C). Physical examination revealed an irregular cardiac rhythm without murmur, a soft abdomen, cyanotic skin, and a garlic odor to the

breath. An intravenous line of 0.9% sodium chloride (NaCl) was established and blood was drawn for laboratory analysis. The physicians performed an orogastric lavage and recovered a small amount of grain-like material. The child was transferred to a pediatric intensive care unit at regional pediatric hospital, where on arrival she only responded to painful stimuli. Her vital signs were: systolic blood pressure 50 mm Hg; pulse 160 beats/min; respirations 44 breaths/min; and temperature 94.1Â°F (34.5Â°C). Laboratory data was unremarkable except for an inorganic phosphorus level of 5.2 mg/dL (normal 3â€“4.5 mg/dL). An electrocardiogram showed premature atrial contractions.

The child was treated with a gastric lavage of potassium permanganate 1:5000 solution, followed by administration of a cathartic. Supportive measures improved her vital signs, but 2 hours after her admission she had a cardiopulmonary arrest, and could not be resuscitated.

History and Epidemiology

The word phosphorus comes from the ancient Greek â€œphos,â€• which means light, and â€œphorus,â€• which means bringing. Phosphorus was initially identified in specimens of distilled urine by an alchemist named Hennig Brandt in Hamburg in about 1669. The clinical use of phosphorus first appeared in a medical text in 1720. It was touted as a treatment for colic, tetanus, apoplexy, and gout. Phosphorus also gained a popular reputation as a tonic and aphrodisiac, and its use was promoted by traveling medicine shows which impressed gullible onlookers with the phosphorescent and explosive nature of the â€œmedicine.â€• Despite its highly toxic nature, it remained in the British Pharmacopoeia until 1932 and was available without prescription in Great Britain until the 1950s.

White phosphorus gained public notoriety as the main ingredient in â€œlucifers,â€• or strike-anywhere matches. Invented by French

chemist Charles Sauria in 1830. Over 3 trillion of these matches were struck per year by the end of the 19th century. However useful these matches were to the population, the history of their production epitomizes workers' struggles with safety during the industrial revolution. Workplace exposure to phosphorus produced â€œphossy jaw,â€• or mandibular osteonecrosis first documented in Germany in 1838. The incidence of this disease was approximately 1% among the young women who worked in match factories at that time. Accounts of patients suffering from phossy jaw describe loss of teeth, softening or destruction of the mandible, and formation of abscesses discharging foul-smelling pus.

Because of the fire hazard presented by strike-anywhere matches, and the health risks posed to their makers, the Berne Convention of 1906 prohibited the use of white phosphorus in matches among its signatories. Although the United States failed to ratify this multinational treaty, the Match Act of 1912 was subsequently passed by Congress. It effectively taxed these matches out of existence. Today, matches are markedly safer and use red phosphorus in the striking pad on the matchbook rather than white phosphorus in the match head.

Phosphorus incendiary bombs were responsible for a large portion of the destruction unleashed on Europe during World War II, typified by the London Blitz of 1940. Numerous murders were attempted or committed in the 19th and early 20th centuries using phosphorus. Although it was readily available, it had the dual disadvantages of a strong garlic odor and a luminescence, which alerted both intended victims and suspicious coroners.

TABLE 107-1. Exposure Limits to White Phosphorus

Agency	Exposure Measure	Value
NIOSH	IDLH	5 mg/m^3
ACGIH	TLV TWA	0.1 mg/m^3
NIOSH	REL TWA	0.1 mg/m^3
OSHA	PEL TWA	0.1 mg/m^3

White phosphorus is used commercially today to manufacture insecticides (organic phosphorus compounds) and fertilizer (phosphoric acid).[14,15,22,23,28,31] White phosphorus itself is used as an incendiary and may be found in hand grenades, mortar rounds, shells, smoke generators, tracer rounds, and fireworks.[21,22,24,28] White phosphorus is used in many countries to create homemade fireworks known as totes, *diablitos*, or Watusi that are commonly used in suicides and occasionally homicides. These fireworks typically weigh about 300 mg, containing up to about 10% white phosphorus, and also include up to 40% potassium chlorate. Quality control is poor and the exact contents are unpredictable.

Elemental phosphorus, primarily the red allotrope, is a key component in the synthesis of illicit methamphetamine, and its sale is now tightly controlled by the Drug Enforcement Administration (DEA). Workplace exposure limits exist for the many industrial applications for which elemental phosphorus is

critical (Table 107-1).

Chemistry

Phosphorus (P) is the 15th element on the periodic table, with an atomic weight of 30.97 Daltons. Elemental phosphorus exists in three allotropes: black phosphorus, a nontoxic compound that does not ignite spontaneously; red phosphorus, a fairly innocuous phosphorus intermediate in reactivity between black and white phosphorus; and white phosphorus, a highly reactive and dangerous element. White phosphorus is a tetramer, P_4, which is a waxy paste, insoluble in water. It has a melting point of 111.2Â°F (44Â°C) and an ignition temperature of 86Â°F (30Â°C) in moist air. It may emit a pale green glow in some circumstances because of low-level reactivity with the surrounding oxygen. The presence of impurities in white phosphorus account for the general description of white phosphorus as yellow phosphorus. White phosphorus undergoes rapid oxidation on contact with oxygen, with the resultant liberation of heat, light, and dense white smoke. The chemical equation which describes this process is as follows:

$4P + 5O_2$ â†’ $2P_2O_5$

This reaction continues until the phosphorus or the oxygen is consumed. Phosphorus pentoxide generates phosphoric acid when dissolved in water:

$P_2O_5 + 3H_2O$ â†’ $2H_3PO_4$

Thus, following the explosion of white phosphorus, not only is white phosphorus broadly disseminated, but it also creates a dense cloud of white smoke with a garlic odor. The smoke is phosphoric acid, which can produce pulmonary, ophthalmic, and dermal irritation.

Red phosphorus differs from the white allotrope by its crystalline form, its lack of phosphorescence, and its markedly reduced reactivity with oxygen. Red phosphorus will slowly degrade to

highly toxic phosphine gas (PH_3) and phosphorous acids. Phosphine is reactive and usually undergoes rapid oxidation (Chap. 112). Black phosphorus is produced by heating white phosphorus with a mercury catalyst, forming a graphite-like sheet of phosphorus atoms. Black phosphorus is the least reactive, does not readily ignite and has little commercial value.

TABLE 107-2. Distribution of White Phosphorus by Various Body Tissues

UPTAKE	High	Moderate	Low
Tissue	Adrenal cortex	Adrenal medulla	Bone
	Bowel mucosa	Endometrium	Brain
	Epidermis	Lung	Fat
	Hair follicles	Myocardium	Myometrium
	Liver	Ovary	Skeletal muscle
	Pancreas	Renal medulla	
	Renal cortex	Spleen	
		Thymus	

Because the majority of toxicity reported from elemental phosphorus is a result of the white allotrope, when phosphorus is mentioned in this chapter, it refers to the white allotrope, unless otherwise specified.

Toxicokinetics

White phosphorus is rapidly absorbed from the intestinal tract. After systemic absorption, it is taken up primarily by the tissues of the liver, renal cortex, bowel mucosa, epidermis, hair follicles, pancreas, and adrenal cortex. Within several hours of ingestion 69â€“73% of the total ingested dose is identified concentrated in the liver.[40] Other tissues absorb the toxin to lesser degrees (Table 107-2).[8]

In rat models, a subcutaneous lethal dose is approximately 10 mg/kg[37] and the intraperitoneal median lethal dose (LD_{50}) is approximately 9 mg/kg.[17] A review of 56 cases of human white phosphorus poisoning suggested a lethal dose of 1 mg/kg, which is the commonly accepted value.[11] This study predates the introduction of intensive care units, so the lethal human dose in the modern day may be significantly higher, although a later prospective study suggests a lower lethal dose.[22]

White phosphorus is highly lipid-soluble, and significant absorption can occur after skin or mucosal exposure. Penetrating wounds and dermal burns enhance the systemic absorption of white phosphorus.

Pathophysiology

Hepatic

White phosphorus increases oxygen consumption in the hepatocyte. Uncoupling of oxidative phosphorylation is the likely mechanism, and there is a decrease in intrahepatocyte adenosine

triphosphate (ATP) levels.[37] Mitochondrial injury, visible as swelling, can be seen on electron microscopy. White phosphorus may affect the transformation of triglycerides into Î²-lipoproteins or the secretion of the latter into the bloodstream, accounting for the increase in observed cytoplasmic fat that is noted.[37] Massive hepatic steatosis is a hallmark of white phosphorus toxicity, with a rise in hepatic triglycerides beginning within 2 hours and peaking in 36 hours. Hepatic necrosis may be prominent, particularly in zone 1, in distinction to most other classic hepatotoxins, such as acetaminophen

and carbon tetrachloride, that produce zone 3 necrosis. Hepatic glycogen stores are decreased, and blood glucose levels fall. Hepatic glucose-6-phosphatase activity increases.[37] A massive increase of rough endoplasmic reticulum may not be pathognomonic for phosphorus-induced liver injury, but it is seen universally in this poisoning and is rarely produced by other xenobiotics.[17,33]

A rat model of chronic white phosphorus exposure showed development of hepatic edema, and hepatitis, followed by fibrosis and cirrhosis.[33]

Skin, Mucous Membranes, and Gastrointestinal Tract

White phosphorus can cause both thermal and chemical injury. The exothermic reaction described earlier is the major mechanism of injury to the skin. There are no data about direct chemical toxicity to the skin of either white phosphorus or phosphorus pentoxide. Phosphoric acid penetrates the skin, but the significance relative to the thermal burn is unclear.[10,21] In exposures involving penetrating dermal injury, subcutaneous tissue damage as a result of generation of phosphoric acid may occur, albeit more slowly than on the exposed skin. The gastrointestinal tract similarly may

be relatively spared compared to equivalent exposure of the skin, likely a result of the low concentration of oxygen in the gastrointestinal tract.[31] The mucous membranes may similarly be affected by white phosphorus, much of it mediated by phosphoric acid.

Cardiovascular

Some postmortem cardiac examinations of victims of phosphorus poisoning revealed no morphologic changes.[5] One report notes interstitial edema and vacuolated cytoplasm with pale linear areas on microscopic examination. The same researchers noted an experimental decrease in rat myocardial protein synthesis after phosphorus poisoning.[41] The likely mechanism of phosphorus-induced dysrhythmias is profound electrolyte abnormalities, including hypocalcemia and hyperkalemia.

Nervous System

The uptake of radiolabeled phosphorus into neural tissue is minimal[8] and there is no information regarding histopathological changes in brain tissue following phosphorus exposure. Nervous system manifestations of white phosphorus poisoning appear to be more related to the development of hypocalcemia than to direct toxic effect on the tissues.

Electrolyte Homeostasis

Hyperphosphatemia is a direct result of absorption and conversion to phosphoric acid and subsequent deproteination. Calcium complexes with phosphate causing hypocalcemia and may precipitate within tissues in forms such as hydroxyapatite. Hyperkalemia may result from the profound hypocalcemia (as in hydrofluoric acid poisoning) or it can occur as a result of renal failure.

Renal

White phosphorus causes injury to the glomerulus following systemic absorption.[1] Microscopic analysis of renal tissue shows fatty degeneration in some cases[8] but in others is described as fatty deposition and necrosis.[37]

TABLE 107-3. White Phosphorus Poisoning

Stage	Characteristics
I Day 1:	GI tract injury, cardiac dysrhythmias, neurologic manifestations, hypocalcemia.
II Days 2â€“3:	Fulminant hepatic failure.
III Days 4â€“8:	Death from liver failure and delayed cardiac toxicity.
IV Day 8:	Recovery

Clinical Manifestations

Overall, the mortality from ingestion ranges from 20â€“50%.[22,29] Indicators of a poor prognosis include ingestion of greater than 1 mg/kg; signs of severe electrolyte disturbance, such as reversal of Ca^{2+}-to-PO_4^{-3} ratio, mental status changes, prolongation of QTc interval, and ST-T wave abnormalities; tenfold or greater increase in alanine aminotransferase (ALT); severe coagulopathy; and peak liver enzymes reached within 36 hours of ingestion.[5,15]

Previous literature describes the course of oral white phosphorus poisoning in 3 stages.[23] The first, which lasts for hours to days, is marked by irritation and injury of the gastrointestinal tract. In the second stage, the gastrointestinal symptoms may resolve. This period can last for several days. In the third stage, patients develop cardiac, hepatic, or renal toxicity. Recovery, if it occurs, takes place over days to weeks.[29] (See Table 107-3.) However, review of 41 fatal reported cases of white phosphorus ingestion suggests a clinical course that differs from this description.[22,23,28,31] Over half the deaths occurred in the first day, and the cause of death, when known, was cardiac in nature, presumably dysrhythmic as a result of electrolyte abnormalities. Deaths as a result of fulminant hepatic failure occur within the first week. Some delayed cardiac deaths occurred between 5 and 8 days after exposure. No additional deaths are reported after day 8.

Hepatic

White phosphorus produces hepatotoxicity in a predictable and dose-dependent manner.[7,18] Abnormal aminotransferases occur in approximately half of phosphorus poisoned patients,[23] and in most patients they begin to rise within 24 hours of exposure. The time to aminotransferases peak levels and the magnitude of the elevation differed significantly between the patients who died and patients who lived. The group which died had an average ALT peak of 16 times normal level, reached in 36 hours. In the survival group, ALT rose to 8 times normal, reaching this peak in 6 days. Coagulopathy was observed in only 17% of patients.[15] The serum triglyceride level may fall as the hepatic toxicity develops, and there may be an increase in serum and urinary ketones.

Skin, Mucous Membranes, and

Gastrointestinal Tract

White phosphorus skin burns are very painful, with a necrotic appearance, yellowish color, and garlic odor.[4] As in the case of chemical burns, they heal slowly and require longer hospital stays than do simple thermal burns.[24] Human experience and animal models suggest that a second or third degree burn of 10â€“15% body surface area may result in death from phosphorus absorption.[4,5] One epidemiological study of military personnel showed an average third-degree burn size of 11.2% and a mortality rate of 4.1%.[24]

Mucosal surfaces that are directly affected by phosphorus suffer the same chemical burns noted on the skin. Following exposure

to phosphorus smoke membranes in exposed areas, such as the mouth, nose and eyes, may develop swelling, injection and other signs of irritation.

Oropharyngeal burns, nausea, vomiting, diarrhea, abdominal pain, and gastrointestinal hemorrhage may occur following ingestion of white phosphorus. Hematemesis occurs in about 30% of patients who ingest phosphorus, and post mortem examinations of the intestines do show diffuse hemorrhages.[37] The vomitus and stool are typically described as having a garlic odor. Nine case reports describe that the effluent emitted smokeâ€”the famous â€œsmoking stoolâ€•â€”and was phosphorescent.[15,30,31]

Cardiovascular System

Early death following white phosphorus exposure is commonly because of cardiovascular collapse.[31] In one case, this was found to be because of decreases in cardiac contractility and systemic vascular resistance.[41] Electrocardiographs performed during the first 12 hours showed abnormalities in 70% of the subjects.[19,36] These included bradycardia, atrial fibrillation, QTc interval

prolongation, ST segment depression, T-wave changes, bradycardia, atrial fibrillation, and low-voltage QRS complexes. These manifestations likely reflect electrolyte abnormalities, such as severe hypocalcemia.[19,36] Cardiac arrest may occur within several hours of oral or dermal exposure. Death from cardiac causes generally occurs in the period from 3â€“8 hours after systemic absorption.[5,23,31] However, some late cases of cardiac death are reported. Cardiovascular collapse, cardiac arrest without dysrhythmias and morphologic myocardial injury are also described.[30] Hypocalcemia may cause cardiomyopathy, heart failure, and mimic myocardial infarction.[9,16,20,26]

Nervous System

Central nervous system signs, which include irritability, anxiety, agitation, confusion, lethargy, delirium, hallucinations, seizures and coma, are often the first manifestations of toxicity. Patients, who develop CNS signs or symptoms before other organ systems are affected, have a mortality rate of 73%.[23] In the peripheral nervous system, hypocalcemic manifests as paresthesias, carpopedal spasm, tetany, and even laryngeal stridor or opisthotonus.[27,23]

Renal

Renal failure and hyperkalemia are not prominent elements of white phosphorus poisoning, but are noted in some cases.[34] In a series of 41 cases reported in the 1970s, nearly half of the patients had an abnormal BUN and creatinine, but only 3 developed transient renal failure.[23] No cases of chronic renal failure are described. Two hypotheses for renal failure are a direct toxic effect of white phosphorus on the kidney, and acute tubular necrosis because of the shock state.[8]

Electrolytes

Rabbits that died from white phosphorus burns within the first 24 hours had profound elevations of serum phosphorus and depressions of serum calcium. The clinical findings of patients with white phosphorus poisoning are suggestive of acute hypocalcemia.

Chronic Exposure

Workers engaged in the early years of white phosphorus production developed an unusual mandibular osteonecrosis known as â€œphossy jawâ€• and cachexia, anemia, and fatigue.[2] A case-controlled study of workers at a white phosphorus plant in China from 1973 to 1984 showed that 22 of 58 had osteolytic or osteosclerotic lesions on radiography of the mandible. Ten years later, 13 of the 22 had complete resolution of their lesions, 2 had remaining lesions that were improved, and 7 had no changes in their previous abnormalities. Hepatomegaly was noted in 6â€“9%, leukopenia in 18â€“20%, and pulpitis or tooth decay in 20â€“57%. The concentration of white phosphorus measured in the factory air was 0.13 mg/m^3. Longer employment was associated with increased incidence of pathology, with an exponential rise at year 5.[35]

Assessment and Management

Protection of Healthcare Personnel

Care must be taken to prevent exposure of healthcare personnel. White phosphorus contained in vomitus or stool can be hazardous; one case report of a suicide by white phosphorus ingestion contains a picture of a hole burned through a bed sheet by a patient's feces.[30] Given the low melting point, white phosphorus may be present in the liquid phase in a patient's clothing, and may ignite spontaneously at room temperature.[21,24] Personnel must

wear protective equipment to prevent direct contact with phosphorus. As discussed below, patients must be decontaminated and thoroughly wetted.

Supportive and Standard Care

Life support measures, such as airway protection and fluid resuscitation, should be provided. A complete blood count, hepatic enzymes, PT, PTT, electrolytes, bun, creatinine, serum phosphate, and serum calcium should be measured. Hypocalcemia, hyperphosphatemia, and hyperkalemia should be expeditiously treated using standard modalities. Frequent measurement of vital signs and continuous cardiac monitoring are essential. Renal function and urine output, must be evaluated. Most patients with white phosphorus exposure should be admitted to hospital. Ophthalmic irrigation should be performed if eye irritation is present.

Skin Decontamination

The patient with a cutaneous exposure should be immediately doused with, or immersed in, water. Irrigation is the only treatment shown to decrease burn size, length of hospital stay, and mortality.[10,12,13] Any areas where white phosphorus may remain must be kept wet at all times, as the substance may re-ignite if it is exposed to ambient oxygen.[21]

Copper sulfate solutions are occasionally recommended for conversion of particulate phosphorus to the less harmful copper phosphate, which is black, making debridement easier.[3] However, copper sulfate can inhibit glucose-6-phosphate dehydrogenase, leading to lethal hemolysis[34] and raising a significant concern about its potential benefit. Remaining particulate phosphorus may be identified using a Woods lamp, as phosphorus fluoresces easily. Alternatively, the application of silver nitrate may prevent ignition

of the phosphorus by depositing a film of silver on the surface of the phosphorus.[32] After combustion has been prevented and particles identified, a thorough debridement must be performed as any remaining phosphorus can be systemically toxic.

Gastrointestinal Decontamination

Early lavage of the stomach has been recommended without supporting data.[38] Given the high mortality associated with exposure to

white phosphorus and the lack of effective antidotes, lavage should be considered, with appropriate precautions. One case report describes an explosion and fire, which occurred after a nasogastric tube was inserted into the stomach of a phosphorus poisoned patient.[39] This was likely because of entrance of oxygen into the stomach through the tube or exit of phosphorus from the tube. Regardless of the exact circumstance, precautions can be taken to minimize this risk. Connect the external end of the tube to a syringe filled with water; prime the tube itself with water; confirm placement by instilling water rather than air, or by withdrawing gastric contents.

There are no data evaluating the ability of activated charcoal (AC) to adsorb phosphorus, nor of any known clinical benefit.[31] However, white phosphorus is highly toxic in small amounts, no effective antidote exists, and esophageal burns are not prominent. The administration of oral AC therefore is appropriate for patients who have ingested phosphorus.

Whole-bowel irrigation with polyethylene glycol may decrease the absorption of phosphorus by mixing the xenobiotic in a nonabsorbable carrier and removing it from the GI tract.[31,38] Given the highly toxic nature of white phosphorus, this treatment should be attempted for consequential exposures.

Instillation of 1:5000 potassium permanganate solution into the stomach will theoretically convert ingested white phosphorus to a less harmful oxide.[6] This treatment has been used on many patients, but no clinical trial has demonstrated a benefit.[11,14,28] This therapy is not readily available, is high risk from a chemical perspective, has no sound clinical basis, and is therefore not indicated.

N-Acetylcysteine

In another study, a standard intravenous *N*-acetylcysteine (NAC) regimen was given to 9 of 15 patients who had ingested fireworks. Although there was no significant benefit identified in this small, uncontrolled trial, all patients who received the full course survived. As NAC is a benign therapy and may be of benefit, we recommend it in cases of white phosphorus poisoning.

Other Antidotal Therapy

A prospective human study reached the conclusion that corticosteroids are not helpful in reducing the hepatotoxic effects of white phosphorus.[22] In small-animal studies, ubiquinone, cysteine, and sulfate treatments were shown to prevent liver damage to some degree. No human data evaluates these therapies.[33,37]

Enhanced Elimination

The correction of hyperphosphatemia, hyperkalemia, and hypocalcemia can be most rapidly done through the use of hemodialysis. However, its use for these electrolyte disturbances in the setting of acute phosphorus poisoning is not reported. Exchange transfusion is reported in humans, but too few data were collected to draw a conclusion about its value in this situation.[22] However, whole blood cross circulation appears to have a

significant positive effect on survival in a controlled animal study. In the control arm, the mortality was 90%, compared to 20% in the treatment arm.[7] This result suggests that exchange transfusion may be beneficial.

Summary

White phosphorus is used in military and industrial applications, and in fireworks. Poisoning carries a mortality of greater than 20%. Early death is generally due to cardiac dysrhythmias, secondary to electrolyte abnormalities, such as hypocalcemia and hyperkalemia. Death after the first 24 hours is generally due to hepatic failure. Management must include protection of healthcare personnel, as any remaining exposed phosphorus may ignite or explode. Patients with dermal exposure must be doused with water and kept wet to prevent spontaneous ignition of white phosphorus. Treatment of patients with oral exposure includes gastric lavage and administration of AC. Intensive supportive care is required, the mainstay of which is electrolyte homeostasis. Intravenous *N*-acetylcysteine may be of benefit in preventing hepatic injury.

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Chapter 108
Strychnine

Yiu-Cheung Chan

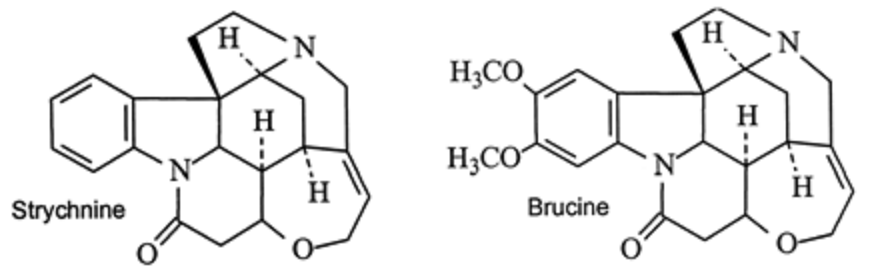

Figure. No Caption Available.

A 45-year-old woman who had been injecting heroin for a long period of time presented to an emergency department (ED) shortly after self-injecting heroin, complaining of generalized muscular

aches and twitching. Over a short period of time she developed repeated episodes of uncomfortable diffuse muscular twitching, but remained alert. She was otherwise in good health, although her tetanus vaccination status was unknown.

On arrival in the ED, her vital signs were: blood pressure 134/58 mmHg; pulse 97 beats/min; respiratory rate 22 breaths/min; temperature 100Â°F (37.2Â°C), and oxygen saturation by pulse oximetry 100% on room air. Respiratory and cardiovascular examinations were unremarkable. The abdomen was rigid and the neck was stiff during the muscular contractions, but both examinations were normal in between the contractions. Her cranial nerve and sensory examinations remained intact and there were no focal signs. The remainder of her neurologic examination revealed involuntary muscular contractions in all limbs and an increased reflex jerk. Clinical investigations revealed normal ECG, chest radiograph, and CT scan of the brain. Blood tests, including glucose, electrolytes, arterial blood gas, renal function, and liver function were also all within normal limit. A complete blood count was remarkable only for mild leukocytosis.

Either strychnine poisoning or tetanus was considered the most likely diagnosis, and the patient was treated with 5-mg diazepam intravenously, tetanus immunoglobulin (Hypertet), and other general supportive measures. Over the next few hours in the ICU, the muscular spasms gradually improved and her hemodynamic status remained stable. This rapid improvement made tetanus unlikely and strychnine the probable etiology for the patient's spasm. After 4 days, the patient was discharged from the hospital with a normal examination and no sequelae. A urine specimen was positive for strychnine.

History

Strychnine alkaloid can be found naturally in *Strychnos nux vomica*, a tree native to tropical Asia and North Australia, and in

Strychnos ignatii and *Strychnos tiente*, trees native to South Asia. The alkaloid was first isolated in 1818 by Pelletier and Caventou.[5,17] It is an odorless and colorless crystalline powder that has a bitter taste when dissolved in water. Besides strychnine, the dried seeds of *Strychnos nux vomica* contain brucine, a structurally similar, although less potent, alkaloid.[88] In addition to the naturally occurring alkaloidal form, strychnine is available from commercial sources in its salt form, usually as nitrate, sulfate, or phosphate.

Strychnine was first introduced as a rodenticide in 1540, and was subsequently used medically as a cardiac, respiratory, and digestive stimulant,[49] as an analeptic,[92] and as an antidote to barbiturate[91] and opioid overdoses.[60] Nonketotic hyperglycemia,[9,40,80] sleep apnea,[75] and snake bites[17] were all once also considered indications for strychnine use. In 1982, at least 172 commercial products were found to contain strychnine, including 77 rodenticides, 25 veterinary products, and 41 products for human use.[82] Currently, strychnine is used mainly as a pesticide and rodenticide (for moles, gophers, and pigeons),[82] and a research tool for the study of glycine receptors. Most commercially available strychnine-containing products contain about 0.25â€“0.5% strychnine by weight.[82]

Epidemiology

In the past, strychnine poisoning caused significant mortality, especially in children. Between 1926 and 1928, strychnine killed more than three Americans every week.[5,30] In 1932, it was the most

common cause of lethal poisoning in children[5,82,98] and one third of the unintentional poison-related deaths in children younger than 5 years were attributed to strychnine.[85] Currently, strychnine poisoning is rare in United States, but deaths are still reported.

The Toxic Exposure Surveillance System (TESS) data of the American Association of Poison Control Centers (AAPCC) reports 1601 strychnine exposures during the past 10 years with 0â€“3 deaths annually (Chap. 130).

Strychnine poisoning has resulted from deliberate exposure with suicidal and homicidal intent,[12,30] from unintentional poisoning by a Chinese herbal medicine (Maqianzi),[18] a Cambodian traditional remedy (slang nut),[52,56,86] and adulteration of street drugs.[14] Maqianzi is used to treat limb paralysis, severe rheumatism, and inflammatory disease, whereas slang nut is used to treat gastrointestinal illness. The bitter taste of strychnine allows it to be substituted for heroin,[46] and cocaine.[14,25,64] There are also reports of strychnine poisoning from adulterated amphetamines,[25] ecstasy (MDMA, 3-4 methylenedioxymethamphetamine),[28] Spanish fly,[13] and from the ingestion of gopher bait.[54]

Toxicokinetics

Standard references list the lethal dose of strychnine as approximately 50â€“100 mg[20,36,37,70,94] (1â€“2 mg/kg). However, mortality resulting from doses as low as 5â€–10 mg[6] and, alternatively, survivals following ingestions of 3.75 g and 15 g of strychnine are reported.[20,97] Some of this variation may be attributed to the route of administration, with parenteral administration being more toxic than oral, and the limitations of self reports of exposure quantities.

Strychnine is rapidly absorbed from the gastrointestinal tract, mucous membranes, and via the parenteral route. There is also one case report of poisoning as a result of dermal absorption of strychnine from an alkaline solution, in which strychnine exists in the nonionized, alkaloid form.[38] Protein binding is minimal and strychnine is rapidly distributed to peripheral tissues[93] with a large volume of distribution (13 L/kg).[43] Based on postmortem findings, the highest concentrations of strychnine are found in the

liver,[58,70,78] bile,[70] blood,[70] and gastric contents.[70,78] Relatively less strychnine is identified in kidney, urine, and brain.[78]

Strychnine is metabolized by hepatic P450 microsomes[1,61] producing strychnine-N-oxide as the major metabolite,[1] and this metabolism is increased by P450 induction.[47,51] Several urinary metabolites are identified,[65] and 1â€“30% of strychnine is excreted unchanged in urine,[10,69] in decreasing proportions when larger amounts are ingested.[81,93] In human case reports, strychnine follows first order elimination kinetics with a half-life of 10â€“16 hours.[29,69,96]

Pathophysiology

The pharmacologic effects of strychnine are well understood. Glycine, one of the major inhibitory neurotransmitters in the spinal cord, mediates its effects by opening a ligand-gated chloride channel, thus allowing the inward flow of Cl^-[21] (Chap. 14). As Cl^- moves into the cell, it becomes hyperpolarized or inhibited. Strychnine competitively inhibits the binding of glycine to the Î±-subunit of the glycinergic chloride channel.[14,95,98] Although strychnine affects all parts of the central nervous system in which glycine receptors are found, the most significant effect is in the spinal cord. With the loss of the glycine inhibition to the motor neurons in the ventral horn, there is a loss of inhibitory influence on the normally suppressed reflex arc. The result is increased impulse transmission to the muscles producing generalized muscular contraction. Rabbits pretreated with glycine were found to have a 40% increase in the strychnine â€œseizureâ€• threshold, illustrating the competitive nature of strychnine and glycine activity on the glycinergic chloride channel.[77] For comparison, tetanus toxin (tetanospasmin) causes the identical clinical syndrome of muscular contractions, although tetanospasmin prevents the release of presynaptic glycine and does not function as a competitive antagonist. In dogs, strychnine

also has positive chronotropic and inotropic effects on the heart,[83] but this effect is unlikely to exert a major effect in human poisoning.

Clinical Manifestations

Strychnine poisoning is characterized by a rapid onset of signs and symptoms. Symptoms begin within about 15â€“60 minutes of ingestion,[35] and although less well documented, are expected to occur even sooner after parenteral or nasal administration. Delayed onset of clinical effects are rarely reported.[26,37] The typical symptoms of poisoning are involuntary, generalized muscular contractions resulting in neck, back, and limb pain. The contractions are easily triggered by trivial stimuli (such as turning on a light) and each episode usually lasts for 30 seconds to 2 minutes[82] with the period of recurrent episodes lasting as long as 12â€“24 hours. Differences in the strength of various muscle groups result in the classic signs of opisthotonus, facial trismus, and risus sardonicus, with flexion of the upper limbs, and extensions of lower limbs. Hyperreflexia, clonus, and nystagmus[11,62] are also evident on examination. Because strychnine affects glycine inhibition mainly in the spinal cord, the patient typically remains fully alert until metabolic complications arise. The combination of convulsive motor activity involving both sides of the body in the conscious patient has often resulted in imprecise descriptions such as â€œconscious seizureâ€• or â€œspinal seizure.â€• Hemodynamically, hypotension,[27,29,64] or hypertension[14,32,63] in the presence of bradycardia[16,27,29,64] or tachycardia[14,16] are all reported. Hyperthermia, presumably from increased muscular activity, is typical, and temperatures as high as 109.4Â°F (43Â°C) are reported.[14] Other nonspecific signs and symptoms include dizziness, vomiting, and chest and abdominal pain.[62]

Early in the course of strychnine poisoning, mortality is mainly due

to hypoventilation and hypoxia secondary to muscular contractions.[32] Later, life-threatening complications include rhabdomyolysis with subsequent myoglobinuria and acute renal failure,[16] hypoxia- or hyperthermia-induced multiorgan failure, aspiration pneumonitis,[84] anoxic brain injury, and pancreatitis.[45] Rarely, local neuromuscular sequelae such as weakness, myalgia, and anterior tibial compartment syndrome are reported.[14] As might be expected, the prognosis is related to the duration and extent of the episodes of muscle contractions.[34]

Differential Diagnosis

The diagnosis of strychnine poisoning is mainly established on clinical grounds, although several differential diagnostic etiologies need to be considered. Tetanus produces similar muscular hyperactivity, but with less rapid onset and lasting much longer than strychnine poisoning. Frequently, the diagnosis of tetanus is suggested by a history of recent injury, or the finding of an obvious wound. In general, patients with tetanus have a deficient record of tetanus immunization.

Strychnine poisoning can be differentiated from generalized seizures by the presence of a normal sensorium during the period of diffuse convulsions. That is, most patients with bilateral convulsions

are having generalized seizures, which by definition involve the reticular activating system, producing unconsciousness. It is conceivable, although extraordinarily rare, to have bilateral focal seizures producing apparent â€œgeneralizedâ€• convulsions; in this case because the reticular activating system may not be involved, the patient's mental status may be preserved. The diagnostic utility of the presence of consciousness in a patient with a generalized convulsion for diagnosing strychnine poisoning or tetanus is true at least in the time period of the clinical course. At

later times this finding may be obscured by metabolically induced alterations in sensorium. When this occurs an electroencephalogram may be helpful, if it documents an absence of focal neurological deficits. A CT can help to exclude structural brain lesions, and a lumbar puncture is helpful to exclude meningitis or encephalitis. Hypocalcemia, hyperventilation, and myoclonus secondary to renal or hepatic failure are evaluated by appropriate routine laboratory testing. Although a drug-induced dystonic reaction should be considered when there is a relevant drug history, dystonic reactions are usually static, and strychnine poisoning results in dynamic muscular events. Serotonin syndrome, malignant hyperthermia, neuroleptic malignant syndrome, and stimulant use should be considered, if the medical history is supportive.

Diagnostic Testing

Both respiratory and metabolic acidosis are commonly found in strychnine-poisoned patients. Metabolic acidosis correlates with serum lactate levels,[14] whereas respiratory acidosis is secondary to hypoventilation resulting from diaphragmatic and respiratory muscle failure. Survival is well documented in patients with serum pHs in the range of 6.5â€“6.6.[14,32,33,35,55,96] The lowest pH and highest lactate reported in a patient who subsequently had full recovery was 6.5 and 32 mmol/L,[14,196] respectively. Thus, profound acidosis in strychnine poisoning is not necessarily associated with poor prognosis. One proposed reason is that the serum pH does not correlate with the intracellular pH in the vital organs, namely the brain and heart.[7,8,14,73] In contrast to the lactic acidosis seen in shock, the lactic acidosis of strychnine poisoning results from overactivity of the muscle instead of undersupply or underutilization of oxygen and nutrients.

Besides acidosis, other laboratory abnormalities expected from prolonged muscular activity include evidence of rhabdomyolisis,[14]

hyperkalemia,[14] and acute renal failure. There is also stress induced leukocytosis,[14,45] elevated liver enzymes,[45,62,90] hypocalcemia,[14,43] hypernatremia,[35] and hypokalemia.[31,62,84] The electrocardiogram is expected to remain normal or reflect changes consistent with the above electrolyte disturbances.[43] Chest radiography may show evidence of aspiration pneumonia or acute lung injury.

Strychnine can be detected by various methods such as thin layer chromatography,[48,67,89] high performance liquid chromatography,[2,23] ultraviolet spectrometry,[67] a simple colorimetric reaction,[67] gas chromatographyâ€"mass spectrometry,[15,16,58,69,78] gas chromatographyâ€"flame ionization detector,[94] and capillary electrophoresis.[99] With the exception of the bedside colorimetric reaction, none of these tests are routinely available in a time frame useful to assist in clinical decisions. Strychnine is also detectable in amounts as low as 0.01 ppm in tissue,[2,24,59,72] and it resists postmortem putrefaction. Additionally, even when available, quantitative levels do not correlate with clinical toxicity. Reported blood strychnine levels in fatal poisoning ranged from 0.5 to 61 mg/L.[94] Conversely, the highest initial blood level associated with survival was 4.73 mg/L from blood drawn at 1.5 hours postingestion;[96] a level as low as 0.06 mg/L was found in a patient reported to have muscular irritability.[29]

Management

Induced vomiting is absolutely contraindicated because of the risk of aspiration and loss of airway control following rapid onset of muscle contractions in strychnine poisoning. Orogastric lavage should be considered on an individual basis after evaluating potential benefits and risks.[3] When gastric lavage is thought to be indicated, it may be important to protect and secure the airway with an endotracheal tube before attempting lavage. Activated

charcoal (AC) binds strychnine effectively at a ratio of near 1:1; 1 g of AC will bind 950 mg of strychnine.[4,88] In animal models, pre-[66] and post-[71] treatment with AC increases the median lethal dose of 50% of test subjects (LD_{50}) for strychnine. Clinical evidence of the effectiveness of AC on strychnine dates back to 1831, when in front of the French Academy of Medicine Professor Touery took a lethal dose of strychnine with AC and survived.

Currently, there is no evidence to recommend the use of multiple-dose AC or whole-bowel irrigation in strychnine poisoning. Although forced diuresis was once suggested as an effective means of enhancing the elimination of strychnine,[88] subsequent data failed to demonstrate an increase in drug clearance[81] and it is therefore no longer recommended. Peritoneal dialysis, hemodialysis, and hemoperfusion have not been extensively studied. Because strychnine is rapidly distributed out of the blood[93] into a large volume of distribution (13 L/kg), extracorporeal drug elimination procedures are unlikely to be useful and therefore not justified given their risks.

Supportive treatment remains the most important aspect of management in the majority of cases. The focus of care is to stop the muscular hyperactivity as soon as possible to prevent the metabolic and respiratory complications. At all times, unnecessary stimuli and manipulation of the patient should be avoided, as these activities trigger muscle contractions. Benzodiazepines remain the first-line treatment for strychnine-induced muscular hyperactivity.[82,96] Although much of the evidence concerning the efficacy of benzodiazepines is based on diazepam,[41,50,53,64] any of the commonly used benzodiazepines (diazepam, midazolam, lorazepam) would likely have similar effects. The initial dose of the benzodiazepine chosen should be the standard dose used for other indications, although doses of more than 1 mg/kg diazepam or its equivalent may be needed.[44,57] In case of failed intravenous access, lorazepam or midazolam can be given intramuscularly. Dosing should be repeated until the patient's muscles relax and

the contractions cease. Besides benzodiazepines, barbiturates (phenobarbital, pentobarbital) are also effective in stopping the strychnine induced hyperactivity[42,56,74,87] and are considered second-line treatment if benzodiazepines fail. Both benzodiazepines and barbiturates work through agonism of Î³-aminobutyric acid (GABA) receptor chloride complexes to increase the inhibitory neurotransmission to the spinal cord from the brain, and thus raise the reflex arc threshold.[79] If these measures fail to control the muscular hyperactivity, a nondepolarizing neuromuscular blocking (NMB) agent should be administered. Only nondepolarizing NMB agents should be used, as succinylcholine itself induces muscle contractions.[14,29,56,64,81] It is important to remember that strychnine has no direct effects on consciousness, so that sedation must always accompany attempts at neuromuscular blockade. Generally, therapy is continued for about 24 hours, at which time the medications are slowly withdrawn, as tolerated.

The most important therapy for the metabolic complications of strychnine poisoning is to stop the further production of metabolic products by terminating the muscular hyperactivity as soon as possible. Hyperthermia should be treated aggressively by active cooling with ice water immersion, cooling blanket or mist and fan,

depending on the degree of temperature elevation. Means to prevent rhabdomyolysis-induced acute renal failure includes adequate fluid administration to ensure good urine output (>1 mL/kg/hr), the potential use of urinary alkalinization with sodium bicarbonate,[76] and temporary renal replacement therapy, if acute renal failure occurs. Metabolic acidosis rapidly resolves when muscular activity is controlled.[14,68]

Thus, effective management in the first few hours of strychnine poisoning is crucial for survival. If the patient can be supported adequately for the first 6 hours, this may be considered a good prognostic sign.[14,37] All significantly poisoned patients should be

managed in an intensive care unit with the help of a regional poison control center or medical toxicologist. For those patients unintentionally exposed to strychnine who remain asymptomatic, an observation period of 12 hours is sufficient to exclude significant risk.

Summary

Strychnine is a lethal poison not frequently encountered, except in areas that favor its use to exterminate small animals. A â€œconscious seizureâ€• is the characteristic presentation of strychnine toxicity, and is rapidly followed by life-threatening metabolic and respiratory consequences. The mainstay of treatment is supportive care with the goal of rapidly terminating muscular contractions, providing adequate airway management, and rapidly treating hyperthermia, and or metabolic abnormalities. Although benzodiazepines are generally sufficient, neuromuscular paralysis with a nondepolarizing NMB agent may be required. Generally, the prognosis of strychnine poisoning is good, if the patient can be adequately supported and survives the first few hours of toxicity.

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Chapter 109

Insecticides: Organic Phosphorus Compounds and Carbamates

Richard F. Clark

A 40-year-old suicidal man was brought by relatives to the emergency department (ED) after drinking two sips of 50% malathion about 3 hours earlier. The patient was awake but confused and extremely diaphoretic. He had the odor of hydrocarbons on his breath; however, there was no evidence that the liquid had spilled onto his clothes. His initial vital signs in the ED were: blood pressure 210/120 mm Hg; pulse 100 beats/min; respiratory rate 22 breaths/min; temperature 98.6Â°F (37Â°C); and oxygen saturation 95% on room air. Physical examination demonstrated midsized pupils, minimal crackles in all lung fields, and copious vomiting and diarrhea. The patient was drooling between episodes of vomiting.

Initial evaluation demonstrated the patient's airway was patent and he was not in immediate respiratory distress. He was administered oxygen by face mask, placed on a cardiac monitor, an intravenous (IV) line was inserted and 2 mg atropine administered. Additional atropine was

obtained and placed at the bedside.

Even with supplemental oxygen and atropine given, the victim's oxygen saturation on pulse oximeter began to fall soon after arrival in the ED. His heart rate also rapidly increased to 120 beats/min, and an electrocardiogram demonstrated a prolonged QTc interval (560 msec). A portable chest radiograph showed bilateral pulmonary edema with normal heart size. The poison center was contacted immediately on his arrival, and recommended administration of more atropine and pralidoxime. After administration of an additional 3 mg atropine and pralidoxime 1 g intravenously, his breath sounds improved. But, despite therapy, his oxygenation continued to fall to 87%, and he began coughing up pink-tinged, frothy sputum. He continued to have large amounts of vomiting and diarrhea. A pralidoxime bolus of 1 g was administered intravenously, over 15 minutes and an infusion at 500 mg/h was initiated. The poison center also advised giving additional 2-mg atropine doses every 5â€“15 minutes as needed to control his secretions.

Although the emesis, diarrhea, and bronchorrhea diminished after a total of 20 mg of atropine, the clinicians elected to intubate the patient. He was sedated with 3 mg IV midazolam and paralyzed with 10 mg IV vecuronium. His oxygen saturation following intubation was 98% on 100% FIO_2 at an intermittent mandatory ventilation (IMV) rate of 16/min, and his vital signs were: blood pressure, 175/90 mm Hg; and pulse, 125 beats/min. A nasogastric tube was inserted and lavage of the stomach contents performed, followed by administration of 75 g of activated charcoal (AC). He was transferred to the intensive care unit (ICU).

In the ICU, the pralidoxime infusion was continued at 500 mg/h, and atropine was administered intermittently throughout the first 24 hours of admission for a total dose of 30 mg. Hematologic studies were normal except for a white blood cell count (WBC) of 19,000/mm^3. His other laboratory studies were remarkable for a glucose of 195 mg/dL, potassium of 3.2 mEq/L, and bicarbonate of 20 mEq/L. The chest

radiograph dramatically improved over the first 24 hours, and by the second day was only remarkable for a right-upper-lobe infiltrate. The patient was kept sedated with midazolam and intubated for another 24 hours to better monitor his pulmonary status. His ECG gradually improved by the second day, with a heart rate of 105, and normalization of his QTc interval.

On hospital day 2, because oxygenation was normal on room air, his sedation was terminated and he was extubated. His nausea and vomiting had largely improved, and no further frothy sputum was observed. The diaphoresis and diarrhea had resolved, but he continued to smell of solvents. Cholinesterase measurements sent initially showed virtually no detectable red blood cell (RBC) or butyrylcholinesterase (plasma) activity. All other laboratory results had normalized by the second day. He was transferred to a step-down unit for observation, and did not require any further atropine that day. The pralidoxime infusion was maintained at 500 mg/h, and penicillin started for presumed aspiration pneumonia after his sputum turned purulent. In view of the persistent presence of a hydrocarbon odor, the PC advised to wash the victim's skin and hair at least on a daily basis.

On hospital day 3, the patient reported feeling much better. His pralidoxime infusion was stopped and he was evaluated by the psychiatric service. That afternoon, he reported 2 episodes of diarrhea and some nausea; as a result, atropine 2 mg IV was administered and the pralidoxime infusion was restarted with resolution of symptoms once again.

The patient required no further atropine during his hospitalization. Pralidoxime infusion was stopped on hospital day 5, and he was discharged to a psychiatric facility on hospital day 7.

History

The first potent synthetic organic phosphorus anticholinesterase was

tetraethylpyrophosphate (TEPP), which was synthesized by Clermont in 1854. Clermont's report described the taste of the compound, a remarkable achievement because a few drops should be rapidly fatal.[69] In 1932, Lange and Krueger wrote of choking and blurred vision following inhalation of dimethyl and diethyl phosphorofluoridates.[78] This account inspired Schrader in Germany to begin investigating these agents, initially as pesticides, and later for use in warfare (Chap. 126). During this research, Schrader's group synthesized hundreds of compounds, including the popular pesticide parathion and the chemical warfare agents sarin, soman, and tabun. Allied scientists were also motivated during the same period by the work, and independently discovered other extremely toxic compounds such as diisopropylphosphofluoridate (DFP).[165] Since that time, it is estimated that more than 50,000 organic phosphorus compounds have been synthesized and screened for pesticidal activity, with dozens being produced commercially.[18]

The history of carbamates was first recorded by Westerners in the 19th century when they observed that the Calabar bean (*Physostigma venenosum Balfour*) was used in tribal cultural practice in West Africa.[164] These beans were imported to Great Britain in 1840, where, by 1864, Jobst and Hesse isolated an active alkaloid component they named â€œphysostigmine.â€• [164] VÃ©e and Leven (1865) claimed to have obtained it in crystallized form, and named it *eserine*, from Ã©sÃ©re, the African term for the ordeal bean. Physostigmine was first medicinally used to treat glaucoma in 1877.[70,79] In the 1930s, the synthesis of aliphatic esters of carbamic acid led to the development and introduction of carbamate pesticides, marketed initially as fungicides.[169] In 1953 the Union Carbide Corporation developed and first marketed carbaryl, the insectivide being prepared at the plant in Bhopal, India, during the catastrophic release of methyl isocyanate in 1984 (Chap. 2).[102]

Epidemiology

Organic phosphorus compounds and carbamates are the two groups of cholinesterase-inhibiting pesticides that commonly produce human toxicity. Although the term organophosphate is traditionally used in clinical practice and in the literature to refer to all phosphorus-containing pesticides that inhibit cholinesterase, phosphates are compounds in which the P atom is surrounded by four O atoms, and there are other derivatives of phosphoric and phosphonic acids such as phosphonates that can exhibit cholinesterase inhibition. Some chemicals, such as parathion, contain thioesters, whereas others are vinyl esters. Those cholinesterase-inhibiting (anticholinesterase) insecticides that contain phosphorus will be collectively termed organic phosphorus compounds in this chapter. Those that contain the OC=ON linkage will be termed carbamates.

During the 5-year period of 1998â€“2002, the American Association of Poison Control Centers (AAPCC) recorded more than 55,000 exposures to organic phosphorus compounds and more than 25,000 exposures to carbamates. Although these totals are large, the number of reported organic phosphorus compound exposures reported to the AAPCC in the last 2 years of this period declined by almost 20%, perhaps owing to mass marketing and use of less toxic pesticides. However, the number of fatalities reported to by the AAPCC remained constant, during this time averaging about 8 per year. These insecticides still rank as the most frequent lethal insecticides in use in the United States, and among the most lethal poisonings (Chap. 130). In Taiwan, where insecticides are often more accessible than medications in rural areas, fatality rates recorded with exposures to these compounds are as high as 23%.[150] Similarly, organic phosphorus insecticides were responsible for as much as high as 50% of all poisonings deaths in India in the past 25 years,[153] and may account for up to 75% of all poisonings in that country today.[130] The World Health Organization (WHO) estimates that at least one million unintentional poisonings and two million suicide attempts occur annually worldwide from these insecticides.[19] However, these figures undoubtedly omit numerous unreported and possibly unrecognized illnesses resulting from lower level

environmental exposure to these chemicals.

Typically patients present following unintentional or suicidal ingestion of anticholinesterase insecticides or after working in areas recently treated with these compounds.[67] Children and adults can develop toxicity while playing in or inhabiting a residence recently sprayed or fogged with organic phosphorus insecticides by a pesticide applicator.[183] Direct dermal contact with certain types of these insecticides may be rapidly poisonous.[105] Outbreaks of mass poisoning have occurred from contamination of crops or food.[19,34,43,118,144,145,167] Recently, epidemics of cholinergic toxicity have been reported among groups illegally importing and using the potent carbamate aldicarb.[124,132] Organic phosphorus agents have also been used for homicide.[118,119]

Pharmacology

Organic Phosphorus Compounds

Poisoning from organic phosphorus compounds results in a rise in the concentration of acetylcholine (ACh) at muscarinic and nicotinic cholinergic receptors, which, in turn, leads to the syndrome of cholinergic excess. Figure 109-1 shows the basic formula for cholinesterase-inhibiting organic phosphorus compounds. The â€œXâ€• or â€œleaving groupâ€• determines many of the characteristics of the compound and provides a means of classifying organic phosphorus insecticides into four main groups (Table 109-1). Group 1 compounds contain a quaternary nitrogen at the X position, and are collectively termed phosphorylcholines. These chemicals originally developed as weapons of war[51] are powerful cholinesterase inhibitors and can also directly stimulate cholinergic receptors, presumably because of their structural resemblance to Ach. Group 2 compounds are called fluorophosphates because they possess a fluorine molecule as the leaving group. Like group 1 compounds, these compounds are volatile and highly toxic, making them well-suited for

chemical warfare. The leaving group of group 3 compounds is a

cyanide molecule or a halogen other than fluorine. The most well-known agents in this group are cyanophosphates such as tabun. The fourth group is the broadest and comprises various subgroups based on the configuration of the R_1 and R_2 groups, with the majority falling into the category of either a dimethoxy or diethoxy compound. Most of the insecticides in use today fall into this last class.[51]

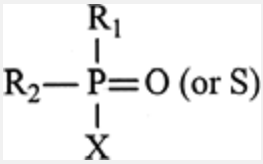


Figure 109-1. General structure of organic phosphorus insecticides. X represents the leaving group. R_1 and R_2 may be aromatic or aliphatic groups that can be identical.

Group 1–phosphorylcholines
Leaving group: substituted quarternary nitrogen
Echothiophate iodide

Group 2–fluorophosphates
Leaving group: fluoride
Dimefox, sarin, mipafox

Group 3–cyanophosphates, other halophosphates
Leaving group: CN, SCN, OCN, halogen other than fluoride
Tabun

Group 4–multiple constituents
Leaving group:
Dimethoxy
Azinphos-menthyl, bromophos, chlorothion, crotoxyphos, dicapthon, dichlorvos, dicrotophos, dimethoate, fenthion, malathion, mevinphos, parathion-methyl, phosphamidon, temephos, trichlorfon

Diethoxy
Carbophenothion, chlorfenvinphos, chlorpyriphos, coumaphos, demeton, diazinon, dioxathion, disulfoton, ethion, methosfolan, parathion, phorate, phosfolan, TEPP

Other dialkoxy
Isopropyl paraoxon, isopropyl parathion

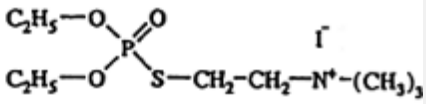
Diamino
Schradan

Chlorinated and other substituted dialkoxy
Haloxon

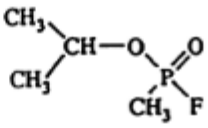
Trithicalkyl
Merphos

Triphenyl and substituted triphenyl
Triorthocresyl phosphate (TOCP)

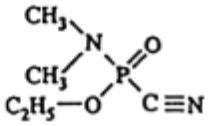
Mixed substituent
Crufomate, cyanofenphos



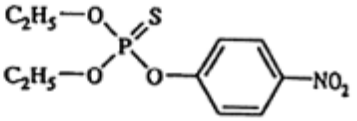
Echothiophate iodide



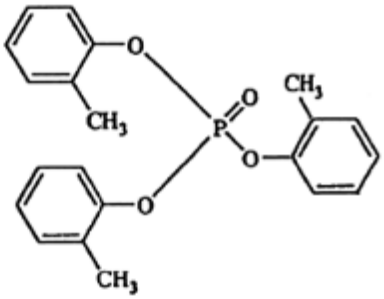
Sarin



Tabun



Parathion



Triorthocresyl phosphate (TOCP)

TABLE 109-1. The Classification of Organic Phosphorus Compounds by Groups. Leaving Groups and Examples of Each Group are Included

â€œDirectâ€•-acting organic phosphorus insecticides can inhibit acetylcholinesterase (AChE) without being structurally altered by the body. However, many of the more popular pesticides, such as parathion and malathion, are â€œindirectâ€• inhibitors or prodrugs requiring partial metabolism (to paraoxon and malaoxon, respectively) within the body to become active. Most of the indirect inhibitors undergo desulfuration in the intestinal mucosa and liver following absorption to form the more active phosphate or â€œoxonâ€• metabolites.[87] The active form is a more potent cholinesterase inhibitor. The covalent bond is completed as the leaving group of the organic phosphorus insecticide is split off by AChE, resulting in a stable but reversible bond between the remaining substituted phosphate of the

organic phosphorus agent and AChE, effectively inactivating the enzyme (Figure 109-2, normal metabolism; Figure 109-3, inactivation, see Figure 12-6 for a more detailed analysis). Although the splitting of the choline-enzyme bond in normal ACh metabolism is completed within microseconds, the severing of the organic phosphorus compoundâ€“enzyme bond can be prolonged.[51,154] In organic phosphorus compound poisoning, the complex becomes irreversibly bound during the next 24â€“72 hours when one of the R groups leaves the phosphate molecule. This step is termed â€œaging.â€•[142] De novo synthesis of AChE is required to replenish its supply once aging has occurred.[136,164,176]

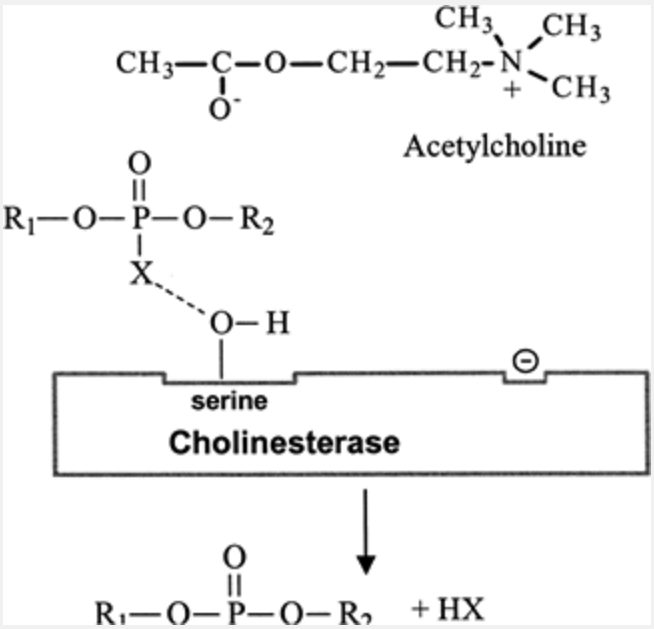


Figure 109-2. Normal metabolism of acetylcholine by acetylcholinesterase to choline and acetic acid.

Carbamates

Carbamate insecticides are *N*-methyl carbamates derived from carbamic acid (Figure 109-4). Medicinal carbamate compounds include physostigmine, pyridostigmine, and neostigmine. Medications such as meprobamate and various urethanes are carbamate derivatives, but do not inhibit cholinesterase.[164] Thiocarbamate fungicides and herbicides (eg, Maneb, Zineb, Nabam, Mancozeb) also do not inhibit AChE and do not produce the cholinergic toxidrome (Chap. 111).

When exposed to carbamate compounds, AChE undergoes carbamylation in a manner similar to phosphorylation by organic phosphorus agents, allowing ACh to accumulate in synapses.[177] Aging cannot occur and the carbamate-AChE bond hydrolyzes spontaneously, reactivating the enzyme. As such, the duration of symptoms in

carbamate poisoning is generally less than 24 hours.

Pharmacokinetics

Organic Phosphorus Compounds

Organic phosphorus insecticides are extremely well absorbed from the lungs, gastrointestinal tract, skin, mucous membranes, and conjunctiva following inhalation, ingestion, or topical contact,[51,99] unlike some xenobiotics percutaneous exposure may cause severe toxicity.[21,59,179] The presence of broken skin and dermatitis and higher environmental temperatures further enhances cutaneous absorption.[51]

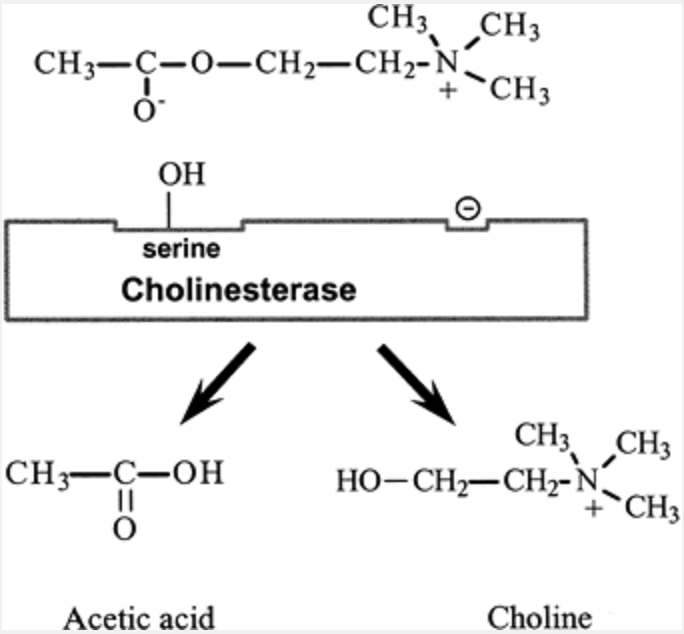


Figure 109-3. Mechanism of inhibition of acetylcholinesterase by an organic phosphorus compound. The X is the leaving group. A serine residue at the active site of the enzyme gives up a hydrogen atom to combine with the leaving group while the active site undergoes phosphorylation and inhibition. This initial inhibition is reversible with pralidoxime. However, as the inhibited

phosphorylated enzyme â€œages,â€• one of the R groups is lost. The aged phosphorylated enzyme is unable to be rejuvenated by pralidoxime.

Cholinesterase-inhibitor poisonings can be chronic or acute, although the differentiation has little clinical relevance. The difficulty in removing these compounds from the skin and clothing may explain some chronic poisonings[21] and inadequate skin and respiratory protection during pesticide application is responsible for most of the remainder.

Most organic phosphorus insecticides are lipophilic.[164] Radiolabeled parathion injected into mice distributes most rapidly into the cervical brown fat and salivary glands, with high levels also measured in the liver, kidneys, and ordinary adipose tissue.[46] Adipose tissue gradually accumulates the highest levels. Cholinergic crisis may recur in patients when unmetabolized organic phosphorus agents are mobilized from fat stores.[50,51] The more lipophilic compounds such as fenthion and chlorfenthion are particularly likely to cause this phenomenon.[173]

Peak levels of most organic phosphorus insecticides are measured around 6 hours after oral ingestion in man.[126] Although serum half-lives of these compounds range from minutes to hours,[78] prolonged absorption or redistribution from fat stores may allow for

measurement of circulating insecticide concentrations for up to 48 days.[25,52,78,140]

Figure 109-4. General structure of carbamate insecticides.

Organic phosphorus insecticides are thought to be metabolized by various mixed function oxidases in the liver and intestinal mucosa, but the exact pathways are not yet well understood.[51,87,159] The phosphorylating ability of these substances is lost when any of the side chains are hydrolyzed. Certain indirect-acting compounds are activated to a more toxic compound by this initial metabolism. Particularly lipophilic organic phosphorus compounds may be protected from metabolism by fat storage, markedly prolonging their elimination half-life.[25,51,107] Inactive metabolites of these compounds are excreted in the urine.[51]

Recently, studies have investigated possible relationships between human serum paraoxonase (PON) activity and susceptibility to acute and chronic effects of organic phosphorus poisoning.[4,22,49,155] Paraoxonase is an A-esterase that can hydrolyze the active (oxon) metabolites of some organic phosphorus insecticides. Activity differs significantly among animal species. Some animal models of organic phosphorus poisoning demonstrate protection from toxicity when exogenous PON is administered, and greater susceptibility to poisoning when enzyme-deficient animals (such as genetically engineered knockout mice) are exposed.[49,155] Some authors have postulated that

genetic polymorphisms in human PON activity may lead to variations in interindividual susceptibility to some organic phosphorus insecticides.[49]

Carbamates

Carbamate insecticides are well absorbed across skin and mucous membranes, and by inhalation and ingestion. Peak serum levels of some compounds are measured 30â€“40 minutes following ingestion.[16] Most carbamates undergo hydrolysis, hydroxylation, and conjugation in the liver and intestinal wall, with 90% excreted in the urine within 3 days.[127] There are two main pharmacokinetic characteristics that distinguish carbamates from organic phosphorus compounds. First, carbamate insecticides do not easily cross into the central nervous system.[51] CNS effects of carbamates are thus limited, although CNS dysfunction may still occur in massive poisonings or may result from hypoxia secondary to pulmonary toxicity and paralysis. Second, the carbamate-cholinesterase bond does not â€œageâ€• as in organic phosphorus compound poisoning; thus it is reversible, with spontaneous hydrolysis occurring usually within several hours.

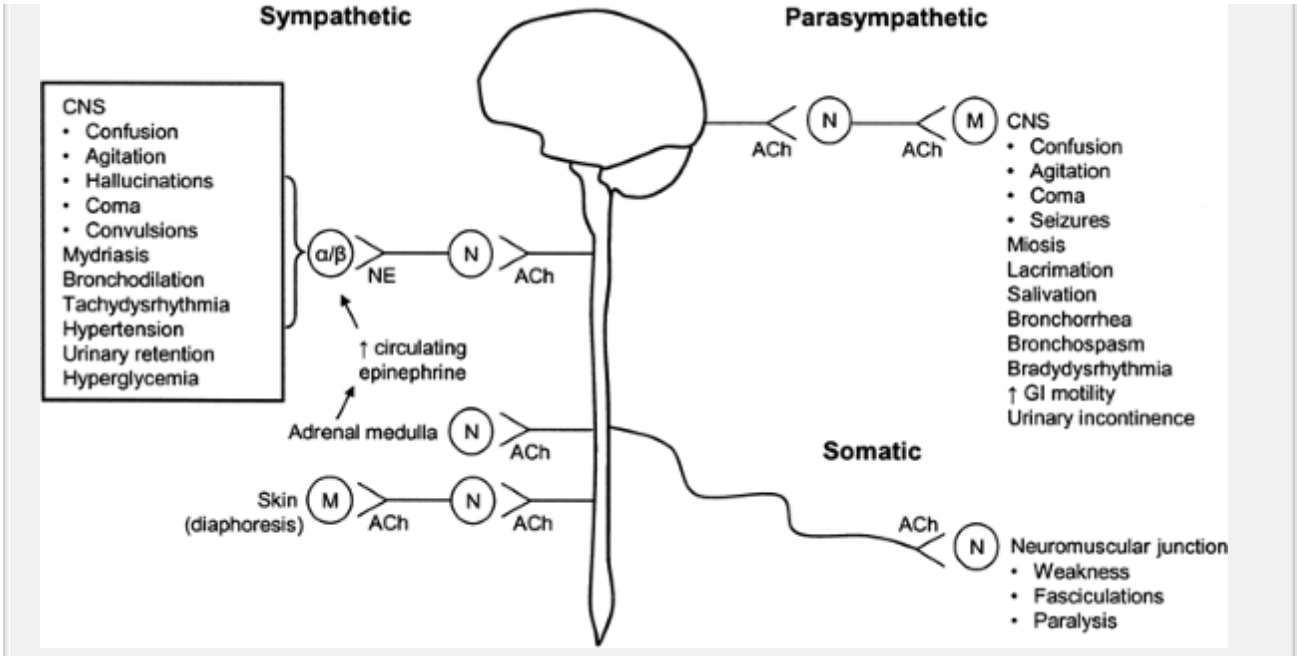


Figure 109-5. Pathophysiology of cholinergic syndrome as it affects the autonomic and somatic nervous systems.

Pathophysiology

Acetylcholine is a neurotransmitter found at both parasympathetic and sympathetic ganglia, skeletal neuromuscular junctions, terminal junctions of all postganglionic parasympathetic nerves, postganglionic sympathetic fibers to most sweat glands, and at some nerve endings within the central nervous system (Figure 109-5).[51] As the axon terminal is depolarized, vesicles containing ACh fuse with the nerve terminal, releasing ACh into the synapse or neuromuscular junction. Acetylcholine then binds postsynaptic receptors leading to activation (G proteins for muscarinic receptors and ligand-linked ion channels for the nicotinic receptors). Activation alters the flow of K^+, Na^+, and Ca^{2+} ionic currents on nerve cells, and alters membrane potential of the postsynaptic membrane, resulting in propagation of the action potential.[15]

Acetylcholinesterase (AChE) is an enzyme that hydrolyzes ACh into two inert fragments: acetic acid and choline. Under normal circumstances, virtually all ACh released by the axon is hydrolyzed almost immediately, with choline undergoing reuptake into the presynaptic terminal and used to resynthesize ACh.[51,128,164] Organic phosphorus insecticides and carbamates are inhibitors of carboxylic ester hydrolases within the body, including variably chymotrypsin, AChE, plasma or butyrylcholinesterase (pseudocholinesterase), plasma and

hepatic carboxylesterases (aliesterases), paraoxonases (A-esterases), and other nonspecific proteases. Acetylcholinesterase is found in human nervous tissue and skeletal muscle, and on erythrocyte (RBC) cell membranes. RBC cholinesterase activity levels correlate best with the function of nervous system AChE. Butyrylcholinesterase is a hepatic-derived protein that is found in human plasma, liver, heart, pancreas, and brain. Although the function of this enzyme is not well understood, its activity can be easily measured and has important clinical implications in anesthesia (Chap. 66).

Clinical Manifestations

Acute Toxicityâ€”Organic Phosphorus Compounds

Clinical findings of toxicity from these compounds derive from excessive stimulation of muscarinic and nicotinic cholinergic receptors by ACh in the central and autonomic nervous systems, and at skeletal neuromuscular junctions (Figure 109-5). Although the classically described patient with organic phosphorus insecticide poisoning is one who is unresponsive with pinpoint pupils, muscle fasciculations, diaphoresis, emesis, diarrhea, salivation, lacrimation, urinary incontinence, and an odor of garlic or solvents, most presentations are not so typical. The onset of symptoms varies according to the compound, the route, and the degree of exposure. Patients suffering

massive ingestions can become symptomatic as quickly as 5 minutes following ingestion, and deaths have occurred within 15 minutes of ingestion.[51,95] Most victims of acute poisonings become symptomatic within 8 hours of exposure, and nearly all are symptomatic within 24 hours.[118] The longest delays may occur with compounds requiring metabolic activation, such as malathion, or very lipid-soluble agents such as fenthion. Symptoms may last for variable lengths of time, again based on the agent and the circumstances of the exposure. For example, the more lipophilic compounds, such as dichlofenthion, can cause cholinergic effects for several days following oral ingestion.[25]

A variety of CNS findings are reported after exposure. Many patients present awake and alert, complaining of anxiety, restlessness, insomnia, headache, dizziness, blurred vision, depression, tremors, or other nonspecific symptoms.[118] The level of consciousness may deteriorate rapidly to confusion, lethargy, and coma, and patients may display inappropriate behavior or convulsions.[118]

The effects of excessive ACh on the autonomic nervous system may be variable because cholinergic receptors are found in both the sympathetic and parasympathetic nervous systems (Figure 109-5). Excessive muscarinic activity can be characterized by several mnemonics, including â€œSLUDâ€• (salivation, lacrimation, urination, defecation) and â€œDUMBBELSâ€• (defecation, urination, miosis, bronchospasm or bronchorrhea, emesis, lacrimation, salivation). Of these, miosis may be the most consistently encountered sign. Bronchorrhea can be so profuse that it mimics pulmonary edema.[118]

Although muscarinic findings are emphasized in these mnemonics, muscarinic signs usually are not clinically dramatic or initially predominant, except in very severe poisonings. In many cases, parasympathetic findings are offset by excessive autonomic activity from stimulation of nicotinic adrenal receptors (resulting in catecholamine release) and postganglionic sympathetic fibers.[164] Mydriasis is reported in as many as 13% of cases, presumably from nicotinic stimulation of sympathetic receptors.[43] Bronchodilation and

urinary retention can occur as a result of sympathetic activity on smooth muscle.[164] Excessive adrenergic influences on metabolism cause glycogenolysis with hyperglycemia and ketosis that are occasionally mistaken for diabetic ketoacidosis.[106] Hypoglycemia can also occur, although the mechanism is unclear.[72] Increased sympathetic activity usually precipitates white blood cell demargination, resulting in leukocytosis.[118] Hyperamylasemia is occasionally reported in cases of severe organic phosphorus pesticide poisoning, and although pancreatitis may result from spasm of the sphincter of Oddi,[101] hyperamylasemia is most often the result of salivary gland stimulation and not the result of pancreatic dysfunction.[93] Elevations of hepatic enzymes can also occur following organic phosphorus pesticide exposures.[51,131]

The cardiovascular manifestations also reflect mixed effects on the autonomic nervous system.[98] Increased sympathetic tone is often initially present, and most patients manifest a sinus tachycardia,[98,118] and sometimes hypertension. As toxicity becomes more severe, bradycardia with a prolonged PR interval and atrioventricular blocks of various degrees occur because of excessive parasympathetic tone, and possibly because of reduced coronary blood flow.[86,98,118] Unequal sympathetic stimulation of myocardial cells, and interactions with potassium channels and the Na^{+}/Ca^{++} exchanger in the myocardial cell membrane are probably responsible for the occasional prolonged QTc interval.[2,98,114,123] This prolongation in QTc interval can be associated with polymorphic ventricular tachycardia (torsades de pointes).[83,98,123,171] Finally, hypotension may occur because of stimulation of vascular receptors by excessive circulating ACh.

The most common pulmonary complications of these compounds are bronchorrhea and bronchoconstriction. Additionally, because liquid preparations are usually dissolved in a hydrocarbon aspiration frequently results following ingestion in severe poisoning and can lead to hydrocarbon pneumonitis.[123] Respiratory depression is common, and is in part centrally mediated.[118]

Acetylcholine stimulation of nicotinic receptors also governs skeletal muscle activity. The effects of excessive cholinergic stimulation at these sites are similar to that of a depolarizing neuromuscular blocker agent (succinylcholine) initially resulting in fasciculations or weakness. This effect is considered by some to be the most reliable sign of toxicity.[119] Cranial nerve abnormalities are uncommon. As the severity of poisoning progresses, paralysis ensues. Paralysis of the respiratory muscles in combination with bronchorrhea, bronchoconstriction, and CNS depression leads to hypoxemia and respiratory arrest, the most common cause of death.[118,162] Rarely, patients may present only with paralysis from nicotinic effects without any other initial signs and symptoms suggestive of organic phosphorus compound toxicity.[45,54] This is more common with nerve agent weapons of mass destruction. Extrapyramidal effects such as rigidity and choreoathetosis occur uncommonly after severe anticholinesterase poisoning but can persist for several days after cholinergic features have resolved.[11,76]

Acute Toxicityâ€”Carbamates

The effects of poisoning from carbamate insecticides appear identical to those of organic phosphorus insecticides except for the relative inability of the carbamate to penetrate the CNS and the rapid hydroxylation of the carbamate-AChE bond. However, as noted previously, CNS abnormalities may occur in victims of severe carbamate poisonings, especially aldicarb.[166] Some of these CNS effects may result from hypoxia caused by respiratory insufficiency or severe bronchorrhea.

Chronic Toxicity

Illness may also result from chronic exposure to excessive amounts of organic phosphorus insecticides. Chronic exposure most commonly occurs in workers who have regular contact with these compounds, but may also occur in individuals who have repeated contact with excessive

amounts of insecticides in their living environments. Cholinergic ophthalmic preparations can also lead to toxicity in this manner.[100] Although tolerance to acute cholinergic systemic effects of organic phosphorus insecticides (including death in rats) may be observed with long-term exposures,[51] persons who have such repeated contact may begin to describe symptoms after substantial lengths of time. These effects can range from vague neurologic complaints, such as weakness and blurred vision, to miosis, nausea, vomiting, diarrhea, diaphoresis, and other cholinergic effects.[100,109,135,156] Much of the literature on this topic is retrospective. Red blood cell cholinesterase activity is the most sensitive measure of exposure, and workers in contact with these chemicals should have baseline cholinesterase testing for comparison and monitoring.[51,68]

Recent literature has linked Parkinson disease with chronic exposure to pesticides including organic phosphorus insecticides.[11,157] The structures of some pesticides are similar to that of known neurotoxins like 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Some individuals may have a possible genetic susceptibility. Additionally, significant acute exposures to organic phosphorus insecticides can lead to self-limited movement disorders resembling Parkinson that resolve over weeks to months.[11,115] Although statistics derived from some epidemiologic studies suggest the connection,[41,63] others studies have failed to a find an association between organic phosphorus compounds and Parkinsonism.[163]

Delayed Syndromes

Intermediate Syndrome

Delayed muscle weakness often without fasciculations or cholinergic features can occur 24â€“96 hours after acute organic phosphorus compound poisoning.[62,78,129,137,146,158] This phenomenon was first described in 1987, and is termed the â€œintermediate syndromeâ€• because it occurred in between the periods of acute and delayed

toxicity.[146] The majority of reported cases of intermediate syndrome presented initially with cholinergic signs and symptoms that improved with atropine and oxime therapy over the first 1â€“2 days after exposure. Relapse with peripheral neurologic impairment developed about 48 hours after presentation. Intermediate syndrome occurs more often in patients poisoned with parathion, methyl parathion, diazinon, malathion, fenthion, monocrotophos, dimethoate, and methamidophos.[62,146] Redistribution of these lipophilic pesticides and their metabolites from adipose tissue may be responsible,[27,28,29,30,31 and 32,50,148,158] and the syndrome may resolve when the body burden of these metabolites diminish and cholinesterase levels normalize. There is growing speculation that intermediate syndrome may result from inadequate oxime therapy,[26,27,29] although more recent case reports question this theory.[82,158] One recent study suggested that the occurrence of intermediate syndrome strongly correlated with the initial degree of cholinergic crisis, and seemed to be a continuum with the neuromuscular paralysis resulting from the early stages of poisoning.[73] The authors and others propose that muscle injury during early cholinergic crisis may progress to intermediate syndrome.[73,181]

The most frequently encountered clinical findings of intermediate syndrome include upper body weakness, cranial nerve palsies, and areflexia. Fasciculations occur rarely. Level of consciousness is rarely affected. The muscle weakness in these patients can progress to respiratory distress and paralysis.[62,129,137,146] The most commonly affected muscles are the facial, extraocular, palatal, respiratory, and proximal limb muscles.[62,137,146]

Clinical examination remains the most reliable means of identifying the occurrence of intermediate syndrome.[21] Electromyograms will often show tetanic fade in these patients, and suggest both pre- and postsynaptic involvement.[78] However, repetitive nerve stimulation may not always accurately predict the occurrence or severity of intermediate syndrome, but may be beneficial in determining the need for mechanical ventilation.[29]

The treatment of intermediate syndrome is largely supportive with airway protection and ventilatory assistance. There are no substantial data demonstrating that pralidoxime or atropine is effective in the treatment of this disorder, although patients may require these medications to control the cholinergic symptoms resulting from persistent effects at nicotinic receptors on motor nerves proximal to the neuromuscular junction. However, because some reports correlating pralidoxime dose and intermediate syndrome suggest that insufficient dosing may play a part we therefore recommend reinstituting pralidoxime infusion at 500 mg/h when intermediate syndrome is suspected. The weakness and paralysis commonly resolve in 5â€“18 days.[14,62,73,78]

Encephalopathy and Peripheral Neuropathies

Peripheral neuropathies can occur either with chronic organic phosphorus pesticide exposures or days to weeks following acute exposures. This disorder appears to result from inhibition of an enzyme within nervous tissue named neurotoxic esterase or neuropathy target esterase.[74,78] Symptoms seem to be initiated by the phosphorylation of this enzyme, or perhaps of some related compound, followed by aging of the complex.[182] Such neuropathies may even result from exposure to organic phosphorus compounds that do not inhibit red blood cell cholinesterase or produce clinical cholinergic toxicity.[17] The more commonly implicated chemicals include triaryl phosphates, such as triorthocresyl phosphate (TOCP), and dialkyl phosphates, such as mephosfolan, mipafox, and chlorpyrifos.[75,105,118] Pathologic findings demonstrate effects primarily on large distal neurons, with axonal degeneration preceding demyelination.[117]

Contaminated foods and beverages were responsible for epidemics of organic phosphorus compoundâ€“induced delayed polyneuropathies and encephalopathy. In the 1930s, thousands of individuals in the United States became weak or paralyzed after drinking a supplement containing TOCP an outbreak nicknamed â€œGinger Jake

paralysis.â€• [5,108,112,113] Contaminated cooking and mineral oils were responsible for outbreaks of delayed polyneuropathies in Vietnam and Sri Lanka.[34,144,145] Vague distal muscle weakness and pain are often the presenting symptoms and may progress to paralysis.[45,58] The administration of atropine or pralidoxime may not alter the onset and clinical course of these symptoms.[45,118,170] Pyramidal tract signs can appear weeks to months after acute exposures.[78,170] Electromyograms and nerve conduction studies may be helpful in diagnosing this disorder by identifying the type of neuropathy (such as axonopathy, myelinopathy or transmission neuropathy) and differentiating it from similar presentations such as Guillain-BarrÃ© syndrome.[1,148] Recovery of these patients is variable and occurs over months to years, with residual deficits common.[8,113,147]

Delayed neuropathies are not usually associated with carbamate insecticides. One reason for this difference is presumed to be that

aging of the neuropathy target esterase pesticide complex is a requirement for neuronal degeneration. Paradoxically, studies suggest that subgroups of carbamates may actually bind neuropathy target esterase and exert a protective effect against more toxic organic phosphorus compounds.[3] However, several cases of possible delayed neuropathy associated with carbamates are reported.[35,169,182] These cases involve ingestions of carbaryl, *m*-tolyl methyl carbamate, and carbo furan, include both sensory and motor tracts, and tend to resolve over 3â€“9 months. EMG findings in these subjects are variable.

Behavioral Toxicity

Behavioral changes may also occur after acute and chronic exposure to organic phosphorus compounds.[78] Signs and symptoms include confusion, psychosis, anxiety, drowsiness, depression, fatigue, and irritability.[51,107,143,161] Electroencephalographic changes may be noted and can last for weeks.[51,57,68] Single photon emission computed

tomography (SPECT) scanning revealed morphologic changes in the basal ganglia of one child following poisoning.[13] Although no specific treatment is effective, most psychological abnormalities resolve within a year.[53] Behavioral toxicity following carbamate exposure is extremely rare.

Diagnostic Testing

Organic Phosphorus Compounds

When confronted with a patient in cholinergic crisis who presents with a history of acute excessive exposure to an organic phosphorus cholinesterase inhibitor insecticide, the diagnosis is frequently straightforward. However, when the history is unreliable or does not suggest poisoning, the physician must turn to other means to confirm the diagnosis of organic phosphorus or carbamate insecticide poisoning.

The most reliable and appropriate laboratory test for confirming cholinesterase inhibition by insecticides is a test that measures specific insecticides and active metabolites in biologic tissues. Unfortunately, although urine and serum assays for organic phosphorus compounds and their metabolites are being investigated,[7,60,88,122] such testing is rarely obtainable within a few minutes or hours. Moreover â€œnormalâ€• ranges and toxic levels are not established for most compounds. Another useful research tool is the measurement of AChE activity in neuronal tissue, but this requires CNS or neuronal tissue biopsies and, even then this test is not very helpful unless the baseline activity is known. Currently, the only practical diagnostic study for verifying cholinesterase inhibitor poisoning is a measurement of cholinesterase activity in readily accessible tissue, such as the plasma and erythrocytes.[51,118]

Butyrylcholinesterase (plasma cholinesterase) is able to metabolize various xenobiotics, including succinylcholine and cocaine.

Erythrocytes contain a form of AchE that is structurally similar to the enzyme found in neuronal tissue.[20] Inhibition of either red blood cell cholinesterase or butyrylcholinesterase only serves as markers for cholinesterase inhibitor poisoning, as inhibition of these enzymes do not contribute to signs and symptoms of poisoning.

There is tremendous interindividual and interchemical variability in the degree and duration with which the organic phosphorus insecticides affect various cholinesterases. After a significant exposure, butyrylcholinesterase activity usually falls first, followed rapidly by a decrease in red blood cell cholinesterase activity. The sequence may be highly variable, but by the time patients present with acute symptoms, levels of both cholinesterase activities have usually fallen well below baseline values, and often have fallen below detectable limits.[118]

Butyrylcholinesterase activity usually recovers before red blood cell cholinesterase activity often returning to normal within a few days in the absence of a repeat exposure to the inciting agent.[23] However, butyrylcholinesterase activity is less specific for exposure than is red cell cholinesterase activity.[51] Low butyrylcholinesterase activity can be found in patients with a number of disorders, including hereditary deficiency of the enzyme, malnutrition, hepatic parenchymal disease, chronic debilitating illnesses, and iron deficiency anemia.[51,125] Additionally, day-to-day variation in the activity of this enzyme in healthy individuals may be as high as 20%.[51]

Red blood cell cholinesterase activity is thought to more accurately reflect nervous tissue AChE activity than does butyrylcholinesterase because the AChE in red blood cells is true AChE. Some authors suggest that clinical organic phosphorus pesticide poisoning occurs when red blood cell cholinesterase activity falls to below 50% of baseline values.[111,118] Although these statements are generally true, there are several potential pitfalls in interpreting cholinesterase laboratory values. First, it is AChE inhibition in nervous tissue that causes toxicity, and red blood cell and butyrylcholinesterase activity

may not always reflect neuronal enzyme activity. Organic phosphorus insecticides vary in their ability to inhibit butyrylcholinesterase or red blood cell cholinesterase. Because these tests are only markers of neuronal enzyme inhibition, this variation may lead to some patients presenting highly symptomatic after minimal reductions in red blood cell or butyrylcholinesterase, although others can be asymptomatic after losing 50% activity.[23,67,110] The wide normal range of red blood cell and butyrylcholinesterase activity also allows for patients with high normal values to suffer significant falls in cholinesterase activity, yet still register near normal levels of cholinesterase activity on laboratory assay.[23,67,110]

Red blood cell cholinesterase regenerates more slowly than AChE found in neurons.[118] To completely replenish the RBC AChE supply, the red blood cells in circulation at the time of the organic phosphorus insecticides exposure must be replaced, or pralidoxime administered. An average of 66 days may be necessary for red blood cell cholinesterase activity to recover following severe inhibition[23] (assuming no treatment with pralidoxime), and activity may take up to 120 days to return to normal. The patient may have completely recovered neuronal activity of AChE and resolved all cholinergic symptoms, yet still have low red blood cell cholinesterase laboratory values. For this reason, in subacute poisoning with organic phosphorus agents, it is difficult to accurately predict the actual time of onset or duration of exposure when only the red blood cell cholinesterase activity is known. In fact, the ability of red blood cell cholinesterase activity to serve as a historical marker for excessive exposure to organic phosphorus insecticides provides the basis for monitoring red blood cell cholinesterase activity in pesticide workers.[24,33,91,133]

Depressed red blood cell cholinesterase activity may be the result of exposures or conditions other than insecticide poisoning, such as in therapy with antimalarial agents such as chloroquine and pernicious anemia. Genetic and circadian variations are also common, with daily fluctuations within the same individual as high as 10%.[180] Additionally, levels are normally slightly lower in children younger than 4 months of

age, probably increasing as hepatic function matures.[81] Oral contraceptives raise red blood cell cholinesterase activity.

TABLE 109-2. Interpreting Cholinesterase Values

	Red Blood Cell Cholinesterase	Butyrylcholinesterase
Advantage	Better reflection of synaptic inhibition	Easier to assay, declines faster
Site	RBC (reflects CNS gray matter, motor end plate)	CNS white matter, plasma, liver, pancreas, heart
Regeneration (untreated)	1%/day	25â€“30% in first 7â€“10 day
Normalization (untreated)	35â€–49 day	28â€–42 day
Use	Unsuspected prior exposure with normal plasma cholinesterase	Acute exposure
False depression	Pernicious anemia, hemoglobinopathies, antimalarial treatment, oxalate blood tubes	Liver dysfunction, malnutrition, hypersensitivity reactions, drugs (succinylcholine,

		codeine, morphine), pregnancy, genetic deficiency

The most important aspect to consider when interpreting the cholinesterase activity as reported by a laboratory is how it compares with baseline values in that individual (Table 109-2). Because baseline values are usually unavailable in most cases, laboratories report out a â€œreference rangeâ€• of activity. This range is based on the central 95% of values of cholinesterase activity for the general population.

Blood samples for cholinesterase activity must be obtained in the appropriate blood tubes. Tubes containing fluoride will permanently inactivate the enzyme, yielding falsely low activity levels, and should not be used. Specimens for red blood cell cholinesterase are usually drawn into tubes containing a chelating anticoagulant such as ethylenediaminetetraacetic acid (EDTA) to prevent clot formation. Butyrylcholinesterase does not require an anticoagulant and can be drawn into a tube without chelators or anticoagulants. Because laboratory color coding systems for blood tubes vary, laboratory personnel should be contacted to determine the appropriate venipuncture container.

Carbamates

Carbamates inhibit neuronal and red blood cell AChE, and butyrylcholinesterase. The relative ease with which spontaneous decarbamylation of cholinesterase takes place may result in the measurement of relatively normal red cell cholinesterase activity despite severe cholinergic symptoms if the assay is not performed within several hours of sampling.[39,124] As in the case with organic phosphorus pesticide poisoning, the wide â€œnormalâ€• range of cholinesterase values may make interpretation of cholinesterase

activity difficult at times when the patient's baseline values are unknown. Unlike organic phosphorus insecticides, carbamates generally do not produce persistent depressed red blood cell and butyrylcholinesterase activities.

Atropine Challenge

An atropine sulfate challenge may be helpful in diagnosing cholinergic poisoning in a patient who presents with findings suggestive of this disorder, but in whom no history is available to suggest excessive exposure to an organic phosphorus or carbamate insecticide. In an individual not exposed to significant amounts of insecticide a test dose of 1â€“5 mg of atropine in adolescents or adults, or 0.05 mg/kg in children up to an adult dose, should produce classic antimuscarinic findings such as mydriasis, tachycardia, and dry mucous membranes. Conversely, the persistence of cholinergic signs and symptoms after an atropine challenge strongly suggests the presence of organic phosphorus compound or carbamate poisoning.[118] However, some patients suffering from mild-to-moderate anticholinesterase poisoning may respond to these doses of atropine. Therefore, the reversal of cholinergic findings does not exclude poisoning by one of these compounds.

Electromyogram (EMG) Studies

Although measuring cholinesterase levels is the test most often used to estimate tissue and neuronal AChE activity, studies support the use of repetitive nerve stimulation testing as an accurate method of quantifying AChE inhibition at the neuromuscular junction.[9,10,27] Spontaneous repetitive potentials or fasciculations following single-nerve stimulation resulting from persistent ACh at nerve terminals can be a sensitive indicator of AChE inhibition at the motor endplate, and may be useful in the early diagnosis of anticholinesterase poisoning.[10] This type of evaluation may also be of benefit in early detection of rebound cholinergic crisis caused by continued insecticide absorption

or redistribution from adipose, or onset of an intermediate syndrome.[9,27]

Differential Diagnosis

The differential diagnosis for cholinergic poisoning includes 3 main categories (Table 109-3). The first comprises insecticides and other noninsecticidal cholinesterase inhibitors including the medicinal anticholinesterases neostigmine, pyridostigmine, physostigmine, and echothiophate iodide. The most common patients to suffer cholinergic

poisoning syndrome from medicinal cholinesterase inhibitors are patients with myasthenia gravis who are given excessive doses of pyridostigmine. This entire group of xenobiotics should produce low butyrylcholinesterase and low red blood cell AChE activity. Newer agents used to treat Alzheimer disease, such as tacrine, may inhibit ACh, but symptomatic overdose of these agents has not yet been reported.

TABLE 109-3. Categories of Cholinergic Poisoning

Cholinesterase inhibitors
Organic phosphorus insecticides
Organic phosphorus ophthalmic medications
Carbamate insecticides
Carbamate medicinals
Cholinomimetics
Pilocarpine
Carbachol
Aceclidine
Methacholine
Bethanechol
Muscarine-containing mushrooms

Nicotine alkaloids
Coniine
Lobeline
Nicotine

The second category of compounds that produce a syndrome of cholinergic poisoning include agents with cholinomimetic activity. These compounds directly stimulate muscarinic or nicotinic cholinergic receptors, but do not inhibit AChE. In individuals exposed to these compounds butyrylcholinesterase and red blood cell cholinesterase activity should be normal. Cholinomimetic medications include preparations of carbachol, methacholine, pilocarpine, and bethanechol. Non pharmaceutical agents such as muscarine-containing mushrooms can be cholinomimetic (Chap. 113). Finally, a third group of xenobiotics nicotine alkaloids (eg, nicotine, lobeline, and coniine) cause CNS, autonomic, and skeletal muscle symptoms similar to those occurring in organic phosphorus and carbamate toxicity (Chap. 82).

Management

Organic Phosphorus Insecticides

The first cause of death results from respiratory failure and hypoxemia that may result from coma and convulsions, nicotinic effects on skeletal muscles, (weakness and paralysis) and muscarinic effects on the cardiovascular and pulmonary system (bronchospasm, bronchorrhea, aspiration, bradydysrhythmias, or hypotension.) Therefore initial treatment for a patient exposed to organic phosphorus compounds is directed at ensuring an adequate airway and ventilation, and at reversing excessive muscarinic effects. Seizures not secondary to hypoxemia are treated with standard anticonvulsants such as benzodiazepines or barbiturates.

Maintenance of the patient's airway is best assured by early

endotracheal intubation and positive pressure ventilation in patients who are comatose, have significant weakness, or who are unable to handle copious secretions that may accompany the poisoning. Only a neuromuscular blocking agent that is not primarily metabolized by cholinesterases should be used to induce pharmacologic paralysis. The duration of action of the depolarizing agent succinylcholine and the nondepolarizing agent mivacurium, for example, will be extended in the presence of low butyrylcholinesterase activity, resulting in paralysis that can be prolonged up to 24 hours or more.[143,149]

The second management priority is to control excessive muscarinic activity. Atropine sulfate competitively antagonizes ACh at muscarinic receptors to reverse excessive secretions, miosis, bronchospasm, vomiting, diarrhea, diaphoresis, and urinary incontinence.[14,78,118] For adolescents and adults, intravenous doses should begin with boluses of 1â€“5 mg and for children at 0.05 mg/kg up to adult doses depending on the severity of symptoms. Many authors state that repeat doses of 1â€“2 mg should be given every 2â€“3 minutes or more rapidly until atropinization occurs.[51,118,183] We suggest that during the initial resuscitation the dose of atropine should be doubled on each subsequent administration until symptoms such as bronchorrhea are under control. â€œAtropinizationâ€• has been accomplished when the patient exhibits dry skin and mucous membranes, decreased or absent bowel sounds, tachycardia, reduced secretions, no bronchospasm (in absence of other causes such as aspiration), and usually, mydriasis. An improvement in pulmonary secretions is the most important target in atropine therapy and can be guided by following lung sounds and oxygenation. Tachycardia is not a contraindication to atropine therapy. Although the pupils are often helpful in gauging the need for atropine, the miosis encountered in severe ingestions and by direct ocular exposure to organic phosphorus insecticides may respond only to topical ophthalmic atropine.[139] Conversely, a positive pupillary response alone should not be used to discontinue further therapy. Isolated pulmonary manifestations may respond to administration of nebulized atropine or ipratropium, and this treatment can accompany

parenteral administration of these medications.

Large doses of atropine may be needed to reverse the bronchospasm, bronchorrhea, bradycardia, and heart block associated with severe organic phosphorus pesticide toxicity.[51,59,61,99,119] Some patients with mild symptoms need only 1 or 2 mg of atropine to reverse cholinergic toxicity, but the moderately poisoned adolescent or adult commonly requires total doses as large as 40 mg.[38,76] Severe poisonings may necessitate even higher doses. Some adults have received over 1000 mg of atropine in 24 hours (with adequate pralidoxime dosing) without demonstrating antimuscarinic effects,[38,172] and total doses as high as 11,000 mg during the course of treatment have been reported.[71] Children have been managed with continuous infusions of atropine starting at 0.025 mg/kg/h,[13,92,123] and adult infusions of atropine can begin at 0.5â€“1 mg/h and titrated as needed. Continuous infusions have been used for as long as 32 days in severely poisoned patients.[52]

Atropine does not reverse nicotinic effects. Therefore, the patient who improves after receiving atropine must still be closely monitored in an intensive care setting for impending respiratory failure.

When antimuscarinic CNS toxicity becomes evident, yet peripheral cholinergic findings necessitate the administration of more atropine (eg, bradycardia, bronchorrhea, vomiting), glycopyrrolate bromide can be substituted for atropine because its quaternary ammonium structure limits CNS penetration.[134] The initial intravenous dose of glycopyrrolate for adults and adolescents is 1â€“2 mg, repeated as needed or in children 0.025 mg/kg up to adult doses. As with atropine, much higher doses of glycopyrrolate may be required to stabilize patients with severe poisonings. Although scopolamine has also been used in place of atropine,[134] it may cause more pronounced CNS effects. A urinary catheter should be inserted in all atropinized patients to prevent urinary retention. If atropine supplies are exhausted during therapy, other antimuscarinic agents like diphenhydramine may be used.

Pralidoxime

Although phosphorylated AChE undergoes hydrolytic regeneration at a very slow rate, this process can be markedly enhanced by using an oxime such as pralidoxime hydrochloride (2-PAM) (Fig. 109-6).[175] In addition to rejuvenating AChE, pralidoxime may also reverse toxicity by directly inactivating free organic phosphorus molecules and by exhibiting an apparent antimuscarinic effect on nervous tissue.[51,85] Regeneration of AChE lowers ACh concentrations to normal levels, reversing both muscarinic and nicotinic effects. An immediate rise in red blood cell cholinesterase activity, presumably paralleling a rise in neuronal AChE activity, is often noted after the administration of pralidoxime.

Most phosphorylated AChE will presumably be aged within 24â€“48 hours of exposure.[51,164] Pralidoxime is unable to rejuvenate active enzyme from the organic phosphorus compoundâ€“AChE complex that has undergone aging.[38,66] Therefore, pralidoxime therapy is

most effective if started early in the course of toxicity.[37,142,158] The actual rate of aging however, varies significantly among organic phosphorus insecticides. Additionally, circulating organic phosphorus pesticide concentrations have been measured for as long as 48 days after exposure,[25,52] either because of prolonged absorption from the GI tract or, more likely, because of redistribution from fat stores.[13,38,51,52,118] Therefore, some AChE may still be undergoing new inhibition for days or weeks after exposure in symptomatic patients, and such inhibition may be reversible by pralidoxime.[173] Case reports support this reasoning by noting dramatic effects in reversing paralysis, weakness, and cholinergic symptoms even after late administration of pralidoxime.[26,27 and 28,30,107,118,121]

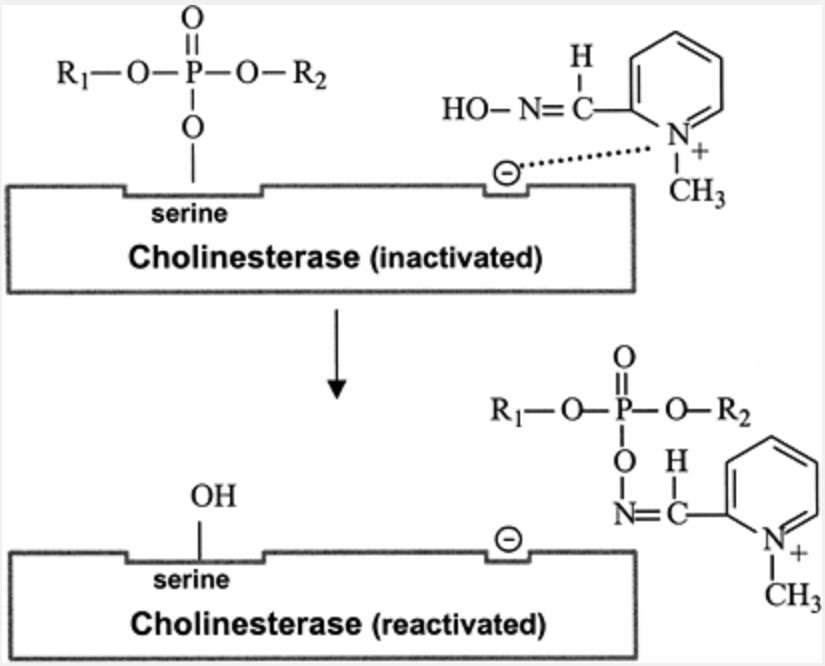


Figure 109-6. Mechanism of reactivation of acetylcholinesterase by pralidoxime. The positively charged aromatic nitrogen of pralidoxime is â€œattractedâ€• to the anionic site of acetylcholinesterase, allowing the reactive oxime portion of the molecule to position itself over the phosphorylated active site of the enzyme. Pralidoxime then becomes phosphorylated, reactivating acetylcholinesterase.

The initial dose of pralidoxime for adolescents and adults is 1â€“2 g intravenously over 10â€“15 minutes and for children 20â€“40 mg/kg IV up to adult doses over 10â€“15 minutes.[78,141] Although minimal serum concentrations of 4 Âµg/mL are estimated to be necessary for maintenance of enzyme reactivation,[158,160] the degree of reactivation may be dependent on the specific identity and concentrations of both oxime and organic phosphorus compound.[173] Bolus dosing of pralidoxime every 4â€“8 hours is ineffective in maintaining these levels,[104] and therefore a constant infusion appears to be more

appropriate. Present recommendations for adults are to begin the maintenance infusion at 250â€“500 mg/h, titrating to symptoms.[78] Alternative dosing by weight reported in other studies suggests using 4â€“5 mg/kg as a loading dose over 15â€“30 minutes, followed by a continuous infusion of 2â€“4 mg/kg/h to maintain serum concentrations.[104,174] WHO-sponsored recommendations note that pralidoxime infusions of up to 8 mg/kg/h or more may be required in some cases.[40] Based on these data, it seems prudent in adults requiring pralidoxime to administer an initial IV loading dose of 1â€“2 g over 15 minutes, and then begin an IV infusion at 500 mg/h. Pharmacokinetics of pralidoxime in children are extremely variable and different from adults.[141] Reports suggest that loading doses for children should be 20â€“40 mg/kg of pralidoxime intravenously over 15â€“30 minutes (up to adult bolus doses), followed by a continuous infusion of 10â€–20 mg/kg/h. This regimen is effective in treating symptoms associated with organic phosphorus pesticide poisoning and does not result in pralidoxime-associated toxicity.[44,141] Of interest, recent research in animals suggests that oral dosing of pralidoxime and atropine (obviously not practical in the majority of severe intoxications) may also improve survival.[14]

Side effects of pralidoxime are usually minimal at normal doses.[56,120] Severely poisoned patients have received 500 mg/h for weeks without adverse effects.[52,118] Rapid infusion can cause mild cholinergic effects because of transient blockade of AChE[118] and has resulted in neuromuscular blockade and central respiratory depression.[78,164] Occasional visual complaints are also reported in patients receiving pralidoxime.

Some effects of pralidoxime are not well understood. The quaternary ammonium compound structure of pralidoxime largely prevents it from crossing the bloodâ€“brain barrier.[105] However, case reports of organic phosphorus compound toxicity describe pralidoxime-induced reversal of convulsions and improvements in mental status and electroencephalograms not attributable to improved ventilation or perfusion.[42,48,64,65,80,96,97,125] These findings could also result from a

neuroprotective effect of antimuscarinic agents.[12,168]

Pralidoxime is not equally effective in reversing cholinergic symptoms in all types of organic phosphorus compound poisonings.[78,118] It is particularly effective in reversing toxicity from parathion, diazinon, methyl parathion, TEPP, dimethoate, and dichlorvos but[51] dimethoxy compounds, such as malathion and methyl demeton, may be more resistant to reversal.[51]

Diazepam

Diazepam may improve survival in victims of severe organic phosphorus pesticide poisoning. Animal studies demonstrate that administering diazepam along with oximes in the treatment of organic phosphorus nerve agents (sarin, soman, tabun, VX) or dichlorvos can increase survival and decrease the incidence of seizures and neuropathy.[36,85,90,97,116,138] Diazepam can also decrease cerebral morphologic damage resulting from organic phosphorus compoundâ€“related seizures.[103,152] One study also suggests that diazepam may help attenuate organic phosphorus-induced respiratory depression,[36] postulating that the benzodiazepines may attenuate the overstimulation of central respiratory centers caused by organic phosphorus insecticides.

Decontamination

Rapid and continuous cutaneous absorption of organic phosphorus pesticides and carbamates necessitates removal of all clothing as soon as possible. Medical personnel should avoid self-contamination by wearing neoprene or nitrile gloves. Double-gloving with standard vinyl gloves may be protective for short intervals. Skin should be triple-washed with water, soap, and water, and rinsed again with water. Although alcohol-based soaps are sometimes recommended to dissolve hydrocarbons,[47] these products can be difficult to find, and expeditious skin cleansing should be the primary goal. Cutaneous absorption can

also result from contact with organic phosphorus and carbamate compounds in vomitus and diarrhea if the initial exposure was by ingestion. Oily insecticides may be difficult to remove from thick or long hair, even with repeated shampooing, and shaving scalp hair may be necessary. Exposed leather clothing or products should be discarded because decontamination is very difficult once impregnation has occurred.

Military institutions are now experimenting with cholinesterase sponges for cutaneous organic phosphorus decontamination.[55] The sponge consists of a cholinesterase enzyme covalently linked and immobilized in a polyurethane matrix. The sponge reportedly is effectively in removing organic phosphorus compounds from skin and surfaces.[55]

In acute ingestions, if emesis has not occurred, evacuation of stomach contents by lavage is recommended. Because the onset of coma, seizures, and paralysis can be rapid, airway protection may be necessary to perform the procedure safely. Although there are data suggesting that AC may adsorb some organic phosphorus insecticides, there are no studies evaluating whether repeat administration of AC changes the outcome or clinical course of these patients and also ileus may develop during atropine therapy. Thus, the present recommendation is that patients with anticholinesterase poisoning receive a single dose of 1 g/kg AC. Healthcare providers must always maintain caution when coming into contact with stomach contents or other body fluids when managing these cases. Individuals have been poisoned by providing mouth-to-mouth resuscitation to a victim of an intentional ingestion of diazinon.[84]

Disposition

Even after atropinization, patients with cholinesterase inhibitor poisoning should be continuously observed for evidence of deteriorating neurologic function and potential paralysis. Patients commonly develop confusion and agitation following large doses of

atropine as a consequence of the central antimuscarinic effects.

Red blood cell cholinesterase and butyrylcholinesterase activities should be measured intermittently after the institution of pralidoxime therapy.[6,77,90,151,173,178] In most case, checking enzyme activity every 12â€“24 hours will be sufficient in symptomatic patients, and can be reduced to once a day testing or less when cholinergic effects have resolved. Butyrylcholinesterase may not normalize with pralidoxime therapy because this enzyme does not contain an anionic site to attract the compound[82] and red blood cell cholinesterase activity may be markedly depressed long after neuronal AChE levels have returned to normal. Therefore, an individual who remains asymptomatic may be discharged home with subnormal cholinesterase activity. However, a significant fall in cholinesterase activity may reflect redistribution of insecticide from fat stores or prolonged absorption and may be accompanied by the redevelopment of cholinergic symptoms 3 or 4 days after initial resolution of symptoms.[38,51,107] Further deterioration of cholinesterase activity should be treated by reinstituting a pralidoxime infusion, even though the patient may still be asymptomatic. After an additional 24 hours of pralidoxime, if the patient remains asymptomatic, pralidoxime can be halted again, and red blood cell cholinesterase and butyrylcholinesterase activities monitored. When available, electromyographic studies to detect signs of motor endplate dysfunction and early AChE inhibition may be a more sensitive method for identifying recurrent cholinergic toxicity.[10]

A patient who becomes asymptomatic, has not needed pralidoxime or atropine for 1â€“2 days, and who has cholinesterase activity documented to be stable, may be discharged. The patient should not be allowed to go home wearing clothing that was worn when the poisoning occurred. (The clothing should be disposed of as medical waste and destroyed.)

Carbamates

The treatment of patients with carbamate poisoning is identical to that of organic phosphorus compound poisoning with two exceptions. First, the use of pralidoxime in monomethyl carbamate exposure is controversial and many providers will not administer it because animal data imply that pralidoxime may increase AChE inactivation in carbaryl poisoning.[51,89,94] However, other studies and subsequent anecdotal experience have found that pralidoxime is useful in treating poisoning from the dimethyl carbamates such as isolan,[51] and may not adversely impact treatment for monomethyl carbamate poisoning in humans. Recent reports suggest aldicarb poisoning may also benefit from oxime therapy.[132] Comparative human data investigating the use of pralidoxime in carbamate poisonings are currently lacking. Fortunately, because of the rapid hydrolysis of the carbamate-AChE complex, symptoms, including weakness and paralysis, usually resolve within 24â€“48 hours without pralidoxime therapy. However, administering pralidoxime to a poisoned patient in a cholinergic crisis is appropriate when it is not known whether the patient is suffering from organic phosphorus or carbamate pesticide poisoning. If the poisoning is from a carbamate pesticide, pralidoxime therapy may not be necessary, but if used, should not prove detrimental.

Second, significant inhibition of red blood cell cholinesterase and butyrylcholinesterase by carbamates generally does not last for more than 1â€“2 days, assuming absorption is complete. Patients exposed to carbamates usually have normal red blood cell and butyrylcholinesterase values by the time of discharge. There are no reported cases of recurrent or delayed poisonings following carbamate insecticide poisoning. Therefore, repeating cholinesterase tests after patients are asymptomatic is usually unnecessary.

Summary

Cholinesterase inhibitors are commonly used pesticides. As the use of these compounds expands, instances of both acute and chronic exposure are likely to become more common. The clinical presentation

of toxicity from these compounds relates to their ability to stimulate the parasympathetic, and, to a lesser extent, the sympathetic branches of the autonomic nervous system. The early clinical findings of cholinesterase inhibitor poisoning may be mixedâ€”a mixture of muscarinic and nicotinic with signs and symptoms that can include weakness, fasciculations, tachycardia, hypertension, vomiting, diaphoresis, diarrhea, salivation, small (or less often large) pupils, and either micturition or urinary retention. As acetylcholine concentrations continue to rise, the clinical course usually changes to reflect mainly muscarinic, skeletal muscle, and CNS abnormalities, with bradycardia, heart block, hypotension, bronchorrhea, bronchospasm, salivation, diaphoresis, lacrimation, vomiting, diarrhea, urinary incontinence, miosis, fasciculations and paralysis, hyperglycemia, and ketosis. Secretions from every orifice may become copious and hinder resuscitation efforts. With supportive care and antidotal therapy, some patients with cholinesterase inhibitor poisoning improve rapidly, signs and symptoms resolving within 2 or 3 days. In other cases, redistribution and absorption of these chemicals may continue for days, leading to prolonged or recurrent cholinergic symptoms and lengthy hospitalizations. Although measuring cholinesterase activity can be helpful when the diagnosis of cholinesterase inhibitor poisoning is unclear or questionable, most laboratories are unable to perform these tests rapidly enough to be useful. Expeditious recognition of the cholinergic syndrome followed by therapy with atropine to control muscarinic activity and an oxime to regenerate acetylcholinesterase coupled with supportive care will improve clinical outcome.

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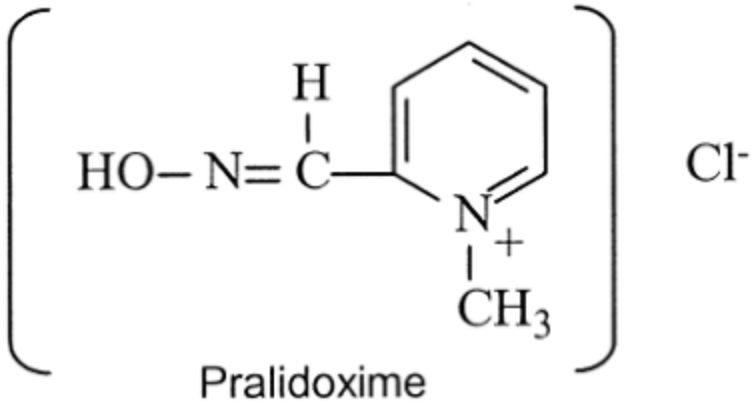
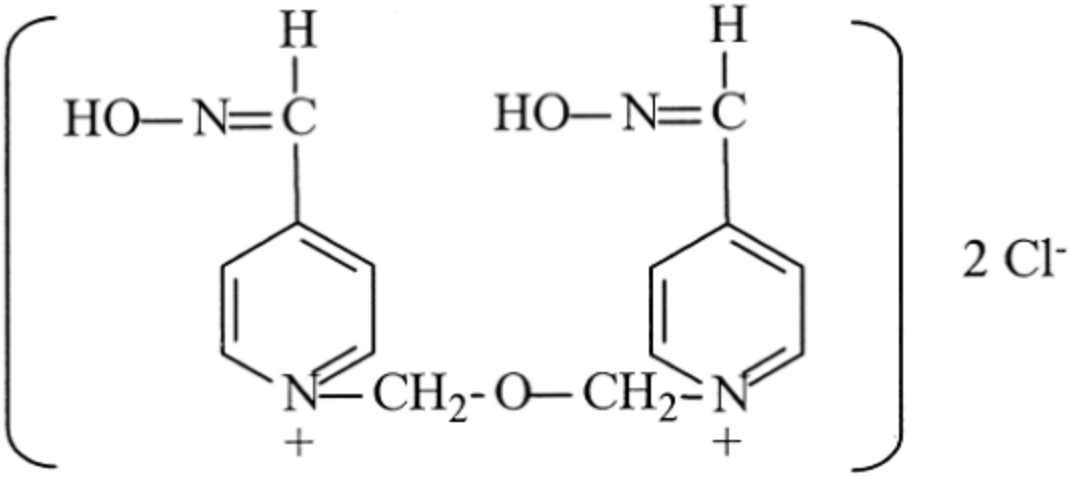
Antidotes in Depth

Pralidoxime

Mary Ann Howland



Pralidoxime



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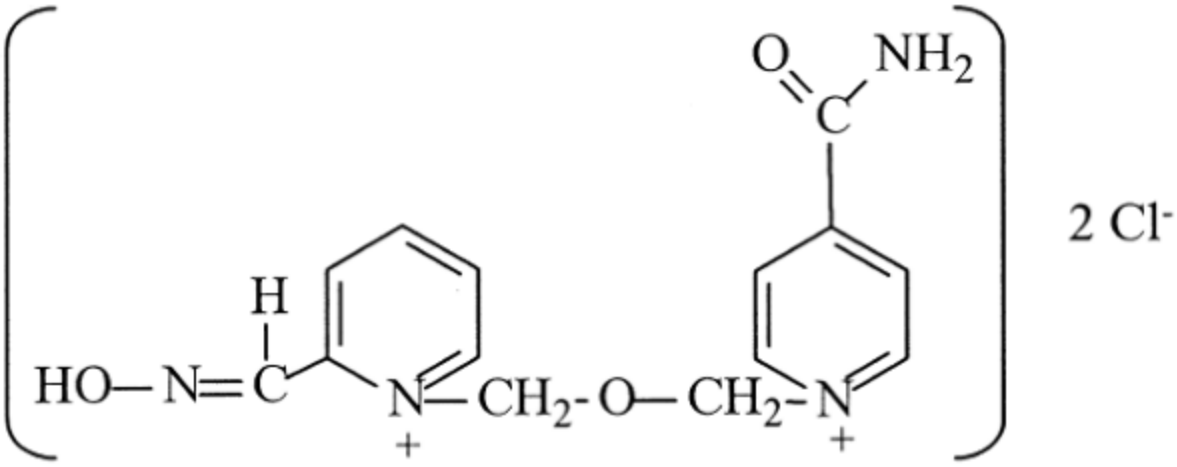

Asoxime (HI6)

Figure. No Caption Available.

Pralidoxime (2-hydroxyiminomethyl-1-methyl pyridinium chloride; 2-PAM) is the only cholinesterase-reactivating agent currently available in the United States.[45] It is employed together with atropine in the management of patients poisoned by organic phosphorus insecticides. Administration should be initiated as soon as possible after exposure, but pralidoxime may remain effective for days after an exposure, and should be administered to all symptomatic patients independent of delay. Continuous infusion is preferable to intermittent administration for patients with serious toxicity and a prolonged therapeutic course may be required.

Chemistry

Pralidoxime is a quaternary pyridinium oxime with a molecular weight of 173 daltons. The chloride salt exhibits excellent water solubility and physiologic compatibility.

Reactivation of Cholinesterases Following Organic Phosphorus Compound Poisoning

Organic phosphorus pesticides are powerful inhibitors of carboxylic esterase enzymes, including acetylcholinesterase (true cholinesterase, found in red blood cells, nervous tissue, and skeletal muscle) and plasma cholinesterase or butyrylcholinesterase (found in plasma, liver, heart, pancreas, and brain).[41] The organic phosphorus compound binds firmly to the serine-containing esteratic site on the enzyme, inactivating it by phosphorylation (Figure 109-2, 109-3 and 109-4).[25,42,63] This reaction results in the accumulation of acetylcholine at muscarinic and nicotinic synapses in the peripheral

and central nervous systems, leading to the clinical manifestations of organic phosphorus poisoning. After the organic phosphorus pesticide binds to cholinesterase, the enzyme is inactivated and can undergo one of three processes: endogenous hydrolysis of the phosphorylated enzyme; reactivation by a strong nucleophile, such as 2-PAM; and aging, which involves biochemical changes that render the phosphorylated molecule inactive.

Endogenous hydrolysis of organic phosphorus compounds can be extremely slow and, for the most part, is considered insignificant in contrast to the rapid hydrolysis of many carbamates. Studies in the 1950s demonstrated the ability of oximes to reactivate cholinesterase bound to organic phosphorus compounds.[71,73] The positively charged quaternary nitrogen of pralidoxime is attracted to the negatively charged anionic site on the phosphorylated enzyme, bringing it in close proximity to the phosphorous moiety (Figure 109-2, 109-3 and 109-4). Pralidoxime then exerts a nucleophilic attack on the phosphate moiety, successfully competing for it and releasing it from the acetylcholinesterase enzyme.[70] This action liberates the enzyme to a variable extent and restores enzymatic function. Organic phosphorus compounds with small substituted side chains are more easily reversed by oximes because of better steric positioning, allowing easier access to the oximes.[73]

The understanding of the pathophysiology of the intermediate syndrome is inadequate to determine whether pralidoxime can prevent the development of the syndrome.[61] Additionally, certain organic phosphorus pesticides may lead to the development of delayed onset neurotoxicity that cannot be prevented by pralidoxime treatment.[15,36]

Efficacy Related to Time of Administration After Poisoning

Early in vitro evidence suggested that the successful use of

cholinesterase reactivators depended on administration within 24â€“48 hours of exposure to the organic phosphorus compounds; afterwards, the acetylcholinesterases would be irreversibly inactivated. However, according to currently available information there is no absolute time limitation on reactivator function. The 48-hour limit was derived from in vitro experiments using a small number of tightly bound compounds and reactivators and data from plasma cholinesterase

enzyme activity, which is now recognized to be relatively resistant to oxime-nucleophilic attack. The early data was accepted without consideration of relevance to human systems, the use of newer and less tightly bound compounds, temperature and pH variation, blood flow, fat solubility, active metabolites, and species specificity. Fat-soluble organic phosphorus compounds redistribute from fat stores over time, acting similarly to sustained-release products. Even if they have not aged, they continue to reinhibit acetylcholinesterase for days. An in vitro experiment assessed the effect of aging on the ability of pralidoxime to regenerate rat erythrocyte and brain cholinesterases using three different organic phosphorus compounds.[67] The rate of reactivation of erythrocyte and brain cholinesterases was significantly decreased over time for fenitrothion and methyl parathion, with no reactivation occurring at 48 hours. This is partly because demethylated organophosphorus pesticides age more quickly than diethylphosphorylated agents.[15] In contrast, a very high reactivation rate for ethyl parathion was still apparent at 48 hours. This demonstrates that the structure of the organic phosphorus compound is important in the rates of aging and reactivation with pralidoxime. Fenitrothion and methyl parathion are both O'O dimethyl organic phosphorus compounds as is dimethoate, whereas ethyl parathion is an O'O diethyl organic phosphorus compound.[67] Other studies also suggest that 2-PAM and obidoxime are effective long after the previously suggested 48-hour window of therapy.[2,4,7,11,14,15,15a,39,69]

Carbamates

Acetylcholinesterases inactivated by most carbamates spontaneously reactivate with half-lives of 1â€“2 hours, and typical clinical recovery occurs in several hours. However, in severe cases, cholinergic symptoms may persist for 24 hours.[9,19] Pralidoxime is rarely indicated for carbamate poisoning, but it is not generally contraindicated as was previously suggested. The conclusion that pralidoxime was contraindicated after a carbamate exposure was based solely on data derived from the study of a single carbamate (carbaryl). This conclusion was inappropriately applied to all carbamates. In vitro experiments had demonstrated that pralidoxime had no effect on the reactivation of erythrocyte acetylcholinesterase carbamylated by aldicarb, methomyl, and carbaryl.[30] However, Pralidoxime decreased the rate of carbamylation of 16 insecticidal carbamates and only modestly increased the rates for 3, 1 of which was carbaryl.[13] Animal studies demonstrated the beneficial effects of pralidoxime and obidoxime in decreasing the lethality of several carbamate insecticides.[43,60] In contrast, obidoxime and pralidoxime worsened the toxicity of carbaryl possibly because the carbamate-oxime complex may actually be a more potent cholinesterase inhibitor than carbaryl alone.[19,43,60] Even in the presence of carbaryl, however the combination of atropine plus an oxime resulted in survival data comparable to that of atropine alone.[19] This evidence suggests that although pralidoxime is not usually a necessary adjunct to atropine in a pure carbamate overdose, it may at least occasionally improve morbidity and mortality.[9] Pralidoxime should not be withheld in a seriously poisoned patient out of concern that a cholinergic xenobiotic may be a carbamate.[30] However, pralidoxime should always be used in conjunction with atropine and should never be the sole therapeutic agent.

Pharmacology

Pralidoxime is most important at nicotinic sites where atropine is

ineffective, often improving muscle strength within 10â€“40 minutes after administration.[42,63] This effect is vital to maintaining the functioning of the muscles of respiration. Pralidoxime is synergistic with atropine and in addition liberates cholinesterase enzyme so that additional acetylcholine can be metabolized. This suggests that 2-PAM should rarely if ever be used alone.[16,42] Some organic phosphorus compounds respond much better to 2-PAM than do other compounds depending on the affinity of pralidoxime for the particular type of phosphorylated enzyme and its reactivating ability and whether ageing has occurred prior to administration.[74]

The CNS benefits of 2-PAM are controversial, as the molecule is a quaternary nitrogen compound not expected to cross the bloodâ€“brain barrier.[35,42] Animal studies suggest conflicting results.[38] Rat studies using radiolabeled pralidoxime demonstrated a lack of any radioactivity in the CNS after IV administration.[66] Following exposure to IV fenitrothion, intravenous administration of pralidoxime in rats failed to improve survival or to reactivate brain cholinesterase, whereas intramedullary pralidoxime partially restored brain cholinesterase and eliminated fatalities.[66] A recent rat experiment using a microdialysis technique demonstrated only 10% CNS penetration of 2-PAM.[54]

Clinical observations however have certainly suggested a CNS action of 2-PAM with a prompt return of consciousness reported in some cases.[41,42,49,70] A 3-year-old child who was comatose from parathion was given 500 mg of 2-PAM IV over 15 minutes with continuous electroencephalographic (EEG) monitoring. Within 2 minutes there was a dramatic response on the EEG, followed rapidly by normalization of consciousness.[31]

Early work with cats led to a proposal that a plasma concentration of â‰¥4 Âµg/mL was a desired therapeutic concentration for pralidoxime.[62] Recent in vitro work with human erythrocytes and a mouse hemidiaphragm model suggests that higher serum concentrations are actually needed.[74] Twenty percent reactivation

was achieved in 5 minutes with serum concentrations of 10 Âµg/mL.[74] A recent simulation and analysis suggests that plasma concentrations between 10 and 15 Âµg/mL (50â€“100 Âµmol/L) are necessary for optimal treatment of severely poisoned patients.[15a] These recommendations await validation in poisoned patients.

Other Reversal Agents

To improve the central effect of pralidoxime, the dihydropyridine derivative of pralidoxime was synthesized.[5] This derivative, known as pro-2-PAM, acts as a â€œprodrug,â€• or drug carrier, which allows passage through membranes such as the bloodâ€“brain barrier. Once across the membranes, spontaneous in vivo oxidation converts pro-2-PAM to the active species, demonstrating a 13-fold higher level of 2-PAM in the brain than when 2-PAM itself is administered under similar conditions. Further experiments support the significantly increased central effects of pro-2-PAM.[53]

The use of sugar oximes (the molecular combination of glucose with 2-PAM derivatives) to promote CNS penetration also appears promising.[50] Obidoxime (Toxogonin) is an oxime used outside the United States that contains two active sites per molecule and is considered by some to be more effective than 2-PAM.[16,74] An in vitro study using human erythrocyte acetylcholinesterase supported the superiority of obidoxime to pralidoxime in reactivating acetylcholinesterase inhibited by the dimethyl phosphoryl and diethyl phosphoryl organic phosphorus compounds paraoxon, mevinphos, and malaoxon. On a molar basis, obidoxime is approximately 10â€“20 times more effective in reactivating acetylcholinesterase than is pralidoxime.[74]

The H series of oximes (named after Hagedorn) were developed to act against the chemical warfare nerve agents. These oximes have superior effectiveness against sarin, VX and certain types of newer pesticides (eg, methyl-fluorophosphonylcholines).[10,26,29,32,52,74,75]

Unfortunately, they are less efficacious for traditional organic phosphorus insecticide poisoning, and their toxicity profile is inadequately defined.[10,26,29,32,52,74,75] In addition to reactivating acetylâ€“cholinesterases, the Hagedorn oximes demonstrate direct central and peripheral anticholinergic effects at supratherapeutic concentrations.[52]

Duration of Treatment

The signs and symptoms of organic phosphorus compound poisoning are usually manifest from within minutes up to 24 hours.[42] Delayed manifestations occur with the fat-soluble organic phosphorus compounds, such as fenthion or chlorfenthion. The route of exposure may also influence the onset of systemic symptoms; for example, there may be a delay following dermal contact, which does not occur following ingestion or inhalation. When either symptoms are delayed or prolonged, or when treatment is delayed, extended therapy with 2-PAM may be indicated.[1,7,39] In one case of poisoning with the fat-soluble organic phosphorus compound fenthion 5 days elapsed before cholinergic symptoms appeared, and some symptoms then persisted for 30 days.[39] Pralidoxime and atropine were administered continuously in varying doses for the time that the patient was symptomatic.

Pharmacokinetics and Pharmacodynamics

Pralidoxime pharmacokinetics are characterized by a two-compartment model. Pharmacokinetics values vary depending on whether calculations are determined in healthy volunteers or poisoned patients. In volunteers, the steady-state volume of distribution is about 0.8 L/kg and the half-life is 75 minutes.[24,47] Pralidoxime is renally excreted, and within 12 hours, 80% of the dose is recovered unchanged in the urine.[59]

A dose of 10 mg/kg of 2-PAM IM to volunteers results in peak plasma concentrations of 6 Âµg/mL (reached 5â€“15 minutes after IM injection) and a plasma half-life of approximately 75 minutes.[59] Following a standard IV 30-minute infusion dose of 1 g of 2-PAM in a 70-kg man, the plasma level fell to less than 4 Âµg/mL at 1.5 hours. In a simulated model, a continuous infusion of 500 mg/h of 2-PAM led to a level greater than 4 Âµg/mL after 15 minutes, which could be maintained throughout the infusion.[64] In a human volunteer study, an intravenous loading dose of 4 mg/kg over 15 minutes followed by 3.2 mg/kg/h for a total of 4 hours maintained pralidoxime serum concentrations greater than 4 Âµg/mL for 4 hours. The same total dose, 16 mg/kg, administered over 30 minutes only maintained those concentrations for 2 hours.[37]

In poisoned patients receiving continuous infusions of pralidoxime as opposed to intermittent infusions, both the volume of distribution and the half-life are increased. A volume of distribution of 2.77 L/kg, an elimination half-life of 3.44 hours, and a clearance of 0.57 L/kg/h were reported in poisoned adults given a mean loading dose of 4.4 mg/kg followed by an infusion of 2.14 mg/kg/h.[70] In poisoned children and adolescents, the volume of distribution varied with severity of poisoning from 8.8 L/kg in the severely poisoned patients to 2.8 L/kg in moderately poisoned patients.[56] After a mean loading dose of 29 mg/kg followed by a continuous infusion of about 14 mg/kg/h, a steady-state serum concentration of 22 Âµg/mL, a half-life of 3.6 hours, and a clearance of 0.88 L/kg/h were calculated.[56]

Oral administration of salts of 2-PAM (not used clinically because of anticholinesterase poisoningâ€“induced vomiting) demonstrated a peak concentration at 2â€“3 hours, a biologic half-life of 1.7 hours, and an average urine recovery of 27% of unchanged 2-PAM in humans, and clinical efficacy in a mice model.[8,28]

Autoinjector administration of 600 mg of pralidoxime chloride in an adult man (9 mg/kg) produced a concentration above 4 Âµg/mL at 7â€“16 minutes, a maximum plasma concentration of 6.5 Âµg/mL at

about 28 minutes, and a half-life of 2 hours.[47,58] Using traditional needle and syringe IM administration requires longer time to achieve comparable plasma concentrations. The autoinjectors more widely disperse the medication in the tissues resulting in faster absorption.[51]

Adverse Effects

At therapeutic doses of 2-PAM in humans, adverse effects are minimal.[17,18,40,41 and 42,49,64] Transient dizziness, blurred vision, and elevations in diastolic blood pressure may be related to the rate of administration.[24,37] Doses of 45 mg/kg produce blood pressure elevations that may persist for several hours, but may be reversed with IV phentolamine.[58] Rapid IV administration has produced sudden cardiac and respiratory arrest because of laryngospasm and muscle rigidity.[44,57,72] Following IM administration, other adverse effects reported to occur in normal volunteers include diplopia, dizziness, headache, drowsiness, nausea, tachycardia, increased systolic blood pressure, hyperventilation, decreased renal function, muscular weakness, and pain at the injection site.[47] Elevations in liver enzymes were observed in volunteers administered autoinjector doses of 1200â€“1800 mg; LFTs returned to normal in 2 weeks.[47]

Pralidoxime is pregnancy category C and should be used as clinically indicated for women.

Dosing and Administration

The optimal dosage regimen for pralidoxime is unknown. Traditionally, the recommended initial adult dose is 1â€“2 g in 100 mL of 0.9% sodium chloride solution given intravenously over 15â€“30 minutes.[48] The pediatric dose is 20â€“40 mg/kg up to a maximum of 2 g as a loading dose given intravenously over 30-60 minutes.[51] These initial doses can be repeated in 1 hour if muscle weakness and fasciculations are not relieved. Thereafter, additional

doses may be needed every 3â€“8 hours as long as signs of poisoning recur.[48]

Patients with reduced renal function may require dosage adjustment, but there are no specific recommendations on how to accomplish this.[45] Alternatively, a loading dose followed by a continuous maintenance infusion has been reported to be safe and effective in a limited number of adults and children.[40,42,56,65,67,70] Serious cholinergic poisoning may require a continuous 2-PAM infusion of 500 mg/h in adults and 10â€“20 mg/kg/h up to 500 mg/h in children. One author suggests a loading dose of 25â€“50 mg/kg (up to a maximum dose of 2 g) in children, depending on the severity of the poisoning, to be followed via continuous infusion of 10â€“20 mg/kg/h.[51,56] In patients with acute lung injury the dose can be given as a 5% solution by a slow IV injection over at least 5 minutes.[45,59]

Although IV administration is preferred, IM administration is acceptable using a 1-g vial of 2-PAM reconstituted with 3 mL of sterile water for injection or 0.9% sodium chloride for injection to provide a solution containing 300 mg/mL (concentrations above 35% weight/volume produce muscle necrosis in animals).[45,59]

Depending on the severity of a nerve agent exposure, 1â€“3 injections with the autoinjector of both atropine and pralidoxime should be administered. The number of autoinjector doses administered to a child depends on the child's age and weight.[20,34] For children ages 3â€“7 (13â€“25 kg), one autoinjector of atropine and one autoinjector of pralidoxime should be administered, which should result in a projected pralidoxime dose of 24â€“46 mg/kg. For ages 8â€“14, two autoinjectors of atropine and two autoinjectors of pralidoxime should be administered. These injections should result in a projected pralidoxime dose of 24â€“46 mg/kg. For patients older than 14 years of age, three autoinjectors of atropine and pralidoxine should be administered. This results in a projected dose of pralidoxime of less than 35 mg/kg. For children younger than 3 years

during an emergency, one autoinjector of atropine and one of pralidoxime may be administered in accordance with a risk-benefit analysis. If time permits and only autoinjector doses are available, its contents after isopropyl alcohol swabbing may be transferred to a small sterile vial for traditional IM administration with a needle and syringe.[21]

In most cases, pralidoxime is continued for a minimum of 24 hours after symptoms have resolved. Extended dosing may be necessary, depending on the patient's clinical condition and the nature of the organic phosphorus compound.[68] Alternatively, if serial determinations of red blood cell cholinesterase activity can be obtained in a timely fashion, restoration of a normal value seems a reasonable endpoint of therapy with the exception of rapidly aging organic phosphorus compounds where a normal AchE cannot be achieved. In all cases, patients should be observed for recrudescent toxicity after termination of pralidoxime. If symptoms return, therapy should be continued for a minimum of an additional 24 hours.

Availability

Pralidoxime chloride (Protopam) is supplied in 20-mL vials containing 1 g of powder, ready for reconstitution with sterile water for injection.[45,48]

The addition of 20 mL of sterile water for injection to the 1-g vial of 2-PAM results in a 5% solution (50 mg/mL). Following reconstitution, the 2-PAM should be used within several hours. This solution can be further diluted to a volume of 100 mL of normal saline for IV infusion.

As noted above pralidoxime chloride is also available for IM administration by an autoinjector containing 600 mg of pralidoxime in 2 mL of sterile water for injection with 20 mg benzyl alcohol and 11.26 mg glycine. The 2-PAM autoinjector also is packaged in a kit containing 600 mg of pralidoxime in 2 mL of sterile water for

injection with 40 mg benzyl alcohol and 22.5 mg glycine accompanied by an autoinjector containing 2.1 mg of atropine in 0.7 mL of a sterile solution containing 12.47 mg glycerin and not more than 2.8 mg phenol. This kit is called a â€œMark 1 Nerve Agent Antidote Kit (NAAK)â€• and is designed to be used IM by first responders in case of a nerve agent attack. The needles are approximately 1 inch in length.

Summary

Pralidoxime is an effective reactivator of acetylcholinesterase in many organic phosphorus compound poisonings. It primarily reverses neuromuscular manifestations but has some CNS effects. New oximes may improve CNS penetration and efficacy. Pralidoxime and atropine are synergistic and should be used together in the management of patients with organic phosphorus poisonings. If a patient requires multiple doses of atropine for muscarinic symptoms, then the use of 2-PAM is indicated. In symptomatic patients, acetylcholinesterase is partially inactivated and will remain so until new enzyme is synthesized or inactivated enzyme is reactivated. The resolution of all signs or symptoms with atropine alone indicates only that acetylcholinesterase inactivation is less than 50% and that endogenous hydrolysis by nonphosphorylated enzyme is sufficient to eliminate symptoms. This clinical response by no means indicates however, that the enzyme systems are fully active; patients may still benefit from enzyme regeneration with the safe and effective antidote pralidoxime.

Finally, because newer fat-soluble organic phosphorus pesticides are currently available, it may be necessary to administer atropine and 2-PAM for more prolonged periods of time than previously indicated based on the clinical manifestations and the predicted kinetics of the highly fat soluble pesticides.[7]

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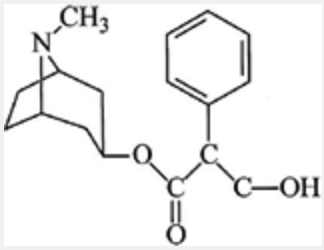
Antidotes in Depth

Atropine

Mary Ann Howland



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Atropine is the prototypical antimuscarinic drug. It is a competitive antagonist at both central and peripheral muscarinic receptors, used to treat symptomatic exposures to muscarinic agonists and

acetylcholinesterase inhibitors such as carbonate and organic phosphorous pesticides and organic phosphorus chemical warfare nerve agents.

History

Many plants contain the alkaloids atropine and/or scopolamine. One notable example is *Atropa belladonna*, named by Linnaeus after Atropos, the goddess of fate in Greek mythology who could cut short a person's life. Belladonna means beautiful woman in Italian and comes from the practice by Italian women of placing belladonna extract in their eyes, to produce aesthetically pleasing dilated pupils.[6] In the early 1800s, atropine was isolated and purified from plants and in the 1860s, Fraser experimented with the dose response relationship between atropine and physostigmine involving various organs such as the heart and the eye.[12] Experiments in the 1940s with cholinesterase inhibitors demonstrated the ability of atropine to reverse many of the effects of these xenobiotics and to protect against doses 2â€“3 times the LD_{50}s in animals.[34]

Chemistry

Atropine (dl-hyoscyamine), like scopolamine (l-hyoscine), is a tropane alkaloid with a tertiary amine structure that allows CNS penetration. Quaternary amine antimuscarinic agents such as glycopyrrolate, ipratropium, and tiotropium do not cross the bloodâ€“brain barrier into the CNS.[6]

Pharmacology

Centrally acting muscarinic antagonists include atropine scopolamine and homatropine. Glycopyrrolate, ipratropium, and tiotropium act peripherally. Scopolamine is about 10 times more potent than atropine.[20]

Cholinesterase inhibitors (eg, organic phosphorous insecticides, carbamates chemical warfare nerve agents) prevent the breakdown of acetylcholine by acetylcholinesterase thereby increasing the amount of acetylcholine available to stimulate cholinergic receptors. Cholinergic receptors are made up of muscarinic and nicotinic receptors. Muscarinic agonists (eg, muscarine, methacholine, and pilocarpine) stimulate muscarinic receptors. They do not have any effect on nicotinic receptors.

Atropine is a competitive antagonist of acetylcholine primarily at muscarinic receptors (M_1â€“M_5).[7] Muscarinic receptors are coupled to G proteins and either inhibit adenylyl cyclase (M_2, M_4) or increase phospholipase C (M_1, M_3, M_5). Muscarinic receptors are widely distributed throughout the peripheral and central nervous systems. The competitive blockade of muscarinic receptors in normal individuals results in dose dependent effects which occur in a hierarchy dependent on the importance of parasympathetic tone.[6] In adults low doses (0.5 mg) of atropine cause a paradoxical bradycardia, and some drying of the mouth and sweat glands. Higher doses of atropine (2 mg) produce noticeable dryness, subjective feeling of warmth, slight flushing, slight tachycardia, reactive slightly dilated pupils blurred near vision, mild drowsiness, some postural hypotension, and urinary hesitation. At higher doses of 3â€“4 mg of atropine all the aforementioned symptoms are exaggerated, hyperthermia, tachycardia, and drowsiness are present. At doses of 5 mg of atropine all of previously noted symptoms are even more marked and in addition the patient has difficulty voiding and GI transit time and tone are decreased. By the time doses of â‰¥10 mg of atropine are employed patients are incapacitated with hot, dry, flushed skin, dilated pupils, blurred vision, very dry mouth, tachycardia, urinary retention, constipation, increased drowsiness or disorientation, hallucinations, stereotypical movements, bursts of laughter, delirium, and finally, coma.[6,14] The duration of action of atropine is dose-dependent and may last as long as 12â€“24

hours.

Miosis from the topical instillation of an cholinesterase inhibitor into the eye will not be reversed by the systemic administration of atropine.[14] The systemic administration of 354 mg of atropine made one patient floridly anticholinergic but did not counteract the ophthalmic effects of a previously instilled topical cholinesterase inhibitor.[14]

This paradoxical bradycardia produced at low doses of atropine is thought to be a consequence of the inhibition of peripheral M_1 presynaptic postganglionic parasympathetic neurons: stimulation of these receptors by acetylcholine inhibits the further release of acetylcholine, and atropine interferes with this negative feedback.[6,33]

Pharmacokinetics and Pharmacodynamics

Atropine is absorbed rapidly from most routes of administration including inhalation, oral, and IM.[2] Oral ingestion of 1 mg of atropine produced maximal effects on heart rate and on salivary secretions at 1 and 3 hours respectively.

The distribution half-life of atropine following IV administration is approximately 1 minute. The apparent volume of distribution (Vd) is about 2â€“2.6 L/kg.[19] As a result of the rapid distribution, 10 minutes after IV administration less than 5% of the dose remains in the plasma. The plasma concentrations of atropine are similar at 1 hour following either 1 mg IV or IM in adults.[2,5] The elimination half-life is 6.5 hours.[27]

Following IM administration of 0.02 mg/kg in adults the absorption rate and elimination rates were comparable for the racemic d,l-hyoscyamine and the active l-hyoscyamine at 8 minutes and 2.5

hours respectively. The mean peak plasma concentration and the area under the curve (AUC) were higher for the racemic mixture indicating a stereochemical difference in metabolism.[19] Renal elimination accounts for 34% of the dose and the majority of renal elimination occurred within 6 hours. Other studies suggest as much as 57% may be eliminated unchanged in the urine.[2] Plasma concentrations of l-hyoscyamine correlate with effects on heart rate and the antisialagogue effects. Plasma concentrations below 0.5 Âµg/L caused bradycardia, whereas higher concentrations caused tachycardia.[19]

Atropine autoinjectors are now given to first-responders for use during chemical terrorist attacks. The administration of 2 mg of atropine by autoinjector was compared to 2 mg administered by conventional needle and syringe into the deltoid of 6 adult subjects.[31] The onset of tachycardia and the time to maximal increase in heart rate occurred sooner with the autoinjector (16 minutes vs. 23 minutes and 34 minutes vs. 41 minutes respectively). An analysis of radiographs of contrast material injected by autoinjector or conventional IM administration into a dog's leg, demonstrated that the autoinjector appeared to â€œsprayâ€• the material into a larger tissue area accounting for a faster rate of absorption.[31]

Ocular instillation of atropine causes mydriasis by blocking the M_3 muscarinic receptor on the iris sphincter muscle.[23] The peak mydriatic effect occurs within 30â€“40 minutes and persists for 7â€“10 days. Ophthalmic atropine also causes cycloplegia by blocking the M_3 muscarinic receptor on ciliary muscle. Peak cycloplegia occurs within 1â€“3 hours and persists for 6â€“12 days.

In contrast, the effects of topical homatropine on the eye occur sooner than topical atropine (10â€“30 minutes for mydriasis and 30â€“90 minutes for cycloplegia) and are shorter in duration (6â€“48 hours).

An investigation of the bioavailability of atropine eye drops in healthy adults revealed on average 65% systemic absorption, but with a wide individual variability.[18] The time to maximum serum concentration was 30 minutes and the elimination half-life was 2.5 hours.

The pharmacokinetics of 3 inhaled doses of atropine was compared to 2 mg of IM atropine in healthy adults.[15] Peak concentrations were comparable for the 2 mg inhaled and 2 mg IM atropine doses. The time to peak concentration following inhalation averaged 1.3 hours.

Clinical Use

One of earliest descriptions of the effectiveness of atropine in parathion and tetraethylpyrophosphate insecticide poisoning was published in 1955.[13] The report emphasized the improvement in survival when atropine was administered early and continued with adequate maintenance doses in conjunction with intubation and ventilation. The report also found that after parathion and tetraethyl pyrophosphate exposure, dogs were more likely to develop heart block and bronchoconstriction, whereas humans were more likely to develop a relative rather than absolute bradycardia. Additionally, humans were more likely to die from respiratory causes stemming from central apnea, diaphragmatic weakness and bronchorrhea.

In 1971, a landmark case series and review of organic phosphorus insecticide poisonings were published. Included in this report was a table classifying the severity of poisoning along with treatment protocols for each level of severity.[24] This regimen served as the foundation of treatment regimens for many years.

In the 1930s and 1940s, the Germans synthesized organic phosphorous insecticides (acetylcholinesterase inhibitors) that were further developed as chemical warfare nerve agents (Chap.

126).[30] Although these agents inhibit acetylcholinesterase in a manner similar to that of traditional organic phosphorous insecticides such as parathion, these so called â€œnerve agentsâ€• also affect other cholinesterases, and at high doses, directly affect nicotinic and muscarinic receptors. Atropine was chosen in the late 1940s as the standard antidote for these nerve agents. The dose of atropine needed to antagonize these nerve agents is much less than that needed to effectively antagonize traditional organic phosphorous insecticides, largely because of differences in pharmacokinetics. The benefits of adding pralidoxime to atropine were noted in the 1950s, and in the 1960s, pralidoxime was established as a standard antidote in addition to atropine for these agents (Antidotes in Depth: Pralidoxime).

Adverse Effects and Toxicity

When atropine is used in the absence of a xenobiotic that increases or mimics acetylcholine, these effects begin at 0.5 mg IV in the adult. However, in the presence of a muscarinic agonist or an anticholinesterase agent, the effects may not occur until many milligrams of atropine are administered.

IV doses of greater than 10 mg of atropine and oral doses of 500â€“1000 mg have been administered with full recovery. Deaths from atropine use, are usually correlated with hyperthermia.

An unintentional atropine dose of 1 g orally resulted in typical manifestations of anticholinergic poisoning which began within a short time and lasted 4 days.[1] In 2 hours the patient went from feeling hot and flushed with blurred vision to stuporous. Over the ensuing 24 hours he became tachycardic, hyperthermic, and comatose with dilated unreactive pupils and shallow respirations. By 40 hours he started to respond to his name and his temperature had normalized, but he remained dry with dilated and nonreactive pupils. He went from comatose to restless,

hallucinating, and paranoid. At 4 days he regained a normal mental status with amnesia for the previous 4 days.

A survey of pediatric emergency departments in Israel reported on 240 children who were unintentionally injected with atropine autoinjectors during the Persian Gulf crisis.[3] Half of the children developed systemic effects that correlated with the doses of atropine administered. Eight percent of effects were serious but there were no seizures or deaths.

Systemic atropine toxicity may occur when too large a dose of atropine is instilled in the eye, especially in children.[26] Excessive absorption from other routes of administration (eg, rectal, inhaled) would also be expected to result in toxicity.[29] In the event of an atropine overdose, physostigmine, a reversible, CNS active, cholinesterase inhibitor, is the antidote of choice (Antidotes in Depth: Physostigmine). Psychiatric patients in the 1950s were often given atropine as a remedy. Within 15â€“20 minutes of getting 32 to 212 mg of IM atropine, patients become restless and often confused. This progresses to muscular incoordination, ataxia, weakness and garbled speech.[11] The patients then pass from being disoriented, with illusions, visual hallucinations, and delirium to being comatose. The coma often lasted for 4â€“6 hours and then patients recovered in a manner that in some respects is the reverse of intoxication. Regardless of the dose of atropine required to induce

the coma, physostigmine 4 mg IM completely reversed it within 20 minutes but the reversal only lasted for 30â€“45 minutes.

Atropine is classified by the Food and Drug Administration (FDA) as pregnancy category C. Atropine crosses the placenta and may cause tachycardia in the fetus near term.[32]

Administration and Dosing

The dosage regimen of atropine for an organic phosphorous pesticide poisoning in adults has never been studied in a randomized controlled trial and there is considerable variation in textbook recommendations.[9] However experience suggests that atropine should be initiated in adults in doses of 1â€“2 mg IV for mild-to-moderate poisoning and 3â€“5 mg IV for severe poisoning with unconsciousness.[24] This dose can be doubled every 3â€“5 minutes.[10] The editors believe that the most important endpoint for adequate atropinization is clear lungs, and the reversal of the muscarinic toxic syndrome. Some authors suggest clear lungs, heart rate â‰¥80 beats/min, and systolic blood pressure â‰¥80 mm Hg as most important, and dry axillae and wider than pinpoint pupils as additional goals.[10] Once these endpoints have been achieved, a maintenance dose of atropine needs to be started. One group suggests administering 10â€“20% of the loading dose as an IV infusion every hour as a starting point with meticulous frequent reevaluation and titration.[9] When too much atropine is administered, the patient demonstrates classic signs of peripheral anticholinergic toxicity: hot dry flushed skin, urinary retention, absent bowel sounds, tachycardia, mydriasis and central anticholinergic activity including restlessness, confusion, and hallucinations or CNS depression.

In the event that a person is exposed to a chemical warfare nerve agent atropine should be administered in a dosage suitable for both the severity of the poisoning and the age of the patient. In a conscious adult patient with mild to moderate cholinergic effects 2 mg of atropine IV or IM should be administered every 5â€“10 minutes until shortness of breath and drying of secretions occurs.[30] One adult autoinjector contains 2 mg of atropine and therefore multiple injectors are often required. Total doses of 2â€“4 mg of atropine are usually all that is needed. Patients who are unconscious or apneic require higher total doses with 5â€“15 mg usually sufficing.[30]

The appropriate total autoinjector doses for children depend on

age and weight.[16,21] For ages 3â€“7 (13â€“25 kg), 1 autoinjector (2 mg) of atropine and one autoinjector of pralidoxime (600 mg) should be administered resulting in a projected atropine dose of 0.08â€“0.15 mg/kg. For ages 8â€“14, two autoinjectors of atropine and two autoinjectors of pralidoxime should be administered resulting in a projected atropine dose of 0.08â€“0.15 mg/kg. For patients older than 14 years of age, three autoinjectors of atropine and pralidoxime should be administered. This results in a projected dose of atropine of less than 0.11 mg/kg. In an emergency for children younger than 3 years of age a risk-benefit analysis would suggest injecting one autoinjector of atropine and one of pralidoxime. If time permits and only one autoinjector is available for use, its contents may be transferred to a small sterile vial for traditional IM administration with a needle and syringe.[17]

Availability

Atropine sulfate injection, is available in many different strengths, with the following concentrations in each 1 mL vial or ampule: 50 Âµg, 300 Âµg, 400 Âµg, 500 Âµg, 800 Âµg and 1 mg.

The AtroPen Auto-Injector is a prefilled syringe designed for IM injection by an autoinjector into the outer thigh.[4] It is available in 4 strengths: 0.25 mg, 0.5 mg (Blue Label), 1 mg (Dark Red Label), and 2 mg (Green Label).

Atropine is also packaged in a kit with a second autoinjector containing 600 mg of pralidoxime in 2 mL of sterile water for injection with 40 mg benzyl alcohol and 22.5 mg glycine. The pralidoxime injector is accompanied by an atropine autoinjector containing 2.1 mg of atropine in 0.7 mL of a sterile solution containing 12.47 mg glycerin and not more than 2.8 mg phenol. This particular combination kit is called a â€œMark 1 Nerve Agent Antidote Kitâ€• (NAAK) and is designed for IM use in case of a nerve agent attack. The needles are approximately 1 inch in

length.[22]

Atropine is available orally in 300-Âµg, 400-Âµg, and 600-Âµg tablets.

In case of a shortage during an emergency, in vitro evidence suggests that outdated atropine retains its potency and that an extemporaneously prepared atropine solution from powder is stable for at least 3 days.[8,28]

Summary

Atropine has many clinical uses as a competitive antagonist at both central and peripheral muscarinic receptor sites. The use of atropine is extensive for patients with bradycardias, in advanced cardiac life support and those exposed to acetylcholinesterase inhibitors in the workplace, in the home, and potentially on the battlefield.

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Chapter 110

Insecticides: Organic Chlorines, Pyrethrins/Pyrethroids, and DEET

Michael G. Holland

A 2-1/2-year-old (14-kg) boy got into the medicine cabinet and swallowed lindane shampoo (150 mg, or 10.7 mg/kg). Shortly thereafter his mother tonic-clonic seizures. When emergency medical services arrived, the child by the time he arrived at the emergency department (ED) he was more a vomited once.

On examination he was lethargic with no seizure activity. Vital signs were heart rate 110 beats/min; respiratory rate 24 breaths/min, and temperat were clear to auscultation. The poison center was called and the poison recommended achieving IV access, observation, and the administration c should seizures recur. The child was admitted to the pediatric intensive c postictal confusion rapidly cleared, and his mental status remained norma subsequent seizures. His vital signs remained normal. He was discharged completely asymptomatic. His parents received poison prevention educat

Organic Chlorine Pesticides

History and Epidemiology

Until the 1940s, commonly available pesticides included highly toxic arse and nicotine.[100] When Nobel Prize-winning chemist Paul MÃ¼ller demons of dichlorodiphenyltrichloroethane (DDT) in the early 1940s, a whole new introduced.[32] The organic chlorine insecticides were inexpensive to proc stable, and had relatively low acute toxicity when compared to previous chlorines have a negative temperature coefficient, making them more ins and less toxic to warm-blooded organisms (Table 110-1).[125] Widespread occurred from the 1940s until the mid-1970s. They were highly effective agriculture, allowing unprecedented crop output from each acre of arable organic chlorines were used extensively in structural protection and soil health applications of DDT and its analogues were also found in the contr malaria by eliminating the mosquito vector.[25] By 1953, DDT alone was c 50 million lives, and with averting one billion cases of human disease.[33] I this consequential impact on human health, DDT is the single most impor explosion that occurred between 1950 and 1970.[33]

However, the properties that made these chemicals such effective insectic environmental hazards: they are slowly metabolized, lipid soluble, chemi persistent. In her 1962 book, *Silent Spring* , Rachel Carson, a biologist w Service, demonstrated that organic chlorines are bioconcentrated and bior She alleged that this persistence could eventually lead to increases in car publications since then have stated that organic chlorine residues in pred peregrine falcons, bald eagles, and pelicans, caused eggshell thinning an success.[32] However, these theories were not actually demonstrated when administered in high concentrations to experimental birds. Testing on dor Japanese quail,[16 , 18 , 90] chickens,[4] and mallard ducks[120] showed little o before the Environmental Protection Agency (EPA) regarding DDT registrat disproved fear of placing future generations at risk of cancer. This, and t residues in humans, led to the severe restriction or total ban of DDT and North America and Europe.[25] There is considerable evidence that since D replacements have placed many more millions at risk for malaria, and is

millions of deaths from this disease.[70 , 88 , 89] Not surprisingly, DDT is st mosquito control agent with a low order of acute toxicity, and is very ine replacement insecticides. For these reasons, the World Health Organizatior list of banned pesticides, and it is still widely used for malaria control pr will likely be for the foreseeable future.

Organic chlorine pesticides are complex, cyclic polychlorinated hydrocarb generally in the range of 300â€“550 Da. They are nonvolatile solids at ro central nervous system stimulants.

Hexachloro-cyclohexanes
Lindane (gamma isomer) 58â€“89â€“9
Kwell
Topical scabicide; Seed treatment: RED[2] 2001
Moderate
High
Low
Topical scabicide: Seizures, CNS excitation; musty odor
DDT and Analogues
DDT-Dichlorodi-phenyltrichlor-oethane 50â€“29â€“3
Neocid, Ixodex, Anofex, others
Cancelled 1972
Low to moderate
Low
Highest
Tremors, CNS excitation; odorless
Methoxychlor 72â€“43â€“5
Marlate
Suspended 2000
Low
Low
Moderate
Less toxic DDT substitute
Dicofol 115-32-2
Kelthane

Residential Use Banned 1998; Cotton, Citrus, Apple
Low
Low
Low

Chlorobenzilate 510-15-6
Benzilan, Benzo-Chlor
Citrus miticide
Low
Low
Low
Much less environmenta persistence than DDT
Cyclodienes and Related Compounds
Aldrin 309-00-2
Aldrex, Octalene, Toxadrin
Cancelled 1974
High
High
High
Rapidly metabolized to Dieldrin; mild â€œchemicalâ€• odor
Dieldrin 60-57-1
Dieldrite, Octalox, Quintox
Cancelled 1974
High
High
High
Stereoisomer of Endrin; Early & late seizures; odorless
Endrin 72-20-8
Hexadrin
Cancelled 1974
Highest
High
None
Most toxic organic chlorine; Rapid onset seizures, status epilepticus

Chlordane 57-74-9
Octachlor, Toxichlor, others
Cancelled 1988
Moderate
High
High
Early & late seizures occur
Endosulfan 115-29-7
Thiodan, Cyclodan, others
RED 2000
High
High
Low
Strong sulfur odor
Heptachlor 76-44-8
Drinox
Restricted: fire ant control soil treatment
Moderate
High
High
Toxic metabolite heptachlor epoxide; odor of camphor
Isobenzan 297-78-9
Telodrin
Never Registered
High
Moderate
High
Also inhibits Mg^{++} -ATPase; mild â€œchemicalâ€• odor
Dienochlor 2227-17-0
Pentac
Cancelled
NA
Low
Low

Toxic metabolite binds to GSH
Toxaphene (Polychlori-nated Cam-phene) 800-35-2
Alltox, Chemphene, Toxakil, others
Cancelled 1982
Moderate to high
Low
Low
Seizures; turpentine-like odor, often mixed with parathion
Chlordecone and Mirex
Chlordecone 143-50-0
Kepone
Cancelled 1977
Moderate
High
High
â€œKepone shakesâ€•; seizures not seen, structurally similar to mirex
Mirex 2385-85-5
Dechlorane
Cancelled 1976
Low
High
High
(?) Converted to chlordecone, toxicity identical.
[1]. Chemical Abstracts Service #-provided here to facilitate Toxline, Medli Registration Eligibility Decision.

Classes of Organic Chlorines	Specific Organic Chlorine; CAS[1] Registry #	Brand Name(s)	Current EPA Registration (US)	Acute Oral Toxicity (Man)	Derma Absorpti

TABLE 110-1. Classification of Organic Chlorine Pesticides

In contrast, chlorinated hydrocarbon solvents and fumigants are low mol that are volatile liquids or gases, and that generally have CNS-depressant

The organic chlorine pesticides are grouped into four categories based on similar toxicities: (a) DDT and related analogues; (b) cyclodienes (the re endrin; and heptachlor, endosulfan), and related compounds (toxaphene, hexachlorocyclohexane (lindane, the Î³ isomer; with the commonly used hexachloride), the primary organochlorine pesticide still in common clinica United States. Isomerism is important, because the Î² and Î´ isomers are insecticidal properties.[1,23,81] and (d) mirex and chlordecone (Table 11 compounds differ

substantially, both between and within groups, with respect to toxic dose metabolism, and elimination.[25] The signs and symptoms of toxicity in hu similar within each group.

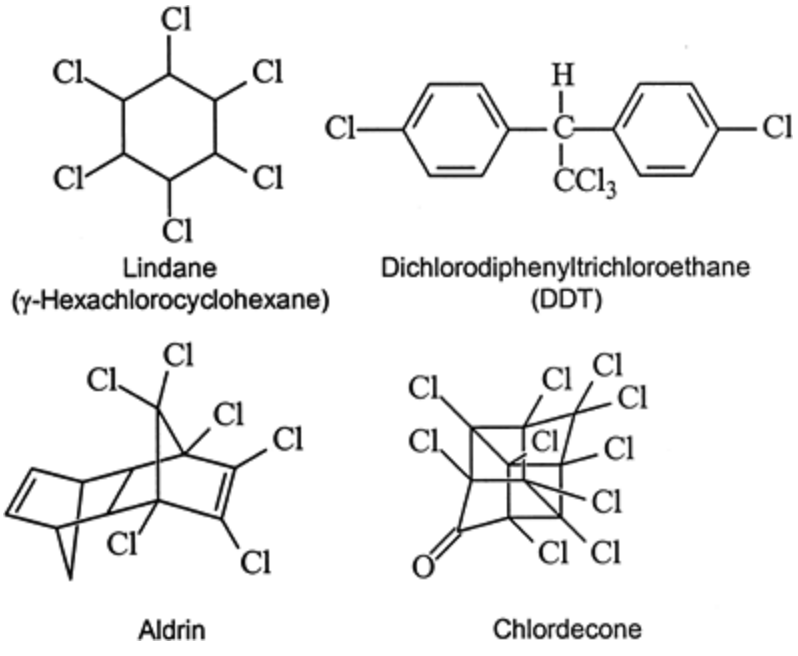

Figure 110-1. Structures of various organic chlorine pesticides.

Toxicokinetics

Absorption

All of the organic chlorine pesticides are well-absorbed orally and by inh variable, depending on the particular compound. Absorption by any route and the physical state (solid or liquid) of the pesticide. None of the orga and are usually either dissolved in organic solvents or manufactured as p

DDT and its analogues methoxychlor, dicofol, and chlorobenzilate are ve unless the pesticide is dissolved in a suitable hydrocarbon solvent.[87] DDT concentrations are usually low, and toxicity by the respiratory route is u

All of the cyclodienes have significant transdermal absorption rates. Cuta approximately 50% that of the oral route.[25] Oral absorption of the cyclod poisonings have occurred when foodstuffs were contaminated with these absorbed through the skin in both acute and chronic exposures.[99]

Lindane is well absorbed after skin application, and in adults has a docu rate of 9.3% of a topically applied dose over 24 hours.[36] Anatomic sites v capacities: axillary rates are 3.6 times greater, although scrotal absorptior of forearm rates.[11 , 40 , 53 , 107] Animal studies and case reports suggest malnourished, and those who receive repeated topical doses may have ir increased toxicity.[82] Hot baths, occlusive clothing or bandages the vehicle cutaneous integrity, such as eczema, fissures and other violations of the penetration.[107 , 108] The state of hydration of the skin also affects the a just prior to application can enhance absorption and increase the likelihoc stable compound, and volatilizes easily when heated. It was used extensiv vaporizers, and toxicity was common via inhalation, and when vaporizer ingested by children.[25] Review of data when lindane was ingested therap demonstrates that 40 mg/d for 3â€“14 days generally produced no symp

Mirex and chlordecone are efficiently absorbed via skin, by inhalation, an

Distribution

All organic chlorines are lipophilic, a property that allows penetration to t serum ratios at equilibrium are high, in the range of 660:1 for chlordane; 150:1 for dieldrin.[26] Central nervous system redistribution of the organic to fat may account for the apparent rapid CNS recovery despite the pers burden. In the rat model, there is a direct correlation between the concer brain and the clinical signs produced after a single dose of the insecticide

Serum lindane levels peak at 6 hours, and have a half-life of 18 hours a

Metabolism

The high lipid solubility and very slow metabolic disposition of DDT, DDE dichloroethylene, metabolite of DDT), dieldrin, heptachlor, chlordane, mir significant adipose tissue storage and increasing body burdens in chronic Organic chlorines that are rapidly metabolized and eliminated, such as en endosulfan, lindane, methoxychlor, dienochlor, chlorobenzilate, dicofol, and persistence in body tissues, despite being highly lipid soluble.[87]

Most organic chlorines are metabolized by the hepatic microsomal enzym oxidation, with subsequent conjugation. However, metabolism may result i metabolite with more toxicity than the parent compound, such as heptacl chlordane to oxychlordane, and aldrin to dieldrin.

In animals, most organic chlorine pesticides are capable of inducing the systems.[24 , 100 , 128] Enzyme induction changes the biodegradation of the certain animal models the acute toxicity of organic phosphorus compounds reduced by the administration of organic chlorines. This protective effect hepatic microsomal metabolism of the organic phosphorus compound beca administering piperonyl butoxide, an inhibitor of the liver microsomal enz induction of hepatic enzymes has not been described in man, except in ra with concomitant neurologic findings.[35 , 44]

Elimination

The half-lives of fat-stored compounds and poorly metabolized organic chl

chlordecone are measured in months or years. The elimination half-life of The primary route of excretion of the organic chlorines is in the bile, but urinary metabolites. However, as with other compounds excreted in bile, have significant enterohepatic or enteroenteric recirculation such as mire of the lipophilic compounds are excreted in maternal milk.[91]

Mechanisms of Toxicity

The same neurotoxic properties that make the organic chlorines lethal to potentially toxic to higher

forms of life. The organic chlorines exert their most important effects in Electrophysiologic studies demonstrate that the organic chlorine insecticid membrane by either interfering with repolarization, by prolonging depolar maintenance of the polarized state of the neuron. The end result is hype system and repetitive neuronal discharges.

DDT primarily affects the axon, by causing the voltage-dependent Na^+ ch depolarization, allowing repetitive action potentials.[74, 109] Low-level stim responses, seen clinically as prominent tremors and abnormal startle refle Evidence of this mechanism of action is the amelioration of DDT-induced phenytoin, a sodium channel blocker, which reduces the ability of voltag recover from inactivation.[51, 118]

The cyclodienes and lindane act as Î³-aminobutyric acid (GABA) antagonis the $GABA_A$ -receptor-chloride ionophore complex in the CNS, by interactir site.[1, 7, 23, 38, 43, 46, 75, 81] In fact, the degree of binding at this sit amount of Cl^- influx inhibited and the relative neurotoxicity of each insec , and 110-2). Indeed, development of cyclodiene resistance seems to be $GABA_A$ -receptor-chloride ionophore complex in these affected insects.[9] , of GABA agonists, such as benzodiazepines and phenobarbital, in treating of the cyclodienes[47] and lindane.[130] Toxaphene also inhibits GABA bindin chloride ionophore complex.[99]

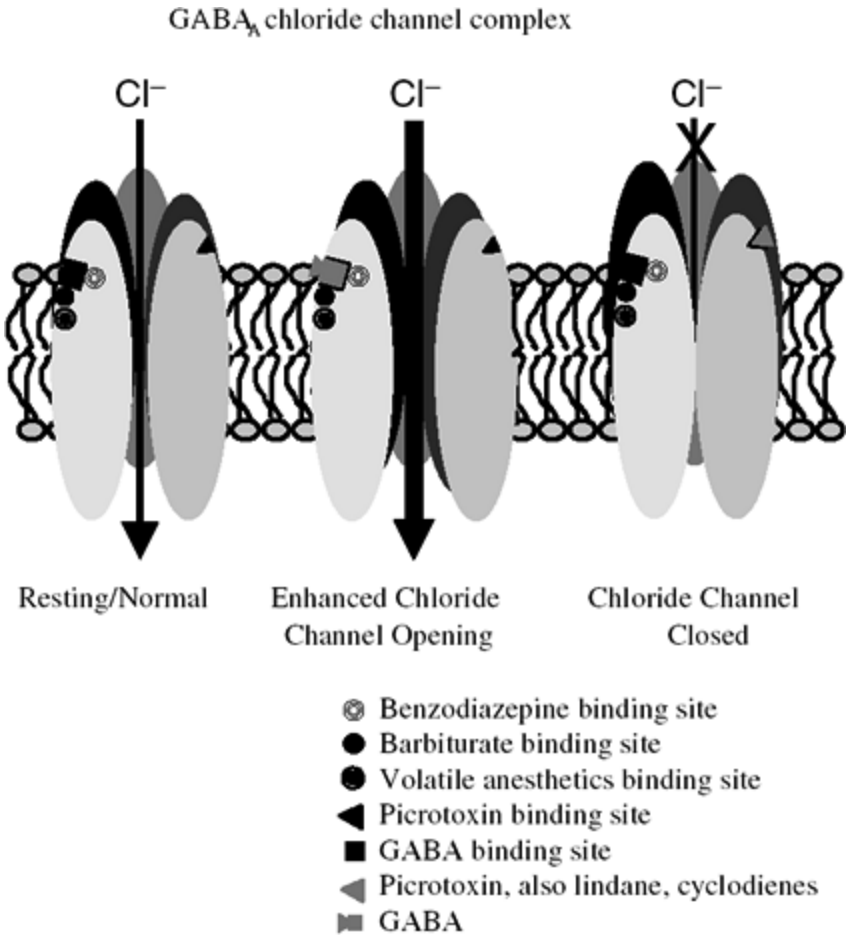

Figure 110-2. Chloride channel. Under resting conditions, a tonic influx cell in a polarized state. Binding of GABA or an indirect-acting GABA ag volatile anesthetic) opens the chloride channel. The subsequent chloride membrane, making the neuron less likely to propagate an action potential GABA antagonists, such as picrotoxin, close the chloride channel, reducin decreased membrane polarity causes the neuron to become hyperexcitable normally subthreshold in nature (Chap. 14).

The mechanisms of action of mirex and chlordecone are not as well unde ATPase, and Ca^{+2} -ATPase. However, lindane, DDT, and the cyclodienes a produce very different symptoms of toxicity, suggesting that these effects clinical manifestations seen in mirex/chlordecone toxicity. Phenytoin and the prominent tremor seen with chlordecone intoxication, but conversely poisoning, which further supports a different mechanism than the sodium

and chlordecone are poor inhibitors of GABA binding at the $GABA_A$ -recep therefore their mechanism of action is likely not at this site.[8] Seizures are chlordecone.

Organic chlorines sensitize the myocardium to endogenous catecholamines dysrhythmias, presumably in a fashion similar to the chlorinated hydrocar

Drug Interactions

There are theoretical consequences of liver enzyme induction, such as er therapeutic drugs and/or reduced efficacy. Dysfunctional uterine bleeding contraceptive metabolism induced by chlordane, but this was in a single exposure to chlordane.[44] A large group of workers poisoned by chlordecon increased hepatic microsomal activity, but no evidence of drug interaction Thus, induction of the hepatic microsomal enzyme system by organic chlo extended, substantial exposure.[87] There are no definitive reports of enha drugs or adverse reactions because of microsomal enzyme induction in m

Clinical Manifestations

Acute Exposure

In sufficient doses, organic chlorines lower the seizure threshold (DDT ar agents) or remove inhibitory influences (antagonism to GABA effects) and resultant seizures, respiratory failure, and death.[15, 17, 21, 32, 46, 47, exposure, tremor may be the only initial manifestation. Nausea, vomiting, face, paresthesias of face, tongue, and extremities, headache, dizziness, agitation, and confusion may subsequently occur. Seizures only occur afte only after ingesting large amounts.[32, 47, 58] Single, acute, oral doses of usually necessary to produce symptoms.[47] However, with lindane, the cy often are no prodromal signs or symptoms, and more often than not, the a generalized seizure.[15, 17, 32, 33, 47, 58, 93, 111] If seizures develop, hours of ingestion when the stomach is empty, but may be delayed as mu ingestion follows a substantial meal.[47]

Seizures related to dermal application of 1% lindane for treatment of ect

following a single inappropriate application,[63, 82, 116] or, more common exposures.[59, 84] The time from application to seizure onset can vary fror are often self-limited, but

may recur or result in status epilepticus. An epidemic of lindane poisonin substitution of lindane powder for sugar in coffee demonstrated a delay of the onset of nausea, vomiting, dizziness, facial pallor, severe cyanosis of collapse, convulsions, and hyperthermia. Affected patients ingested an ave a single dose.[25]

The cyclodienes are also notable for their propensity to cause seizures tha following an acute exposure. If the seizures are brief and hypoxia has no complete. Electroencephalographic (EEG) abnormalities have been recorde seizures.[58] Hyperthermia secondary to central mechanisms, increased mu pneumonitis is common.[33]

The ingestion of combinations of xenobiotics may result in significantly ir synergy. This has been demonstrated for DDT and lindane.[48]

Lindane: Specific Risks

Patients are at risk for developing central nervous system toxicity from i such as exceeding recommended application times or amounts, repeated following hot baths, and use of occlusive dressings or clothing shortly af occurs after unintentional oral ingestion of topical preparations. Young ch possibly because of greater skin permeability, increased ratio of body surf liver enzymes.[48] The elderly may also be at increased risk because of in atrophic skin, and perhaps age-related increased sensitivity. Preexisting of seizures include chlorpromazine treatment, CNS disease, or skin abso [, 77, 82, 84, 107, 108, 115, 116]

Despite the availability of safer and equally or more effective treatments continues to be used because of its low cost and generally good safety p English-language case reports and those submitted to the U.S. Food and toxicity into those associated with concentrations of lindane greater than cases could be considered probably related to 1% lindane;[4] of these, 6 c

or inappropriate skin application. The sale of lindane-containing products f banned in California because of its toxicity and environmental concerns.[1

Chronic Exposure

Chlordecone (Kepone), unlike the other organic chlorines, produces an in related to its extremely long persistence in the body. Because of poor inc makeshift chlordecone factory in Hopewell, Virginia, 133 workers were hea 1974â€“1975. They developed a clinical syndrome which became known a epidemic,â€• which consisted of a prominent tremor of the hands, a fine trembling of the entire body, known as the â€œKepone Shakes.â€• Othe opsoclonus (rapid, irregular, dysrhythmic ocular movements), ataxia, mer loss, and elevated liver enzymes.[35] Idiopathic intracranial hypertension, sperm motility were also found in some of these workers.[22] Severely affec exaggerated startle response, remarkably similar to that seen in animal s intense that some workers went home covered with chlordecone, and sev neurologic symptoms, presumably from exposures while laundering their

DDT and Breast Cancer

DDT and other organic chlorine insecticides have estrogenic effects.[28 , 1 estrogenic compounds adversely affect birds because differentiation of the estrogen-dependent.[41] Breast cancer incidence rates in the United States year since the 1940s, coinciding with, among many other factors, the wor lifetime exposure to excess estrogen is a known risk factor for human bre postulated that women who have higher levels of estrogenic organic chlo polychlorinated biphenyls [PCBs]) may be at risk for developing breast c

Several small case-control studies of women with breast cancer showed th higher average body burdens of DDT, DDE, and PCBs than their age-mat implicated the organic chlorines as a possible cause of human breast can larger studies have shown no increased risk of breast cancer because of and that currently accepted hereditary and lifestyle risk factors were pres cancer.[52 , 60 , 96 , 97] Additionally, other natural dietary estrogens such a and fungal metabolites are present in the human diet, and the organic c minimal by comparison.[42]

Organic Chlorines and Other Malignancies

The organic chlorines can induce liver tumors in mice, but have not been s hamsters.[48] Some reports suggest an association between long-term exp pesticides and blood disorders such as aplastic anemia, leukemia, and c purpura.[47 , 85 , 94] However, there is no convincing evidence that any of humans. Workers heavily exposed to DDT and dieldrin do not have an in Epidemiologic evidence suggests that the incidence of deaths from liver c since 1930, which includes the more than 50 years since the introduction is some evidence that DDT can be a facilitator of carcinogenesis induced aflatoxin, and that chlordane may have the same facilitative character recent comprehensive review found no evidence of human cancer risk fro dieldrin.[112]

Diagnostic Information

The history of exposure to an organic chlorine pesticide is the most critic exposure is otherwise rare. By law, the package label of these products r concentrations, and the vehicle. The EPA-registered use of the insecticide which agent is involved (Table 110-2). The presence of an unusual odor on the skin may be helpful. Toxaphene, a chlorinated pinene, has a mild endosulfan has a unique â€œrotten eggâ€• sulfur odor (Table 110-1). radiograph may reveal the presence of a radiopaque chlorinated pesticide radiopacity of the xenobiotics (Chap. 6).[30] A large number of other xeno first manifestation of toxicity, and must be considered in the differential c 14 and 19).

Ants

Baygon, bendiocarb, chlorpyrifos, diazinon, permethrin, resmethrin, silica boric acid

Bedbugs

Permethrin

Cockroaches

Baygon, bendiocarb, chlorpyrifos, diazinon, permethrin, resmethrin, silica

boric acid
Fleas
Baygon, bendiocarb, chlorpyrifos, d-limonene, permethrin, pyrethrins, sili tetramethrin
Flies (house)
Allethrin, pyrethrum, resmethrin, tetramethrin
Mosquitoes
Allethrin, pyrethrum, pyrethrins, resmethrin, tetramethrin
Silverfish
Baygon, bendiocarb, boric acid, chlorpyrifos, diazinon, silca gel pyrethrur
Spiders
Baygon, bendiocarb, chlorpyrifos, diazinon, permethrin, pyrethrins, resm
Termites
Effective pesticides restricted in use for application bycertified applicators
Ticks
Baygon, chlorpyrifos, diazinon, malathion, tetramethrin
Reproduced, with permission, from Guide to Safe Pest Management Aroun College of Agriculture and Life Sciences of Cornell University, 1997/1998, Cornell University.

Pest Usual Recommendation

TABLE 110-2. Common Household Pesticides

Laboratory Testing

Gas chromatography can detect organic chlorine pesticides in serum, adip confirmation is necessary for legal purposes, it may be necessary to mea chlorines. If the patient's history and toxidrome are obvious, then labora as this determination will not alter the course of management, and these an emergent basis. At present, there are no data correlating health effec Routine surveillance of serum levels in the occupationally exposed is not

Most humans studied have measurable levels of DDT in adipose tissue. In

very large exposure to DDT, serum DDT levels increased proportionally w were not associated with any apparent adverse health effects, but there v increasing levels of the liver enzyme Î³-glutamyltransferase (GGT), but s seen.[61] Serum lindane levels document exposure, and most laboratories exposed workers with chronic neurologic symptoms showed a blood lindan limited series of patients with acute lindane ingestion suggests that a ser with sedation, and that 0.20 mg/L is associated with seizures and coma.[3] lindane levels in the CNS are 3â€“12 times higher than serum levels.[31] , with a prolonged exposure to chlordecone, clinical signs and symptoms o levels.[22]

Management

As with any patient who presents with an altered mental status, the adm thiamine should be considered. Skin decontamination is essential, especial Clothing should be removed and placed in a plastic bag disposed of appr waste, and the skin washed with soap and water. Healthcare providers sh gloves and aprons. Because these pesticides are almost invariably liquids, to suction and lavage gastric contents, if clinically indicated. This is most recent ingestion (Chap. 8). Activated charcoal (AC) can be used after or lavage is not indicated.[47] , [68] However, the ability of AC to adsorb the va adequately studied, and mixtures containing petroleum distillates would pr the organic chlorines are all neurotoxins, the risk of complications associ outweighs the risk of any of the GI decontamination strategies in most ac lindane toxicity following intragastric administration showed a trend, but benefit, of AC.[56] The use of cholestyramine, a nonabsorbable bile acid-bi the same murine model did show a statistically significant benefit by raisi the lethal dose.[56] Oil-based cathartics should never be used, as they ma some evidence that sucrose polyester (olestra, a nonabsorbed synthetic c increase excretion of a wide variety of fat-soluble organic chlorine chemi inexpensive and more palatable alternative to cholestyramine to increase increased body burdens from chronic toxicity.

Seizures should be controlled with a benzodiazepine followed by pentobar if necessary, neuromuscular blockade to control the peripheral manifestat

preventing metabolic acidosis and rhabdomyolysis. Phenytoin is much less particularly with the GABA-chloride ionophore antagonists lindane, toxaph , [97] Hyperthermia should be managed aggressively with external cooling.

Cholestyramine should be administered to all patients symptomatic from organic chlorines. Chlordecone undergoes both enterohepatic and enteroe be interrupted by cholestyramine at a dosage of 16 g/d.[22] Cholestyramine of chlordecone 3â€“18-fold in industrial workers exposed during the Hope clinical improvement.[22]

Pyrethrins and Pyrethroids

The pyrethrins are the active extracts from the flower *Chrysanthemum* insecticides are important historically, having been used in China since th developed for commercial application by the 1800s. They are produced b ground Chrysanthemum flowers. The resulting concentrates have greater first pyrethrin identified, consists of 6 esters derived from chrysanthemic insecticides are highly effective contact poisons, and their lipophilic nature penetrate insect chitin (exoskeleton), and paralyze their nervous systems blockade.[20 , 73 , 87 , 109] When applied properly, they have essentially no because of their rapid hydrolysis. Pyrethrins break down rapidly in light a no environmental persistence or bioaccumulation. This fact makes them m must be constantly reapplied.

The pyrethroids are the synthetic derivatives of the natural pyrethrins (Ta They were developed in an effort to produce more environmentally stable pyrethroids were divided into two groups based on the intoxication syndro animals. The T syndrome

(for tremor seen in rats) was produced by intravenous administration of p the pyrethroids that did not contain a cyano group at the central ester lin syndrome (for choreoathetosis and salivation) was produced by 12 of the cyano group at the ester linkage. The original studies delineating the T o not test several new currently registered pyrethroids pesticides, and the intravenous or intracerebral administration, which are not relevant to hu

Type I
Allethrin 584-79-2
Pynamin
1st generation; First synthetic pyrethroid, 1949
Bioallethrin 584-79-2
D-trans
2nd generation, 1969: trans isomer of allethrin
Dimethrin 70-38-2
Dimetrin
Phenothrin 26002-80-2
Fenothrin, Forte, Sumithrin
2nd generation, 1973
Resmethrin 10453-86-8
Benzofluroline, Chrysron, Crossfire, Premgard, Pynosect, Pyretherm, Syn
2nd generation, 1967; 20X strength of pyrethrum
Bioresmethrin 28434-01-7

2nd generation, 1967; 50X strength of pyrethrum, isomer of resmethrin
Tetramethrin 7696-12-0
Neo-Pynamin
2nd generation, 1965
Permethrin 52645-53-1
Ambush, Biomist, Dragnet, Ectiban, Elimite, Ipitox, Ketokill, Nix, Outflanl
Pertox, Pounce, Pramex etc
3rd generation, 1972; Effective topical scabicide & miticide, low toxicity
Bifenthrin 82657-04-3
Capture, Talstar
4th generation
Prallethrin 23031-36-9
SF, Etoc
4th generation
Imiprothrin 72963-72-5
Multicide, Pralle, Raid Ant & Roach
4th generation; 1998

Type II

Fenvalerate 51630-58-1

Belmark, Evercide, Extrin, Fenkill, Sanmarton, Sumicidin, Sumifly, Sumip

3rd generation, 1973

Acrinathrin 103833-18-7

Rufast

4th generation

Cyfluthrin 68359-37-5

Baythroid, Bulldock, Cyfoxylate, Eulan SP, Solfac, Tempo 2

4th generation

Cyhalothrin 91465-08-6

Demand, Karate, Ninja 10WP, Scimitar, Warrior

4th generation

Cypermethrin 52315-07-8

Ammo, Barricade, CCN52, Cymbush, Cymperator, Cynoff, Cypercopal; Cy

KafilSuper, Ripcord, Siperin, others

4th generation

Deltamethrin 52918-63-5

Butoflin, Butox, Crackdown, Decis, DeltaDust, DeltaGard, Deltex, K-Othri

4th generation

Esfenvalerate 66230-04-4

Asana, Asana-XL, Sumi-alpha

4th generation

Fenpropathrin 39515-41-8

Danitol, Herald, Meothrin, Rody

4th generation, 1989

Flucythrinate 70124-77-5

AASTAR, Cybolt, Fluent, Payoff

4th generation

Fluvalinate 102851-06-9

Evict, Fireban, Force, Mavrik, Raze, Yardex

4th generation

Tefluthrin 19538-32-2

Demand, Force, Karate, Scimitar

4th generation
Tralomethrin 66841-25-6
Dethmor, SAGA, Scout, Scout X-tra, Tralex
4th generation

Pyrethroid Class	Generic Name, CAS #	Brand Names	Generation of

TABLE 110-3. Synthetic Pyrethroids in Common Use

A newer classification scheme was developed that predominates in the lite the structure of the pyrethroid, their clinical manifestations in mammalia on insect nerve preparations and their insecticidal activity. Type I pyrethr the central linkage without a cyano group. Commonly used type I pyreth allethrin, tetramethrin, and fenothrin. The type II pyrethroids have a cyan ester linkage. Type II pyrethroids in common use include cypermethrin, fluvalinate, and fenvalerate. The Î± cyano group greatly enhances neurot in both mammals and insects, and type II agents tend to produce the CS are generally considered more potent and toxic than the type I pyrethroid [106 , 86]

The development of the pyrethroids can be divided into â€œgenerations,â of introduction.[126] The first generation began in 1949, with the developm generation began in 1965, with the introduction of tetramethrin. The majo generation was a dramatic increase in potency compared with the pyreth introduced in the 1970s and including fenvalerate and permethrin, were agricultural use. They were more potent, and more environmentally stabl lasting 4â€“7 days. The current fourth generation includes mostly type II greater insecticidal activity, and environmental stability for nearly 10 day

There are more than 1000 pyrethroids, of which 6â€“10 are in widespread and pyrethroids are found in more than 2000 commercially available prod rapid paralytic effect (â€œknock downâ€•) on insects.

Most mammalian species are relatively resistant, because the pyrethrins c cleavage and oxidation.[80] Toxicity of the pyrethrins and pyrethroids is en

with microsomal enzyme inhibitors such as piperonyl butoxide or *N* -octy

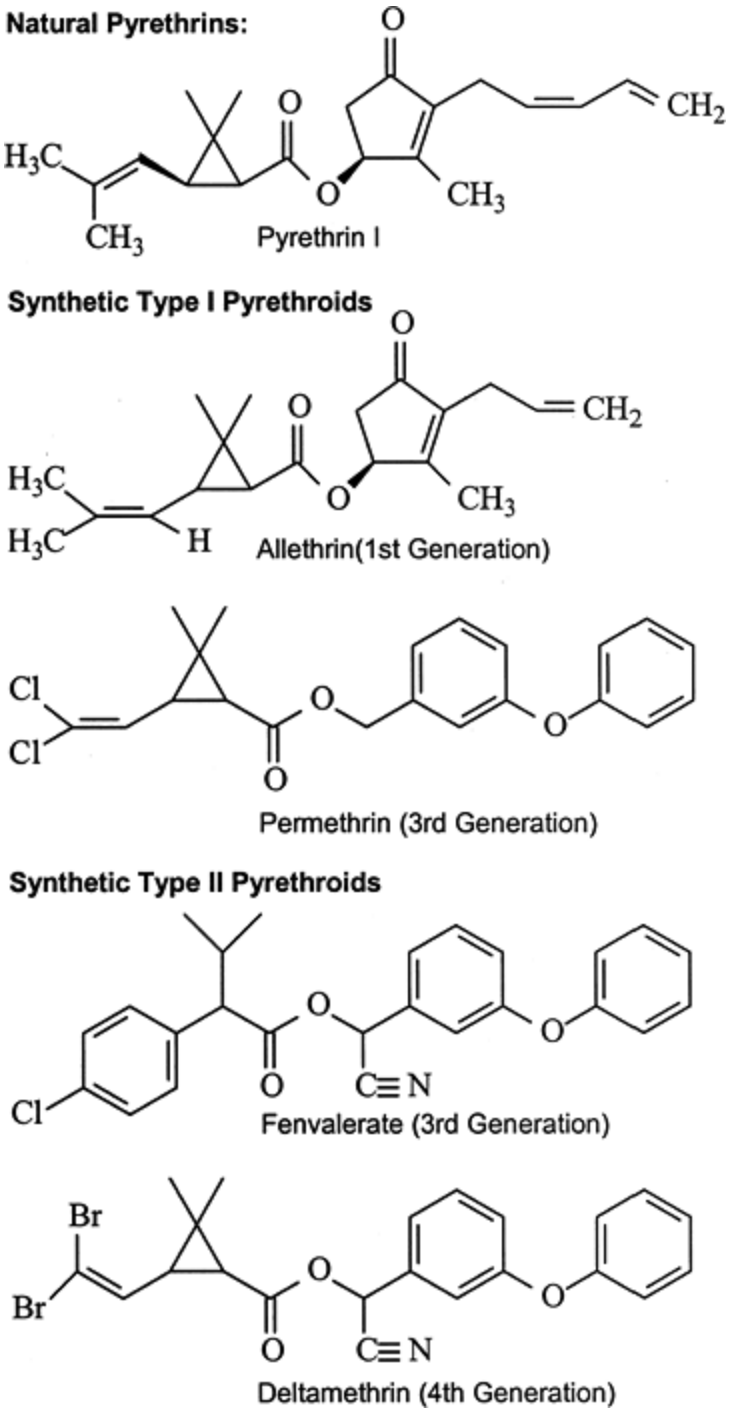

Figure 110-3. Representative structures of pyrethrin and pyrethroids.

Permethrin, a type I pyrethroid, is used medicinally for topical treatment humans, and impregnated in clothing for its insect repellant properties. It with approximately 2% or less absorbed systemically through the skin.[67] have confirmed that 5% permethrin is the drug of choice for scabies trea versus safety profile of topical treatments for scabies and lice.[92 , 125] The resistance to the 1% over-the-counter product, but comparison trials still lindane.[13]

Since West Nile Virus was first identified in the United States in 1999, the most U.S. states. Outbreaks of encephalitis caused by West Nile virus (WI summer and early autumn months annually in New York City since 1999. and transmission to humans occurs via mosquito vectors. Many states ha in an effort to control mosquitoes, the vector of this disease. Most spray insecticides because of their favorable safety profile, and their efficacy ag widespread spraying programs have increased the potential for human ex Centers for Disease Control and Prevention study of pyrethroid spraying d detectable pyrethroid metabolites in the general public living in the spray asthma surveillance showed no increases in emergency department visits conditions for the periods after pyrethroid spraying.[55]

Toxicokinetics

Absorption

The oral toxicity of pyrethrins in mammals is extremely low, because they inactive compounds. Their dermal toxicity is even lower, owing to their s metabolism.[33 , 80]

The pyrethroids are more stable than the natural pyrethrins, and systemi ingestion.[49] Absorption probably also occurs through the oral mucosa, as Chinese insecticide sprayers who frequently used their mouths to clear c exposures are from dermal absorption, the rate of which may vary depen Direct absorption of pyrethroids through the skin to the peripheral senso the facial paresthesias that occur in these cases, as symptoms were prom contact.[19 , 64] The pyrethroids are also absorbed via inhalation; however, sprayers, inhalation was not found to be a clinically significant route of e

zone assays.[19]

Distribution

The pyrethroids and pyrethrins are lipophilic and as such are rapidly distr system.[33] Because they are rapidly metabolized, there is no storage or chronic toxicity.[32]

Metabolism

The pyrethroids are readily metabolized in animals and man by hydrolase dependent microsomal system. The metabolites are of lower toxicity than Piperonyl butoxide, a P-450 inhibitor, enhances the potency of pyrethroid insects. It is often added to insecticide preparations to ensure lethality, a effect of a pyrethroid alone is not always lethal to the insect.[32]

Elimination

There is no evidence that the pyrethroids undergo enterohepatic recircu from the urine of exposed workers within 12 hours, and fenvalerate disap compounds, and metabolites of the pyrethroids, are found in the urine.[87] is used in population-based studies for pesticide exposures. However, a r studies revealed that commonly assayed pyrethroid metabolites also occur natural degradation. These metabolites included 3-phenoxybenzoic acid (of multiple pyrethroids), cis-3-(2,2-dichloroethenyl)-dimethyl cyclopropane metabolite of cis-permethrin, cypermethrin, cyfluthrin], trans-DCCA (met

cypermethrin, cyfluthrin), and 3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopro metabolite of deltamethrin). Therefore the detection of these metabolites i subject's exposure to the parent compound or from its metabolite in the

Pathophysiology

Like DDT, pyrethrins and pyrethroids prolong the activation of the voltag binding to it in the open state, causing a prolonged depolarization[38 , 73 , voltage-sensitive sodium channels is responsible for the insecticidal activity

pyrethroids to nontarget species. Natural pyrethrins and type I synthetic â€œburst dischargesâ€• following a single stimulus, but they have little potential. Type II pyrethroids cause the Na^+ channel to remain open long depolarization of the resting membrane potential.[109, 124] Type II pyrethr lead to significant after-potentials and eventual nerve conduction block. dependent sodium channel, unlike the insect, has many isoforms, and ma resistance in mammalian species. Different pyrethroids have varied effect channels, and the effects are not additive, and in fact may be antagoni is important as well, because some pyrethroid trans isomers at the ester the cis isomers are, and some isomers are insecticidal but lack mammalia isomerism.[105] Pyrethroids also have activity at certain isoforms of the v which may explain the neurotransmitter release that occurs in pyrethroi pyrethroids block voltage-sensitive chloride channels in test animals, prod CS syndrome. These effects may contribute to enhanced CNS toxicity.[105] interference of the type II pyrethroids with the GABA-mediated inhibitory high concentrations.[20, 73] Suppression of the GABA chloride channels like pyrethroid toxicity.[73]

Type I pyrethroids have a negative temperature coefficient, similar to DD to nonâ€“warm-blooded target species. Type II pyrethroids have a positi makes them more insecticidal at higher ambient temperatures.[126] This pr greater mammalian toxicity of type II pyrethroids as compared to type I.

Clinical Manifestations

Pyrethrum probably has an LD_{50} of well over 1 g/kg in man, as extrapola of toxicity associated with the pyrethrins are the result of allergic reactio allergic reactions are patients who are sensitive to ragweed pollen, 50% chrysanthemums (ragweed and chrysanthemum are in the same botanica actually may result from other natural components present in the extract generally do not induce allergic reactions.[12, 80]

In animals, type I pyrethroid poisoning most closely resembles that of DI twitching, increased metabolic rate, and hyperthermia. Excluding the rare allergy, the type I pyrethroids are unlikely to cause systemic toxicity in h are generally more potent, and cause profuse salivation, ataxia, coarse

seizures in animals. In humans, type II pyrethroids cause paresthesias (s effects in sensory nerves), salivation, nausea, vomiting, dizziness, fascic coma, seizures, and acute lung injury.[49 , 64] A review of more than 500 poisoning from China highlights some similar manifestations between a m overdose and an organic phosphorus compound overdose.[49] However, ser has resulted when poisoning from a type II pyrethroid was mistaken for and treatment was directed at these seemingly cholinergic signs.[49] Featur may be because of solvents and surfactants present in the agricultural p pyrethroids contain a cyanide moiety, cyanide poisoning does not occur a not indicated.

Most exposures are dermal, and local symptoms predominate in the majo feature is local paraesthesias in the areas of contact. Ocular contact caus including immediate pain, lacrimation, photophobia, and conjunctivitis.[6]

Treatment

Initial treatment should be directed toward skin decontamination, as mos exposures by this route. Patients with large oral ingestions of a type II p a single standard dose of AC, provided the diluent of the pyrethroid does Contact dermatitis and acute systemic allergic reactions should be treated corticosteroids and Î²-adrenergic agonists as clinically indicated.

Treatment of systemic toxicity is entirely supportive and symptomatic, be Benzodiazepines should be used for tremor and seizures. Topical vitamin especially effective in preventing and treating the cutaneous paresthesias exposures.[25 , 80]

DEET

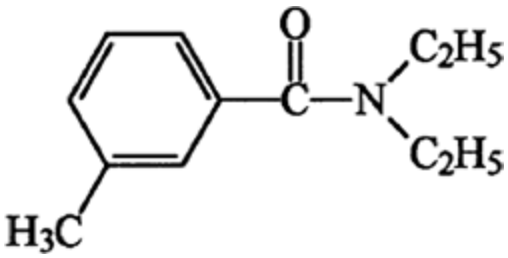

Figure. No Caption Available.

The topical insect repellant, *N* ,*N* -diethyl-3-methylbenzamide (DEET, for *m* -toluamide), was patented by the U.S. Army in 1946, and commercially since 1956. Currently, it is used worldwide by more than 200 million pers that 38% of the U.S. population uses DEET each year. With the spread of 1999, reducing the incidence of mosquito bites has become a public healt of an annoyance arthropod. Mosquito repellants therefore have become im most effective repellant available.[39]

DEET can be purchased without prescription in concentrations ranging from formulations of solutions, creams, lotions, gels, and aerosol sprays. DEET interfering with the chemoreceptors that attract the insects to their hosts

Toxicokinetics

DEET is extensively absorbed via the gastrointestinal tract.[83] Skin absorp the vehicle and the concentration. It does not bind to stratum corneum, a remains in the skin 8 hours after application.[83] DEET is lipophilic, and sk within 2 hours, although it is eliminated from plasma within 4 hours. The in the range of 2.7â€“6.21 L/kg in animal studies. DEET is extensively m hydroxylation by the hepatic microsomal enzymes, primarily by the isozyr 2A6.[121] DEET is excreted in the urine within 12 hours, mainly as metabol as the parent compound.[38 , 83]

Pathophysiology

The exact mechanism of DEET toxicity is unknown. A recent review of ad 26 cases with major morbidity including encephalopathy, ataxia, convuls hypotension, anaphylaxis, or death, particularly after ingestion or dermal [76 , 78 , 117 , 122] These primarily neurologic adverse reactions occurred m involved prolonged use and excessive dosing beyond what is currently re involved a child who was known to be heterozygous for ornithine carban and death was because of a Reye-like syndrome with hyperammonemia.

episodes of hyperammonemia unrelated to DEET use, and DEET does not by, OCT activity in humans.[79] There is currently no evidence that enzyme metabolism or influences individual susceptibility to toxicity.

Although single, large, acute oral doses (1â€“3 g/kg) in rats produced se smaller acute doses (500 mg/kg and less) and chronic multigenerational c produced no obvious toxicity.[101] Teratogenicity studies in rats and rabbits except at the highest doses,[102 , 131] and DEET was not found to be carci of applications, the number of reports of toxicity appears exceedingly sm wide margin of safety.[38 , 45 , 79 , 83]

Clinical Manifestations

Most calls to poison control centers regarding DEET exposures involve mir symptomatic exposures occur primarily when DEET is sprayed in the eyes suicidal ingestions, most serious reactions consist of seizures in children route; in fact, some of these cannot be definitely attributed to DEET.[45 , without treatment and the majority of patients with serious toxicity recov

Treatment

DEET exposures are treated with supportive care aimed at the primarily r dermal exposures skin decontamination should be a priority to prevent f intentional oral ingestions should receive a single dose of AC if clinically

Avoiding the overuse of DEET seems prudent. The American Academy of DEET concentrations of 10% or less for use on children,[104] and most cor for use on children are approximately 5â€“7%. One application lasts 4â€“ reapplication is unnecessary. Soaking the skin is not more effective and r should be applied only to exposed skin. One should avoid abraded skin, o be taken to avoid exposure to eyes and sensitive skin areas. Avoid use or child does not wipe on eyes, mouth, genitalia, and so on. Adults should a and then wipe onto the child's face, rather than spraying onto a child's f most active for a few hours preceding and following dusk, DEET should b skin when protection is no longer needed. Avoid using combination produc DEET, when the repellant component is not needed. Other options for pr

means, such as mosquito netting.

Insecticides, DEET, and the Gulf War Syndr

During operations Desert Shield/Desert Storm, nearly 700,000 Americans
Some returning troops began reporting a variety of symptoms and illness
exposure to burning oil well fires in Kuwait. Approximately 10% of these
the Persian Gulf Registry Health Examination Program. This program was
veterans were experiencing adverse health effects related to exposures e
War. The most common symptoms are largely nonspecific and multiorgan
headache, muscle aches, memory problems, dyspnea, insomnia, and gas
studies and expert panels have been unable to identify a causative xenob
â€œPersian Gulf syndrome.â€•

Some investigators have suggested that combinations of DEET, permethri
additive neurotoxic effects and could be a cause of the symptoms.[62] Altho
of synergistic neurotoxicity when large doses of these xenobiotics are gav
animals,[2 , 65] it is difficult to apply this to human experience in the Gulf
veterans were primarily dermal, and concomitant use at toxic dosages for
unlikely. Given the diversity and multisystem nature of symptoms experie
unlikely that use of these xenobiotics is responsible for the symptom-co

The prevalence of this complex of symptoms is staggering among the Gulf
U.S. veterans of the war has sought federal healthcare for these symptoms
War have symptoms of â€œGulf War syndrome.â€• Similar postwar syndr
fatigue, depression, and other symptoms have plagued returning soldiers a
century. These syndromes have gone by a variety of names such as Da
shell shock, neurocirculatory asthenia, and battle fatigue. After more than
more than 250 million dollars of federally funded medical research, the c
unexplained syndrome remains in dispute, but likely represents, at least i
posttraumatic stress disorder (PTSD).[34]

Legal Standards for an Insecticide Label

The Federal Insecticide, Fungicide and Rodenticide Act of 1962 (Table 10
â€œsignal wordâ€• on an insecticide label, which implies the degree of t

LD_{50} . Also, the label on the original container of these products is usual be brought to the medical facility (Chap. 104).

Summary

The ideal insecticide is one that has low acute toxicity to humans and n DDT), is inexpensive to apply and produce (organic phosphorus compound environmental persistence or bioaccumulation (organic phosphorus compo production techniques, some of the newer pyrethroids may come closer to commonly used today. Until that goal is achieved, the neurotoxic organic used. In January 2000, the Associated Press reported that 21 people in Ir when DDT powder was inadvertently used in food preparation instead of America and Europe, organic chlorine pesticides are still widely used in ot have important implications for toxicologists for some time to come.

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Chapter 111
Herbicides

Rebecca L. Tominack

A 39-year-old 60-kg man came to the emergency department (ED) about 6 hours after intentionally drinking 120 mL of a 41% glyphosate isopropyl amine salt and surfactant herbicide concentrate. He vomited immediately after the ingestion and again after he drank a few sips of water. He complained of a burning mouth, sore throat, and substernal burning chest pain. His vital signs were: blood pressure 110/72 mm Hg; pulse 90 beats/min, respiratory rate 12 breaths/min; and temperature 98.3Â°F (36.8Â°C) and oxygen saturation was 95% on room air. The electrocardiogram showed sinus rhythm without evidence of ischemia. Physical examination was normal except for significant pharyngeal erythema with ulceration and epigastric tenderness. An intravenous line was inserted and volume replacement begun, which was successful in raising blood pressure. Maintenance fluids were then substituted to avoid volume overload. No gastrointestinal decontamination was attempted because of the late presentation. He was transferred to the intensive care unit.

The admission chest radiograph was normal. The only laboratory abnormality was moderate leukocytosis. An upper gastrointestinal endoscopy was performed. The pharynx was edematous and inflamed. There were erythema and superficial ulcerations in the esophagus and stomach. The treatment plan was supportive care for GI tract injury, intravenous H_2 antagonists, and close observation for hypotension, respiratory compromise, and complications of the GI injury. Repeat endoscopy 1 week later showed satisfactory healing of the superficial erosions and ulcers. The patient was discharged on the 9th day after admission.

The term pesticides includes insecticides, herbicides, fungicides, and rodenticides. Herbicides are intended to kill unwanted vegetation or regulate some aspect of the growth cycle of plants. Most of the developed world operates stringent approval and registration systems for herbicides and other pesticides. Because of this intense, ongoing regulatory oversight, herbicides are among the best-studied chemicals in modern society.

History and Epidemiology

In the late 1800s, farmers had few options for weed control. Often there was no attempt to control weeds at all; crop seeds were scattered in a field, nature took its course, and separation of mature weeds from crop was done at the harvest. Smothering weeds before planting by turning the soil with a plow was a standard agricultural practice that only recently is being replaced with an alternative â€œno-tillâ€• practice. In the early 1700s, farmers began sowing seed in rows to facilitate mechanical weed removal after the crop emerged. However, pulling weeds by hand or chopping them with a hoe are prohibitively labor-intensive solutions, particularly for field crops. The first serious attempts to find chemical agents for weed control culminated in the success of Bordeaux mixture (copper sulfate and lime) and Paris Green (copper acetoarsenite) in controlling fungal diseases affecting the French

vineyards. Heavy metal salts such as iron sulfate, copper nitrate, and arsenates and various inorganic chemicals such as borates and chlorates were investigated and found marginally acceptable, primarily to control broadleaf weeds among cereal grain crops on small, intensively cultivated farms. Thus, before the second World War, only a limited number of chemicals were available as herbicides, and these were of relatively low potency, relatively high toxicity to nontarget species, and undesirably persistent in the environment.

In the 1940s, the first herbicidal chemical based specifically on plant physiology was discovered, 2,4-dichlorophenoxyacetic acid (2,4-D). This xenobiotic interferes with growth-regulating compounds called auxins produced by the plant. It was a great success because of its effectiveness against broadleaf weeds in crops, its low cost, higher potency, lower toxicity, and lack of persistent residues. The period since the 1940s has been characterized by the steady introduction of a large number of active herbicide ingredients into the marketplace. Over 200 chemicals are currently registered for use as herbicides in the United States and approximately 500 chemicals in use worldwide; nearly half of these have been introduced in the last 15 years.

In 2001, 1.87 billion pounds of herbicide active ingredients were used worldwide representing 37% of the 5.05 billion pounds of all pesticides used worldwide. In that same year US use of herbicide active ingredients totaled 553 million pounds, or 46% of the 1.2 billion pounds of conventional pesticides used in the United States that year. US herbicide use is currently 5-fold higher than insecticide usage and 8-fold higher than fungicide usage. The largest sector of US use is agriculture, accounting for 78% of total herbicide poundage applied, followed by 13% in home and garden sectors, and 9% in industrial and commercial market sectors. Herbicide use in both agricultural and industrial/commercial sectors has actually decreased over the last 20 years, whereas home usage has nearly doubled over the same time. The highest-use agricultural

herbicides in pounds for 2001 were glyphosate, 88 million pounds; atrazine, 77 million; metolachlor, 41 million; acetochlor, 33 million; and 2,4-D, 31 million pounds. Although the number of

pounds used in the home and garden market, are much smaller, the potential for human exposures is probably greater.[31]

Chemistry

Typical classification schemes organize herbicides by mechanism of action on the plant and subcategorize them by general chemical structure. Herbicides within the same chemical group usually share qualitatively similar toxicologic profiles. About 10% of herbicides have unique structures and are therefore unclassified.

Most contemporary herbicides are organic chemicals, and some of the behavior of a herbicide in plants, animals, and the environment can be predicted from its organic chemistry. Aliphatic chain structures with polar, nonhalogen substitutions (N, O, P, S) tend to be readily degraded in the environment by microbiota. Conversely, aromatic structures, particularly if halogenated, tend to be more difficult to degrade and may persist in the environment. Although some degree of herbicide persistence may be desirable for crops with a long growing season, persistence from one growing season to another or any bioaccumulation is generally undesirable.

Many herbicide structures include an organic acid or other polar groups that can participate in salt formations. The parent acids are often not sufficiently water-soluble for water-based application. Organic salts, often amine, ammonium, sodium, or potassium ionize in water and are more often encountered commercially. Salts are also relatively nonvolatile, which prevents loss to the atmosphere and adds an increased margin of safety against inhalation exposure by the human applicator. In dermal or eye exposure, the primary concern will be local irritation. Allergic contact dermatitis is possible if the formula contains a sensitizing active or adjuvant ingredient or

an ethoxylated surfactant that has formed sensitizing aldehydes and other oxidation products.[30] Because most herbicide active ingredients are water-soluble, their penetration through the skin is usually minimal.

In potential spray exposure, the droplet size generated by the equipment is a primary consideration in evaluating the extent of airborne exposure. Spray equipment and nozzles used in agriculture are intended to deliver relatively large droplets, which fall quickly to minimize spray drift onto nontargeted plants. Generally more than 95% of droplets generated are larger than 100 Âµm and are not considered respirable particles, capable of being retained by the lung.[19] Most particles over 10 Âµm are filtered out by impacting in the nasopharynx and large airways. However, during heavy, prolonged, or overhead spraying, sufficient numbers of large mist droplets can enter the nose and mouth and may result in symptoms such as bad taste and irritated nose and throat. These symptoms are usually self-limiting.

Ingestion of most herbicides that have been diluted with water for use is unlikely to cause severe toxicity, even in relatively large quantity, although notable exceptions include paraquat and diquat. Because most active ingredients based on plant physiology show a reduced level of toxicity to mammals, the toxicity of any particular formulation may not be related to the active ingredient. Instead, the surfactants and other adjuvants may pose the higher risk of toxic effect. Ingestion of concentrated formulations that carry high loads of active ingredient, solvent, surfactant, and other adjuvants may result in significant toxicity that may be life-threatening. Local and systemic surfactant effects must be anticipated and any target organ damage inherent to the active ingredient.

Because of the nature of the commercial herbicide industry, active ingredients and different salts are introduced, combined in a nearly endless series of product formulations and names, and then withdrawn from the market. Formulations also vary by country. Risk

of toxicity depends on the amount and concentration of active ingredient and formulation adjuvants in the preparation to which the patient was actually exposed. Once a concentrated product is diluted with water for use, the label and safety data sheet information likely overstate the hazard of exposure.

Glyphosate

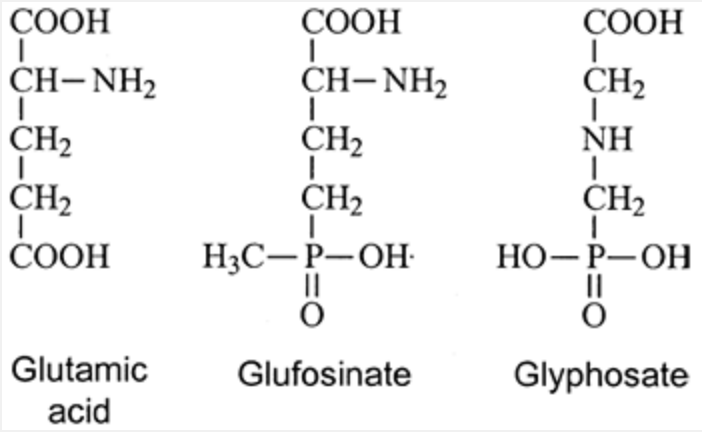


Figure. No Caption Available.

Glyphosate is the classic example of an active ingredient of low human toxicity that is formulated and sold with other, more toxic ingredients that are primarily responsible for the acute health effects. In serious exposures such as intentional ingestions, the healthcare provider tends to ascribe the toxic effects to the active ingredient. This assumption is generally applicable to other types of pesticides such as insecticides and rodenticides whose active ingredients are quite toxic to humans because they affect specific targets in insects or rodents which are present and affected in humans also. Glyphosate targets synthesis of chlorophyll-related molecules in plants, and has no target in humans. Human toxicity of glyphosate formulations is not dependent on the glyphosate content

primarily, but on the type and concentration of the surfactant, the preservative, the salt partner of glyphosate, and other adjuvants.

Large volume ingestions of the original glyphosate formulation concentrate (41% isopropyl amine salt of glyphosate, 15% polyethoxylated tallow amine surfactant, and water) were characterized by risk of severe irritant damage to GI mucosa, shock, and acute lung injury with 7â€“15% mortality. This is likely systemic surfactant toxicity. Although formulations are in constant flux regarding adjuvants, the need for some sort of surfactant or surfactant system remains a constant. Therefore, the basic toxic effects of significant acute exposure to concentrated formulations will likely be similar, but with somewhat unpredictable changes in dose-response relationship and timing of onset.

Characteristics

Glyphosate [*N*-(Phosphonomethyl)glycine] has been commercially available nearly 35 years and is now the most common herbicide in US and worldwide agriculture.[28,41] A related chemical is glyphosine [*N*,*N*-Bis(phosphonomethyl)glycine], which is a dimer of glyphosate used a plant growth regulator.

Glyphosate is a â€œpostemergentâ€• herbicide that is applied after the plant has emerged from the soil and is nonselective in its action,

killing any green plant. It inhibits the enzyme 5-enolpyruval shikimic acid 3-phosphate (EPSP) synthetase, which is important in the biosynthesis of aromatic amino acids. The lethal effects in the plant can be reversed by supplying L-phenylalanine and L-tyrosine.

There is no equivalent enzyme in animal systems; thus, this is the mechanism of its selective toxicity to plants and relative lack of effect in animals. Additionally, it has limited activity as a nonspecific metal chelator, an effect that does not appear important

clinically.

Current Use and Formulations

Glyphosate is registered for use in over 130 countries. The original glyphosate formulation concentrate (Roundup Herbicide, Monsanto) contained the isopropyl amine salt of glyphosate (41% w/v), a polyethoxylated tallow amine surfactant (15.4% w/v), and water. Glyphosate is now available as a generic ingredient, and there are thousands of products containing it marketed under various names by many large and small companies worldwide. There are many differences among the products in addition to differences in glyphosate concentration. Most products contain the original isopropyl amine salt, but some contain the mono-ammonium, di-ammonium, sodium sesqui-, potassium, trimethyl sulfonium (trimesium) or other salts of glyphosate, some of which appear to have different toxicity. Some products are dry formulations; some contain different surfactant systems, or greater or lesser amounts of total surfactant, or no surfactant at all. Glyphosate is also sold in combination with other herbicide active ingredients including diquat, various chlorophenoxy compounds, simazine, linuron, and picloram or with a fertilizer to boost plant growth, which enhances plant lethality. These variations affect the risks of exposure and complicate assessment of the effects of an exposure on a particular patient, and hinder application of published clinical literature to new exposure cases.

Mechanism of Toxicity of Glyphosate and Formulations

The glyphosate molecule itself has a relatively favorable acute toxicity profile in animals. Its acute oral toxicity is relatively low (rat oral LD_{50} = 5600 mg/kg), as is its systemic toxicity from dermal exposure. It is not a contact sensitizer. It is noncarcinogenic

(US EPA category E), nonmutagenic, and devoid of developmental toxicity. There is no serious chronic toxicity in 2-year animal feeding studies. Because glyphosate is used commercially in salt form, and with various surfactants and other adjuvants, the acute toxicity profile of the particular formulation is more important than the profile of glyphosate alone. An animal oral LD_{50} can be obtained from the material safety data sheet (MSDS) of every formulation registered in the United States, and should be compared with the oral LD_{50} of the original glyphosate formulation. This comparative toxicity measure will permit an estimate of the dose-response range of the formulation in question compared to the formulation represented in the published literature.

Because of the selective toxicity of glyphosate to plant life and corresponding low mammalian toxicity, as contrasted with the formulation adjuvants, the surfactant is suspected to be the primary culprit of the toxic syndrome described in large series of ingestions of concentrated glyphosate formulation (<41% isopropyl amine salt and â‰¥15% polyethoxylated tallow amine surfactant). The relative contribution of the surfactant, the glyphosate, and its salt to the toxic syndrome remains controversial. Many of the clinical features identified in glyphosate-surfactant poisonings occur regularly with reported cases of large-volume ingestion of herbicide concentrates irrespective of the active ingredient. The common factor is the presence of surfactant. This is observational evidence that a systemic surfactant syndrome accompanies many serious herbicide ingestion poisonings and is a primary determinant of the toxic symptoms in the early phase of acute poisoning.[71] Although the original surfactant paired with glyphosate is described as nonionic, its tertiary nitrogen is largely protonated at physiologic pH, and it clinically produces effects more traditionally associated with a cationic surfactant. Clinical descriptions of ingestion of benzalkonium chloride, a quaternary ammonium cationic surfactant, share striking similarities with those of the tallow amine-containing original brand name formulation.[16] These include superficial

necrosis of mucous membranes, severe GI tract irritation with erosions, glottic edema, acute lung injury, profound hypotension, oliguria, renal failure, and cardiovascular collapse.

An in vivo intravenous study in dogs confirmed the role of surfactant in causing hypotension through myocardial depression at exposure levels comparable to human poisonings.[69] It compared the cardiovascular physiologic effects of infusions of equivalent doses of isopropyl amine glyphosate alone, polyethoxylated tallow amine surfactant alone, or the two combined as in the formulated herbicide. The endpoint of infusion was a 50% fall in mean arterial pressure. Both the surfactant alone and the combination reduced mean arterial pressure, heart rate, cardiac output, and left ventricular stroke work index and elevated peripheral vascular resistance, whereas the glyphosate infused alone did not. These findings suggest that the hypotension produced was primarily related to myocardial depression and was caused by surfactant.

It is theoretically possible that isopropyl amine itself may exhibit cardiac or other actions. It represents 30% by weight of the isopropyl amine salt of glyphosate, is used as an emulsifying agent and wax remover, and has a rat oral LD_{50} of 820 mg/kg.

Issues of relative contribution of various formulation ingredients to the clinical effects have not been fully investigated and current understanding remains limited. Soon after the first large series of cases of suicidal ingestions was published, the amount of surfactant in the original brand name formulation sold in the United States was significantly reduced; thus, the published literature probably overstated the toxic potential to humans who might have ingested this revised formula. The myriad of different glyphosate formulations currently sold as options to the original formulation share this tenuous connection to the literature. Publications based on a particular archaic glyphosate formulation are becoming irrelevant to contemporary clinical information needs on glyphosate because the marketed formulations continue to change and

diversify. However, as clinical descriptions of agrochemical surfactant poisonings, the literature will have enduring applicability.

The moderate skin irritation of the original brand name formulation is caused by the polyethoxylated tallow amine surfactant. One hundred percent surfactant solution is corrosive to skin in animal tests, and progressively less irritating as the concentration is lowered. Similarly, as the surfactant content is progressively reduced in the concentrated formulation or by dilution of the concentrate in preparation for use, the potential for irritation declines.

Toxicokinetics

Absorption

Glyphosate kinetics and metabolic fate have been extensively characterized in animals, and human clinical data appear

to follow the same general patterns. Approximately 20â€“30% is absorbed orally, and there is evidence of an enhanced absorption ratio at higher doses.

Dermal absorption of glyphosate is poor, less than 2.5%. Water or soap and water washing removes glyphosate from skin; 50% can still be removed by washing delayed 24 hours after exposure.

Elimination

Glyphosate is not metabolized in mammalian systems but a minor metabolite, amino methyl phosphonic acid, may be detected in amounts â‰¤0.5% of glyphosate. It is theorized to originate from colonic bacterial metabolism. Glyphosate is rapidly excreted unchanged in the urine. Experience in human poisoning suggests an elimination half-life from the blood of 2â€“3 hours, assuming renal function is normal. Half-life becomes prolonged as renal function

progressively deteriorates. The absorption, distribution, and disposition of the polyethoxylated tallow amine or other surfactants are not known. They are generally composed of related assortments of large molecules that are unlikely to be well-absorbed intact from the normal gut, with possibly increased absorption occurring after it damages the mucosal surface.

Clinical Manifestations

The range of clinical effects produced by ingestion of the original glyphosate formulation include irritation, edema, and erosions of the oropharynx and GI tract; nausea, vomiting, diarrhea, and midchest and abdominal pain; leukocytosis, metabolic acidosis, elevated salivary amylase, tachypnea, hypoxia, acute lung injury, and volume-responsive hypotension followed by cardiovascular hypotension unresponsive to fluids and pressor amines. Secondary organ dysfunction may occur in the CNS, liver, and kidneys. Aspiration pneumonitis is a potential complication. Fatality rates in the large published series of large volume ingestions of formulations with high concentrations of glyphosate and surfactant range from 7.5 to 16%. Those who ingest large volumes of highly concentrated herbicide (>200 mL of 41% glyphosate isopropylamine and â‰¥15% surfactant) and those developing acute lung injury or cardiogenic shock are at more risk of a fatal outcome. Endoscopic evaluation shows esophageal injury and gastric injury in 70% of patients, and duodenal injury in fewer than 20%. Laryngoscopy shows significant laryngeal injury in the majority of patients, and this correlates with longer hospital stay and risk of aspiration pneumonitis.[27]

Oral and gastrointestinal irritation (burning of mouth and throat, vomiting, abdominal pain) develop rapidly after ingestion. Hypotension may develop within hours of very large ingestions. Some patients may appear to be relatively stable for the first 8â€“12 hours and then develop hypotension and respiratory

distress.

Recent case reports of ingestion of the trimesium salt describe dramatically accelerated fatality, and the reason is not clear. A 6-year-old who unintentionally drank a mouthful of glyphosate-trimesium died within minutes. An adult who ingested 150 mL intentionally also collapsed and died rapidly. Autopsy findings in the child included severe irritation of the gastrointestinal tract and airways, acute lung injury, cerebral edema, and dilated right atrium and ventricle; and in the adult included irritant injury of the pharynx, esophagus, and duodenum and acute lung injury.[65] Obviously it is important to recognize this particular herbicide in a clinical setting. The common name by which this herbicide is described is in flux. It may appear as glyphosate-trimesium, â€œsulfonate,â€• trimethyl sulfonium glyphosate, trimesium salt of glyphosate, and â€œsulfonium, trimethyl-salt with *N*-(phosphonomethyl)glycine (1:1).â€• The latter is the current US EPA nomenclature.

It is difficult to correlate ingested amount with severity of clinical effect because of the unmeasured loss through vomiting. However, in general, severity follows a dose-related trend. In one large series, there were 11 fatalities among 41 cases (27%) of patients who ingested an estimated 150 mL or more of concentrated formulation (41% isopropyl amine glyphosate, â‰¥15% surfactant) but none among 51 who ingested <150 mL.[75] In another large series, an average ingestion of 17 Â± 16 mL (range 5â€“50 mL) produced no symptoms; 58 Â± 52 mL (5â€“150 mL), mild symptoms; 128 Â± 114 mL (20â€–500 mL), moderate symptoms; and 184 Â± 70 mL (85â€–200 mL), severe symptoms or death.[59] Risk of death appears to be higher in older patients.

Once diluted for use to glyphosate concentrations around 1% and surfactant concentration around 0.4%, the various glyphosate formulations offer little risk of adverse effects except temporary, minor eye, membrane, or skin irritation, and systemic effect after

ingestion. Some dry formulations may contain sodium sulfite, which could cause bronchospasm in sulfite-sensitive patients. Allergic contact dermatitis is possible if a sensitizing preservative such as 3-iodo-2-propanyl butyl carbamate or a benzisothiazolone is contained in the particular formulation. The latter preservatives are also phototoxic. Additionally, ethoxylated surfactants undergo decomposition with time to release a variety of aldehydes including formaldehyde. This is known to be a potent contact sensitizer and may account for many skin rashes previously judged to be unrelated to glyphosate herbicide formulations.[69]

Laboratory

In some fatal cases serum glyphosate levels have been reported to exceed 3000 mg/L, although many are significantly lower.[69] However, serum levels are not useful clinically in assessing the severity of exposure or poisoning. Furthermore, glyphosate levels are not readily available. Surfactant analysis is not feasible because the surfactant itself is a complicated mixture of compounds, which vary by carbon-chain size and ethoxy chain size. Patient status can be assessed by determinations of oxygenation status, renal and hepatic function, electrolytes, and acidâ€“base balance. Leukocytosis and increased serum amylase and lipase may be noted. The chest radiograph may be normal or show evidence of acute lung injury or aspiration. The electrocardiogram shows no abnormalities specific to the ingestion but may document possible abnormalities in patients with severe cardiorespiratory compromise.

Treatment

Gastric Decontamination

Ingestion of less than 2 mouthfuls of concentrated herbicide in an adult is unlikely to cause serious illness, and ingestions of nearly any amount of dilute (<2% glyphosate) solution are inconsequential

other than risk of bad taste, nausea, and perhaps vomiting. After significant ingestions of herbicide concentrate, spontaneous vomiting usually occurs rapidly and obviates the need for the induction of emesis or lavage. The potential risk to the patient who may have suffered severe mucosal damage to the esophagus and stomach and the timing of the procedure relative to ingestion must be considered before lavage is attempted.

Activated charcoal (AC) apparently adsorbs the principal toxic component in formulated herbicide, whether it be glyphosate, the surfactant or both. Pretreatment of rats with activated charcoal

before administration of an LD_{100} oral dose of the original glyphosate formulation or an equivalent dose of surfactant prevents mortality. Likewise, in vitro mixing of either with activated charcoal and administration of the supernatant is not lethal. This suggests that the primary toxic component is adsorbed by AC and that it is probably the surfactant. The binding characteristics of glyphosate and AC are unknown.

Extracorporeal Removal

Hemodialysis is effective in removing glyphosate from blood. AC hemoperfusion of cow blood in an in vitro system failed to remove glyphosate.[59] It is not expected that hemodialysis would remove surfactant because of its large molecular size. Because of the rapid elimination of glyphosate by normal kidneys and its uncertain role in the toxic syndrome, there is no proven benefit to accelerating glyphosate removal by hemodialysis. This should be reserved for renal indications. Although, theoretically, hemoperfusion may remove surfactant, this has not been proven experimentally or in patients, largely because the surfactant composition does not permit analysis. Additionally, improved clinical outcome has not been demonstrated for hemoperfusion; therefore, this technique cannot be recommended.

Supportive Care

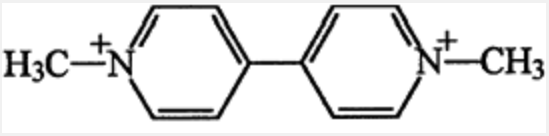
There are no specific therapies or antidotal measures for glyphosate-surfactant poisoning. Fluids and electrolytes should be administered IV in sufficient volume to replace GI tract losses and maintain high normal urine output and normal hemodynamics. However, in severe poisoning, hypotension from cardiovascular compromise may supervene; fluid overload may precipitate or worsen hypoxemia and respiratory distress. In such cases, hemodynamic monitoring may be necessary to optimize management.

Hypoxemia occurs frequently even in the absence of abnormal chest radiograph and should be monitored and corrected; patients should be endotracheally intubated and mechanically ventilated if necessary.

Prognosis

Fatalities generally occur in the first 2 days after ingestion, and possibly very rapidly when sulfonium, trimethyl-salt with N-(phosphonomethyl)glycine (1:1) is involved. Development of respiratory distress severe enough to require intubation, renal failure severe enough to require dialysis, and shock are poor prognostic signs.[42] In survivors recovery is complete.

Paraquat



Paraquat

Paraquat is the classic example of a herbicide that is safe when used as directed on plants but is capable of extreme toxicity when misused. Because of its low cost, rapid action, and favorable environmental characteristics, paraquat remains a widely used herbicide throughout the world. The combination of ready availability and severe toxicity results in continued appearance of serious and fatal poisonings, many with suicidal intent. Paraquat induces pulmonary fibrosis mediated by free radicals; once initiated, even heroic medical interventions cannot save a the patient. Poor worker-protection practices are also problematic in subacute and chronic toxicity.

Characteristics

Paraquat (1,1â€²-dimethyl-4,4â€²-bipyridylium dichloride, CAS 1910â€“42â€“5) is a growth regulator primarily used on field crops, fruit and nut crops, and nonagricultural areas such as airports, commercial buildings, and storage yards. It rapidly damages and kills plants on contact by intercepting electrons moving through photo system I, the photosynthesis pathway in plants that

generates reducing equivalents. In the presence of light, paraquat generates reactive oxygen radicals including hydrogen peroxide that disrupt cell membrane integrity. The above-ground portion of the plant collapses rapidly (â€œburn down,â€•) although regrowth can occur from the roots of perennials. It is rapidly inactivated by adsorption to soil.

Paraquat dichloride is marketed most commonly as an aqueous solution concentrate containing 200 g paraquat dichloride/L (20% w/v), sometimes in combination with diquat or other herbicides. In the United States, paraquat is registered as a restricted use pesticide available in concentrations from 23â€“43.5% dichloride salt. Spray dilutions are typically in the range of 1â€“5 g/L (0.1 to 0.5% w/v). The aqueous concentrates also contain appropriate adjuvant agents as described above and sometimes deterrent adjuvants to prevent or mitigate unintentional ingestion. If no blue dye is added, the concentrate is colored dark brown like cola, for which it can be mistaken, especially if decanted into a soft drink bottle.

Epidemiology

Most cases of paraquat poisoning result from the deliberate ingestion of one of the liquid formulations containing 20â€“40% paraquat. Thousands of deaths have been reported since paraquat was first marketed in 1962, mostly in adults with intentional ingestions. Unintentional ingestions can occur, particularly when the product has been handled or stored incorrectly. Death has also been reported from homicidal use, massive dermal exposure, intravenous administration, and prolonged occupational spraying. Suicidal ingestion of paraquat has been a particular problem in some countries. Measures taken by the manufacturer and by regulatory agencies have curbed the incidence of unintentional ingestions and reduced the mortality rate. These measures include marketing thickened or gel formulations with reduced paraquat concentration,

capping the maximum concentration allowed in commerce and for spray application, placing restrictions on open sale and availability, designing improved product labeling, providing education programs discussing correct use, using marker blue dyes, adding pyridine stenchants to make the product smell bad and taste worse, and including emetics in the formulations. In the 4-year period immediately after the 1988 institution of the color change from brown to blue and the addition of both a stenchant and an emetic to paraquat formulations in the United States, there was a nearly 50% decline in the proportion of all pesticide exposures represented by paraquat ingestion compared with the number of cases in the four years preceding these changes in the formulation. This indicates that such measures indeed have an impact on unintentional exposures. However, they are unlikely to influence those truly intent on suicide.

Toxicokinetics

Absorption

Splash or diluted spray mist exposure to skin, eyes, and upper airways leads to minimal systemic absorption despite

the risk of local tissue damage. Repeated or continuous dermal contact, especially with a concentrated solution, may lead to some absorption into the bloodstream if the integrity of the stratum corneum is impaired.[2] Dermal exposure to burned skin and chronic occupational exposure are reported to have resulted in sufficient paraquat absorption to cause death. Following ingestion, systemic absorption of paraquat is rapid but incomplete (<30% of the dose). Absorption occurs predominantly from the small intestine and is facilitated by active transport of the herbicide across the mucosal cells. If the GI mucosa is compromised, the percentage absorbed is likely to be higher because of additional absorption by passive

diffusion. Peak plasma concentrations of paraquat generally occur within 2 hours after ingestion. Paraquat's volume of distribution is about 1â€“2 L/kg. It distributes rapidly to most tissues, with highest concentrations in the kidneys and the lungs. Higher renal concentrations reflect the role of the kidney in the elimination of paraquat. The high concentrations in the lung result from time- and energy-dependent uptake of paraquat by type I and II alveolar epithelial cells via the polyamine uptake pathway. The uptake results from the structural similarity between paraquat and endogenous diamines and polyamines such as putrescine and spermidine. These are taken up actively into the lung by a membrane transport system[15] that has specificity for molecules with two positively charged quaternary nitrogen atoms separated by a distance of approximately 0.6â€“0.7 nm (Figure 111-1).

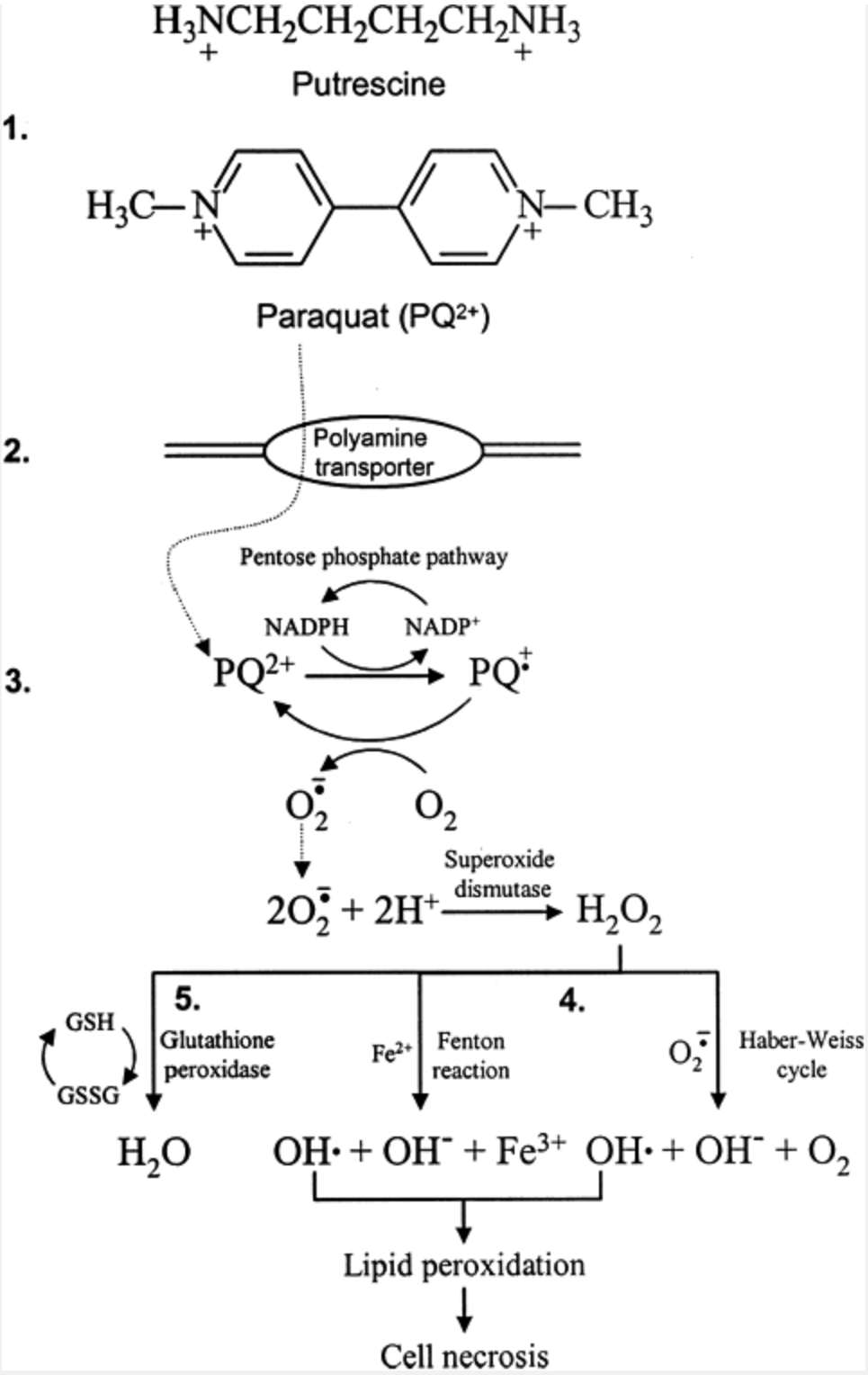


Figure 111-1. Mechanisms of toxicity of paraquat in the type II

alveolar epithelial cell. 1. Structure of paraquat and putrescine, showing the distance between the 2 nitrogen atoms of each. 2. Putative receptor responsible for the active uptake of paraquat by the alveolar epithelial cells. 3. Redox cycling of paraquat and oxygen. 4. Formation of the OHâ€¢ radical. 5. Detoxification of hydrogen peroxide (H_2O_2). *(Reprinted, with permission, from Smith LL: Mechanism of paraquat toxicity in lung and its relevance to treatment. Hum Toxicol 1987;6:31â€“36).*

Elimination

More than 90% of the absorbed dose of paraquat is eliminated by the kidneys as the parent compound within the first 12â€“24 hours after the ingestion. Even in patients who have ingested a toxic dose, renal function and paraquat clearance remain unaffected for several hours. When renal function is normal, the renal clearance of paraquat is higher than that of creatinine because of net tubular secretion of the molecule. As renal function deteriorates as a result of the poisoning, clearance of paraquat falls concurrently, and the half-life becomes prolonged, from about 12 hours to more than 24 hours. Redistribution from lung and muscle into the bloodstream is slow, with a half-life of about 24 hours, and accounts for the detection of low concentrations of paraquat in the urine for several days after the ingestion.

Mechanism

Paraquat produces tissue damage in the mouth and upper GI tract. Damage to organs such as kidney, heart, liver, pancreas, and muscle is assumed to be related to redox cycling and oxygen toxicity, but this has not been proven. The mechanism of toxicity has been determined most clearly in the lung when it is exposed to lower concentrations consistent with an ingested dose of 20–40 mg cation/kg (equivalent to 27–54 mg/kg of the dichloride salt found in 10–20 mL of the 20% concentrate). Once actively transported inside the pneumocyte, paraquat is reduced by an nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reaction to the mono-cation radical ($PQ^{+\bullet}$; Figure 111–1). This radical spontaneously reacts with molecular oxygen to form a superoxide radical ($O_2^{-\bullet}$) and regenerating the original paraquat dication, which now can undergo the reduction–oxidation cycle again. The nearly inexhaustible supply of electrons and oxygen in the lung sustain this redox cycling. It is further augmented over time by an increasing supply of paraquat molecules as they are accumulated from the blood against a concentration gradient and sequestered in the lung.

The recycling participation of paraquat in activating molecular oxygen explains why oxygen enhances the toxicity of paraquat and paraquat enhances the toxicity of oxygen. Like many superoxide radicals initially formed in the reaction of oxygen with PQ^+, paraquat can transfer its free electrons, forming other free radicals and resulting in chain reactions that are very damaging to cellular structures. For example, two superoxide radicals can be catalyzed by superoxide dismutase to hydrogen peroxide (H_2O_2), which in turn can be detoxified by catalases or peroxidases to nontoxic water molecules. On the other hand, in the presence of iron both the initial superoxide and hydrogen peroxide can also be catalyzed to yield the potent hydroxyl radical (•OH), which is thought to be the ultimate toxic free radical species derived from paraquat. The OH• generates additional free radicals by interacting with biomolecules such as proteins or membrane fatty acids. For example, OH• can take a hydrogen atom from polyunsaturated fatty acids, forming a lipid radical and subsequently lipid peroxides or hydroperoxide. These in turn pass on the free electron to other lipids, and a chain reaction of lipid damage occurs. This process, known as lipid peroxidation, leads to degradation of cell membranes. The reactive oxygen species formed by the initial interaction with $PQ^{\ddagger}$ interact with molecular sites on DNA, proteins, and cell membranes, disrupt cellular functions, and cause cell death. Cascading free radical production explains why the cellular injury from paraquat and other free radical generators far exceeds that produced by the initial reaction products.

NADPH is consumed during the initial reduction of paraquat to $PQ^{\ddagger}$ and by the glutathione peroxidase and reductase enzyme systems as they detoxify the superoxide radicals and their products. In response, the pentose phosphate and fatty acid synthesis pathways are activated to regenerate NADPH. Restoration of NADPH cellular reducing equivalents promotes the continuous redox reaction involving paraquat and oxygen and thus the continuous generation of more toxic oxygen species.

Antioxidant systems, such as the enzymes superoxide dismutase, catalase, and glutathione peroxidase and vitamins C and E, cannot respond in the same way, and so their capacity to extinguish the runaway free radical chain reaction is limited. This imbalance explains why the doseâ€“response curve for paraquat toxicity is very steep. Once a threshold dose is attained that begins to overwhelm the antioxidant defense system and damage cells, it requires very little increase in dose to attain the maximum toxic effect in a test population.

Clinical Manifestations

The clinical features of paraquat poisoning are summarized in Table 111-1. Ocular exposure causes gradually developing irritation that reaches a maximum about 12â€“24 hours after exposure as a result of stripping of the superficial epithelium of the cornea and conjunctiva. The severity of the injury is directly proportional to the concentration of the formulation. Dermatitis and nail damage can follow dermal contact with paraquat, particularly if it is not washed off quickly. The nails can become deformed by white bands, ridging, disruption of the nail bed, and impaired growth. Spray mist droplets impacting on the upper respiratory tract mucosa can produce inflammation, epistaxis, cough, and chest pain.

The severity and course of paraquat ingestion poisoning can be divided into three categories that broadly reflect dose-response.[76] Mild-moderate poisoning usually results from an ingestion of 10 mL

or less of 20% paraquat dichloride concentrate in a 70-kg person, equivalent to 20 mg paraquat cation/kg or 28.6 mg paraquat dichloride salt/kg. The possible effects include none/asymptomatic, oral mucosal ulceration, nausea and vomiting, and transient impairment of renal, hepatic or respiratory function. Recovery is expected and is complete.

TABLE 111-1. Clinical Features of Paraquat Poisoning by Organ System

Cardiovascular Hypovolemia, shock, dysrhythmias Central nervous Coma, convulsions, cerebral edema Dermatologic Corrosion of skin, nails, cornea, conjunctiva, and nasal mucosa Endocrine Adrenal insufficiency caused by adrenal necrosis as part of multiple organ failure Gastrointestinal Oropharyngeal ulceration and corrosion; nausea, vomiting, hematemesis, diarrhea, dysphagia,	Genitourinary Oliguric or nonoliguric renal failure caused by acute tubular necrosis; proximal tubular dysfunction Hematopoietic Leukocytosis early, anemia late Respiratory Cough, aphonia, prominent pharyngeal membranes (pseudodiphtheria), mediastinitis, pneumothorax, hemoptysis, acute lung injury, hemorrhage, pulmonary fibrosis

perforation of esophagus, pancreatitis, centrilobular hepatic necrosis, cholestasis	

Moderate-severe poisoning occurs in patients who ingest between 20 and 40 mg paraquat cation/kg (10â€“20 mL of the 20% concentrate in a 70-kg person). They characteristically exhibit early development of upper GI tract corrosion, acute renal tubular necrosis and hepatic injury. CNS involvement may appear as headache, dizziness, drowsiness, and incoordination, and as respiratory failure and coma if severe. Patchy infiltrates may appear on chest radiograph. Patients generally survive the acute phase and experience delayed but progressive pulmonary inflammation, fibrosis, and profound hypoxemia, which is the cause of death. Mortality occurs 5 days to several weeks after the ingestion. The proliferative lesion may not become evident until a week or more after the ingestion. However, cellular damage from free radicals begins immediately and initiates the destructive phase characterized by loss of both type I and II alveolar cells and of surfactant, infiltration by inflammatory cells, and hemorrhage. Hemorrhagic acute lung injury may occur. The subsequent proliferative phase is characterized by loss of alveolar integrity, proliferation of fibroblasts, and deposition of collagen in the interstitium and alveolar spaces. The fibrosis, which is in part cytokine mediated, is not specific for paraquat-induced injury but is seen in response to acute alveolitis induced by many pulmonary toxins. Survival is possible but residual restrictive lung disease may be a long-term sequelae.

A fulminant course of poisoning occurs in patients who ingest more than 40 mg paraquat cation/kg (>20 mL of 20% concentrate in a 70-kg person.) They do not survive long enough to demonstrate pulmonary fibrosis. Patients exhibit severe vomiting and diarrhea,

oropharyngeal and gastrointestinal ulceration, renal and hepatic failure, acute pulmonary injury and alveolitis, cardiac dysrhythmias, shock, and coma. They usually die within 1â€“4 days after ingestion from multiorgan failure, shock, or corrosive destruction of the GI tract. Death from esophageal perforation and mediastinitis can occur within 2â€“3 days of the ingestion.

The diagnosis can be missed if paraquat ingestion is unsuspected. Sudden appearance of rapidly progressive pulmonary fibrosis in the 2 weeks following an illness characterized by oral ulceration and upper GI symptoms must include surreptitious paraquat ingestion in the differential diagnosis.

Diagnostic Testing

Urine and plasma should be sent to the laboratory promptly for qualitative and, if available, quantitative determination of paraquat concentrations. If possible, specimens should be placed in plastic containers because paraquat binds to glass. Rapid, qualitative analysis in urine is performed by reducing paraquat to its blue mono-cation radical with sodium dithionite under alkaline conditions and comparing the result with appropriate positive and negative controls. A fresh alkaline sodium dithionite solution is made by adding 100 mg of sodium dithionite (nonoxidized) to 5 mL of 5 M NaOH. An aliquot sample (250 ÂµL) of this solution is added to 1 mL urine. If paraquat is present in a concentration of 2 Âµg/mL or greater, a concentration-dependent blue to black color is evident. Diquat is reduced similarly to form a yellow-green color.

Plasma or urine paraquat concentrations can be measured quantitatively by a variety of techniques, the most common being radioimmunoassay, gas chromatography, spectroscopy, and high-performance liquid chromatography. It is usually relatively easy to identify a laboratory that can perform the spot test but more difficult to find one to do the quantitative measurements. Many

manufacturers support a 24-hour emergency service that should provide this information for each country. The telephone number for the service in countries in which it is available can be found either on the product label or via a poison center or other emergency facility. In many areas, quantitative assay results are not available in a timely manner to assist with management of the patient. In this case, the management must be guided by the clinical and other laboratory findings. Clinical chemistry abnormalities reflect the developing necrosis of the renal tubules, liver, lung, pancreas, and muscle.[68] Hematologic abnormalities, if any, are usually nonspecific and related to bleeding, infection, or stress. If paraquat concentrations in blood exceed about 10 mg/L, measured values of creatinine and lactic acid dehydrogenase (LDH) may be elevated artificially because of interference with the colorimetric methods used to measure them.[11]

Tissue destruction of the esophagus and mediastinum can be associated with pneumomediastinum and pneumothorax. Typically the resultant changes in the lung parenchyma are obvious on the chest radiograph, first as cystic and linear opacities and later as consolidation, particularly in the perihilar regions. Figure 111-2 shows a chest radiograph, taken on the ninth day after the ingestion of paraquat in a patient who died 3 days later. It shows diffuse consolidation most marked in the perihilar regions.

Management

Early treatment is a very important determinant of survival in paraquat-poisoned patients. The â€œwindow of opportunityâ€• for any effective treatment of paraquat poisoning is very short, only a few hours at most. Therefore, any patient who has been exposed to paraquat, particularly if a concentrated liquid formulation is involved, should be treated as a medical emergency, even if there are no symptoms or signs of toxicity at the time of presentation. All attempts should be made to obtain an accurate history for any

agrochemical ingestion.

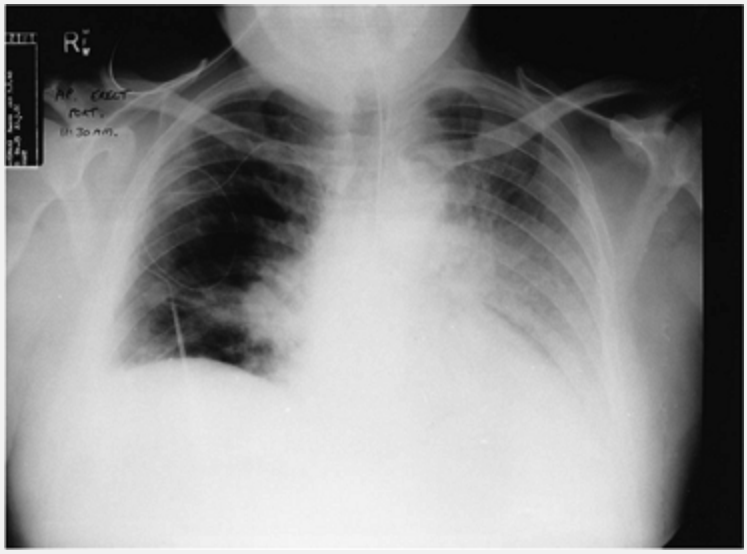


Figure 111-2. Chest radiograph taken 9 days after the ingestion of 70 mL of 20% paraquat, demonstrating diffuse alveolar consolidation, most marked in the perihilar regions.

If there has been dermal exposure, either primarily or secondarily from contact with contaminated vomitus, the clothing should be removed immediately and the skin washed gently but thoroughly with soap and water. Harsh scrubbing should not be conducted because the resultant skin abrasion could actually increase the transdermal absorption of paraquat. If the eyes have been splashed, ocular irrigation with copious amounts of water should continue for 15 minutes. These patients should be seen by an ophthalmologist for further management.

Gastric Emptying

If paraquat was ingested only minutes earlier, measures to remove it or prevent its absorption from the gastrointestinal tract should be

instituted immediately. Spontaneous vomiting is a near certainty in significant ingestions because both the irritant effects of paraquat and the emetic added to many formulations. Induced emesis should not be attempted. Even if the patient has already vomited, further gastrointestinal decontamination should be considered. As a first aid measure, in the field, a slurry of AC, Fuller earth, bentonite, or garden clay can be considered, especially if there will be a substantial delay in reaching a medical facility. In most developed countries, resorting to nonpharmaceutical clay will not need to be seriously considered. Naso- or orogastric lavage may have applicability only in patients who present immediately after ingestion. However, substantial mucosal damage in the esophagus and stomach caused by paraquat formulation places these structures at risk for perforation by the large-bore lavage tube. A better alternative is administering an oral adsorbent as quickly as possible.[47]

Adsorbents

Oral adsorbent options include 1 to 2 g/kg of AC, 1 to 2 g/kg of Fuller earth in a 15% (w/L) aqueous suspension, or 1 to 2 g/kg bentonite in a 7% (w/v) aqueous slurry. All three adsorbents bind and retain paraquat effectively; ready availability determines the choice of adsorbents.[9] If the patient vomits the first dose, another should be given, through a nasogastric tube if necessary. Rapid control of repeated vomiting with antiemetics and promotility agents is essential when the patient cannot retain the adsorbent.

Extracorporeal Removal

Methods to maintain or increase the rate of elimination of paraquat from the body should be considered. Hemoperfusion across a cartridge containing AC enhances elimination of paraquat from the blood. Although significant reduction in mortality can be

demonstrated in dogs 2â€“12 hours after an LD_{50} or LD_{100} dose of paraquat,[20,79] there is no clinical evidence that hemoperfusion is efficacious in humans. Many factors may account for this. Most patients ingest much more than a potentially fatal dose; even if hemoperfusion removes an amount equivalent to several fatal doses, many fatal doses may remain in the body. Many patients present hours after ingestion during which time the paraquat is actively removed from the blood and sequestered in the lung, where it is inaccessible to hemoperfusion. When renal function is normal, hemoperfusion contributes very little additional clearance, so it has proportionately less effect on survival. Likewise, because most of the absorbed dose is eliminated by the kidneys during the first 12 hours after the ingestion; hemoperfusion after this time has little proportional effect on total clearance. Last after the initial plasma phase the slow redistribution phase from the muscles and lungs back to plasma limits the removal rate of paraquat.[51,52] Because of these factors, charcoal hemoperfusion should be begun only if it can be initiated within 4 hours of ingestion and continued for 6â€“8 hours. Based on current clinical and experimental evidence, there is no indication for repeated hemoperfusion. Although hemodialysis can equal or exceed renal clearance of paraquat, particularly when renal function is impaired, it has not reduced mortality. Hemodialysis therefore should only be considered for paraquat removal when hemoperfusion is not available.

Continuous arteriovenous hemofiltration can reduce the marked rebound in plasma paraquat concentrations that occurs after hemoperfusion as a result of redistribution of paraquat from the tissues but no clinical benefit from this procedure has been demonstrated. Forty-four patients receiving continuous venovenous hemofiltration (CVVH) after hemoperfusion had the same overall mortality rate as 36 patients not receiving CVVH (67% vs 64%). However, death was delayed an average of 2.5 days and was a result of respiratory failure rather than circulatory collapse in those receiving CVVH.[35]

Supportive Care

Supportive and palliative care are the most important components of the management of paraquat-poisoned patients. Fluids and electrolytes should be administered IV in sufficient volume to replace GI tract losses and maintain normal hemodynamics and high-normal urine output. Analgesia may be needed for the pain associated with the mucosal ulceration. Patients should be monitored frequently for the development and progression of renal and respiratory failure. Supplemental oxygen is a double-edged sword in that it accelerates paraquat-induced oxygen radical toxicity as it temporarily relieves the distress of hypoxia.[5,6] Generally, supplemental oxygen should be withheld until the arterial oxygen tension falls below 50 mm Hg and/or the patient expresses respiratory distress. The potential contribution of oxygen to the pathologic process and the ultimate decline of the patient should always be considered.

Investigational Treatments

Although many treatments have been proposed and attempted empirically based on the pathologic mechanism of toxicity, none are supported by convincing clinical efficacy.[3] Some authors claim success based solely on the results achieved in a single patient. Few controlled trials of these interventions have been performed, and results of published case series are inconsistent. Major deficits in assessing clinical benefit from various interventions and their combinations include the lack of a uniformly used prognostic indicator that reliably predicts risk of death at an early stage in the poisoning; and small numbers of patients receiving a particular intervention.

Partially evaluated treatments include those that could reduce circulating paraquat (Fab or recombinant single-chain antibody),[8] prevent the accumulation of paraquat by the lung (various

polyamines, *d*-propranolol), increase efflux of paraquat from the lung (cyclophosphamide, *d*-propranolol), reduce or prevent the consequences of the redox cycling (reduction of inspired oxygen FIO_2, vitamin E, superoxide dismutase, ascorbic acid, deferoxamine, selenium, niacin, *N*-acetylcysteine (NAC), or S-carboxy methylcysteine), or reduce the extent or consequences of pulmonary fibrosis (corticosteroids, immunosuppressive agents, fibrinolytic agents, colchicine, radiotherapy, and inhaled nitric oxide).[4]

Two studies with promising preliminary results found reduced mortality in severely poisoned patients given pulse therapy with cyclophosphamide and high-dose methylprednisolone compared to conventionally treated control patients comparable in age, gender, urine dithionite results, and time since ingestion. In the first study series of nonrandomized patients, mortality in the pulse therapy group (n = 16) was reduced compared to the control group (n = 17) (25% vs. 71%).[43] In a prospective, randomized follow-up study by the same authors,[44] all patients received gastric lavage followed by AC instillation, two 8-hour hemoperfusion sessions against activated charcoal, and 10 mg intravenous dexamethasone every 8 hours for 14 days. The patients randomized into the treatment group also received at the end of hemoperfusion 1 g of intravenous methylprednisolone daily for days 1, 2, and 3 and cyclophosphamide 15 mg/kg daily for days 2 and 3 of pulse therapy. Patients with mild poisoning as predicted by a light blue or clear color on the admitting urine dithionate test (n = 21), and those retrospectively assessed as having fulminant poisoning (n = 71) were not included in the data analysis. Exclusion of the latter is a point which has received some criticism.[10] The pulse treatment group had reduced mortality (4/22, 18%) compared to the conventionally treated control group (n = 16/28, 57%). When an intention to treat analysis is done to include those retrospectively excluded as fulminant poisoning, a trend for increased survival is present but does not reach statistical significance. This treatment strategy addresses acute pulmonary

inflammation as the key pathophysiologic target in fatal hypoxemia rather than subsequent fibrosis. The cause of death in fulminant poisoning is not pulmonary inflammation or fibrosis; therefore, salvage of such patients with pulse therapy seems medically doubtful. In a single case reported separately, recovery was achieved in a severely poisoned paraquat patient by a second pulse of methylprednisolone on day 30 when pulmonary inflammation and hypoxemia emerged despite steady daily therapy of dexamethasone after the first pulse therapy. More study of a larger number of severely poisoned patients must be performed to confirm or refute benefit of this approach before it can be recommended as a standard treatment.

Lung Transplantation

Lung transplantation has been performed in a few patients, but only one survival is reported in the literature. In that case, a single

lung was transplanted 44 days after paraquat ingestion; recovery was complicated by subsequent removal of the other poisoned native lung, and severe myopathy prevented weaning from mechanical ventilation.[77] Therefore, single or bilateral lung transplantation can be considered if a patient survives for 3 weeks or longer with end-stage respiratory failure and otherwise meets criteria for transplantation. In this context of prolonged medically supported survival, other serious, long-term effects of paraquat are revealed. For example, patients given lung transplants who survived for several months after paraquat exposure have developed progressive toxic myopathy, which proved fatal in one case.

Prognosis

Survival is dose-dependent. Not all patients who ingest paraquat die, but the mortality has been as high as 75% in some series of patients. Typically a patient who survives does not develop

significant pulmonary injury and has no or few residual effects. Some of the few survivors with residual pulmonary fibrosis have progressively improved over time. Patients who ingest paraquat intentionally usually take a higher dose than those who ingest it unintentionally and therefore typically have a worse prognosis. Similarly, the incidence of death is higher the more concentrated the formulation ingested.

There are proposed prognostic tools to estimate the chance of survival or mortality using serum paraquat concentration or urine dithionate assay results along some time axis following ingestion. Others use physiologic parameters such as APACHE scoring. They all share a major limitation in that they have not been adequately validated in a prospective manner. This hampers the interpretation of studies that investigate the effect of various treatments on survival. An example of such a prognostic tool is presented in Figure 111-3.[22,54] Plasma concentrations of paraquat measured within 28 hours after the ingestion are useful in estimating the prognosis according to the nomogram. This nomogram was derived empirically from clinical data and not by statistical means, and is not infallible. Patients with higher concentrations than those predicted from the nomogram to be associated with survival, have nevertheless survived; conversely, some patients with lower concentrations have died.[54] When experience with the nomogram in 166 cases was reviewed, it correctly predicted the outcome in 93% of cases who died and in 64% who survived.[54] Therefore, reports in the literature of unexpected survival in individual patients based on the nomogram should be attributed only with caution to one or another innovative treatment because of the somewhat inadequate nature of the predictive values. The extension of this nomogram beyond 28 hours has similar predictive efficacy. It appears that whenever the initial plasma concentration of paraquat exceeds 3 mg/L, mortality is 100%. The mode of death is cardiogenic shock within 24 hours of the ingestion in those whose paraquat levels exceed 10 Âµg/mL.

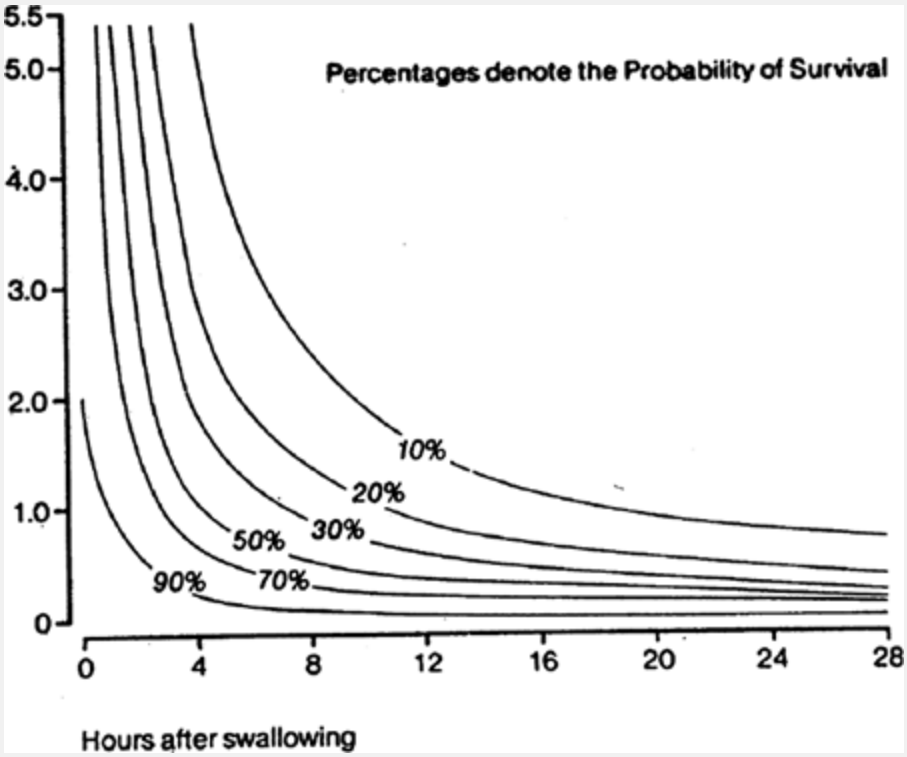


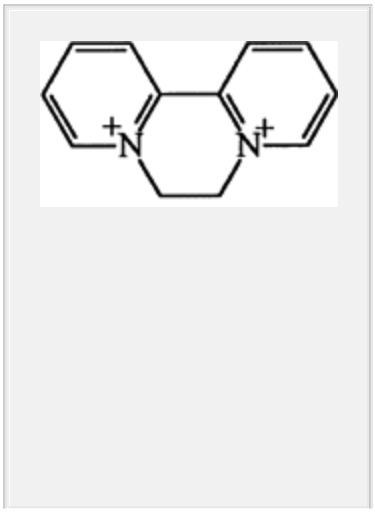
Figure 111-3. Nomogram showing the relationship among the plasma concentrations of paraquat on the ordinate (Âµg/mL), time after ingestion on the abscissa, and the probability of survival. *(Reprinted, with permission, from Hart RB, Nevitt A, Whitehead A: A new statistical approach to the prognostic significance of plasma paraquat concentrations [Letter]. Lancet 1984;2: 1222â€“1223.)*

Concentrations of paraquat in urine obtained within the first 24 hours of ingestion can also be used to estimate prognosis.[61,62] Of 53 patients studied, 15 who had urinary concentrations of paraquat below 1 Âµg/mL within the first 24 hours, survived. Urinary concentrations in those who died within 24 hours ranged from approximately 10â€“10,000 Âµg/mL; concentrations in those who died later from pulmonary fibrosis were between 1 and 1000

Âµg/mL.[61,62]

Several indices using physiologic and clinical data have been proposed.[54,67] Examples include predicting the risk of mortality or change of survival based on rate of increase in plasma creatinine over a 5-hour period[55] and abnormal alveolar permeability found by lung scintigraphy.[29] Several factors can moderate the amount of paraquat absorbed and thus decrease the plasma and urinary concentrations. When paraquat is swallowed on a full stomach, its absorption is reduced because of delayed gastric emptying and the adsorption of the herbicide by the food. The presence of ulceration in the upper gastrointestinal tract is a poor prognostic sign because it may reflect the concentration and the dose of paraquat in the formulation. In one series of patients who had upper GI endoscopy between 3 hours and 3 days after the ingestion, 9 of 14 patients with gastric and esophageal ulcerations died. Conversely, all 6 who had no gastric ulcerations survived.[5] The development of renal failure heralds a poor prognosis. In the same report, 19 of 20 patients developed renal failure died.[5]

Diquat



Diquat

Diquat (1,1â€²-ethylene-2,2â€²-dipyridylium dibromide) is used agriculturally for the same purposes as paraquat and for the control of aquatic weeds. It is sometimes combined with paraquat. Recently, it has also been combined in dilute formulations with glyphosate to provide complementary herbicidal actions of rapid burn-down and elimination of viable root remnants. Diquat is similar to paraquat in terms of acute oral toxicity as measured by LD_{50} in rats (150â€“250 mg ion/kg), caustic local effects, kinetics, and

mechanism of toxicity, with one important exception. Diquat lacks the structural features necessary for active transport by the polyamine uptake pathway into the lungs. Therefore, the extent of pulmonary injury and fibrosis following the ingestion of toxic doses of diquat is much less than paraquat. Instead, the predominant target organ is the kidney. Ingestion of diquat rapidly causes nausea, vomiting, watery diarrhea, and pain. Because of severe irritation or ulceration of the oropharynx, esophagus, and gastrointestinal tract. Progression of toxicity may include airway compromise, hemodynamic collapse, respiratory failure, seizures, and renal failure with attendant clinical complications. Intracranial hemorrhage and brainstem infarction have also been reported in several severe poisonings. In comparison to paraquat, there have been relatively few cases of diquat poisoning. Among 11 adult cases, the lethal dose of diquat was 6â€“12 g.[5] Fatalities occurred despite treatment such as forced diuresis, hemoperfusion, and antioxidants. In one fatal case, the serum diquat level 4 hours was 64 Âµg/mL after ingestion of 60 g of diquat cation. The patient exhibited progressive anuria, coma, and seizures and died 26 hours after ingestion from cardiovascular collapse. Extracorporeal removal techniques yielded 1.09 g of diquat. Postmortem findings included marked renal tubular and some glomerular damage.[21] Another

patient ingested 200 mL of diquat dibromide diluted to 1.84% and remained asymptomatic for 8 hours afterward. Subsequently he developed esophagitis, epiglottitis, and acute renal failure, from which he slowly recovered.[74] In another case, intravaginal instillation of 20 mL of concentrated diquat formulation resulted in local corrosion, renal failure, diffuse slowing on EEG, and spastic quadaparesis lasting 3 months.[57]

Local effects of dermal exposure include chemical burn and injury to nail beds. The dermal LD_{50} of diquat dibromide in rabbits is also of the same magnitude as paraquat dichloride (both approximately 200â€“300 mg/kg). Although as an ionized molecule diquat is poorly absorbed through intact skin, it can itself damage skin after repeated or prolonged contact and facilitate its own absorption. Skin exposure has been experimentally shown to be capable of causing systemic poisoning and death in test animals. Ocular exposure to diquat causes irritation and delayed superficial tissue injury. Damage is mediated by oxygen radicals and may cause visual impairment that takes weeks to resolve. This risk can be substantially mitigated by rapid and thorough rinsing of the eyes with water.

Treatment of diquat-exposed patients is similar to the treatment provided to those exposed to paraquat and includes gastric decontamination, adsorbents, hemodialysis and perfusion, and supportive care. Extracorporeal removal techniques remove diquat from the circulation as renal failure ensues, but they have not appeared to affect mortality among the small number of reported cases. Diquat can be detected qualitatively in the urine by the same colorimetric dithionite test for paraquat, in this case producing a yellow-green color instead of purple-blue. At extremely high serum levels, diquat may also introduce an artifact into certain laboratory assays for serum creatinine.

2,4-D and Chlorophenoxy Herbicides

Characteristics

2,4 dichlorophenoxyacetic acid (2,4-D) was introduced as the first selective herbicide in 1946 and remains one of the most widely used agents worldwide. It is the prototype and representative of a large group of related agents including diclofop, MCPA (methyl chlorophenoxy acetic acid), MCPB (methyl chlorophenoxy butyric acid), MCPP (mecoprop, methyl chlorophenoxy propionic acid) and silex. This group is composed of chlorinated and methyl-substituted phenoxyl acetates, butyrates and propionates and their various salts, amines, and ester forms. The chlorophenoxy herbicides are selectively toxic to broad-leaf plants (eg, clover, dandelion) and not to monocotyledonous species such as grass, wheat, barley, oats, sorghum, corn, and sugarcane. Thus they find great applicability for suppressing weeds in cropland, rangeland, and residential lawns; 2,4-D is the â€œweedâ€• in weed-and-feed formulations. The chlorophenoxy herbicides are synthetic plant hormones, which mimic natural auxins involved with growth responses such as cell elongation and cell division. Growth becomes deranged with cupped leaves and twisted stems appearing before plant death. The exact mechanism of lethality to plants is not known but it appears to involve inhibition of nucleic acid synthesis.[64] Monocotyledons are resistant because they have enhanced ability to glycosylate the herbicide after absorption, which inactivates it.

Use on home lawns provides more opportunity for exposure of both adults and children to 2,4-D than herbicides confined to agriculture or industrial markets. Despite this general availability, reports of poisoning are rare and largely confined to intentional ingestions. The role of chronic or recurrent exposures to chlorophenoxy herbicides in farm work or Vietnam-based exposure to 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) in Agent Orange as the etiology of certain cancers and other adverse health effects is still uncertain. Of the latter, much evidence points to contaminating dioxin as the responsible agent.[12]

Toxicokinetics

Absorption

2,4-D is rapidly and nearly completely absorbed after ingestion (>90%) under experimental conditions. The actual dose absorbed after ingestion is very difficult to estimate because there is typically loss as a result of rapid vomiting. After ingestion, peak tissue concentrations occur in 4â€“12 hours.[34,58] 2,4-D is poorly absorbed through the skin (2â€“6%) and is influenced by the salt or ester form of the chlorophenoxy acid and formulation parameters, occlusion, ambient temperature, and the integrity of the stratum corneum. A radiolabeled skin absorption study showed a standard deviation of 50% of the mean value, suggesting wide interindividual variability in dermal transport. Slow continued absorption through the skin continues over 5â€“7 days following a single topical application, despite removal of the deposit residue by external skin washing. Dermal absorption can be significantly increased by the active ingredients in many sunscreen and sunscreen-insect repellent formulations because these act as penetration enhancers.

Distribution

Once absorbed, the toxicity of the various salt and ester forms is represented by the parent acid as rapid hydrolysis of the ester linkage occurs in serum. Experimentally, 2,4-D appeared in brain tissue within 30 minutes of administration, at concentrations slightly lower than in the serum. Onset of toxicity occurred concurrently, implying that the primary target site of poisoning is the CNS. As an organic acid, 2,4-D is highly protein bound. In high-dose situations when protein binding is saturated the free acid distributes

throughout the body. Distribution of the parent acid into the brain,

which should be hindered by the bloodâ€“brain barrier, may have some connection to its transport by a specific organic acid transporter (OAT). In the choroid plexus, its uptake into cells is inhibited by benzylpenicillin, implicating OAT.[3]

Elimination

2,4-D is excreted in the urine mainly unchanged with only a few percent found as a conjugated metabolite. Excretion becomes less efficient at higher serum concentrations, implying saturation of at least some component of renal elimination, probably organic acid tubular secretion. The half-life of elimination appears to be 12 or more hours, with a terminal elimination half-life of approximately 33 hours. Alkaline manipulation of urine pH increases clearance and shortens half-life. The actual mechanism is uncertain, as the â€œion trappingâ€• explanation would be inconsequential at a urine pH range of 5â€“8 given the low pKa of 2,4-D.

Mechanism of Toxicity

Mammals and insects do not respond hormonally to plant hormones or analogs. The toxic mechanisms of chlorophenoxy compounds in humans and animals are not understood but they appear to have multiple effects in biologic systems. Experimental results implicate interference with membrane-based organic acid transporters and exchangers that carry neuronal metabolic substrates. Oxidative membrane stress, apoptosis, and selective regional neurotransmitter interference have also been proposed. Some chlorophenoxy compounds block chloride membrane conductance in striated muscle. Through structural mimicry, these agents appear to be false substrates of both acetyl coenzyme A (CoA) synthase and choline acetyltransferase, producing substituted acetyl-CoA and acetylcholine. Chlorophenoxy false cholinergic messengers are formed at nicotinic and muscarinic sites in nerves and muscles and at extraneuronal sites. The chlorophenoxy herbicides are also weak

uncouplers of oxidative phosphorylation and impede energy metabolism.

Clinical Manifestations

2,4-D is severely irritating to eyes. It is not considered irritating to skin but applicators of chlorophenoxy herbicide formulas report burning eyes, nose and throat that persists for several days following exposure. It is not a sensitizer.

Organs that bear most of the symptoms of chlorophenoxy poisoning appear to be the central nervous system and the neuromusculature.[64] Adverse effects of poisoning are compatible with neurotoxicity, uncoupling of oxidative phosphorylation, and skeletal muscle toxicity. Ingestion produces rapid onset of oral and abdominal distress characterized by burning pain in mouth, throat and esophagus/chest, nausea, vomiting that may persist for 12 or more hours, dysphagia, and diarrhea. Patients may then demonstrate hypotension, tachypnea, tachycardia or tachydysrhythmias, hyperthermia, diaphoresis, flushing, dizziness, lethargy, confusion, ataxia, and in severe poisoning, seizures or coma. Direct cardiac effects are suggested by various ECG changes and dysrhythmias; ventricular fibrillation is often the terminal event experimentally. Peripheral neuromuscular effects have included increased or decreased reflexes, hypotonia, weakness, muscle aching and tenderness, and fibrillatory twitching. Electromyograms are abnormal. Dyspnea and hypoxia secondary to mechanically inadequate respiration may occur. Myotonia (delayed muscle relaxation after contraction) is a characteristic effect of 2,4-D in animals but only rarely reported in human poisonings.

In 1962, observations on the empiric use of 2,4-D for potential therapeutic response in a patient with disseminated coccidiomycosis were reported. Over a period of 34 days, the patient received 12.7 g of the sodium salt of 2,4-D, most of it intravenously. The most frequently administered daily doses were 800 or 960 mg; however,

the last dose was 2,000 mg IV. This 2-g dose produced no complaints from the patient and resulted in no changes in the physical examination. On the following day 3,600 mg of 2,4-D was given intravenously and the patient developed toxicity at the end of the infusion. Observations included depressed consciousness, diffuse myofibrillations that persisted for several hours. Coma responsive to painful stimuli hyporeflexia, and urinary incontinence ensued. No other neuromuscular manifestations developed in the 2 weeks prior to his death from the fungal disease.

There is still considerable controversy whether exposure to 2,4-D can result in peripheral neuropathy.[13,14] It is not a consistent sequela in patients who survive large-volume ingestions. Most case reports follow relatively minor skin exposure. Because a dose-response relationship is not evident, and there is no plausible mechanism for this specific toxicity, no conclusion can be made causally linking peripheral neuropathy to chlorophenoxy herbicide exposure, unless it be an uncharacterized or rare idiosyncratic response.

Laboratory

Analysis of biologic specimens for chlorophenoxy herbicide is not readily available and not needed for managing the patient. Elevated creatine phosphokinase, and myoglobinuria may occur as a result of muscle damage. Myoglobin release from substantial rhabdomyolysis may jeopardize renal function beyond some minor proteinuria which may occur as a direct toxic effect. Minor-to-moderate injury to liver may be manifest as elevation of hepatic aminotransferases.

Similarly to salicylic acid, another organic acid uncoupler of oxidative phosphorylation, sufficiently high dose may produce complex acidâ€“base disturbances, which include one or more elements of respiratory alkalosis and metabolic acidosis.

Management

Initial treatment consists of removing herbicide from the body and supportive care. AC may be considered in patients with significant ingestions.

Urinary Alkalinization

There is some anecdotal evidence supporting the claim that alkalinization of the urine enhances the excretion of chlorophenoxy herbicides. In one case, renal clearance of 2,4-D rose nearly 5-fold for every unit increase in urine pH.[6,53] Clinical improvement of the patient appeared to follow decline of the serum concentration. Effectiveness of this intervention in removing the herbicide is increased by concurrent high urine flow. Urinary alkalinization may be shown to be of limited value, but is unproven, whereas hemodialysis is a better option in severely poisoned individuals if it is available. Because of striated muscle toxicity, rhabdomyolysis represents an independent indication for urinary alkalization to preserve renal tubule integrity.

Extracorporeal Removal

Hemodialysis is effective in removing chlorophenoxy herbicides from the blood. It should be considered in all patients who manifest CNS or neuromuscular toxicity.

Other Treatment

A single case report observed relief of muscle tenderness with the administration of quinidine sulfate given every 4â€“6 hours to treat an unspecified cardiac dysrhythmias. In a separate case report, quinidine administered to treat intermittent nodal tachycardia also relieved muscular hypertonia. These reports constitute inadequate

evidence to recommend quinidine or quinine as effective in treating the muscle symptoms of chlorophenoxy poisoning.

Glufosinate and Bialaphos

Description

The soil fungus *Streptomyces hygroscopics* produces the tripeptide phosphinothricin-alanine-alanine, also known as bialaphos, and this is metabolized in plants and animals to phosphinothricin, also known as glufosinate. Glufosinate is a unique amino acid (2-amino-4-hydroxymethylphosphinyl butanoic acid) that is an analogue of glutamic acid. It exerts a nonselective herbicidal action by inhibiting glutamine synthetase, an enzyme important in amino acid metabolism, nitrogen transformation, and detoxification of ammonia. The accumulation of ammonium is phytotoxic. The parent molecule bialaphos has limited commercial use as an herbicide. Its active moiety, glufosinate, is synthesized and used in many areas around the world for control of weeds and weedy grasses, especially among permanent crops as in plantations, forests, orchards, and vineyards. It is also used to desiccate certain crops to facilitate harvest. Glufosinate is marketed as the ammonium salt in various products including Basta, Ignite, Challenge, and Finale. The surfactant included with Basta has been characterized as anionic, sodium polyoxyethylene alkyl ether sulfate.

Toxic Mechanism

Glufosinate inhibits mammalian glutamine synthetase in various tissues but causes accumulation of ammonia and glutamate only when administered at near-lethal levels.[18] The mammalian system, unlike plants, apparently can compensate to some degree for inhibition of glutamine synthetase by other metabolic pathways. Glufosinate also inhibits glutamate decarboxylase, leading to a decrease in Î³-aminobutyric acid (GABA). Glufosinate and bialaphos

are centrally neurotoxic in humans. Both seizures and profound CNS depression can occur concurrently. Clinical improvement lags behind the physical elimination of the compound, implying prolonged effect at the target site(s). In one case of bialophos poisoning, serum glutamate levels were followed and found to be abnormally high on day 5 of the poisoning and did not return toward normal until day 26.[49] This finding is in keeping with the clinical observation. The circulatory failure noted in patients with severe acute oral poisoning may be because of systemic surfactant syndrome. This was experimentally demonstrated in an in vivo and in vitro animal model by induction of the characteristic vasodilatation and cardiac depression effects caused by either the surfactant alone or the formulated herbicide containing the surfactant but not by glufosinate alone.[37]

Toxicokinetics

Glufosinate and bialaphos are partially absorbed orally. Onset of serious CNS symptoms is delayed many hours to more than a day after a large volume ingestion of herbicide concentrate. Glufosinate is excreted renally unchanged. The serum glufosinate concentration was measured every 3â€“6 hours in a 65-year-old man who ingested an estimated 60 g as 300 mL of a 20% w/v concentrate. Total urinary excretion was measured every 24 hours. The distribution half-life ($t_{1/2}$ Î±) was 1.84 hours and the elimination half life ($t_{1/2}$ Î²) was 9.6 hours. The apparent volume of distribution was estimated to be 1.4 L/kg. Renal clearance was calculated at 78 mL/min, and represented nearly all of the whole body clearance.[23] Because glufosinate is a racemic mixture of D and L enantiomers, some analytic work has been attempted to distinguish the enantiomers in poisoned patients. In the single patient reported to date, the D enantiomer kinetics best fit a 1-compartment model, but the L enantiomer best fit a 2-compartment model and had a longer half-life of elimination.[25] Both enantiomers were found in the CSF at the time of onset of significant CNS depression at

concentrations approximately one third of the concurrent serum levels. Existence of a specific uptake mechanism is postulated as the ionic nature of this small molecule would normally exclude it from crossing the bloodâ€“brain barrier.[24] More work must be accomplished to evaluate the clinical significance of this finding.

Clinical Manifestations

Early symptoms of the systemic surfactant syndrome may appear very soon after ingestion of concentrate and include oral irritation, nausea, and vomiting. Death from cardiovascular failure has occurred in at least 2 patients who ingested at least 300 mL of the surfactant-formulated herbicide. Onset of CNS symptoms is delayed for 4â€“8 hours after large ingestion with significant symptoms such as coma and respiratory depression usually delayed for 24 hours or longer. One author reports a delay in onset of 60 hours after ingestion.[38] CNS symptoms may continue to progress for 24â€“48 hours. Typical CNS symptoms include drowsiness, ataxia, disordered eye movement, disorientation, tremor, stupor, deep coma, and central apnea and respiratory arrest.[38,39,70,73] Convulsions are a late manifestation of poisoning and appear in only approximately 50% of those seriously poisoned. There may be seizure onset from 7.5â€“29 hours after ingestion.[36,70,72] Seizures are always preceded by loss of consciousness and in fact may begin after the patient begins to awaken from deep coma. Seizures are repetitive and can be prolonged; status epilepticus is possible. Secondary organ damage that may result from seizure activity includes fever, rhabdomyolysis, and myopathy.

During the recovery period, the patient may experience loss of short-term memory (both retrograde and anterograde amnesia).[78] This effect is also a feature of amnestic shellfish poisoning, which involves domoic acid, another excitatory amino acid neurotransmitter. Recovery from glufosinate poisoning is prolonged and extubation may need to be delayed for a week or more.

Normalization of higher functions may require weeks. Some patients have required discharge to a rehabilitation facility. Diabetes insipidus developed approximately 14 hours after admission in one reported case of glufosinate poisoning.[70] The peak urine output was >300 mL/h, serum sodium was 167 mEq/L, plasma osmolality 332 mOsm/kg, urine osmolality 200 mOsm/kg, and plasma antidiuretic hormone was abnormally low.

The patient responded to intranasal desmopressin given 40 hours after admission, with normalization of affected physiologic parameters within 48 hours.[70]

Ingestions of the related chemical bialaphos are less frequent because of its limited commercial availability. In one documented case of ingestion of 100 mL of 32% w/v bialaphos plus ethanol, the patient exhibited early vomiting, respiratory distress, and metabolic acidosis. Ten hours after ingestion he developed nystagmus, which lasted for 19 days. Respiratory arrest occurred 36 hours after ingestion.[44] Hours after ingestion, seizure episodes lasting 80 seconds, followed by 40 hours of complete apnea, developed. The patient recovered and was discharged without apparent sequelae.[46] In another case of intentional ingestion of formulated bialaphos, the patient rapidly developed nystagmus, coma, respiratory arrest, and convusions.[49]

In one series, 5 patients who reportedly ingested 0.3â€“1.8 mL/kg (~20â€“100 mL) of 18.5% glufosinate ammonium formulation remained asymptomatic, but 6 who ingested 1.7â€“9.1 mL/kg (100â€–500 mL) developed CNS dysfunction 8â€–34 hours later. The acute neurotoxic dose of glufosinate was thereby estimated to be approximately 300 mg/kg. Ingestion in adults of more than 1 or 2 mouthfuls of concentrate should be evaluated in a healthcare facility because the onset of CNS dysfunction may occur 24 hours or more later.

Laboratory

There is no readily available laboratory test to document ingestion of glufosinate or bialaphos or determine serum levels. High-performance liquid chromatography (HPLC) has been used in research settings to measure glufosinate in plasma, urine, and CSF. Serum should be monitored for elevations of lipase and hepatic aminotransferases, and creatine phosphokinase monitored in patients with multiple seizures. Clinicians should be aware of the potential for diabetes insipidus and suspect it if the urine output, serum sodium, and serum osmolarity become abnormally high without attendant concentration of urine. There are no clinical data on serum ammonia levels.

Management

Gastric Decontamination

Orogastric or nasogastric lavage and AC may be indicated for particular patients with substantial exposures. Spontaneous vomiting commonly occurs after significant ingestions of formulated herbicides because of the surfactant content; and may therefore make it unnecessary to attempt gastric lavage. Particular attention must be exercised in protecting the airway because of the obtundation and coma that may develop many hours after ingestion. Gastric lavage plus extracorporeal removal failed to prevent progression of CNS effects to coma and seizures in two patients who presented 30 minutes and 3.5 hours after ingestion.[72]

Extracorporeal Removal

Hemodialysis is superior to AC hemoperfusion in eliminating glufosinate from blood in vitro.[73] However, several clinical authorities perform both procedures in tandem in an herbicide-poisoned patient.[63,70,72] In theory, any circulating surfactant would

more likely be removed by hemoperfusion, and any water-soluble herbicide is more likely to be removed by dialysis. Improved clinical outcome has not been demonstrated for this practice. Early hemodialysis/hemoperfusion resulting in documented significant reductions in plasma glufosinate levels, failed to avert the progression of CNS pathology or hasten recovery. In one case the serum glufosinate level was reduced from 3.11 Âµg/mL to 0.91Âµg/mL. In the other case it was reduced from 1.56 Âµg/mL to 0.68 Âµg/mL. Midpoint in this dialysis, the concentration was 0.75 Âµg/mL at the inlet and 0.10 Âµg/mL at the outlet.[72] Onset and resolution of clinical symptoms lag behind serum glufosinate levels.[23,72] Thus, serum levels appear to underestimate the degree of toxic effect at the tissue target level.

Supportive Care

Central respiratory failure and arrest may develop suddenly and require emergent intubation and ventilation. Prophylactic intubation is indicated for any glufosinate- or bialaphos-poisoned patient who becomes stuporous. Additionally, hypotension, airway edema, or acute lung injury may develop in patients with large-volume herbicide ingestion as a result of systemic surfactant syndrome. Patients should be carefully monitored for adequate organ perfusion, respiratory effort, and oxygenation. Seizures respond to intravenous benzodiazepines. A single case of diabetes insipidus responded to intranasal desmopressin.[70]

Prognosis

There were 6 fatalities among 34 cases of glufosinate poisoning reported by the Japanese Poison Center.[73] Recovery may be prolonged, but other than anterograde memory loss, appears to be complete. More clinical experience is required to better understand this poisoning.

Inorganic Herbicides

Inorganic herbicides were generally introduced prior to WW II and include sodium chlorate, arsenicals, dinitrophenols, cyanates, and ammonium sulfamate. Because of nonspecific mechanism of toxicity they tend to have more mammalian toxicity than later herbicides based on plant physiology. Many are still in use.

Nitrophenolic Herbicides

Dinitrophenol (DNP) and substituted nitrophenolic compounds (Binapacryl, dinitroorthocresol [DNOC]) and salts, dinoterb, dinoterb, dinoseb, and salts, dinofen) inhibit cellular energy production in plants, fungi, and insects as the basis for their use as herbicides, miticides, fungicides, and wood preservatives. Because elements of this fundamental biochemistry are also shared by mammals, nitrophenylic compounds are predictably toxic to humans and animals. 2,4-Dinitrophenol is the prototype and classic example of a chemical that uncouples oxidative phosphorylation, the process by which the electron transport system in mitochondria creates an electrochemical gradient that allows the production of adenosine triphosphate (ATP). There are no current registrations for any of these compounds for any pesticidal purpose in the United Sates, although opportunity for exposure still exists in other parts of the world, through leftover products, and through environmental contamination in some unregulated chemical waste sites.

History and Current Use

In the July 1893 edition of *The Manufacturer and Builder: A Practical Journal of Industrial Progress*, 4,6-dinitro-o-cresol was introduced by the name antinonnin (derived from the German name for the gypsy moth, Nonnenraupe) for which â€œâ€¦extraordinary virtues are claimed as an exterminator

of insects destructive to plants or vegetation, parasites on animals, mice and rats and other vermin, and as an effectual protector of wood or lumber against mildew and dry rot. It is interesting and important to note that fact that antinonnin, when used in the state of correct dilution, is quite safeâ€¦â€• From this beginning came an entire class of pesticidal nitrophenolic compounds, of which Dinocap, the last one remaining on the US market in the 1990s, underwent voluntarily cancellation of its FIFRA registration in 2004. Therefore, there are no current legal pesticidal uses of dinitrophenol compounds within the United States, although tolerances remain for some specific uses for imported food (e.g., Dinoseb on apples). Dinitrophenol pesticides have included the prototypes dinitroorthocresol and dinitrophenol (DNP), Dinobuton, Dinocap, dinopenton, dinoprop, dinosam. Dinoseb, dinosulfon, and Dinoterb. Those still in use in the United States in the 1980s were subject to emergency suspension, cancellation or data call-in by the EPA in response to new studies showing developmental toxicity and imperiled male fertility/sperm damage, in addition to acute toxic risks.

Another use which exploits the toxic mechanism of DNP is that as a weight loss agent (Chap. 39). Following its introduction in the 1930s toxic reactions and deaths were rapidly reported, the FDA had no authority to act but only to warn the public under the existing Pure Food and Drug Act of 1908. An epidemic of bilateral cataracts, primarily in women who had taken dinitrophenol, cooled most of the remaining enthusiasm in the medical community, although the agent was still available in over-the-counter (OTC) products. It was not until the 1937 elixir of sulfanilamide epidemic focused congressional attention on the need for drug safety was the revamped FDA ability to put dinitrophenol on a list of agents too toxic for any medical use, and act on it as mislabeled. Use in weight loss clinics re-emerged in the early 1980s. FDA has subsequently reaffirmed the prohibited classification of this chemical for therapeutic use, as have most other countries. However, internet

sites for weight control and body-building provide detailed information on obtaining and using dinitrophenol, in some cases describing how to measure wetted, industrial material to pack one's own capsules.

Mechanism of Toxicity

Dinitrophenol (DNP) is considered the classic uncoupler of mitochondrial oxidative phosphorylation, one of the key processes contributing to mitochondrial ATP formation. The electron transport system reoxidizes NADH and $FADH_2$ formed during the tricarboxylic acid cycle and conserves the energy released from the glucose molecule, by pumping protons across the inner mitochondrial membrane. This creates an electrochemical gradient of protons, which is then used to synthesize ATP. There is a â€œcouplingâ€• of the two processes: electron transport requires ATP generation and ATP generation requires electron transport. If the gradient is lessened by loss or leakage of protons back through the membrane, the production of ATP will diminish. DNP is a weak acid that dissociates into DNP^- and H^+. The extra electron of DNP^- delocalizes over the entire molecule; thus it remains relatively hydrophobic and can readily pass the mitochondrial inner membrane. It picks up a proton on one side of the membrane, diffuses across the membrane, and releases the H^+ on the other side. Net movement of H^+ occurs in the direction of the concentration gradient, which of course, is the gradient created by pumping of protons by the electron transport system. The net effect is reduction of both the proton gradient and subsequent ATP synthesis. Salicylic acid, another hydrophobic weak acid, uncouples by the same mechanism of increasing the permeability of the inner mitochondrial membrane to protons by carrying them across it, and thereby dissipating the electrochemical gradient. The electron transport system proceeds to maximum activity but ADP is not phosphorylated to ATP. No work is done, and the excess energy is liberated as heat. Increased glycolysis ensues to provide substrate for the ineffective system.

Serum glucose may be normal, elevated or low, but does not reflect cellular stores and energy production. Metabolic acidosis may occur as lactate generating anaerobic metabolism attempts to provide cellular energy.

Toxicokinetics

DNP and other nitrophenylic herbicide compounds are rapidly absorbed through oral and inhalation routes, and of significant but lesser degree through skin. Maximum increase in basal metabolic rate occurred in 1 hour after ingestion of DNP in human subjects. Peak plasma levels of DNP were attained within 0.5â€“4 hours in dogs. Toxicity may be somewhat delayed by transcutaneous absorption. Serious illness is possible from breathing dusts or overspray during mixing, loading and application of nitrophenylic herbicides. Cumulative toxicity of small, frequent doses is possible. DNP is primarily excreted in the urine as glucuronide conjugates of hepatic reduction metabolites, principally 2- amino-4 nitro phenol. Some is excreted unchanged. A two compartment kinetic model is proposed after study in animals, in which the terminal half-life is 8â€“10 hours. Elimination from renal tissue may have a half-life of days. Intervening hepatic injury may prolong the elimination half-life. The illness runs a rapid course: death or recovery occurs within 24 to 48 hours. If production of heat exceeds the capacity for its dissipation, fatal hyperthermia may result. These compounds may cross the placenta.

Clinical Effects

Dinitrophenol and substituted derivatives such as Dinoseb and Dinocap, are quite toxic with rodent oral LD_{50}s of approximately 30â€“50 mg/kg. As little as 1 g cumulative dose of DNP over several days has been fatal in humans. The classic clinical presentation of uncoupled oxidative phosphorylation is that of hypermetabolism and energy failure: increased body temperature, increased respiratory

and heart rates, intense fatigue, profuse sweating, thirst, flushed skin, malaise, dyspnea, headache, dizziness, anxiety, confusion, cardiovascular collapse, convulsions, and coma.[13] Pulmonary edema is possible. If death occurs it may be sudden, and rigor mortis appears sooner than expected. In nonfatal exposures, renal and hepatic damage may occur within days after symptom onset. The threshold for increased metabolic rate in humans is around 1 mg/kg of DNP. Hypermetabolism is evident at approximately 4 mg/kg.

Systemic immunologic hypersensitivity reactions have occurred in some 10â€“20% of patients from small doses of DNP used for weight reduction. Such reactions have included isolated pruritus, urticarial or maculopapular eruptions, severe desquamating dermatitis, and generalized edema. Reactions subside with cessation of exposure. Chemically induced bilateral cataracts have occurred in women taking small doses of DNP for weight reduction. Risk of cataracts does not correlate with duration of exposure, but may be a manifestation of a genetically determined vulnerability. Cataract development may occur rapidly; most reported epidemic cases occurred within a year of exposure.[26] Bone marrow toxicity of neutropenia and agranulocytosis are reported. Interference with synthesis and pituitary feedback control for thyroid hormones have been reported.[14]

Local effects of ingestion exposures may also cause irritation or corrosion of oropharyngeal and upper GI mucosa, salivation, nausea, vomiting, and bright yellow stools. Local skin effects include yellow staining, erythema, irritation, and blisters. Many nitrophenylic herbicides are sensitizers, repeated or prolonged exposure may result in allergic contact dermatitis. Local eye exposure effects may include burning pain, lacrimation, and eyelid inflammation and present risk of systemic absorption and toxic effects.

Laboratory

Analysis of serum or urine for dinitrophenolics or metabolites may be possible to confirm exposure, but will likely be unavailable in time to guide clinical management. Serum glucose, electrolytes, hepatic enzymes and renal function should be monitored.

Management

Externally contaminated patients pose a risk of secondary contamination to others. Gentle but thorough soap and water washing of potentially exposed body areas including hair, ears, fingernails should be done with protective gloves and apron. Decontamination will not remove any yellow staining; attempts to do so will damage the skin and perhaps increase absorption of the toxin. Aggressive supportive care may be necessary, including large-volume fluid replacement if hypovolemia is present. Hyperpyrexia, which may be life-threatening, must be rapidly corrected by mechanical means as would be done for heat stroke, for example, cooling blanket. Do not use salicylates for fever reduction. If the exposure was oral, AC may be considered. The hypermetabolic illness runs its course rapidly, usually within 24â€“48 hours. Illness beyond this time in survivors is a consequence of organ damage. Although pharmacologic treatment of hyperpyrexia with dantrolene has been anecdotally reported, there are insufficient information and lack of support mechanistically to recommend its use in dinitrophenolic poisoning. Likewise there is no support for the use of Î²-receptor antagonists, haloperidol, and antithyroid medication.

Sodium Chlorate (NaClO3) (Chap. 98)

Chlorate is the chlorine analog of nitrate and kills all green plants by oxidizing and inactivating a critical nitrate reductase complex. It is phytotoxic by both foliar and soil application, and is also used to sterilize soil, where it may persist for months to years.[66] Recent

research shows a potential application for gut sterilization in cattle prior to slaughter to reduce cross-contamination of meat with *Escherichia coli* and other enteric bacteria. Its major herbicidal uses are control of roadside vegetation and to desiccate crops before harvest. It is a strong oxidant, having three oxygen molecules to donate. Although not itself combustible, it reacts violently with reducing and combustible materials such as clothing, wood, and dried foliage. Formulations usually carry a fire suppressant such as urea or sodium borate to counter this fire hazard. Sodium chlorate is sold alone or in combination with atrazine, 2, 4-D, bromacil, diuron, or sodium metaborate. Minor amounts are also produced when chlorine dioxide is used to disinfect drinking water.

Mechanism of Toxicity

As a potent oxidizer, sodium chlorate oxidizes hemoglobin to methemoglobin causing inadequate oxygen transport. Oxidant stress may also denature and precipitate hemoglobin as Heinz bodies, which prompts removal of these damaged red cells from the circulation by the spleen and liver. Severe acute intravascular hemolysis may occur with its consequent hyperkalemia and risk of acute tubular necrosis. Induced hemolytic anemia in concert with methemoglobin in the remaining red cells produces catastrophic hypoxia. Chlorate action on hemoglobin may be somewhat delayed in a concentration dependent manner, unlike nitrite, which rapidly oxidizes hemoglobin. After the prolonged presence of chlorate, methemoglobin becomes unresponsive to reduction by methylene blue. Red cell membrane enzymes are cross-linked and inactivated by chlorates, including glucose-6 phosphate dehydrogenase, which must be intact for successful methylene blue action. Loss of maintenance enzyme activity makes erythrocyte cell membranes rigid, permeable to cations and fragile. Adding to the pathogenic potential, the chlorate ion itself is not inactivated as it oxidizes hemoglobin, as are other methemoglobin formers such as nitrites, and can therefore continuously produces methemoglobin

autocatalytically until it is excreted.[48] Sodium chlorate is irritating to eyes, skin, and membranes; ingestions are characterized by severe gastrointestinal distress.

The lowest fatal doses in adults are reported to be 100â€“200 mg/kg (10â€“15 g), although typical fatal doses are on the order of 50â€“100 g and higher. Conversely, patients have survived 100-g doses with aggressive care. A two-gram dose was fatal in a child.

Toxicokinetics

As a water-soluble salt, sodium chlorate is not well-absorbed through skin, and ingestion is the primary route of poisoning. Animal data with small doses show a half-life of absorption of about 1.5 hours, and a half-life of elimination of 36 hours. It is excreted in the feces and urine.

Clinical Manifestations

Ingestion produces vomiting, abdominal pain, methemoglobinemia and its cyanotic coloring, severe acute intravascular and extravascular hemolytic, hyperkalemia, renal failure, and disseminated intravascular coagulation (DIC).[17,32] Attendant clinical complications of hypoxia include shock, acidosis, cardiac dysrhythmias and arrest, respiratory failure, and central nervous system dysfunction. Because of a slight delay in onset of hematologic events, do not dismiss patients who do not initially appear severely ill as not being severely poisoned.

Treatment

Ingestions of sodium chlorate are potentially life-threatening, and gastric decontamination by lavage should be considered according to accepted guidelines. AC is not effective in binding small inorganic molecules like chlorate.

Once toxicity is underway, patient stabilization may become

challenging and must incorporate multimodal therapy including standard treatments for shock with fluids and vasopressors, and intubation for respiratory failure. One hundred percent oxygen following intubation will maximize oxygen dissolution in plasma. Acute hemolytic anemia and methemoglobin concurrently will catastrophically reduce oxygen carrying capacity of blood, and consideration must be given to red cell transfusions and possible plasma exchange. Rapid development of acute renal failure is likely in severe poisoning. Robust urine flow and urinary alkalinization should be considered. Hemodialysis should be considered early to compensate for loss of urinary chlorate excretion as renal failure develops and will restore electrolyte balance, and provide renal replacement. Other complications should as DIC should be managed by existing standards of care.

Specific Antidotal Therapy

Methylene blue therapy must be used early in the poisoning when methemoglobin first appears, or

not at all, Because of inactivation of G6PD and consequent loss of methylene blue effectiveness with time. Methylene blue will not reverse Heinz body formation and extravascular hemolysis. If initially successful, repeated doses may be necessary as methemoglobin may re-form. Once therapeutic effect diminishes, or evidence of hemolysis appears, methylene blue should be stopped as it may add to the oxidant stress on hemoglobin instead of reversing it.

Oral or IV administration of 25% sodium thiosulfate solution has been proposed as therapy to convert chlorate ion into chloride ion. Ascorbic acid, vitamin E, and NAC have been suggested as a supplemental antioxidant treatment for chlorate-induced methemoglobin. Actual experience with these proposed antidotes seems lacking, and they cannot then be recommended as standard

effective therapy.

Laboratory

Chlorate measurements are not readily available. A qualitative colorimetric test for chlorate using aniline as the reagent has been used to detect its presence in gastric contents. Ion chromatography has been used to measure chlorate concentrations in blood and urine.

Herbicidal Borates

Boric acid and borates are used as algaecides, fungicide/wood preservative, insecticides (ants, roaches grain weevils, silverfish), and herbicides. Although necessary micronutrients in plants, in excessive amounts of borates are desiccating and interrupt photosynthesis. The primary herbicidal borates are sodium metaborate tetrahydrate and sodium tetraborate. Herbicidal borates are usually found in combination with other active ingredients such as monuron, bromacil and trichlorobenzoic acid. A common use is vegetation control along rights of way, especially in concert with sodium chlorate for which it also provides a fire retardant action. Sodium tetraborate is corrosive to the eyes and irritating to respiratory mucous membranes. Workers exposed to airborne dusts or spray droplets report eye irritation, dryness of the eyes, nose and throat, and cough. Chronic high-dose exposure is selectively toxic to testes; workers exposed to dusts during manufacturing have reduced sperm counts and motility. Acute low-dose ingestions as typically occurs nonintentionally are often asymptomatic but may result in vomiting, diarrhea, and abdominal pain. Symptoms of mild CNS depression such as headache, lethargy, and lightheadedness may follow. Very high-dose ingestion may result in pronounced toxicity involving CNS depression and seizures, metabolic acidosis, shock renal failure, and hepatic injury. Nonspecific cellular toxicity may be due in part to enzyme inhibition (Chap. 98).

Arsenicals

Arsenic compounds are legacy pesticides in long use against various types of pests including fungi/mold, plants, insects, and animals because of the nonspecific mechanism of toxicity that affects life at all levels of organization (Chap. 85). In addition to arsenic trioxide, pesticidal arsenic compounds include a variety of trivalent salts (various arsenites, derived from arsenic trioxide in water) and pentavalent salts (various arsenates, derived from arsenic pentoxide in water). Compounds better suited against mold or insects include arsenic trioxide, copper acetoarsenite (Paris Green) lead arsenate, lead hydroxy arsenate (basic lead arsenate) and calcium arsenate.

Compounds suitable for herbicidal use in the United States have included organic arsenicals such as cacodylic acid (dimethylarsinic acid, Agent Blue) and sodium cacodylate, calcium hydrogen methane arsenate, disodium methane arsenate, monosodium methane arsenate, monomethylarsonic acid (MMA^{+5}), and monoammonium methane arsenate. Many are still have U.S. registrations to kill weedy grasses such as crabgrass and nut grass and to defoliate cotton before harvest. In mid-1988, the EPA canceled the registrations for most inorganic arsenicals used for purposes other than wood preservation. Exceptions included lead arsenate for use as a growth regulator in grapefruit, and calcium arsenate in flowable form for turf use. Inorganic arsenicals such as sodium arsenite and other organic arsenicals may still be used in other world areas as herbicides. Various nonherbicidal pesticide uses of inorganic compounds may continue as well.

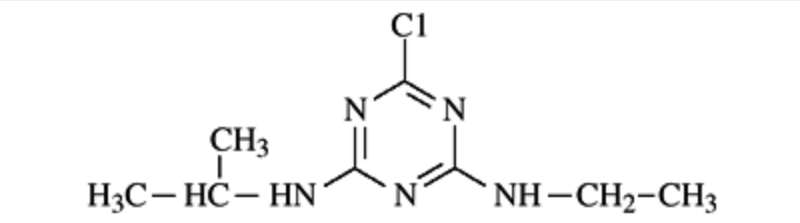
Chromated Copper Arsenate (CCA) Wood Preservative

The contemporary issue about lumber treated with CCA is that of long-term environmental exposure and risk of cancer. Wood for use

in outdoor areas is preserved by pressurized saturation with a solution of chromated copper arsenate against degradation by dry rot, mold, termites, and other pests. Studies suggest that arsenic slowly leaches from CCA-treated wood but the rate varies by amount of CCA applied, local climate conditions, and age of the wood product. Although no unacceptable risk has yet been identified, as of 2004 CCA-treated wood is no longer permitted in new construction in residential areas such as in decks, walkways, fences, gazebos, picnic tables, and playground equipment. Nonresidential uses including highway noise barriers, sign posts, utility posts, and retaining walls are still permitted. Structures already in place are not affected, but as an extra precaution, regular application of certain penetrating coatings such as oil-based, semitransparent stains will minimize potential exposure.

For all pesticidal arsenicals refer to Chapter 85 for details regarding toxic properties and treatment.

Atrazine and Other Chlorotriazines



Atrazine 6-chloro N^2 ethyl N^4 isopropyl-1,3,5-triazine-2,4-diamine

The chloro-S-triazine herbicides, including atrazine, simazine, cyanine, and others, comprise one of the most extensively used herbicide class in the United States.[45] Their primary uses are to control broadleaf and grassy weeds in crops such as corn, sugar cane, and conifers and for nonselective weed control in noncrop rights of way and industrial land. There are few reports of acute human toxicity related to any of these agents.

There are many types of formulations, some with very high loads of actives (80â€“90%) and multiple-active products. Liquid formulations are likely to contain a hydrocarbon solvent.

Kinetics and Clinical Effects

The chlorotriazines are slowly and incompletely absorbed through skin: experimentally less than 5% in 20 hours, but are well absorbed orally (80%).[1] Metabolism is by cytochrome P450 and metabolites,[40] including a glutathione conjugate, are excreted renally.[7]

These herbicides can induce cell-mediated hypersensitivity after prolonged or repeated contact with the skin, and are mildly to moderately irritant to skin, eyes, and mucous membranes. A single case report is published of intentional atrazine ingestion of 500 mL of a concentrate containing 100 g atrazine, 25 g amitrole, and 25g ethylene glycol plus an uncharacterized amount of surfactant.[50] The patient developed coma, shock, metabolic acidosis, gastrointestinal bleeding, renal failure, hepatic necrosis, and DIC, and died on the third day. Much of this is compatible with surfactant toxicity except kidney and liver damage.[33]

Management

The toxic dose of atrazine or other triazene herbicides in their various formulations is unknown, but is apparently relatively high.

Gastric decontamination may be indicated in any particular patient according to accepted guidelines.[33] Because liquid formulations are likely to be emulsifiable concentrates containing both surfactant and a hydrocarbon solvent, precautions must be taken to avoid both aspiration and esophageal trauma.

Hemodialysis removed only 120 mg of atrazine in 4 hours in the man who had ingested a total of 100 g.[50] Unless renal impairment intervenes, it is unlikely that hemodialysis will materially affect the clinical course. Experience with acute toxicity is too limited to permit adequate characterization of effects or treatment. There are no antidotes or specific treatment measures.

Hypotension, airway edema, or acute lung injury may develop in patients with large-volume herbicide ingestion as a result of systemic surfactant syndrome. Patients should be carefully monitored for adequate organ perfusion, respiratory effort, and oxygenation.

Analysis of atrazine in biologic specimens is not routinely available.

Summary

The expanding diverse worldwide agricultural role of herbicides has led to increasing availability and risk as suicidal agents or unintentional exposures of great potential concern.

The exposure of various populations to paraquat and diquat has led to highly lethal complex toxicologic emergency often encountered in developing countries. Glyphosate and glufosinate are additional examples of high-risk herbicides. Evaluation of the supposedly inert components of these formulations has been emphasized. The increasing interest in the toxic potential of these agents is timely, particularly as society attempts to assess the risks and benefits of these agents.

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Chapter 112
Methyl Bromide and Other Fumigants

Keith K. Burkhart

A 46-year-old healthy man employed in a nursery was brought to the em complained of nausea, vomiting, and dizziness. The supervisor reported th been exposed to gas used to fumigate the greenhouse. He had transporte to the greenhouse in the morning, about 2â€“3 hours prior to admission. I canisters into the cab of his pick-up truck and then driving them to the g be used. When he went to unload them, he noticed that one of them see Concerned that it may have leaked during transport, he lifted the canister anything. Because he felt fine, he did not mention the event to his super he started to feel ill.

Physical examination revealed a well-developed and well-nourished man wh appeared to be in mild discomfort. Vital signs were: blood pressure 120/7 and regular; respirations 16 breaths/min; and temperature 99Â°F (37.2Â° at 80 kg. The skin was moist, and there was erythema noted on his neck the shirt collar. His neck was otherwise normal. Examination of the head, was only remarkable for mild conjunctival injection. The chest was remarl rhonchi. Cardiac examination revealed normal S1 and S2 and no murmurs were normal. The abdomen was mildly tender in the epigastrium, without

hepatomegaly were noted. Neurologic examination revealed a normal mer nerves, symmetrical reflexes, and normal sensory and motor examinations reached out to steady himself.

The 12-lead ECG demonstrated normal sinus rhythm with a normal QRS c laboratory assessment including CBC, electrolytes, BUN, creatinine, glucos amylase, lipase, and arterial blood gases were normal.

In the emergency department (ED) the patient had a generalized tonic-clo respond to 20 mg of diazepam. The patient underwent rapid-sequence in mg/kg as an IV loading dose. Two hours later the patient remained coma activity.

On the second day in the ICU, he developed acute respiratory distress sy FiO_2 . His seizure activity returned and required higher doses of phenoba insufficiency complicated his clinical course, but these all resolved with st week ICU stay. He made a partial neurological recovery that left him whe induced myoclonus and difficulty performing activities of daily living. Fum rodents, nematodes, insects, weed seeds, and fungi anywhere in the soil, commodities.[29] Many different chemical classes have been used historically remain in use today in the United States. Most fumigants were abandoned of which were halogenated solvents. The list of discontinued halogenated tetrachloride, chloroform, dibromochloropropane, 1,2-dichloropropane, eth dichloride. Chapter 99 discusses paradichlorobenzene and naphthalene. Cl halogenated fumigant often added in mixtures because of its warning pro in its role as a lacrimator (Chap. 126). For the last few decades methyl prominently, although the Montreal Protocol banned its use beginning in phosphides are also used extensively in the United States.[10] Many reports reported from India and the Middle East.[1 , 16 , 67]

Although fumigants exist in all 3 physical states, they are most commonly explaining why inhalation is the most common route of exposure (Table 1 fumigants are generally heavier than air. Several, such as methyl bromid colorless and the toxic concentrations are below the odor threshold, mak Methyl bromide evaporates from soil after a liquid application. Phosphides although the resultant phosphine gas may have a garlic odor. Metam sodi

A number of sulfur containing compounds are also used as fumigants. Su fumigant used in some regions of the United States. Sulfur dioxide (Chap. fumigant, whereas carbon disulfide use was discontinued. The dithiocarba Metam sodium is one of the most frequently used members of this class ethylene oxide, formaldehyde, oxirane, and paraformaldehyde are aldehyd used as fumigants, but they will not be reviewed in this chapter.

Methyl Bromide

History and Epidemiology

Methyl bromide (CH_3 Br) was used as an anesthetic in the early 1900s, It was employed as a fire retardant during World War II, a role that pers

in Europe.[37] Like many other halogenated xenobiotics, methyl bromide wa methylating agent, chemical precursor, and in fruit packaging.[36 , 66] Indu occurring environmental production in oceans have lead to low levels of r water, and food.[42]

MW (Daltons)
164
111
188
129
95
34
102
Color
Noneâ€“Yellow-Green
Yellow
Clear
White
None
None

None
State
Liquid
Liquid
Liquid
Powder turns
Yellow-Green
Liquid
Gas
Solid â†’ Gas
Gas
Flammable
No
No
Low
No
No
High
No
Odor
Intense
Garlic
Sweet/Chloroform
Sulfur
None
Rotten Fish Garlic
None
Use current
Soil**
Soil
Soil, crop**
Soil
Soil, structural, crop**
Rodenticide**

	Chloropicrin	Dichloropropene	Ethylene Dibromide*	Metam Sodium	Met Bror
Structural					
Historical use					
Fire Extinguisher					
Fire Extinguisher					

*Ethylene dibromide has been banned and is no longer in use, but is inc
**Commodity fumigant, wihich is a class term used by the Environmental fumigation of a food or agricultural product.

TABLE 112-1. Physical Properties and Industrial Use of Fumigants

Hazardous materials incidents are reported for methyl bromide, both duri Residents and plant employees, living or working adjacent to agricultural applied, are occasionally exposed secondary to inadvertent releases.[10, 2] possibly other fumigants have also escaped from fumigated structures to resulting in severe illness and fatalities.[38, 49] Underground pipes adjoinin have led to exposures.[39] Fatalities have occurred when workers entered residues.[45] The transfer of methyl bromide between containers has resul sequelae.[21] Defective or leaking canisters of methyl bromide are another Europe, indoor and outdoor exposures to old fire extinguishers have caus fatalities.[7, 37, 70, 75] Rarely, intentional exposure to fumigants by inhal been used as a means of suicide.[34, 50, 65] Most symptoms reported by t chloropicrin, which is usually formulated as 2% of the methyl bromide co irritant and nonspecific symptoms of methyl bromide and chloropicrin mal differentiate at the time of the exposure.[29]

Diets high in marine products and fruits may cause an increased environ bromide.[42] The 1987 Montreal Protocol was an international agreement to

chemicals. Methyl bromide was scheduled to be phased out in 2005, but applied for and were granted exemptions.[58] Historically, stored or importe by the public, despite restricted use or bans.[61]

Occupational Exposure

Methyl bromide fumigation may expose workers to high concentrations at Methyl bromide can be detected at the joint connections to the vaporizer of 50 parts per million (ppm) have been recorded. Depending on ventila to 55 ppm occurred when the plastic sheets were removed 7 days after a exposures may occur during application secondary to employee error or rubber gloves may absorb methyl bromide. Tight-fitting clothing may trap Because of these properties, leather and rubber should be avoided for all should be changed after the application.

Methyl bromide is listed in the International Agency for Research on Canc classifiable as to its carcinogenicity in humans. One small human cohort s cancer in which the expected number was 0.11. Animal studies have pro mice, gavage produced fore-stomach squamous cell carcinomas, but then show an increased rate. One rat study showed increased pituitary adenom

The American Conference of Governmental Industrial Hygienists (ACGIH) TWA (time-weighted average) of 3.9 mg/m^3 for methyl bromide; 1 mg/m^3

Toxicokinetics

The dermal absorption of methyl bromide appears to contribute to its tox dermal exposure developed persistent peripheral motor neuropathy, highl systemic toxicity after dermal exposure.[47]

Significant individual variability exists for methyl bromide metabolism. P transferase is believed responsible for some of this variability.[9] Pharmacog pharmacogenomics may ultimately explain individual variability. Three of high hemoglobin adduct levels despite performing the same job.[40] S-meth hemoglobin adducts may persist for weeks.[9] Cysteine residues number 104 Î² chain appear to be preferentially methylated.[25] Which biomarker will pr determined.

Bioactivation and then alkylation also appear to be responsible for toxicity ethylene dibromide. The antifertility effects and toxicity of ethylene dibro alkylating, mustard-like, activity.[23] Human in vitro and rat liver models v assessment of ethylene dibromide carcinogenicity.[59] Ethylene dibromide

both conjugative metabolism via glutathione S-transferase and oxidative CYP 2E1, 2A6, and 2B6. The conjugative pathway produces an episulfoniu a carcinogen.

Pathology/Pathophysiology

Pathologic examinations demonstrate the neurotoxic potential for methyl of a man who died 30 days after methyl bromide exposure from a corrod demonstrated that the inferior colliculi and the cerebellar dentate nuclei h gliosis. The brain stem and spinal cord were normal, although the dorsal neuronal loss. The peripheral nerves showed axonal and myelin loss with lesions to the inferior colliculi and the dentate nucleus were also described 5 years after severe poisoning.[32] The cerebral lesions are reportably simi Wernicke encephalopathy. Methylation of the sulfhydryl groups of metaboli common mechanistic pathway.[46 , 70]

Clinical Manifestations

Exposure to high concentrations of methyl bromide may lead to immedia including a rapid loss of consciousness followed by seizures, dysrhythmias symptoms may be delayed for days following low-level exposure.[36] Cardio neurological toxicity may develop following toxicity from methyl bromide a fumigants (Table 112-2).

Some individuals may initially manifest irritant symptoms of the eye, na These irritant symptoms may help differentiate upper respiratory and ga from methyl bromide exposure. In more severe poisonings pulmonary sym shortness of breath that may rapidly progress to bronchitis, pneumonitis, hemorrhage. In some cases, the initial symptoms of methyl bromide pois influenza or a viral-like illness such as gastroenteritis.[49 , 66]

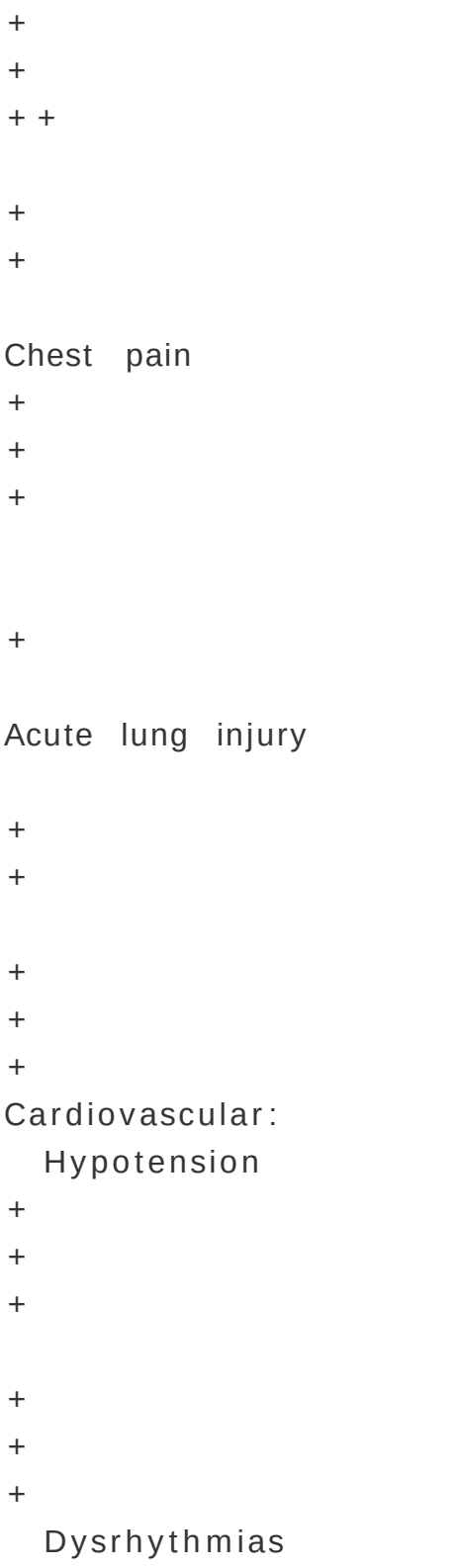
Mucus membrane irritation
+ +
+
+ +
+ +
-/+ High concentration
+ +
-/+ High concentration
Dermatitis

+
+
+
+

+
Burns (frostbite)
+

+
+

+
Gastrointestinal:
Nausea, vomiting, abdominal pain
+
+
+
+
+
+
+
Hepatic dysfunction


Chest pain
Acute lung injury
Cardiovascular:
Hypotension
Dysrhythmias

+
Late

+
+ +
+ +
Nephrotoxicity
+
+
+ +

+
+

Mental status changes
+
+
+
+
+
+
+
+ = presence
- = absence
Â± = variable
++ = very substantial

Clinical Effect	Chloropicrin	Dichloropropene	Ethylene Dibromide	Metam Sodium	M Br

TABLE 112-2. Comparison of Clinical Effects of Fumigants

The neurologic effects of methyl bromide poisoning are most consequentia
demonstrate these irritant effects, yet present later with neurological syn

nervous system symptoms may include headache, vomiting, dizziness, d diplopia, dysmetria, dysarthria, and mood disorders or inappropriate affec ataxia, psychotic delirium, intention tremor, fasciculations, myoclonus, sei reported case of methyl bromide poisoning, the initial diagnosis was Rey

Six patients developed skin lesions including erythema, vesicles, and bulla predominantly in moist areas or pressure points, including groin, axilla, an wristband.[80] In another report, erythema and multiple vesicles developed who used protective respiratory gear.[47] This patient's skin lesions healed persistent peripheral neuropathy.

Patients with chronic exposures may present with varied neurologic featu nystagmus, paresthesias, dysesthesias, hyporeflexia and hyperreflexia.[14] with optic nerve degeneration may be permanent.[14] One chronically expos presentations for psychosis before the underlying etiology of methyl bron determined.[79]

Chronic exposure to methyl bromide is associated with hepatotoxicity an that acute poisoning produces similar effects and that critically ill patients manifest fulminant hepatic failure. Autopsy findings have included acute degenerative nephritis.[49 , 75] Recovery is typical in survivors.[53]

Diagnostic Testing

Standard baseline laboratory tests should be obtained although they will following poisoning. Hepatic

dysfunction should be assessed with serum hepatic aminotransferases and bromide levels are not readily available in most laboratories. Although a s facilitate the clinical management of a methyl bromide poisoned patient, t diagnosis.[50] Serum bromide levels may remain elevated for a week or m The elevation of the serum bromide, however, does not always correlate v exposure.[27 , 39] An elevated serum bromide level may also cause a false when assayed using an ion selective electrode meter.[54 , 77] Alternatively, bromide exposure, the residual air concentration of methyl bromide can b

Treatment

Treatment for methyl bromide poisoning relies on general and supportive for management of dysrhythmias, coma, seizures, ALI, and hepatic and r common and difficult to control with traditional anticonvulsants such as Pentobarbital coma and neuromuscular blockade have been required for r

Decontamination should include the removal of clothing, as methyl bromid including rubber and leather. Irrigation of the eyes with saline and skin c water should be performed. Because of the systemic toxicity of the halog reasonable to administer at least one dose of oral activated charcoal (AC

Extracorporeal removal of bromide by hemodialysis can rapidly clear seru neurological improvement is described, but severe disabilities may still re following fumigant exposure occurs as the bromide is released into the se methylation of neuronal proteins has already occurred and that hemodialy outcome.

Chelators and *N* -acetylcysteine (NAC) have been proposed as antidotes, to be effective. The use of NAC as a sulfhydryl donor and antioxidant to insult, needs further study, as does the role of NAC to help recovery fron Injury, especially neurological, most likely occurs shortly after exposure an manifestations.

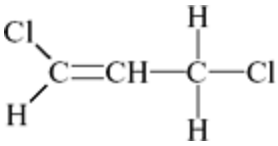
Prognosis

Most patients who develop seizures and coma will not survive. The few s exposure described in the literature, with rare exception, will have neur These sequelae may or may not be permanent and have included cogniti depression, anxiety, mood disorders with rapid behavioral swings, and su [36 , 62 , 66]

Nine months after an acute exposure to methyl bromide complicated by c woman had severe sequelae that included ataxia with action-induced my therapy.[66] A 46-year-old fumigator wearing a defective face mask had m exposures to methyl bromide that led to status epilepticus.[62] His recovery ataxia and action myoclonus interfering with his activities of daily living.

epilepticus that developed several hours after exposure to methyl bromide neuromuscular blockade after the failure of diazepam, phenytoin, nitrous administration. This patient also had ataxia, intention tremor, and fasciculu and died from a pulmonary embolus.[7] A young girl had electrophysiologic the conclusion that it was multifocal and generalized, occurring spontan stimuli and during voluntary movements demonstrated on the EEG by gia somatosensory evoked potentials (SEPs).[73] The myoclonus was refractory intensity did decrease during a 2-year follow-up. A 12-year-old girl deve and dysarthria after exposure to leaking fire extinguishers, but made a d that became complete after a year.[37] Recovery from peripheral neuropath

Dichloropropene



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History and Epidemiology

Dichloropropene was introduced in 1945 and is primarily used as a soil f Exposures are reported both during production and also by ingestion. Trac D.

Occupational Exposure

Chronic subclinical changes have been reported in soil fumigators using bulb occupations.[8] Hematologic cancers including lymphoma and histiocyti firemen after dichloropropene exposure.[48] The TLV for dichloropropene is exposure limit is 5 mg/m^3 .[8]

Toxicokinetics

The metabolism of dichloropropene probably is similar to that of other c

such as carbon tetrachloride and chloroform. Glutathione depletion has be model.[26]

The dose and route correlate with toxicity and outcome in rodent models At 100 mg/kg in mice, hepatotoxicity occurs by the intraperitoneal route, 700 mg/kg administered by the intraperitoneal route hepatic failure and correlated with a 130-fold increase in dichloropropene epoxide formation isozymes. In a rat hepatocyte model, pretreatment with the antioxidant, hepatotoxicity.[71]

The inhalational route is the primary method of toxicity for dichloroproper dermal absorption of dichloropropene was only 2â€“5% of inhalational a

Clinical Manifestations

There are a few reports of systemic dichloropropene toxicity. A patient d ingestion of dichloropropene.[34] The victim drank a glass of dichloroproper Immediately recognizing that it was not water; he vomited. Within 2 hou tachypnea, hypotension, sweating, and abdominal pain, followed by hema death at only 38 hours postingestion. The ingestion also produced rhabd and hyperglycemia.[34]

A hazardous materials incident exposed nine firemen to dichloropropene. neck pain, nausea and difficulty breathing.[48] Individuals may develop cor allergies to dichloropropene.[19] Healing of the skin lesions may leave pig

Diagnostic Testing

Hepatic and renal function should be monitored following acute poisoning, extensive necrosis after ingestion.[34] No additional tests are recommended supportive care.

Biomonitoring for exposure to dichloropropene is being developed.[8] Hepat fumigators but the increase was not statistically significant. This finding, enzyme induction. Erythrocyte GST (glutathione S-transferase) and GSH controls, fumigators had increased serum creatinine and increased urine

retinol binding protein.

Management

The patient's clothes should be removed and bagged to avoid continued of the patient and the healthcare worker. If ingestion occurs, one dose of There are no data to support specific therapies beyond supportive care, a therapy and NAC warrant further study.

Phosphides

History and Epidemiology

Phosphides are usually found as powders or pellets, usually in the form o (Zn_3P_2 and Al P, respectively). Calcium and magnesium phosphides are (PH_3) is formed from phosphides after contact with water, particularly if moisture may react with tablets to decrease their potency after the packa tablets are often placed in grain stores, such as ships, allowing the phosp storage sites are sealed. Phosphine is also available as a compressed gas exposures and toxicity, both from phosphide salts or from compressed ga fumigation in both transport and storage areas, particularly if entry to the proper ventilation.[28,78] Phosphine poisoning was also reported when the shop to another business in the same building.[61]

Many reports of serious phosphide poisoning including fatalities originate countries.[56] The consumption of aluminum phosphide is a common choice

Clandestine methamphetamine laboratories that use the ephedrine/hydric manufacturing method may generate phosphine gas at high reaction tem venue are reported, and first responders have also been exposed to high

Toxicokinetics and Pathophysiology

Phosphides produce toxicity rapidly, generally within 30 minutes of ingesti less than 6 hours.[2] The ingestion of fresh unopened tablets consistently r phosphine gas results in nearly instant toxicity.

Phosphine disrupts mitochondrial function by blocking cytochrome c oxidas energy failure in cells, free radical generation increases, resulting in lipid Phosphine also inhibits cholinesterases in rats.[52] Phosphide ingestions ove

Clinical Manifestations

Phosphides are potent gastric irritants; profuse vomiting and abdominal pa symptoms.[16] Respiratory signs and symptoms include tachypnea, hyperpn tightness that may progress to ALI over days. Tachycardia, hypotension, develop.[3,22,51,68] Phosphine-induced dysrhythmias include atrial fibrill and ventricular tachycardia and fibrillation.[69] Central nervous system tox and delirium.[2,51]

Diagnostic Testing

The diagnosis is usually made from the history. Further laboratory testing supportive care. Phosphine tissue concentrations are not routinely availa

Management

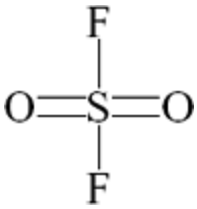
Patients who ingest phosphine frequently vomit from the irritant effects o emesis, theoretically, may expose healthcare workers to phosphine fumes in sealed containers and disposed of properly, as wet phosphides will cor gas. A physician performing an autopsy became symptomatic when the st containing phosphide was exposed.[41]

Vomiting makes AC administration difficult and raises the risk of aspiration what extent AC would bind phosphides,[16] the likely effectiveness of gastri the lack of clinical outcome data for AC, aggressive administration of oral

Comprehensive supportive care is recommended. Dilution with bicarbonate recommended,[30] as bicarbonate is believed to decrease the gastric hydr assists in the conversion of phosphides to phosphine gas. Also unproven i permanganate to oxidize the phosphides.[30] Trimetazidine is used for the as it may diminish the oxidant stress caused by phosphine.[17] Trimetazidine States. Preliminary research using rat models in India suggests possible

survival time with the use of NAC and pralidoxime.[4 , 52] These therapies,

Sulfuryl Fluoride



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History and Epidemiology

Sulfuryl fluoride (Vikane) has been used as a structural fumigant insectici insects such as termites in homes since 1957. Although it is commonly u Washington, a recent 5-year review of fumigant illness did not contain ar toxicity.[10] Structure or tent fumigation is performed by completely enclos in plastic or a tarpaulin; the sulfuryl fluoride is pumped in as a compress sulfuryl fluoride with chloropicrin added as a warning agent, are the mos

Toxicokinetics and Pathophysiology

Little is known about the toxicokinetics of sulfuryl fluoride in humans. At 4000 ppm) rats developed seizures followed by respiratory arrest.[55] At lo chronic exposure, rats and rabbits developed respiratory inflammation, re vacuolation.[24] The mechanism of toxicity is not understood. The measura suggests that the release of fluoride may be a major pathophysiologic m of chronic, low concentration exposures fluorosis developed.

The TLV-TWA (Threshold Limit Value-Time Weighted Average) for SF is 5 Term Exposure Limit) is 10 ppm; IDLH (Immediately Dangerous to Life ar fluoride was not found to be teratogenic in rats nor rabbits.[31]

Clinical Manifestations

Case reports of sulfuryl fluoride exposure describe acute and subacute co similarities to methyl bromide. Initial symptoms may be gastrointestinal, diarrhea and abdominal pain, or respiratory, including cough and dyspnea may produce salivation, lacrimation with conjunctivitis, and nasopharyngitis studies, severe exposures in humans affect the cardiopulmonary and ner

A husband and wife reentered their home after it was cleared by the fum residual sulfuryl fluoride levels were not provided.[57] Within 24 hours both husband complained of dyspnea and cough that became severe. Approxim exposure, he had a seizure followed by cardiopulmonary arrest. His wife vomiting. Over 3 days she became progressively weaker and unable to w dyspnea followed by ventricular fibrillation. She had a plasma fluoride leve exposure began. Autopsies listed the cause of death as pulmonary edema

Another report describes suspected suicide by sulfuryl fluoride inhalation. second person reentered a tented structure while a worker was found nea tank. A 19-year-old woman who reentered apparently to retrieve some p She was found unconscious, but became alert after removal from the hor coughing and chest pain. Approximately 6 hours later she developed carp cardiac dysrhythmias followed by death. Her serum fluoride level was 20 remarkable for pulmonary edema.

Neurotoxicity may also result from low level acute or chronic exposures. applicator developed nausea, vomiting, and abdominal cramps along with transient.[72] On three subsequent evaluations he complained of difficulty memory and dexterity testing were noted in structural fumigation workers bromide and sulfuryl fluoride.[12]

Diagnostic Testing

Patients with sulfuryl fluoride exposure require frequent monitoring of ser calcium complexes with the fluoride ions (See chapter 101). Continuous the QTc interval, as hypocalcemia may precipitate dysrhythmias. Serum f helpful for the acute management, may help with confirmatory diagnostic

Management

After removal from the scene to fresh air, the patient should be disrobed gassing of any sulfuryl fluoride gas. In treating sulfuryl fluoride poisoning hypocalcemia may be needed. Patients should have ECGs performed and cardiac monitoring to observe for QTc prolongation. Similar to the manag supportive care may be needed for the seizures, cardiac dysrhythmias and bronchospasm.

Metam Sodium

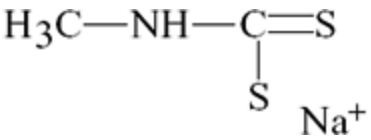

Figure. No Caption Available.

Metam sodium, which breaks down into methyl isothiocyanate, is a potent more common causes of occupational exposure to fumigants.[10] In Sacram derailment resulted in a metam sodium release with persistent air concer exposed individuals developed irritant-induced asthma or reactive airways following the spill.[18] In the cleanup, prolonged exposure to water with 20 caused dermatitis.[44]

Summary

The search for the ideal fumigant continues. It is likely that the use of p bromide use declines during its phase out period. Iodomethane or methyl by the Environmental Protection Agency (EPA). A few reports from Europe methyl iodide may be similar to that of methyl bromide.[33 , 63]

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Chapter 113
Mushrooms

Lewis R. Goldfrank

A 58-year-old woman presented to the emergency department (ED) with severe, crampy, abdominal pain and profuse diarrhea. She had spent the summer morning picking wild mushrooms in a local park, as she had done for many years. She found numerous edible species and ate quite a few while picking them. Her symptoms began within 1 hour of returning from the park.

She explained that she was an expert in selecting edible mushrooms, that she picked at the same place every year, and that she never previously had trouble. Prior to coming to the United States she had foraged in the woods of Poland for years without difficulty. She insisted that the mushrooms could not be at fault because they were found growing on dead wood and that slugs had mutilated several of the mushrooms.

The patient had no known allergies and did not drink alcohol. No other family members had been ill recently. Physical examination revealed a pale, diaphoretic, dyspneic, and anxious woman who was persistently gagging. Her vital signs were: blood pressure, 110/60 mm Hg; pulse,

120 beats/min supine; respiratory rate, 24 breaths/min; temperature 98.6Â°F (37Â°C).

The patient's head was atraumatic. Her pupils were 4 mm, equal, and reactive. Sclerae were anicteric; and conjunctivae were pink. Her mucosa was moist with no excessive lacrimation or salivation, and her throat was unremarkable. There were no cutaneous abnormalities. Lungs were clear, heart sounds were normal, and abdominal examination revealed diffuse tenderness with hyperactive bowel sounds. Liver and spleen were unremarkable. The extremities were normal.

The patient was vehemently resistant to the suggestion that she stay in the hospital. However, her dizziness upon standing convinced her to remain. Blood samples were drawn, and an IV was started with 0.9% sodium chloride solution at 300 mL/h. The patient was admitted for observation and volume repletion.

As the patient prepared herself for admission, she gave her belongings and clothing to her daughter. At that point the staff noticed a large bag filled with mushrooms. The patient was so convinced of the quality of these mushrooms that she wanted to give them to her daughter to take home, but eventually she was persuaded to leave the mushrooms in the ED for further examination.

Her hematocrit was 42%, white blood cell count (WBC) was 8300/mm^3 (72% polymorphonuclear leukocytes, 20% lymphocytes, 4% monocytes, 4% eosinophils), and prothrombin time was 13 seconds. Blood glucose was 220 mg/dL; blood urea nitrogen (BUN) was 21 mg/dL; sodium was 140 mEq/L; potassium was 3.7 mEq/L; chloride was 101 mEq/L; and bicarbonate was 30 mEq/L. The chest radiograph was normal, and abdominal radiographs showed a nonspecific ileus pattern.

Despite the patient's certainty that the mushrooms were edible, her presentation persuaded the staff to have the mushrooms investigated. Microscopic spore assessment methods to identify toxic mushrooms

conducted by a mycologist confirmed that the patient had mistakenly picked the jack-o'-lantern (*Omphalotus illudens*), an orange, bioluminescent mushroom,[3] believing it was the edible species of chanterelle (*Cantharellus cibarius*). This error is frequently reported.[38,92]

Epidemiology

Unintentional exposures to mushrooms represent a small but relatively constant percentage of consultations requested from Poison Control Centers (see citations for American Association of Poison Control Centers [AAPCC] data in Chap. 130) A summary of the 19 years of AAPCC data reveals that mushrooms represent less than 0.5% of the reported exposures to poisons. Combined data accumulated by the AAPCC and the Mushroom Poisoning Registry of the North American Mycological Association indicates that approximately 5 patient exposures to toxic mushrooms per 100,000 population occur per year. Some variations result from geographic and climatic conditions and mycologic habitats.[90] Although the methods of analysis of patients with mushroom exposures have changed over the past 19 years, cumulative AAPCC Toxic Exposure Surveillance System (TESS) data consistently demonstrate the relative benignity

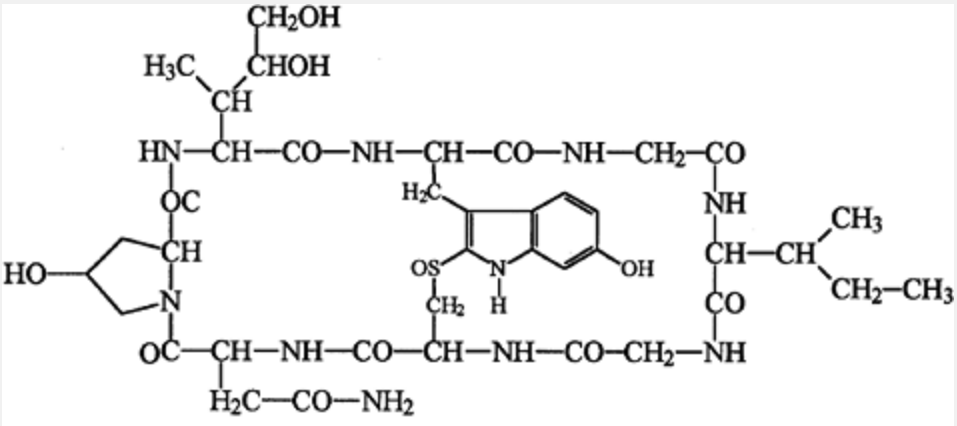
of the vast majority of exposures. The inability of most healthcare providers to correctly identify the ingested mushroom and the rarity of lethal ingestions are demonstrated by the accumulated data. In more than 95% of cases, the exact species was unidentified,[90] and only approximately 10% of the mushroom groups ingested were known. More than 50% of exposed individuals had no symptoms. Twenty-five percent of the patients were treated in healthcare facilities annually; of these 10â€“15% had minor toxicity, less than 5% had moderate toxicity, and approximately 0.3% had major toxicity. During the 19-year period covered by TESS, only 22 of the patients died of their ingestions. Of the mushrooms associated with a death, 14 probably were *Amanita* spp, 2 hallucinogens, 1 *Boletus* spp, 1 presumed

gyromitrin-containing mushroom, and 4 unidentified. All reported deaths occurred in adults. Of the mushroom groups identified in intentional abuse and poisonings, hallucinogens and gastrointestinal (GI) toxins were the most common, yet accounted for less than 10% of ingestions. All other groups represented less than 2% of the total number of identified. Because 90% of mushrooms involved in exposures are never identified, a strategy for making significant decisions with incomplete data is needed.

Classification and Management

Because mushroom species vary widely with regard to the toxins they contain and because identifying them with certainty is difficult, a clinical system of classification is more useful than a taxonomic system (Table 113-1). In many cases, management and prognosis can be determined with a high degree of confidence from the history and initial symptoms.[41,54,55] Ten groups of toxins are identifiable: cyclopeptides, gyromitrin, muscarine, coprine, ibotenic acid and muscimol, psilocybin, general GI irritants, orellinine, allenic norleucine, and myotoxins.[41,54]

Group I: Cyclopeptide-Containing Mushrooms



Î±-Amanitin

Most mushroom fatalities in North America and worldwide are associated with cyclopeptide-containing species.[4,24,102] These mushrooms include a number of *Amanita* species, including *A. verna, A. virosa*, and *A. phalloides*, *Galerina* spp, including *G. autumnalis, G. marginata*, and *Galerina venenata*, and *Lepiota* species, including *L. helveola*, *L. josserandi*, and *L. brunneoincarnata*. (See ILAMANITAPHALLOIDS and ILAMANITAVIROSA in the Image Library at http://www.goldfrankstoxicology.com)

Early differentiation of cyclopeptide poisonings from other types of mushroom poisoning is difficult. Patients poisoned with cyclopeptides may present to an ED with a seemingly innocuous picture of nausea, vomiting, abdominal pain, and diarrhea, which often is attributed to other causes. Such patients may be sent home, only to return moribund on a subsequent day. The delayed onset of more serious symptoms is typical of cyclopeptide poisoning and is a critical consideration in assessing any potential poisoning.

Amanita phalloides contains 15â€“20 cyclopeptides with an approximate weight of 900 daltons. The amatoxins (cyclic octapeptides), phallotoxins (cyclic heptapeptides), and virotoxins

(cyclic heptapeptides) are the best studied.[27,51,97] Of these three chemically similar cyclopeptide molecules, phalloidin (the principal phallotoxin) appears to be a rapid-acting toxin, whereas amanitin tends to cause more delayed manifestations.[79] Phalloidin crosses the sinusoidal plasma membranes of hepatocytes by a carrier-mediated process. This process is shared by bile salts and can be prevented in the presence of extracellular bile salts, suggesting a competitive inhibition. A sodium-independent bile salt transporting system may be responsible for phalloidin hepatic uptake, elimination, and detoxification.[61] Phalloidin interrupts actin polymerization and impairs cell membrane function, but because of its limited oral absorption it appears to have minimal toxicity, restricted mostly to GI dysfunction. There is no evidence for the toxicity of virotoxins in humans.

The amatoxins appear to be the most toxic of the cyclopeptides, leading to hepatic, renal, and central nervous system (CNS) damage. These polypeptides are heat stable, insoluble in water, and lose activity over a period of years upon desication.[27] Î±-Amanitin is the principal amatoxin responsible for human toxicity following ingestion. Approximately 1.5â€“2.5 mg amanitin can be obtained from 1 g dry *A. phalloides*, and as much as 3.5 mg/g can be obtained from some *Lepiota* spp.[66,70,97] A 20-g mushroom contains well in excess of the 0.1 mg/kg amanitin considered lethal for humans.[25]

Î±-Amanitin absorption appears to be facilitated by a sodium-dependent bile acid transporter. Several studies demonstrate that the sodium taurocholate cotransporter polypeptide facilitates hepatocellular Î±-amanitin uptake.[40] In vitro studies show that Î±-amanitin is cytotoxic based on its interference with RNA polymerase II, preventing the transcription of DNA.[59,83] The LD_{50} of Î±-amanitin in mice is 0.1â€“0.75 mg/kg, and the LD_{50} of Î²-amanitin in mice is 0.2â€“0.4 mg/kg,[25] suggesting the two amanitins have comparable toxicity.

In animals, cimetidine (a potent cytochrome P450 system inhibitor) may have a hepatoprotective effect against Î±-amanitin by inhibiting

metabolism,[77] but it shows no protective effect against phalloidin toxicity.[79] Cimetidine is proposed as a therapeutic intervention,[78] but no available human data support its use. The amanitins are poorly but rapidly absorbed from the GI tract,[45] and Î±-amanitin may be enterohepatically recirculated. Target organs are those with the highest rate of cell turnover, including the GI tract epithelium, hepatocytes, and kidneys. Amatoxins do not appear to cross the placenta, as demonstrated by the absence of fetal toxicity in severely poisoned pregnant women.[6,11,88]

Amatoxins show limited protein binding and are present in the plasma at low concentrations for 24â€“48 hours.[45] In an intravenous radiolabeled amatoxin study in dogs, 85% of the amatoxin was recovered in the urine within the first 6 hours, whereas <1% was found in the blood at that time.[26] Amatoxins can be detected by high-performance liquid chromatography,[45] thin-layer chromatography, and radioimmunoassay in gastroduodenal fluid,

serum, urine, stool, and liver and kidney biopsies for several days following an ingestion.[25,27,50]

Genus/Species	Toxin	Time of Onset of Symptoms	Primary Site of Toxicity	Symptoms	Mortality	Specific Therapy[a]
I. *Amanita phalloides, A. tenuifolia, A. virosa* *Galerina autumnalis G. marginata, G. venenata* *Lepiota josserandi, L. helveola*	Cyclopeptides Amatoxins Phallotoxins	5–24 h	Hepatic	Phase I: GI toxicity-N V D Phase II: Quiescent, Phase III: Gastroenteritis, jaundice, ↑ AST, ↑ ALT	10–30%	Activated charcoal Hemoperfusion Penicillin G Silibinin
II. *Gyromitra ambigua, G. esculenta, G. infula*	Gyromitrin (metabolite: monomethylhydrazine)	5–10 h	CNS	Seizures, abdominal pain, N/V, weakness, hepatorenal failure	Rare	Benzodiazepines, Pyridoxine, 70 mg/kg IV
III. *Clitocybe dealbata, Omphalotus olearius* Most *Inocybe* spp	Muscarine	0.5–2 h	Autonomic nervous system	Muscarinic effects-salivation, bradycardia, lacrimation, urination, defecation, diaphoresis	Rare	Atropine: Adults: 1–2 mg Children: 0.02 mg/kg with a minimum of 0.1 mg
IV. *Coprinus atramentarius*	Coprine (metabolite: 1-aminocyclopropanol)	0.5–2 h	Aldehyde dehydrogenase	Disulfiramlike effect with ethanol, tachycardia, N/V	Rare	—
V. *Amanita gemmata, A. muscaria, A. pantherina*	Ibotenic acid, muscimol	0.5–2 h	CNS	GABAergic effects, rare delirium, hallucinations, dizziness, ataxia	Rare	Benzodiazepines during excitatory phase
VI. *Psilocybe caerulipes, P. cubensis* *Gymnopilus spectabilis* *Psathyrella foenisecii*	Psilocybin, psilocin	0.5–1 h	CNS	Ataxia, N/V, hyperkinesis, hallucinations	Rare	Benzodiazepines
VII. *Clitocybe nebularis* *Chlorophyllum molybdites, C. esculentum,* *Lactarius* spp *Paxillus involutus*	Various GI irritants	0.5–3 h	GI	Malaise, N/V/D	Rare	—
VIII. *Cortinarius orellanus, C. speciosissimus, C. rainierensis*	Orelline, orellanine	>24 h Days-weeks	Renal	Phase I: N/V Phase II: Oliguria, renal failure	Rare	Hemodialysis for renal failure
IX. *Amanita smithiana*	Allenic norleucine	0.5–12 h	Renal	Phase I: N/V Phase II: Oliguria, renal failure	None	Hemodialysis for renal failure
X. *Tricholoma equestre*	Unidentified myotoxin	24–72 h	Muscle (skeletal and cardiac)	Fatigue, nausea, muscle weakness, myalgias (↑CPK), facial erythema, diaphoresis, myocarditis	25%	—

D = diarrhea; N = nausea; V = vomiting.
[a]Supportive care (fluids, electrolyes, and antiemetics) as indicated.
Adapted, with permission, from Lincoff G, Mitchel DH: Toxic and Hallucinogenic Mushroom Poisoning: A Handbook for Physicians and Mushroom Hunters. New York, Van Nostrand Reinhold, 1977, pp. 246–247.

TABLE 113-1. Mushroom Toxicity

Some of the toxicokinetic analyses following unquantified ingestions demonstrate 12â€“23 Âµg amatoxin excretion in the urine over 24â€“66 hours, of which 60â€–80% occurred during the first 2 hours of collection. The extreme variabilities of the type and quantity of ingestant, the host, and the management make interpretations exceedingly difficult.[93] In another series, total maximal urinary Î±- and Î²-amanitin excreted over 6â€“72 hours were 3.19 and 5.21 mg, respectively. Two thirds of the patients had total amanitin toxin excretion >1.5 mg.[45] Urinary amanitin excretion concentrations differ by several orders of magnitude. Whether the variation results from exposure dose, time following ingestion, or laboratory technique is unclear. Several techniques for evaluating urinary amanitin presence qualitatively and quantitatively are under investigation. The sensitivity and specificity of these determinations are under investigation.[14,15,70,87] Most studies suggest that no circulating amatoxins are present by the time the need for transplantation is evident.[23]

Clinical

Phase I of cyclopeptide poisoning resembles severe gastroenteritis, with profuse watery diarrhea not occurring until 5â€“24 hours after ingestion. Supportive fluid and electrolyte replacement leads to transient improvement during phase II, which occurs between 12 and 36 hours after ingestion.[70,102] However, despite such supportive care, phase III, manifested by hepatic and renal toxicity and death, may ensue 2â€–6 days after ingestion.[4] Pancreatic toxicity may rarely occur.[32] The initial hepatotoxicity begins within the second phase, but clinical hepatotoxicity (Chap. 26) with elevated concentrations of bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), hypoglycemia, jaundice, and coma are not

manifest until 2â€“3 days after ingestion. Pathologic manifestations include steatosis, central zonal necrosis, and centrilobular hemorrhage, with viable hepatocytes remaining at the rims of the larger triads. Lobular architecture remains intact.[4]

Cyclopeptide poisoning alters the hormones that regulate glucose, calcium, and thyroid homeostasis, resulting in widespread endocrine abnormalities.[48] Insulin and C-peptide concentrations are elevated at a stage of poisoning prior to hepatic and renal compromise.[22,48] These findings are suggestive of direct toxicity to pancreatic Î² cells, resulting in release of preformed hormone or induction of hormone synthesis. This insulin release necessitates vigilance for hypoglycemia prior to hepatocellular damage. Serum calcitonin concentrations may be elevated, and hypocalcemia may be present. Thyroxine concentrations may be depressed and triiodothyronine concentrations undetectable, whereas thyroid-stimulating hormone concentrations may not be elevated. These thyroid-related findings were reported in a single study and merit further investigation.[48]

In a series of 10 patients poisoned by diverse *Lepiota* spp, 50% developed a mixed sensory and motor polyneuropathy. Most of the patients spontaneously recovered within 1 year, although a single patient developed progressive clinical and electromyographic deterioration.[72] These neuropathic findings have not been recognized in other case reports.

Treatment

The search for treatments has been vigorously pursued in Europe because of the persistently large number of amatoxins victims each year.[31] Thioctic (Î±-lipoic) acid initially was reported to be beneficial in treating the amatoxin-induced liver toxicity in several different animal models, and a number of uncontrolled clinical trials in humans followed.[4] Because of its potential effects as a coenzyme in the tricarboxylic acid cycle or as a free radical scavenger, thioctic acid, was credited for the survival of 39 of 40 patients reportedly poisoned

by *A. phalloides*.[52] Hypoglycemia is a common feature of thioctic acid therapy for *Amanita* poisoning, but whether hypoglycemia results from direct toxicity of the drug or is secondary to hepatic damage is not clear.

Despite the initial success, thioctic acid was not effective in various other studies.[33,34] Survival rates of patients poisoned by *A. phalloides* who received any of the following: supportive care, fluid and electrolyte repletion, high-dose penicillin G, dexamethasone, and thioctic acid are between 70% and 90%.[31,44,63,64,102]

Several laboratory investigations in mice and rats suggest that 1 g/kg penicillin G (l g = 1,600,000 units) may have a time- and dose-dependent protective effect.[35,36] These results are limited because the amatoxins were administered intraperitoneally, resulting in the death of untreated animals 12â€“24 hours later. Additional investigations demonstrated that 1 g/kg penicillin G administered 5 hours after sublethal doses of Î±-amanitin decreased clinical and laboratory toxicity.[35] The mechanisms suggested include displacing Î±-amanitin from albumin, blocking its uptake from hepatocytes, binding circulating amatoxins, and preventing Î±-amanitin binding to RNA polymerase. None of these mechanisms is substantiated. Although the hepatoprotective effects of penicillin remain unclear,[24] a dose of 1,000,000 units of penicillin G/kg/d IV is recommended as safe and possibly efficacious.[49,50,81]

The active complex of milk thistle (*Silybum marianum*) is silymarin, which is a lipophilic extract composed of 3 isomeric flavonolignans: silibinin, silychristin, and silydianin. Silibinin represents approximately 50% of the extract, but is 70â€“80% of the marketed product.[43] Silibinin may modify or occupy cell membrane receptor sites, thereby inhibiting hepatocellular penetration by Î±-amanitin. Use of silibinin 50 mg/kg in dogs, 5 and 24 hours following exposure to Î±-amanitin, suppressed chemical evidence of hepatotoxicity and lethality. Although silibinin is routinely available in health food stores and appears to be safe and well tolerated in patients with chronic liver disease, no

reduction in mortality, improvement in histology at liver biopsy, or biochemical marker has been identified in a systematic review and meta-analysis.[43] Silibinin 20â€“50 mg/kg/d is recommended for use in humans, even though this xenobiotic is not approved by the FDA for use in the United States.[50,96] Activated charcoal both adsorbs the amanitins and improves survival in laboratory animals.[25] Emesis, lavage, and catharsis are not necessary unless the patient is seen shortly after the ingestion, because the toxin usually induces emesis and catharsis. Activated charcoal is safe, logical, and a valuable therapeutic strategy. Although the clinical presentation often is delayed, 1 g/kg body weight of activated charcoal should be given orally every 2â€“4 hours (if the patient is not vomiting) or by continuous nasogastric infusion. Fluid and electrolyte repletion and treatment of hepatic compromise are essential. Intravenous 0.9% sodium chloride solution and electrolytes usually are necessary because of substantial fluid loss due to vomiting and diarrhea. Dextrose repletion may be necessary because of nutritional compromise, hepatic failure, or glycogen depletion. Because of its hepatoprotective effects, *N*-acetylcysteine is also suggested as an antidote, but no evidence for any specific benefit has been demonstrated.

Forced diuresis, hemodialysis, plasmapheresis,[46,47] hemofiltration, and hemoperfusion[29] may be effective shortly after ingestion, but most studies neither offer clinical evidence of benefit nor supportive

pharmacokinetic data for any of these therapies.[50,69,70,93,95] Plasmapheresis, which is dependent on effective clearance, high plasma protein binding, and a low volume of distribution, does not remove more than 10 Âµg amatoxin. Because of the absence of prospective controlled studies of exposure to amatoxins in addition to the extreme variability of success with many regimens, multiple-dose activated charcoal and supportive care remain the standard therapy. Early recognition of exposure to amanitin is an indication for hemoperfusion, but most patients likely will not have the potential for

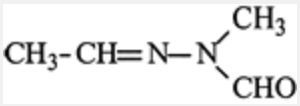
benefit at the time they develop clinical manifestations of toxicity.[47] Future therapeutic interventions may be dependent on improved understanding of the hepatocellular bile acid transporter system.[40,53]

Extracorporal albumin dialysis[28] and molecular absorbent regenerating system[19] are variant detoxification techniques used in patients with fulminant hepatic failure to remove water soluble and albumin bound toxins while providing renal support. These two techniques permit time for hepatic regeneration or sufficient bridging time to orthotopic liver transplantation. The criteria and timing for liver transplantation in this setting are far less established than for fulminant viral hepatitis, where grade III or IV hepatic encephalopathy, marked hyperbilirubinemia, and azotemia are the well-established criteria for transplantation[68] (Chap. 26). When fulminant hepatic failure is present, *N*-acetylcysteine should be administered until the patient recovers from the encephalopathy because of its presumptive benefits under these circumstances (Antidotes in Depth: *N*-Acetylcysteine). Successful transplantations were performed in individuals whose resected livers showed 0â€“30% hepatocyte viability. In these cases, the authors did not wait for progression past grade II encephalopathy or for development of azotemia or marked hyperbilirubinemia.[68] Criteria for patient selection are essential to avoid unnecessary risk while offering the potential for survival to appropriate candidates who have no functional liver. The grim prognosis associated with hepatic coma secondary to *Amanita* poisoning has led several transplant groups to consider hepatic transplantation for encephalopathic patients with prolonged INRs, persistent hypoglycemia, metabolic acidosis, increased concentrations of serum ammonia and AST, and hypofibrinogenemia.[39,49,68] There are now case reports of successful liver transplantation for fulminant hepatic failure from presumed *Amanita ocreata*,[49,101] *A. phalloides*[45,68] *Amanita vivosa*,[13] *Lepiota helveola*,[62] and *Lepiota brunneoincarnata* poisoning.[72]

To enhance the likelihood of success, several authors suggest that individuals who manifest symptoms suggestive of hepatotoxic *Amanita, Galerina*, or *Lepiota* spp exposure should be told of the potential need

for transplantation and, with their consent, rapidly transferred to a regional liver transplantation center.

Group II: Gyromitrin-Containing Mushrooms



Gyromitrin

Members of the gyromitrin group include *G. esculenta, G. californica, G. brunnea*, and *G. infula. Gyromitra esculenta* is a good example of a mushroom with a â€œJekyll and Hydeâ€• personality, enjoying a reputation of being edible in the western United States but of being poisonous in other areas. These mushrooms are found commonly in the spring under conifers and are easily recognized by their brainlike appearance. Poisonings with these mushrooms are exceptionally uncommon in the United States, representing <1% of all recognized events, whereas these poisonings are considered more common in Europe. Certain cooking methods may eliminate the toxin, but inhalation of the fumes while cooking may cause poisoning. Because of the potential for toxicity, all members of this mushroom family should be avoided. The most common error occurs in the spring, when an individual seeking the nongilled brainlike *Morchella esculenta* (morel)

finds the similar *Gyromitra esculenta* (false morel). (See ILGYROMETRA in the Image Library.)

Gyromitra mushrooms contain gyromitrin (*N*-methyl-*N*-formyl hydrazone), which on hydrolysis splits into acetaldehyde and *N*-methyl-*N*-formyl hydrazine. Gyromitrin is unstable and therefore unlikely to exist in its free form. Subsequent hydrolysis, yields monomethylhydrazine (CH_3NHNH_2). The hydrazine moiety reacts with pyridoxine, resulting in inhibition of pyridoxal phosphate-related enzymatic reactions. This interference with pyridoxal phosphate disrupts the function of the inhibitory neurotransmitter Î³-aminobutyric acid (GABA).[54] The implications of this decrease in GABA, which is thought to contribute to intractable seizures associated with isoniazid or gyromitrin toxicity in a fashion identical to isoniazid toxicity, is discussed in Antidotes in Depth: Pyridoxine.

The initial signs of toxicity for these mushrooms occur 5â€“10 hours after ingestion and include nausea, vomiting, diarrhea, and abdominal pain. Patients manifest headaches, weakness, and diffuse muscle cramping. Most patients improve dramatically and return to normal function within several days. Rarely, early in the clinical course patients develop delirium, stupor, convulsions, and coma. Infrequently, patients develop a hepatorenal syndrome and require extensive in-hospital care.

Activated charcoal 1 g/kg body weight should be given. Benzodiazepines such as diazepam or lorazepam are appropriate for initial management of seizures. Under most circumstances, supportive care is adequate treatment. Pyridoxine in doses of 70 mg/kg IV may be useful in limiting seizures (Antidotes in Depth: Pyridoxine).

There are no rapid diagnostic strategies in the laboratory, although thin-layer chromatography, gas-liquid chromatography, and mass spectrometry can be used for subsequent (delayed) identification of the various hydrazine and hydrazone metabolites.

Group III: Muscarine-Containing Mushrooms

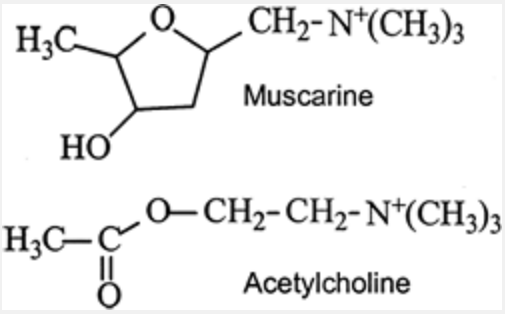


Figure. No Caption Available.

Mushrooms that contain muscarine include numerous members of the *Clitocybe* genus, such as *C. dealbata* (the sweater) and *C. illudens* (*Omphalotus olearius*), and the *Inocybe* genus, that in turn include *I. iacera* and *I. geophylla. Amanita muscaria* and *Amanita pantherina* contain limited quantities of muscarine. (See ILCLITOCYBEDEALBATA and ILOMPHALOTUSOLEARIUS in the Image Library.)

Muscarine and acetylcholine are similar structurally and have comparable clinical effects at the muscarinic receptors. Peripheral manifestations typically include bradycardia, miosis, salivation, lacrimation, vomiting, diarrhea, bronchospasm, bronchorrhea, and micturition. Central muscarinic manifestations do not occur because muscarine, a quaternary ammonium compound, does not cross the bloodâ€“brain barrier (Chap. 14). No nicotinic manifestations occur.

The effects of muscarine often last longer than those of acetylcholine. Because muscarine lacks an ester bond, it is not susceptible to

acetylcholinesterase hydrolysis. Clinical manifestations, which typically are mild, usually develop within 0.5â€“2 hours and last several additional hours. Significant toxicity is uncommon, limiting the need for more than supportive care. Rarely, atropine (1â€“2 mg given IV slowly for adults or 0.02 mg/kg with a minimum of 0.1 mg IV for children) can be titrated and repeated as frequently as indicated to reverse symptomatology.

No current, clinically available, analytic techniques can identify muscarine, although high-performance liquid chromatography would be appropriate for investigative purposes.

Group IV: Coprine-Containing Mushrooms

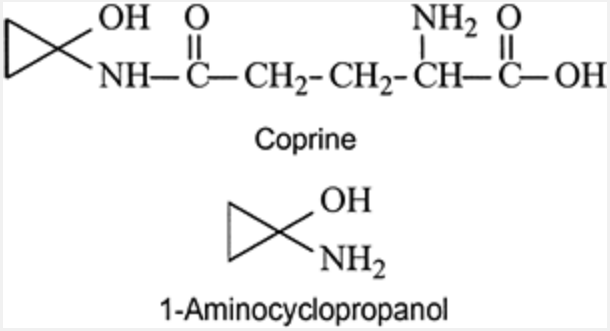


Figure. No Caption Available.

Coprinus mushrooms, particularly *C. atramentarius*, contain the toxin coprine. (See ILCOPRINUSATRAMENTARIUS in the Image Library.) These mushrooms grow abundantly in temperate climates in grassy or woodland fields. They are known as â€œinky capsâ€• because the gills that contain a peptidase autodigest into an inky liquid shortly after picking. The edible member of this group, *Coprinus comatus* (shaggy mane) is nontoxic, and probably its misidentification results in

collectors' errors. Coprine, an amino acid, its primary metabolite, 1-aminocyclopropanol,[17,60,89] or, more likely, a secondary in vivo hydrolytic metabolite, cyclopropanone hydrate, has a disulfiramlike effect.[100] Although both of these metabolites appear to inhibit aldehyde dehydrogenase, the most stable in vivo inhibitory effect is present in cyclopropane hydrate.[100] Inhibition of acetaldehyde dehydrogenase results in buildup of acetaldehyde and its accompanying adverse effects, which occur if the patient ingests alcohol concomitantly or for as long as 48â€“72 hours after the mushroom ingestion. Within 0.5â€“2 hours of ethanol ingestion, an acute disulfiram effect is noted, with tachycardia, flushing, nausea, and vomiting. Interestingly, alcohol ingested simultaneously does not result in clinical manifestations because inhibition of aldehyde dehydrogenase is slightly delayed during coprine metabolism. Treatment is symptomatic with fluid repletion and antiemetics such as metoclopramide, although clinical manifestations usually are mild and resolve within several hours. Prophylactic use of fomepizole immediately following ingestion of ethanol and coprine-containing mushrooms has a theoretical basis, but no case reports or studies are published. This group of mushrooms rarely causes fatalities (disulfiram is discussed further in Chap. 77).

Group V: Ibotenic Acid- and Muscimol-Containing Mushrooms

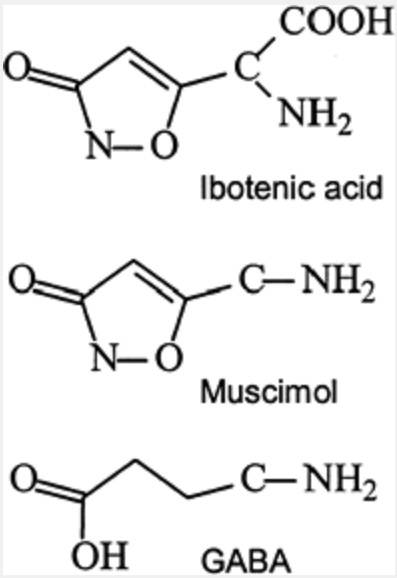


Figure. No Caption Available.

Most of the mushrooms in this class are primarily in the *Amanita* genus, which includes *A. muscaria*, (fly agaric) *A. pantherina*, and *A. gemmata*. (See ILAMANITAMUSCARIA1, ILAMANITAMUSCARIA2 and ILAMANITAMUSCARIA3 in the Image Library.) They exist singly and are scattered throughout the US woodlands. The brilliant red or tan cap (pileus) is that of the mushroom commonly depicted in children's books and is easily recognized in the fields during summer and fall.

Small quantities of the isoxazole derivatives ibotenic acid and muscimol are found in these mushrooms, which have been used in religious customs throughout history. Ibotenic acid is structurally similar to the stimulatory neurotransmitter glutamic acid. The stereochemistry of muscimol is very similar to that of the neurotransmitter GABA and may act as a GABA agonist.

Most patients who develop symptoms intentionally ingested large quantities of these mushrooms while seeking an hallucinatory experience. Within 0.5â€“2 hours of ingestion, these compounds

produce the GABAergic manifestations of somnolence, dizziness, hallucinations, dysphoria, and delirium in adults, whereas the excitatory glutamatergic manifestations of myoclonic movements, seizures, and other neurologic findings predominate in children.[7]

Treatment is invariably supportive. Most symptoms respond solely to supportive care, although a benzodiazepine such as diazepam or lorazepam is appropriate for excitatory CNS manifestations.

Group VI: Psilocybin-Containing Mushrooms

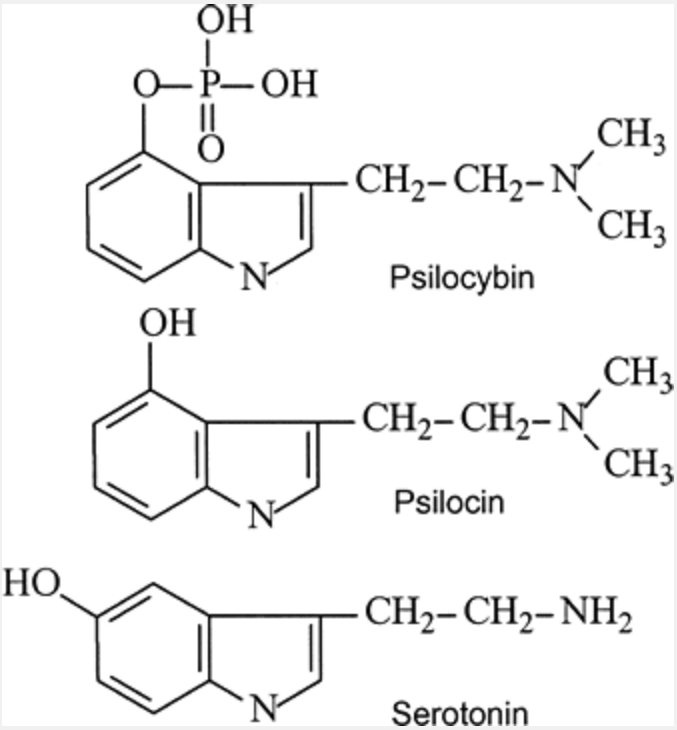


Figure. No Caption Available.

Psilocybin-containing mushrooms include *Psilocybe caerulescens*,

Psilocybe cubensis, *Conocybe cyanopus*, *Panaeolus foenisecii, Gymnopilus spectabilis,* and *Psathyrella foenisecii.* (See ILPSILOCYBECYANESCENS, ILPSILOCYBECAERULIPES, and ILGYMNOPILUSSPECTABILIS in the Image Library.) These mushrooms have been used for native North and South American religious experiences for thousands of years. They grow abundantly in warm, moist areas of the United States. Drug culture magazines and Internet sources advertise mail-order kits containing *P. cubensis* spores to grow â€œmagic mushroomsâ€• domestically.

Toxicity from this group is common because of the popularity of hallucinogens.[9] The quality, quantity, and variety of mushroom ingested may or may not be related to the hallucinogenic effects. Psilocybin is rapidly and completely hydrolyzed to psilocin in vivo. Serotonin, psilocin, and psilocybin are very similar structurally and presumably act at a similar 5-HT_2 receptor site. The effects of psilocybin as a serotonin agonist and antagonist are discussed in Chaps. 14 and 80.

The psilocybin and psilocin indoles, like those of lysergic acid diethylamide (LSD), rapidly (within 1 hour of ingestion) produce CNS effects, including ataxia, hyperkinesis, visual hallucinations, and illusions.[42] Rare cases of renal failure,[37,71] seizures, and cardiopulmonary arrest[9] are associated with psilocybin-containing species. However, such associations should always be questioned when reported in a substance-using population potentially simultaneously exposed to other toxins.

Some patients manifest tachycardia, anxiety, hallucinations, tremor, agitation, and mydriasis. Anxiety and light-headedness may develop quite rapidly (<1 hour), and most manifestations are recognized within 4 hours of ingestions with a return to normalcy within 6â€“12 hours. A single patient who intravenously administered an extract of *Psilocybe* mushrooms experienced chills, weakness, dyspnea, headache, severe myalgias, vomiting associated with hyperthermia, hypoxemia, and mild methemoglobinemia.[20]

Treatment for hallucinations usually is supportive, although a benzodiazepine such as diazepam or lorazepam may be necessary when reassurance proves inadequate.

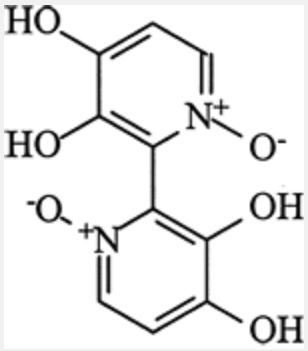
Group VII: Gastrointestinal Toxin-Containing Mushrooms

By far the largest group of mushrooms is a diverse group that contains a variety of ill-defined GI toxins. Many of the hundreds of mushrooms in this group fall into the â€œlittle brown mushroomâ€• category. Some *Boletus, Lactarius* spp, *Omphalotus olearius, Rhodophyllus* spp, *Tricholoma* spp, *Chlorophyllum molybdites*, and *Chlorophyllum esculentum* are mistaken for edible or hallucinogenic species. (See ILRUSSULAEMETICA and ILCHLOROPHYLLUMMOLYBDITES in the Image Library.) The toxins associated with this group are not identified. The malabsorption of proteins and sugars such as trehalose and the ingestion of a mushroom infected or partially digested by microorganisms or allergy may be responsible for symptoms. GI toxicity occurs 0.5â€“3 hours after ingestion when epigastric distress, malaise, nausea, vomiting, and diarrhea are evident. Treatment with regard to fluid resuscitation, vomiting, and diarrhea is supportive. The clinical course is brief and the prognosis excellent.

Others have described a *Paxillus* syndrome, which may be associated with involutin, one of the constituents of *Paxillus*.[50] A small number of patients with ingestions of *Paxillus involutus*, and possibly *Clitocybe claviceps* and *Boletus luridus*, develop a mild GI syndrome followed by an immune-mediated hemolytic anemia, hemoglobinuria, oliguria, and renal failure. IgG antibodies to a *Paxillus* extract were detected by a hemagglutination test in these patients.[98,99]

Rarely, clinical presentations are life threatening, with hypovolemic shock necessitating fluids and vasopressors.[84] Resolution of symptoms usually occurs within 6â€“24 hours. The clinical courses associated with specific mushroom ingestions are variable.[7] Death is rare.

Group VIII: Orellanine-and Orellinine-Containing Mushrooms



Orellanine

Cortinarius mushrooms, such as *Cortinarius speciosissimus.* (See ILCORTINARIUSSPELIOSISSIMUS in the Image Library.) and *Cortinarius orellanus*, are commonly found throughout Europe. *Cortinarius rainierensis* is a common North American species.[16,80] The *C. orellanus* toxin orellanine is reduced by photochemical degradation to orellinine, another bipyridyl agent that is further reduced to the nontoxic orelline.[2,65,74] The toxic compound orellanine is a hydroxylated bipyridine compound activated by its metabolism through the P450 system. Toxicologically, these molecules are similar to paraquat and diquat and may have comparable mechanisms of action, although precise knowledge is limited (Chap. 111). Other nephrotoxins, such as cortinarines, are isolated from certain *Cortinarius* species[87] and result in tubular damage, interstitial nephritis, and fibrosis.

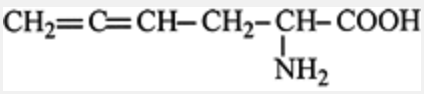
Initial symptoms occur 24â€“36 hours after ingestion and include headache, chills, polydipsia, anorexia, nausea, vomiting, and flank and abdominal pain. The largest case review demonstrated that numerous

patients repetitively ingested the *Cortinarius* spp prior to diagnosis.[21] Oliguric renal failure may develop several days to weeks after initial symptoms.[10] The only initial laboratory abnormalities may be hematuria, leukocyturia, and proteinuria. Nephrotoxicity is characterized by interstitial nephritis with tubular damage and early fibrosis of injured tubules with relative glomerular sparing.[16,80] Hepatotoxicity is rarely reported.[10] Hemoperfusion, hemodialysis, and renal transplantation are used for treatment.[10,21] No evidence suggests that secondary detoxification by plasmapheresis or hemoperfusion is of any benefit in preventing chronic renal failure even when initiated in the first 48 hours.[21,50,73] The data are inadequate to define management or prognosis precisely, as many patients improve rapidly, while some require acute hemodialysis and others require chronic therapy for renal failure.[10] No laboratory or clinical parameters to assist in predicting the individual reactions to the toxins are available. Although case reports in the literature commonly lack definitive proof of ingestion or confirmation of toxin presence, the more

rapid the onset of GI and renal manifestations, the greater the risk of both acute and chronic renal failure appear to be.[21]

Orellanine is rapidly removed from the plasma within 48â€“72 hours and concentrated in the urine in a soluble form. It can be detected in the plasma at the time of clinical symptoms by some investigators[73] but not by other investigators.[75] Thin-layer chromatography on renal biopsy material can detect orellanine long after clinical exposure.[73,75]

Group IX: Allenic Norleucine-Containing Mushrooms



Allenic norleucine

This relatively new diagnostic group is associated with ingestion of *Amanita smithiana*. (See ILAMANITASMITHIANA in the Image Library.) The 13 cases of *A. Smithiana* poisoning reported have all occurred in the Pacific Northwest.[56,91,94] Because the mature specimen often lacks any evidence of a partial or universal veil, these mushrooms are not recognized as *Amanita* species. It appears that all of the poisoned individuals were seeking the edible pine mushroom matsutake (*Tricholoma magnivelare*), a highly desirable look-alike. (See ILTRICHOLOMAMAGNIVELARE in the Image Library.) The *A. smithiana* and *A. abrupta* possess 2 amino acid toxins: allenic norleucine (amino-hexadienoic acid) and possibly l-2-amino-4-pentynoic acid.[18,67,103] In vitro renal epithelial tissue cultured with allenic norleucine developed morphologic changes similar to those that occur following *A. smithiana* ingestion.[67] In mice the extract of *Amanita abrupta* was also hepatotoxic, which suggests that other toxic agents in addition to the two described amino acids were present.[103]

Initial symptoms were noted from 30 minutes to 12 hours following ingestion of either raw or cooked specimens. GI manifestations, including anorexia, nausea, vomiting, abdominal distress, and diarrhea, occurred frequently, accompanied by malaise, sweating, and dizziness.

In some cases, vomiting and diarrhea persisted. The patients were oliguric or anuric upon presentation. Acute renal failure manifested 4â€“6 days following ingestion with marked elevation of BUN and creatinine. ALT and lactate dehydrogenase concentrations frequently were elevated, whereas amylase, AST, alkaline phosphatase, and bilirubin were only infrequently abnormal.

Risk of toxicity was greatest in older patients and in patients with underlying renal insufficiency. Patients who required hemodialysis underwent the procedure 2â€“3 times per week for approximately one month. None of the patients in the three series died.

There is no known antidote for these nephrotoxins. Activated charcoal, although of no proven benefit, should be used in standard doses when a patient in the northwest United States presents with early GI manifestations after mushroom ingestions. The clinician will be forced to consider the circumstances of ingestion to assess the probability of *A. smithiana* ingestion as opposed to ingestion of mushrooms containing a GI toxin.

In view of the substantial morbidity associated with *A. smithiana* ingestions, historic, clinical, and/or temporal evidence of this ingestion should lead to activated charcoal hemoperfusion or hemo-dialysis as a strong consideration when the patient presents in the early phase of exposure. When a patient presents with renal compromise several days, as opposed to weeks, following mushroom ingestion and with a history of early, as opposed to delayed, GI manifestations, the clinician may be able to differentiate *A. smithiana* from *Cortinarius* spp exposure.

Group X: Rhabdomyolysis-Associated Mushrooms

Twelve patients who ingested *Tricholoma equestre* (*T. flavovirens*) mushrooms for three consecutive days developed severe rhabdomyolysis that was lethal in three cases.[5] All patients developed

fatigue, muscle weakness, and myalgias 24â€“72 hours following the last mushroom meal. The individuals also developed facial erythema, nausea without vomiting, and profuse sweating. The mean maximal creatine phosphokinase (CPK) was 226,067 units/L in women and 34,786 units/L in men, with some values >500,000 units/L. Electromyography revealed muscle injury with myotoxic activity. The biopsies showed myofibrillar injury and edema consistent with an acute myopathy.

Dyspnea, muscle weakness, pulmonary congestion, acute myocarditis, dysrhythmias, cardiac failure, and death ensued in three patients. Autopsy demonstrated myocardial lesions identical to those found in the peripheral muscles. Although muscle toxicity was reproduced using *T. equestre* extracts in a mouse model, the etiology of the toxicity is not defined.[5] All the triterpenoids, sterols, indoles, and acetylenic compounds extracted from these mushrooms previously were assumed to be without toxicity. Currently all the clinical experience originates from Europe; no cases are reported in the United States.

Management

Because ingestion of certain mushrooms may lead to toxicity with substantial mortality, patients with suspected mushroom ingestions require rigorous management. A serious effort at precise identification of the genus and species involved will make assessment, management, and followup easier and more logical. The basic regimen of adsorption should be initiated if potentially toxic mushrooms are ingested. If nausea and vomiting persist, an antiemetic can be used to ensure that the patient can retain activated charcoal 1 g/kg. Appropriate life support measures should be instituted as necessary. Fluid, electrolyte, and glucose repletion are essential.

There is a wide variability in quantity and type of toxin present in mushrooms according to geography, local conditions, and individual susceptibility. The clinical course for *A. smithiana* poisoning has led us to suggest an alteration in the initial approach to patients in the

northwest United States who have early onset (0.5â€“3 hours) of GI distress following mushroom ingestion. Until recently, all patients who had early onset of nausea, vomiting, diarrhea, and abdominal cramps were presumed to be poisoned by a member of the groups containing either the GI toxins or muscarine. However, a better understanding of *A. smithiana* led us to limit the use of an algorithm we and others frequently used in the past (see Goldfrank's Toxicologic Emergencies, 6th edition, Figure 75-1). The routine use of specific antidotes should be avoided because they usually are unnecessary.

Disposition

It is important to remember that many patients with mushroom ingestions present with signs and symptoms suggestive of mixed

poisonings. Whereas some ingestions produce â€œpurerâ€• symptom complexes than others, some ingestions, such as those of *A. muscaria*, produce GI and CNS effects, and still other ingestions, such as of *Cortinarius* spp, have acute GI and delayed renal manifestations. Treatment or partial treatment may further confound the assessment. In addition, it is essential to remember that any acute GI disorder actually may be the manifestation of mushroom toxicity. In the spring and fall, in areas with moderate weather and humidity, it is particularly important to consider intentional or unrecognized exposure to mushroom toxins, although a logical approach to management is impossible in the absence of a precise history.

Because the clinical course of mushroom poisoning can be deceptive, all patients who manifest early symptoms (<3 hours) and remain symptomatic despite supportive care (Tables 113-1 and 113-2) should be admitted to the hospital. In this group of patients inhabiting the Pacific Northwest, *A. smithiana* should be of particular concern. Patients whose delayed initial presentation (â‰¥5 hours) is suggestive of amatoxin exposure should be hospitalized, as should any patient postingestion who cannot be followed safely or reliably as an

outpatient. Tables 113-1 and 113-2 list the characteristic times of appearance and evolution of symptoms caused by mushroom toxins and groups. Confusion may result from atypical clinical manifestations or, commonly, ingestion of several different mushrooms species, some of which may produce early symptoms and others delayed toxicity. Patients with certain types of ingestions may appear to improve initially with only supportive care. This latency period, which is characteristic of *Amanita* spp, may not be appreciated when several different species are eaten simultaneously. However, because hepatotoxicity leading to death may not appear until 2â€“3 days after ingestion (amatoxins) and nephrotoxicity may not appear for 3â€“21 days (orellanine and allenic norleucine), all patients with symptoms require subsequent followup.

Visualizing and analyzing the gross, microscopic, or chemical characteristics of the ingested mushroom remain vital strategies that are infrequently used. When the whole mushroom or parts are unavailable, the diagnosis must be based on the clinical presentation. No rapidly available studies in emergency departments or clinical chemistry laboratories are available to assist with management. The development of a rapid clinical test for amatoxins,[14,15,50] gyromitrin, orellanine, and allenic norleucine would be useful and permit early use of hemoperfusion and greater vigilance with regard to use of hemodialysis. We have not yet achieved the ability to use thin-layer chromatography, high-performance liquid chromatography, gas chromatography, or gas chromatography-mass spectrometry for clinically relevant circumstances.

TABLE 113-2. Mushroom Toxicity: Correlation Between Symptomatology and Time of Onset of Symptoms

	Early <3 h	Middle 5â€“24 h	Late >24 h
Gastrointestinal	Muscarine	Amatoxin	Orelline and orellanine
	Gastrointestinal toxins	Allenic norleucine	
	Allenic norleucine	Gyromitrin	
Hepatic			Amatoxin Gyromitrin
Neuropsychiatric	Ibotenic acid and muscimol Psilocybin	Gyromitrin	
Renal			Orelline and orellanine Allenic norleucine

Lycoperdonosis

Lycoperdonosis is not related to either the toxic or hallucinogenic

characteristics of a mushroom. This syndrome occurs in patients following acute inhalation of spores as a folk medical therapy for epistaxis[85] and in adolescents for various experimental reasons.[86] Puffball mushrooms (*Lycoperdon perlatum*, *Lycoperdon pyriforme*, or *Lycoperdon. gemmatum*), which are edible in the fall and can (upon decay or drying) release large numbers of spores by compression or agitation. (See ILLYCOPERDONPYRIFORME and ILLYCOPERDONPERLATUM in the Image Library.) Massive inhalation, insufflation, and chewing of spores can lead to the development of nasopharyngitis, nausea, vomiting, and pneumonitis within hours. Over a period of several days, cough, shortness of breath, myalgias, fatigue, and fever develop. Rarely patients require intubation because of pulmonary compromise associated with diffuse reticulonodular infiltrates.[86] Lung biopsy demonstrates an inflammatory process with the presence of *Lycoperdon* spores.[85] Patients treated with prednisone and antifungal agents such as amphotericin B recovered within several weeks without sequelae.

Identification

General

Although mushroom identification is a difficult science, this section may be helpful to the clinician dealing with a suspected case of mushroom toxicity. However, it is generally best to rely on symptomatology, not mushroom appearances, to confirm a diagnosis. As a general rule, positive identification of the mushroom should be left to the mycologist or qualified toxicologist. Digital images sent over the Internet with verbal descriptions to a mycologist have enhanced diagnostic potential, although definitive identification could not be achieved in a limited study.[30]

The most important anatomic features of both edible and poisonous mushrooms are their pileus, stipe, lamellae or gills, and volva.

- *Pileus:* Broad, caplike structure from which hang the gills (lamellae), tubes, or teeth.
- *Stipe:* Long stalk or stem that supports the cap; the stipe is not present in some species.
- *Lamellae:* Platelike or gill-like structures on the undersurface of the pileus that radiate out like the spokes of a wheel. The spores are found on the lamellae. Some mushrooms have pores or toothlike structures on their pili, which contain the spores. The mode of attachment of the lamellae to the stipe is noteworthy in making an identification.
- *Volva:* Partial remnant of the veil found around the base of the stipe in some species.
- *Veil:* Membrane that may completely or partially cover the lamellae, depending on the stage of development. The â€œuniversalâ€• veil covers the underside, the spore-bearing surface of the pileus.

- *Annulus:* Ringlike structure that may surround the stipe at some point below the junction, with the cap that is a remnant of the partial veil.
- *Spores:* Microscopic reproductive structures that are resistant to extremes in temperature and dryness, produced in the millions on the spore-bearing surface (see Lamellae). Of all the characteristics of a particular mushroom species, spores are the least variable, although many mushrooms have similar-appearing spores. A spore print is helpful in establishing an identification. (See ILSPOREPRINT 1 and ILSPOREPRINT 2 in the Image Gallery.) A spore print viewed microscopically is comparable to a bacterial Gram stain. Spore colors range from white to black and include shades of pink, salmon, buff, brown, and purple. Spore color in general is constant for a species.

The Unknown Mushroom

- The most important determinant is whether the ingested mushroom is one of the deadly varieties, especially *Amanita.* Outside of the Pacific Northwest, the onset of GI symptoms within 3 hours of ingestion does not result from amatoxin poisoning. In the Pacific Northwest, symptoms may represent *A. Smithiana* (allenic norleucine) poisoning (Tables 113-1 and 113-2).
- Attempt to obtain either the collected mushrooms or a detailed description of their features. Arrange for transport of the mushroom in a dry paper bag (not plastic). Ensure that the mushroom is neither moistened nor refrigerated, either of which will alter its structure. Remember that gastric contents may contain spores that can be crucial for analysis.
- If the mushroom cap is available, make a spore print by placing the pileus spore-bearing surface side down on a piece of paper for at least 4â€“6 hours in a windless area. The spores that collect on the paper can be analyzed for color. White spore prints can be visualized more easily on white paper by tilting the paper and looking at it from an angle.
- Concomitant with step 3, contact a mycologist and use the best resources available for identification. A botanical garden usually has expert mycologists on staff, or a local mycology club can locate a mycologist. Alternatively, the North American Mycological Association through its Internet site (http://www.namyco.org/) can furnish this information. A regional poison control center almost always can provide this expertise or locate an expert.
- If none of the resources in step 4 is accessible, Melzer reagent can be useful in differentiating look-alike species and defining the presence of an amatoxin. A positive reaction is indicated by the development of a dark blue color upon contact with Melzer reagent.[58] Melzer reagent is a solution of 20 mL water, 1.5 g

potassium iodide, 0.5 g iodine, and 20 g chloral hydrate. Staining a sample of the spores with 1 drop of reagent and then viewing the sample under a microscope helps to determine whether the mushroom is a deadly *Amanita*, with bluish-black â€œamyloidâ€•-reacting round spores.

- An additional test used by some is the Meixner reaction. Several drops of 10â€“12N hydrochloric acid are applied to an amatoxin-containing mushroom sample squeezed onto newspaper, resulting in a blue reaction.[50] The reliability of this test is doubtful, and most mycologists prefer to use Melzer reagent. Although the Meixner test is sensitive, false-negative and false-positive tests are of concern.[8]

Poisoning Principles: Myths and Science

Differentiating myths from science is a difficult task in any field of medicine. This effort is even more complex when discussing mushrooms. The following principles are of great value in developing a logical approach to a potential ingestion.

- Wild mushrooms should never be eaten unless an experienced mycologist can absolutely identify the mushroom. Even experts have trouble identifying some mushrooms, yet some foragers boldly indicate that distinguishing edible from toxic mushrooms is â€œas easy as telling brussels sprouts from broccoli.â€• Remember the saying, â€œThere are old mushroom hunters, and bold mushroom hunters; but there are no old, bold mushroom hunters.â€•
- The toxicology of any species can vary, depending on geographic location.
- If poisoning is suspected, attempt to obtain samples of the mushrooms eaten and identify them. Every ED should have a readily available resource on mushrooms, such as one of the major

mycology field guides.[1,12,57,58,76,82] In any case, identification is best made with the aid of the poison center's consultant mycologist.

- Mushrooms often are implicated as the cause of an illness when, in fact, infections or other diseases are responsible. Other etiologies include the mode of preparation (the sauce or wine) or the cooking utensil.
- There are no absolute generic approaches for evaluating the potential toxicity of a mushroom. Myths suggesting the safety or lack of safety by staining of silver, presence of insects or slugs, peeling off the mushroom cap, or the area of mushroom growth are unreliable or false. Neither odor nor taste is a good predictor of toxicity. Pure white mushrooms, little brown mushrooms, large brown mushrooms, and red- or pink-spored boletus (a mushroom without lamellae) should be considered potentially toxic.
- Cooking may inactivate some toxins but not others. In general, no wild mushroom should be eaten raw or in large quantities. Examples of toxicity associated with lack of cooking include *Armillariella mellea* (honey mushroom), which usually is well tolerated when cooked but not raw, and *Verpa bohemica* (a morel-like mushroom), which is edible but causes illness if eaten in excess.
- Associated phenomena may be responsible for or contribute to toxicity. Could insecticides have been sprayed on the mushrooms? Is it an alcohol-related response? Besides the well-known disulfiram reaction involving *C. atramentarius*, other good edibles, including the black morel *(Morchella angusticeps)* and the sulfur polypore (*Laetiporus sulfureus*), can cause adverse reactions if consumed with alcohol. The etiology of these adverse reactions is not understood.
- â€œEdibleâ€• mushrooms that are allowed to deteriorate become toxic. Therefore, only young, recently matured specimens should

be eaten when adequate mycologic support is available.

- The finding that only some people who ate a mushroom species manifested characteristic toxicity should not exclude the diagnosis of mushroom poisoning. The degree of toxicity may be dose related or genetically determined, or a person may have a pathologic predisposition to toxicity.

- Mushroom allergy can manifest as anaphylaxis.
- Most poisonous mushrooms resemble edible mushrooms at some phase of their growth. For this reason, even careful examination of the ring, cap, consistency, form, and color may not reliably identify the edible species. Also, characteristic features of specific toxic mushrooms may not be present under certain conditions. Although the deadly *A. phalloides* and *A. virosa* usually have remnant patches of tissue from the universal veil that envelops the mushroom in its â€œbuttonâ€• stage, rain may wash these remnants away. Similarly, a subterranean basal cup may not be noticed if the mushroom is cut at the ground level by a novice forager (Figure 113-1).
- Even the new in-vogue â€œwild mushroomsâ€• in the fanciest markets may not be entirely safe.

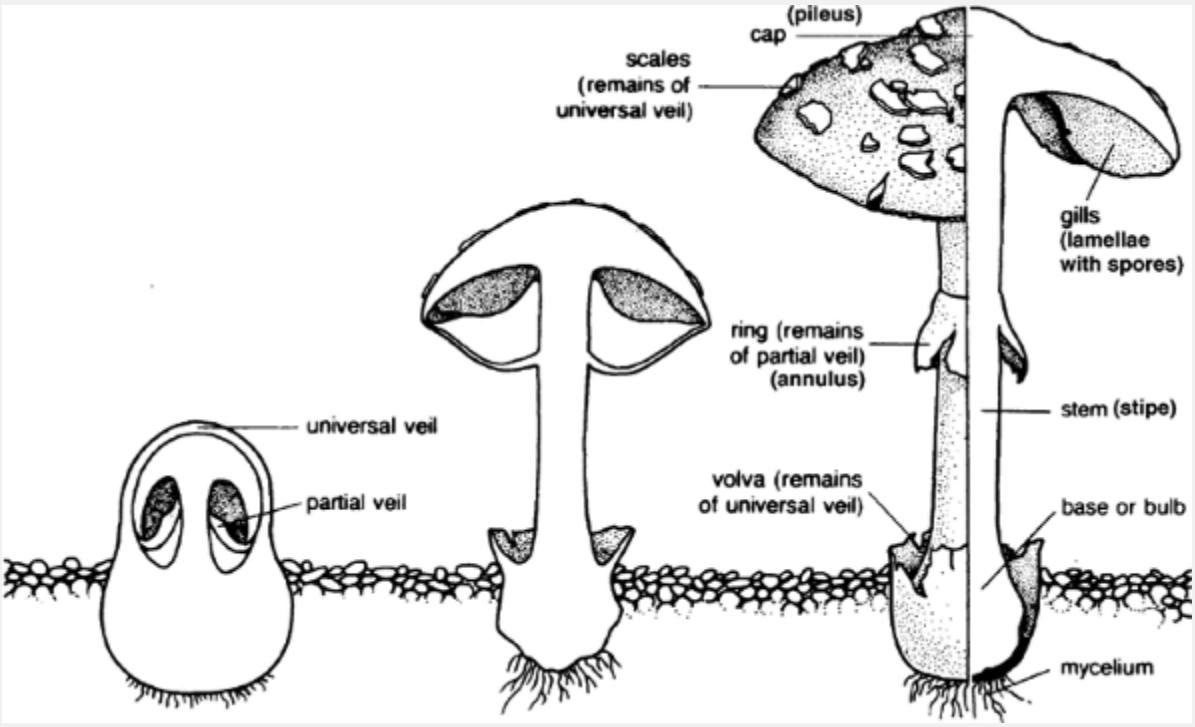


Figure 113-1. In the more highly specialized and evolved mushrooms, various protective tissues cover the fruit body and its constituent parts during its development. In the toadstool shown, an *Amanita* species, 2 veils of tissue are involvedâ€”one an outer enclosing bag, the universal veil, which ruptures as the fruit body expands to leave a volva at the base and fragments on the cap, the other an inner partial veil covering the developing gills, which is pulled away as the cap opens to leave a ring on the stem. (Reprinted, with permission, from Kibby G: Mushrooms and Toadstools, A Field Guide. Oxford, Oxford University Press, 1979, p. 14.)

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Chapter 114
Plants

Mary Palmer

Joseph M. Betz

A 25-year-old man was found unconscious with sustained ventricular tachycardia. He was found with a printout from a web page describing the use of *Aconitum* spp (monkshood) from horticultural sources as a means of committing suicide. His vital signs were: blood pressure, 60 mm Hg palpable; pulse, 120â€“170 beats/min; respiratory rate, 22 breaths/min; temperature 99Â°F (37.3Â°C); and oxygen saturation 100% by pulse oximetry breathing 28% oxygen. His dysrhythmia was responsive to sodium bicarbonate and 100 mg lidocaine IV bolus followed by a 2-mg/min infusion. Urine toxicology for cocaine, amphetamine, salicylate, and acetaminophen was negative. Upon awakening, he would not describe what he had done. Although both urine and serum specimens were obtained, local public health and medical examiner laboratories and 3 commercial natural product laboratories were unable to analyze these specimens for aconitine, one of the active ingredients presumed responsible for his symptoms.

Classification of Plant Xenobiotics

Aconitine, from monkshood, exemplifies the rich history of plant toxicology. It was believed by the Greeks to be the first poisonâ€”â€œlycotonumâ€• â€”created by the goddess Hecate from foam of the river Cerebrus.[18] Alkaloid constituents are responsible for its toxic (and therapeutic) effects. â€œAlkaloidâ€• is one of several classes of organic molecules found in plants as defined by the science of pharmacognosy. The pharmacognosy approach is consistent with the literature of plant efficacy and is applied here to their toxicity (Table 114-1). Unfortunately, the â€œscienceâ€• of pharmacognosy is not always straightforward and varies depending on the pharmacognosist. Hence our approach borrows primarily from two groups of authors[107,296] to keep the classification as consistent as possible. The major groups are as follows:

- *Alkaloids:* Molecules that react as bases and contain nitrogen, usually in a heterocyclic structure. Alkaloids typically have strong pharmacologic activity that defines many major toxidromes.
- *Glycosides:* Organic compounds that yield a sugar or sugar derivative (the glycone) and a nonsugar moiety (the aglycone) upon hydrolysis. The aglycone is the basis of subclassification into saponin or steroidal glycosides (also called cardioactive steroids, Chap. 62), cyanogenic glycosides, anthraquinone glycosides, and others such as atractyloside and salicin.
- *Terpenes and resins:* Assemblages of 5-carbon units (isoprene unit) with many types of functional groups (eg, alcohols, phenols, ketones, and esters) attached. These are the largest group of secondary metabolites; approximately 20,000 are identified. Most essential oils are mixtures of monoterpenes, and the terpene name depends on the number of assemblages. Monoterpenes have 2 units ($C_{10}H_{16}$), sesquiterpenes have 3

isoprene units (C_{15}), diterpenes have 4 isoprene units (C_{20}), triterpenes have 6 (C_{30}), etcâ€¦ These molecules have an active role in plant defense mechanisms.

- *Proteins, peptides, and lectins:* Proteins consist of amino acid units with various side chains, and peptides consist of linkages among amino acids. Lectins are glycoproteins classified according to the number of protein chains linked by disulfide bonds and by binding affinity for specific carbohydrate ligands, particularly galactosamines. The toxalbumins (eg, ricin) are lectins. These components tend to be neurotoxins, hemagglutinins, or cathartics.
- *Phenols and phenylpropanoids:* Phenols have phenyl rings. Phenylpropanoids consist of a phenyl ring attached to a propane side chain. They are devoid of nitrogen, even though some are derived from phenylalanine and tyrosine. They constitute a major group of secondary metabolites and among plant toxins consist of *coumarins* (lactone side chains), *flavonoids* (built upon a flavan 2,3-dihydro-2-phenylbenzopyran nucleus, eg, naringenin and rutin), *lignans* (2 linked phenylpropanoids, eg, podophyllin), *lignins* (complex polymers of lignans that bind cellulose for woody bark and stem), and *tannins* (polymers that bind to protein and can be further hydrolyzed or condensed).

Plant chemistry is complex. Our simplified presentation of one toxin class per plant, per symptom group (Table 114-1) overlooks the fact that plants contain multiple chemicals and chemical classes that work independently or in concert. Additionally, different plant families may contain similar, if not identical, xenobiotics (a form of convergent evolution). In some cases, xenobiotics remain unidentified and are grouped in the section on Unidentified Toxins.

Dissimilar molecules from diverse pharmacognosy classes that

share effects are grouped together for pragmatic purposes in the section on Effects Shared Among Diverse Classes of Xenobiotics. They are further categorized into Plantâ€“Drug Interactions, Sodium Channel Effects, Antimitotic Alkaloids and Resins, and Plant-induced Dermatitis.

TABLE 114-1. Primary Toxicity of Common Important Plant Species

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Our focus is on exposures to flowering plants (angiosperms) related to foraging, dietary, or occupational contact, except for some gymnosperms or algae and, rarely, medicinal contact (medicinal use as herbals is discussed in Chap. 43).[222] Because our understanding of plant toxicity is poor relative to that of pharmaceutical agents, we include animal research to provide a more comprehensive foundation for comparison to human experiences that may otherwise go unrecognized without such precedent or may likewise prove incorrect in time. The science of plant toxicology formally began in the United States as a response to significant poisonings of livestock.[360,361] The overall quality of literature for human exposures is poor and primarily available as case reports.[276]

P.1584

Many of these cases lack clear links between toxin exposure and illness, and qualitative serum concentrations often are unavailable.[157] Uncertainty is compounded by the fact that plants

themselves are inherently variable, and potency and type of toxin depend on the season, geography, local environment, plant part, and methods of processing.[6,126]

Identification of Plants

Positive identification of the plant species should be attempted whenever possible, especially when the patient becomes symptomatic. Communication with an expert botanist or poison center is highly recommended and can be facilitated by transmission of digital images or a fax.[243] Provisionally, simple comparison of the species in question with pictures or descriptions from a field guide or flora may help exclude the plant's identity from among the most life-threatening in Table 114-1. A plant identification also can be compared with those searched in the PLANTOX database (http://www.vm.cfsan.fda.gov/~djw/readme.html) managed by the Food and Drug Administration.[75,359,361] Laboratory analysis is not timely enough to be useful except as a tool in an investigatory or forensic analysis.[133]

In cases where expert identification cannot be immediately achieved, crude recognition of taxonomic families of poisonous plants is the simplest first step to identify or exclude poisonous plants but is most easily achieved when the plant is in flower or fruit. For instance, if the flower is described or looks like a flower from a tomato or potato, it probably is in the Solanaceae family. Plants of this family typically produce gastroenteritis or anticholinergic findings following ingestion. It then would be prudent to begin expectant management (eg, prepare for use of physostigmine). This approach will be less useful for those xenobiotics (eg, pyrrolizidine alkaloids) that occur in numerous different families.

Approach to the Exposed Patient and

Understanding Risk

Faced with the care of an individual who comes seeking medical care, health care givers must determine whether or not the patient needs treatment interventions. Potential symptoms listed in Table 114-1 are organized by plant name but with their *major* organ system effects for quick reference to types of symptoms and whether they might be life threatening.[35] For instance, life-threatening symptoms such as dysrhythmias or seizures can be searched by â€œcardi-â€• or â€œneuro-â€• in the first column and compared with the plant(s) in question. The plants and xenobiotics that present life-threatening symptoms are so noted. Exposures associated with one of these plants or xenobiotics or major organ system symptoms dictates the need for possible prompt gastric emptying, decontamination, individualized therapy, and hospitalization. Note that nonspecific symptoms such as nausea and vomiting are listed only when they are the sole cause of morbidity or mortality (toxalbumins such as ricin), but nausea and vomiting are nearly ubiquitous among acute poisonings of clinical consequence.

Identified plant species most frequently reported during a decade of Poison Center experience are indicated in Table 114-1. In most cases, these species provide reassurance because most offer benign outcomes, and only 2 among these can be life threatening depending on the circumstances of the exposure. Given the relatively poor understanding of toxins and in the absence of complete information about an exposure, expectant management and supportive care are the rule. Even if a plant is not marked as life threatening or commonly reported, the patient should undergo a period of observation and followup given the relatively immature science of plant toxicology relative to that of pharmaceuticals.

The difficult task in human plant toxicology is the lack of adequate data to determine risk (see examples in Chap. 124). Typically, evaluations of risk are based on poison center data and usually

cite the numerous calls without clinical consequence as a part of the risk equation (Chap. 130).[208,209,210,211,212 and 213,260,363] However, poison center data are dominated by pediatric cases and other cases with unsubstantiated clinical manifestations (Chap. 130).[157] These cases often represent small or nonexistent exposures, and their inclusion in the database may mask real risks by diluting â€œtrueâ€• hazardous exposures with trivial or nonexistent exposures. Furthermore, misidentification of the plant may occur because of either similar appearance or similar nomenclature.

In summary, basic decontamination and supportive care should be instituted as fits the situation, with appropriate consultation to a poison center. The most consequential and dangerous plant xenobiotics for humans are discussed here and those that can produce life-threatening signs acutely are denoted in Table 114-1.

Toxic Constituents in Plants, Taxonomic Associations, and Selected Symptoms

Alkaloids: Toxic Manifestations

The term *alkaloid* refers to nitrogen-containing basic xenobiotics of natural origin and limited distribution. They figure prominently in the history of humanâ€“plant interaction, ranging from epidemics of poisoning caused by ergot-infested rye bread in the Middle Ages, to addictions to cocaine, heroin, and nicotine in contemporary time. Numerous examples of toxic constituents of these families are given in the following discussion, which begins with a description of every major toxidrome that involves alkaloids. See also Sodium Channel Effects under Effects Shared Among Diverse Classes of Xenobiotics later in this chapter for description of additional life-threatening alkaloids.

Anticholinergic Effects: Belladonna Alkaloids

The belladonna alkaloids are all from the family Solanaceae and can be identified as members of this family by their characteristic flowers (most familiar from nightshade, potato, or tomato flowers). The belladonna alkaloids have potent antimuscarinic effects. Ingestion produces classic signs of this toxidrome: tachycardia, hypertension, hyperthermia, dry skin and mucous membranes, skin flushing, diminished bowel sounds, urinary retention, agitation, disorientation, and hallucinations (Chap. 3). Since the 1970s, the quest for recreational â€œhighsâ€• has surpassed unintentional ingestions as the main source of toxicity. Hallucinatory effects are sought in seeds and teas, especially in late summer, when jimsonweed *(Datura stramonium)* seeds (see ILDATURASTRAMONIUM1 and ILDATURASTRAMONIUM2 in the Image Library at http://www.goldfrankstoxicology.com) become available.[46,48,71,72,149,152,320] One hundred of these seeds contain up to 6 mg atropine and related alkaloids, and an ingestion of this amount can be fatal.[27]

Although various species and plants within species bear differing concentrations of diverse xenobiotics, the clinical manifestations usually are similar.[290,347] Onset of symptoms typically occurs 1â€“4 hours postingestion, or more rapidly if the plants are smoked or consumed as a tea infusion. The duration of effect is partly dose dependent and may last from a few hours to weeks.[152] The course of anticholinergic poisoning is altered by use of physostigmine, which when consequential may require repetitive dosing, necessitating observation and hospitalization.[307] Moreover, physostigmine may be lifesaving in patients with seizures or agitated delirium (Antidotes in Depth: Physostigmine Salicylate). Anticholinergic toxicity may be produced without detectable

atropine, scopolamine, or hyoscyamine concentrations and is better left as a clinical and not a laboratory diagnosis.[320]

Solanine is contained in other members of the Solanaceae family, but it is not a belladonna alkaloid. It inhibits cholinesterase in vitro, although cholinergic symptoms are not noted clinically. Nonetheless, reports of solanine-induced central nervous system (CNS) toxicity includes hallucinations, delirium, and coma.[244,278] However, most symptomatic patients typically develop nausea, vomiting, diarrhea, and abdominal pain that begins 2â€“24 hours after ingestion, which, like CNS toxicity, may persist for several days.[80,278] Although solanine is present in most of the 1700 species in the genus *Solanum*, solanine toxicity in humans is uncommonly encountered. Green potatoes and green potato tops are most commonly associated with symptoms, which is not surprising because the alkaloids are most concentrated in those items. Most reports of death come from the older literature,[4,162] and consumption of 2â€“5 g of green components per kilogram body weight per day is not predicted to cause acute toxicity.[284]

Nicotine and Nicotine-like Alkaloids: Nicotine, Lobeline, Sparteine, *N*-Methylcytisine, Cytisine, and Coniine

Nicotine toxicity (other than from inhaled sources) occurs via ingestion of leaves of *Nicotiana tabacum*, cigarette remains, organic products and insecticides, and transdermally among farm workers harvesting tobacco (green tobacco sickness).[137,139,289] A dose as little as 1 mg/kg can be lethal to an adult.[238,282] Overstimulation of the nicotinic receptors by high doses of nicotine produces a toxidrome that progresses from gastrointestinal (GI) symptoms to diaphoresis, mydriasis, fasciculations, tachycardia, hypertension, hyperthermia, and seizures, respiratory depression, and death (Chap. 82). Wearing of protective clothing by tobacco farm workers best prevents green tobacco sickness.

These manifestations are also produced by alkaloids other than nicotine.[355] There are no recent reports of nicotinic toxicity from lobeline (found in all parts of *Lobelia inflata)*, but its overenthusiastic use in the 18th century resulted in morbidity and mortality.[44]

Sparteine from broom *(Cytisus scoparius)*[349] and *N*-methylcytisine from blue cohosh *(Caulophyllum thalictroides)*[291] provide additional examples of nicotinelike alkaloids that may be teratogenic.[194] Laburnum or golden chain *(Cytisus laburnum)* contains cytisine, which reportedly is responsible for mass poisonings and fatalities in children and adults who eat the plants or parts thereof (even as little as 0.5 mg/kg, or a few peas).[138,259,293] Unfortunately, such reports have resulted in thousands of unnecessary hospital admissions for patients without morbidity and mortality after ingestion of this plant, demonstrating the difficulty in separating hazard from risk and in obtaining accurate doseâ€“response information in the setting of plant exposures and human variability.[30,121]

The most famous description of the end stages of nicotinic toxicity dates from approximately 2400 years ago by an observer of Socrates' fatal ingestion of a decoction of poison hemlock *(Conium maculatum)*:[342]

> â€¦the person who had administered the poison went up to him and examined for some little time his feet and legs, and then squeezing his foot strongly asked whether he felt him. Socrates replied that he did not and said to us when the effect of the poison reached his heart, Socrates would depart.

Birds do not experience coniine toxicity but provide a vector for poisoning. According to the book of Exodus, quail that fed on seeds

(presumably from poison hemlock) became toxic and passed the toxicity on to the Israelites who ate the fowl. In the 20th century, people have succumbed to hemlock poisoning following their avian repasts. This is especially well documented in Italy, where the toxic alkaloid coniine subsequently was detected in the bird meat, as well as in the blood, urine, and tissue of some victims.[294,314]

The age of the plant seems to be directly correlated with increasing concentrations of coniine, whereas the toxin Î³-coniceine occurs in greater amounts in new growth; hence, the plant remains toxic over the length of the growing season.[91,135] Fatal poisonings are reported on multiple continents,[91,34] and death may result from respiratory arrest.[23] Of 17 poisoned Italian patients, all had elevated liver aminotransferases and myoglobin concentrations, and 5 had acute tubular necrosis. Death developed 1â€“16 days following ingestion.[295]

Cholinergic Effects in Alkaloids: Arecoline, Physostigmine, and Pilocarpine

Betel chewing has been a habitual practice in the East since ancient times. The â€œquidâ€• consists of betel nut *(Areca catechu)* and other ingredients. The effects of acute exposure to arecoline, the major alkaloid, include sweating, salivation, and hyperthermia. Effects of acute use are rarely reported, but are associated with death, at least in susceptible patients.[87] Prolonged use is linked to dental decay and oral cancer.[64,85,90,106,316] Physostigmine is an alkaloid derived from the Calabar bean *(Physostigma venenosum)*, where it is present in concentrations of 0.15%. The miotic effects of physostigmine have been used to reverse mydriatic agents. Its efficacy as an anticholinesterase agent makes it a valuable antidote in anticholinergic poisoning (Antidotes in Depth: Physostigmine Salicylate). Pilocarpine is derived from *Pilocarpus jaborandi* from South America and possesses stimulatory effects on muscarinic receptors. It is of

value in treatment of glaucoma.[106] Reversal of toxicity can be achieved by atropine.

Psychotropic Alkaloids: Lysergic Acid and Mescaline

Hallucinations from the direct serotonin effects of lysergic acid diethylamide (LSD) and its derivatives and from the amphetaminelike serotonin effects of the mescaline alkaloids are reported following ingestion of morning glory seeds (*Ipomoea* spp) and peyote cactus *(Lophophora williamsii)*, respectively (Chap. 80). Ingestion of at least 150 morning glory seeds also produces nausea and vomiting.[68,179,369] Despite their chemical relatedness to LSD, molecules such as lysergacidamide and lysergacidethylamide, found in Hawaiian baby woodrose seeds *(Argyreia nervosa)* and sold for their hallucinogenic effects, produce a syndrome more similar to that of anticholinergic poisoning.[28]

Alkaloidal Central Nervous System Stimulants and Depressants: Ephedrine, Synephrine, Cathinone, and Narcotics

Use of ephedrine-containing *Ephedra* herbal products was banned by

the FDA in 2004 secondary to cardiovascular toxicity and deaths.[357] However, varieties of *Sida cordifolia* also contain ephedrine. Synephrine, another compound structurally related to ephedrine, occurs in *Citrus aurantium*, which is ingested as a plant or as a medicinal. Deaths are reported following ingestion of *C. aurantium* rinds by children.[240] Drug interactions can ensue from their use.[175] Another plant ingested for its CNS stimulant activity is khat *(Catha edulis).* The plant contains cathinone (Î±-

aminopropiophenone) and cathine [(+)-norpseudoephedrine]. In addition, narcotics derived from the poppy plant (*Papaver* spp) are prototypic CNS depressants and analgesics (Chap. 38).

Pyrrolizidine Alkaloids

Pyrrolizidine alkaloids are widely distributed both botanically and geographically. Approximately half of the 350 different pyrrolizidine alkaloids characterized to date are considered toxic. Pyrrolizidine alkaloids are found in 6000 plants and in 13 plant families but are most heavily represented within the Boraginaceae, Compositae, and Fabaceae families. Within these families, the genera *Heliotropium*, *Senecio*, and *Crotalaria*, respectively, are particularly notable for their content of toxic pyrrolizidine alkaloids.[332] These hepatotoxic alkaloids all contain an unsaturated 1-hydroxymethyl pyrrolizidine system.[370] The hepatic cytochrome P450 system converts these compounds to highly reactive pyrroles in vivo. Chronic exposures cause hepatic venoocclusive disease by stimulating proliferation of the intima of hepatic vasculature. Most poisonings occur as a result of contamination of food grain with seeds of pyrrolizidine alkaloid-containing plants or by use of pyrrolizidine alkaloid-rich plants for medicinal purposes. Acute poisoning probably is caused by an oxidant effect resulting in hepatic necrosis.[75,150] An estimated 20% of patients with acute pyrrolizidine alkaloid poisoning die, 50% recover completely, and the rest develop subacute or chronic manifestations of hepatic venoocclusive disease.[14] Pyrrolizidine alkaloids are teratogenic and are transmitted through breast milk.[301] Other types of plant-associated hepatic disorders are discussed in Effects Shared Among Diverse Classes of Xenobiotics.

Isoquinoline Alkaloids: Sanguinarine, Berberine, and Hydrastine

Sanguinarine was detected in 26 family members who consumed a

mustard oil contaminated with seeds of *Argemone mexicana*.[322] All patients suffered GI distress followed by peripheral edema, skin darkening, erythema, skin lesions, perianal itching, anemia, and hepatomegaly. Ascites developed in 12%, and myocarditis and congestive heart failure occurred in approximately a third of affected individuals.[371] Medicinally, sanguinarine is used for dental hygiene.[164] In North America, sanguinarine is found in blood root *(Sanguinaria canadensis)*, which, like *Argemone*, is in the Ranuculaceae family.

Berberine is structurally similar to sanguinarine and reportedly also has cardiac depressant effects. A number of medicinal plants contain berberine, including goldenseal *(Hydrastis canadensis)*, Oregon grape (*Mahonia* spp), and barberry (*Berberis* spp). It causes myocardial and respiratory depression and contraction of smooth muscle in vasculature and the uterus.[240] Strychninelike movement disorders are described following ingestion of hydrastine, which composes 4% of goldenseal.

Miscellaneous Other Alkaloids: Emetine/Cephaline, Strychnine/Curare, and Swainsonine

Emetine and cephaline are derived from *Cephaelis ipecacuanha*, a tropical plant native to the forests of Bolivia and Brazil. They are the principal active constituents in syrup of ipecac, which produces emesis. Chronic use of syrup of ipecac, typically by patients with eating disorders or Munchausen syndrome by proxy,[13,111] can lead to cardiomyopathy, smooth muscle dysfunction, myopathies, electrolyte and acidâ€“base disturbances related to excessive vomiting, and death [154,315] (Antidotes in Depth: Syrup of Ipecac). Poisoning in patients ingesting plant material is not reported.

Strychnine and curare are both derived from plants of the *Strychnos* genus but possess very different clinical effects. The

alkaloids strychnine and brucine result in muscular spasms and rigidity by antagonizing glycine receptors in the spinal cord and brainstem and are derived from the seeds of *Strychnos nux-vomica*. The plant is used as an herbal remedy for arthritis called â€œmaqianzi,â€• which if processed in error produces muscle spasm and weakness, including respiratory muscles[59] (Chap. 108).

Curare is the name given to the unstandardized extract of the bark of certain members of the genera *Strychnos* and *Chondodendron.* The physiologically active principal of curare is (+)-tubocurarine chloride, a competitive antagonist of acetylcholine at nicotinic receptors in the neuromuscular junction. The pharmacology and potential applications of curare are great, as it is the molecule from which most nondepolarizing neuromuscular blockers are derived (Chap. 66). Plant poisoning is recorded solely with its traditional use as a hunting poison.[24,226,286]

Swainsonine is isolated from *Swainsonia canescens*, *Astragalus lentiginosis* (spotted locoweed), *Sida carpinifolia*, other species of *Swainsonia* and *Astragalus*, as well as several species in the genera *Oxytropis* and *Ipomoea*, and several fungi.[69,70] After subsisting on seeds containing swainsonine for nearly 4 months, a naturalist forager manifested profound muscular weakness and died in the wilderness.[207] The compound is teratogenic and causes chronic neurologic disease called â€œlocoism,â€• with weakness and failure to thrive in livestock. Swainsonine inhibits the glycosylation of glycoproteins by Î±-mannosidase II of the Golgi apparatus, resulting in a lysosomal storage disease. Swainsonine was used with some success in clinical trials for treatment of advanced neoplasms. Adverse effects included hepatic, pancreatic, and respiratory manifestations, as well as lethargy and nausea.[148]

Glycosides

Glycosides yield a sugar or sugar derivative (the glycone) and a nonsugar moiety (the aglycone) upon hydrolysis. The aglycone

group is the basis of subclassification. The nonsugar or aglycone group determines the subtype of glycoside. For instance, the cardioactive steroids have saponin (steroid) aglycone groups and are among the saponin glycosides.

Saponin Glycosides: Cardioactive Steroids, Glycyrrhizin, *Ilex* Saponins

Cardioactive Steroids

Poisoning by virtually all *cardioactive steroids* is clinically indistinguishable from poisoning by digoxin (Chap. 62), which itself is derived from *Digitalis lanata*.[296] However, compared to toxicity from pharmaceutical digoxin, toxicity resulting from the cardioactive steroids found in plants has markedly different pharmacokinetic characteristics. For example, digitoxin in *Digitalis* species has a plasma half-life as long as 192 hours (average 168 hours).

The pharmacologic properties are true across taxonomic boundaries.[311] Poisonings by *Digitalis* spp,[267,292,324] squill (*Urginea* spp),[123,345] lily of the valley (*Convallaria* spp [see ILCONVALLARIAMAJALIS in the Image Library at http://www.goldfrankstoxicology.com]),[98,210,215] oleander (*Nerium* spp),[7,161,210,218,220] and yellow oleander (*Thevetia* spp [see ILTHEVETIAPERUVIANA1 and ILTHEVETIAPERUVIANA2 in the Image Library at http://www.goldfrankstoxicology.com]).[26,96,97,235,311,312] are clinically similar. The potency of these effects depends on the specific cardioactive steroid constituents and its dose. For instance, lily of the valley is rarely associated with morbidity or mortality,[98,219] whereas ingestion of only two seeds of yellow oleander by adults can produce severe symptoms, and expected outcome is grave if more than 4 seeds are consumed.[235,311]

Poisonings by oleander and yellow oleander occur predominantly in the Mediterranean and in the Near and Far East. These two plants are attractive ornamentals popular in the United States and Europe, commonly resulting in poisoning in some of these regions.[82]

Patients experience vomiting within several hours, followed by hyperkalemia, conduction delays, and increased automaticity (bradycardia and tachydysrhythmias). Interestingly, the cardiac manifestations may be difficult to distinguish from those produced by plants with sodium channel blockers (see Effects Shared Among Diverse Classes of Toxins). Activated charcoal was beneficial in preventing death after suicide attempts with yellow oleander in Sri Lanka and its use should not be delayed in the face of uncertain plant identity.[86] Antibody therapy reduces mortality 3-fold from yellow oleander poisoning but is too expensive for developing countries where oleander-induced mortality is highest. In addition, various cardioactive steroids respond differently to therapeutic use of digoxin-specific antibody fragments (Fab). Use of very large doses of digoxin-specific antibody (up to 37 vials reported in one case[292]) may be necessary to capitalize on the therapeutic cross-reactivity between antibody and the nondigoxin cardioactive steroids. The potential for success should lead to use of antibody therapy without delay when available.[81,306] Similarly, there is variable cross-reactivity among the individual plant cardioactive steroids with regard to the degree to which each elevates diagnostic polyclonal digoxin assay measurements in clinical laboratories. These measurements can be used only as qualitative proof of exposure but not as quantitative indicators of the exposure, because the elevations can result in marked *underestimation* of the â€œfunctional digoxin concentrations.â€• Until more is known, any positive digoxin concentration following exposure to a plant should be assumed to be significant and treated accordingly.

Because steroidal glycosides were found only in the stomach of a

patient who died after ingestion of common ivy *(Hedera helix)*, it was concluded that hederacoside C, Î±-hederin, and hederagenin did not cause death. Instead, the patient is believed to have asphyxiated on the leaves.[132]

Glycyrrhizin

Glycyrrhizin is a saponin glycoside derived from *Glycyrrhiza glabra* (licorice) and other *Glycyrrhiza* spp. Glycyrrhizin inhibits 11Î²-hydroxysteroid dehydrogenase, an enzyme that converts cortisol to cortisone. When large amounts of licorice root are consumed chronically, cortisol concentrations rise, resulting in pseudohyperaldosteronism because of its affinity for renal mineralocorticoid receptors.[109] Chronic use eventually leads to hypokalemia with muscle weakness, sodium and water retention, hypertension, and dysrhythmias[76,105,108,109,377] Assessment involves evaluation of the patient's fluid and electrolytes and electrocardiogram. Potassium replacement is the most common necessary intervention.

Ilex Species

Holly berries (from >300 *Ilex* spp) are a common and attractive ingestant among children, especially during winter holidays.[353] They contain a mixture of alkaloids, polyphenols, saponin glycosides, steroids, and triterpenes.[367] Saponin glycosides appear to be responsible for GI symptoms such as nausea, vomiting, diarrhea, and abdominal cramping that result from ingestion of the berries. Experimental data in animals describe hemolysis as well as cardiotonic effects similar to those of digoxin.[15,362] CNS depression was reported in a case in which a child consumed a â€œhandfulâ€• of berries; however, this child was also treated with syrup of ipecac.[298] The toxic dose has been suggested to be just two berries,[125] but one study suggested that no untoward effects are to be expected for ingestions of <6 berries.[362]

Symptoms may be expected to be restricted to GI effects, and treatment is supportive.

Cyanogenic Glycosides: *(S)*-Sambunigrin, Amygdalin, Linamarin, and Cyacasin

Cyanogenic glycosides yield hydrogen cyanide on complete hydrolysis. These glycosides are represented in a broad range of taxa and in approximately 2500 plant species.[354] The species that are most important to humans are cassava (*Manihot esculenta* [see ILMANIHOTESCULENTA in the Image Library at http://www.goldfrankstoxicology.com]), which contains linamarin, and *Prunus* spp, which contain amygdalin. Cycad toxins are neurotoxic or pseudocyanogenic. Rare reports of cyanide poisoning associated with *(S)*-sambunigrin in European elderberry *(Sambucus nigra;* sambunigrin) are more severe when these ingestions include leaves as well as berries.[39,49]

Many North American species of plants contain cyanogenic compounds, including ornamental *Pyracantha*, *Passiflora*, and *Hydrangea* spp, which either do not release cyanide or are rarely consumed in quantities sufficient to result in toxicity.[146] On the other hand, although the fleshy fruit of *Prunus* spp in the Rosaceae are nontoxic (apricots, peaches, pears, apples, and plums), the leaves, bark, and seed kernels contain amygdalin, which is metabolized to cyanide.[43] Amygdalin was the active ingredient of Laetrile, an apricot pit extract, promoted in the 1970s for its supposed selective toxicity to tumor cells. Its sale was restricted in the United States because it lacked efficacy and safety.[258] However, patients continued to travel to other countries for laetrile therapy, also marketed as â€œvitamin B-17,â€• and it once again is available through alternative medicine providers.[372] Ingestions of, and poisoning from, *Prunus* seeds continue today.[281,304,336] The manifestations of cyanide poisoning and treatment involving use of the cyanide antidote kit are detailed elsewhere (Chap. 121

and Antidotes in Depth: Nitrates, Sodium Thiosulfate, and Hydroxcobolanin).

Acute and chronic cyanide toxicity (including deaths) associated with consumption of inadequately prepared cassava (*M. esculenta* [see ILMANIHOTESCULENTA in the Image Library at http://www.goldfrankstoxicology.com]) are reported worldwide (Chap. 121).[2,303] Chronic manifestations include visual disturbances (amblyopia), upper motor neuron disease with spastic paraparesis, and hypothyroidism. These findings are associated with protein-deficient states and use of tobacco and alcohol. The ataxic neuropathy resembles that produced by lathyrism (see Proteins, Peptides, and Lectins). A unifying hypothesis about the etiology of these 2 similar diseases from seemingly very different sources is that thiocyanate accumulation may lead to degeneration of the Î±-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA)-containing neurons that are first stimulated and then destroyed in neurolathyrism.[326,329]

Similarly, seeds of cycads contain cycasin and neocycasin, which belong to the family of cyanogenic glycosides, as well as neurotoxins associated with consumption of indigenous food. The cyanogenic glycosides of cycads are considered pseudocyanogenic, with little potential to liberate hydrogen cyanide, but most typically produce violent vomiting 30 minutes to 7 hours after ingestion of 1â€“30 seeds.[58] On the island of Guam, indigenous peoples develop a devastating amyotrophic lateral sclerosis-parkinsonism dementia complex (ALS-PDC) that appears associated with ingestion of *Cycas circinalis* seeds or the flying foxas that feed extensively upon the cycads.[333] The implicated toxin originally was believed to be an amino acid[33] but more recently is identified as a sterol glycoside.[195] Research on the mechanism of this cycad-induced disease is ongoing, with the goal of understanding potential mechanisms of this disease and its links to ALS and Parkinson disease.[321]

Anthraquinone Glycosides: Sennoside and Others

Anthraquinone laxatives are regulated both as nonprescription pharmaceutical ingredients and as dietary supplements. These glycosides, such as sennoside, are metabolized in the bowel to produce derivatives that stimulate colonic motility, probably by inhibiting Na^{+}â€“K^{+}â€“ATPase in the intestine, which also promote accumulation of water and electrolytes in the gut lumen, producing fluid and electrolyte shifts that can be life threatening.[108]

Other Glycosides: Salicin and Atractyloside

Salicin is an inactive glycoside until it is hydrolyzed to produce salicylic acid (Chap. 35). The glycosidic bond is relatively resistant to stomach acid, and the hydrolysis must be accomplished by gut flora. The ability of individual human flora to produce the necessary enzymes varies significantly, resulting in variable clinical effects. However, sufficient hydrolysis to transform salicylic acid occurs in all individuals.

Atractylis gummifera was a favorite agent for homicide during the reign of the Borgias. Atractyloside, the active ingredient, decreases concentrations of cytochrome P450. It also inhibits oxidative phosphorylation in the liver by inhibiting the ADP/ATP antiporter blocking influx of adenosine diphosphate (ADP) into hepatic mitochondria and outflow of ATP to the rest of the cell (Chap. 13). Death or severe illness as a result of liver failure or hepatorenal disease following ingestion is reported.[156,166]

The effects of the glycosides sinigrin (from *Brassica nigra* seed and *Alliaria officinalis* [horseradish] root) and naringen (a polyphenolic glycoside from the grapefruit *Citrus paradisi*) are discussed in the sections on Plant-Induced Dermatitis and Plantâ€“Drug

Interactions, respectively.

Terpenoids and Resins: Ginkgolides, Kava Lactones, Thujone, Anisatin, Ptaquiloside/Thiaminase, and Gossypol

Ginkgolides in *Ginkgo biloba* are associated with antiplatelet aggregation effects. Three reports of spontaneous bleeding associated with ingestion of *Ginkgo* leaf products as an herbal medicine are perhaps explained by this property.[300,302,351] Another xenobiotic found only in the seed, 4-methoxypyridoxine (pyridine alkaloid), is associated with seizures. A mechanism similar to isoniazid-induced seizures is plausible.[129,188,255,358] These cases suggest treatment with pyridoxine phosphate (Chap. 55 and Antidotes in Depth: Pyridoxine). The dermal effects of *Ginkgo* are discussed in Plant-Induced Dermatitis.

Kava lactones are a family of terpene lactones found in kava kava *(Piper methysticum)* that causes central and peripheral nervous system effects or hepatotoxicity.[66] Kava kava has enjoyed a long ceremonial history among islanders of the South Pacific, and observers visiting Oceania have recorded its acute and chronic effects (both pleasant and unpleasant) over the centuries. Importation of kava kava to Australia in 1983 was a measure to assist Aborigines with alcohol abuse problems. However, the kava kava itself became abused, and its subsequent ban has resulted in the growth of a black market for kava kava.[12,45] Proposed mechanisms to explain the effects of kava lactones include effects at $GABA_A$ and $GABA_B$ receptors[83,186] or, more likely, local anesthetic effects.[38,142,275] Acute symptoms following ingestion include peripheral numbness, weakness, and sedation. Chronic use leads to kava dermopathy and weight loss.[36] More than 70 cases of hepatotoxicity, several requiring liver transplantation, are associated with both acute and chronic effects of the kava lactones

on cytochrome oxygenases or other yet to be defined etiologies and prompted regulatory health measures in Europe and North America.[47]

Thujone is one of many terpenes associated with seizures.[34] It is found in the wormwood plant *(Artemisia absinthium)* and its derivative absinthe, and in some strains of tansy *(Tanacetum vulgare).* The Î±- and Î²-isomers of thujone are believed to act much like camphor to produce CNS depression and seizures. Invoking the structural similarity of thujone to tetrahydrocannabinol (THC), one of the terpenoids of marijuana, to explain the psychoactive effects is controversial[250] (Chap. 81).

Absinthism is characterized by seizures and hallucinations, permanent cognitive impairment, and personality changes. Acute and chronic absinthism led to a worldwide ban of the alcoholic beverage absinthe, which contained thujone, in the early 1900s. The essential oil of wormwood is composed almost exclusively of thujone. Wormwood oil currently is available over the Internet and is responsible for at least 2 reports of adverse reactions in people seeking its hallucinatory or euphoriant effects[21,365]

Anisatin found in *Illicium* spp. This terpenoid produces seizures as a noncompetitive GABA antagonist. The Chinese star anise *(Illicium verum)* is sometimes used in teas and occasionally is confused or contaminated with other species of *Illicium*, particularly Japanese star anise *Illicium anisatum*.[140,180] These contaminations have resulted in small epidemics of tonicâ€“clonic seizures, particularly but not exclusively of infants after use of the tea to treat their infantile colic. Recently, in the United States, a case series of at least 40 individuals who had consumed teas brewed from â€œStar aniseâ€• experienced seizures, motor disturbances, other neurologic effects, and vomiting. These cases include at least 15 infants treated for infantile colic with this home remedy. This trend prompted the FDA to issue an advisory regarding the health risk from remedies sharing the common name â€œStar anise.â€•[180]

Ptaquilosides are found in the bracken fern *(Pteridium aquilinum)*, a plant that is extending its range and density worldwide. In foraging animals, consumption of ptaquilosides results in acute hemorrhage secondary to profound thrombocytopenia whereas thiaminases produce cerebral disease.[108,290] Although no acute human poisonings are reported, these xenobiotics are transmitted through cow's milk and are associated with increased prevalence of gastric and esophageal cancer in areas where fern is endemic and consumed by cows whose milk is not diluted. Chronic toxicity through spore inhalation also produces pulmonary adenomas in animals [325,374] More recently, research defined links between alimentary cancer in humans who previously consumed bracken fiddleheads.[5]

Gossypol is a sesquiterpene that is derived from cottonseed oil. It is used experimentally as a reversible male contraceptive. The mechanism for its spermicidal effect is unclear,[75] but the effects have been attributed to inhibition of plasminogen activation and plasmin activity in acrosomal tissue.[337] These effects are not currently reported to produce systemic bleeding. Gossypol also inhibits 11Î²-hydroxysteroid dehydrogenase, as does glycyrrhizin, but typically results in only isolated hypokalemia.[74]

Proteins, Peptides, and Lectins: Ricin and Ricinlike, Pokeweed, Mistletoe, Hypoglycin, Lathyrins, and Microcystins

Lectins are glycoproteins that are classified according to their binding affinity for specific carbohydrate ligands, particularly galactosamines, and by the number of protein chains linked by disulfide bonds. Toxalbumins such as ricin and abrin, are lectins that are such potent cytotoxins that they used as biologic weapons

(Chap. 126). Ricin, extracted from the castor bean (*Ricinus communi* [see ILRICINUSCOMMUNIS1 and RICINUSCOMMUNIS2 in the Image Library at http://www.goldfrankstoxicology.com]), exerts its cytotoxicity by 2 separate mechanisms. The compound is a large molecule that consists of 2 polypeptide chains bound by disulfide bonds. It must enter the cell to exert its toxic effect. The B chain binds to the terminal galactose of cell surface glycolipids and glycoproteins. The bound toxin then undergoes endocytosis and is transported via endosomes to the Golgi apparatus and the endoplasmic reticulum.[309] There the A chain is translocated to the cytosol, where it stops protein synthesis by inhibiting the 28S subunit of the 60S ribosome. In addition to the GI manifestations of vomiting, diarrhea, and dehydration, ricin can cause cardiac, hematologic, hepatic, and renal toxicity. All contribute to death in humans and animals.[7,52,189,203,274] Despite the obvious toxicity of this compound, death probably can be prevented by early and aggressive fluid and electrolyte replacement after oral ingestion (but not injection or inhalation, Chap. 126). Allergic reactions to some of these lectin-bearing plants are noted, particularly to *R. communis*.[265] Occupational exposures to castor oil are a particular hazard,[84,346] and the plant's pollen may be a pneumoallergen.[135]

Just how lethal are ingestions of the ornamental seeds? The highest concentration of xenobiotic is in the hard, brown-mottled seeds. These seeds are both tempting and available, even to children in the United States, because they are attractive enough to be used to make jewelry, and their parent plants are showy enough to have been exported for horticultural purposes outside of their native India (including to the United States).[199] Although mastication of one seed by a child liberates enough ricin to produce death,[203] this outcome (or even serious toxicity) is uncommon, even if the seeds are chewed, probably because GI absorption of the xenobiotic is poor and supportive care is effective.[9,52] Activated charcoal should be administered promptly.

Other *ricinlike lectins* are found in *Abrus precatorius* (jequirity pea,

rosary pea [see ILABRUSPRECATORIUS in the Image Library at http://www.goldfrankstoxicology.com]),[17,82] *Jatropha* spp,[221] *Trichosanthes* spp (eg, *kirilowii* or Chinese cucumber),[187] *Robinia pseudoacacia* (black locust),[73,248] *Phoradendron* spp (American mistletoe), *Viscum album* (European mistletoe),[94,102] and *Wisteria* spp (wisteria).[171,299] These all produce at least one double-chain lectin that binds to galactose-containing structures in the gut or inhibits protein synthesis in a manner similar to ricin.

Pokeweed mitogen of *Phytolacca americana* (pokeweed [see ILPHYTOLACCAAMERICANA in the Image Library at http://www.goldfrankstoxicology.com]) is a single-chain protein that inhibits ribosomal RNA by removing purine groups.[16,177] Given their mechanism, it is not surprising that the lectins are capable of producing GI symptoms, and they otherwise have toxic profiles with variable degrees of overlap in pattern and severity with ricin in humans and animals.

The most commonly ingested toxic plant lectins in the United States are from pokeweed, which is eaten as a vegetable but rarely causes toxicity or death. *Phytolacca* toxin and pokeweed mitogen are found in all plant parts, but the highest concentrations are found in the plant root. The mature deep purple berries are less toxic.[16] Pokeweed leaves are consumed after boiling without toxic effect if the water is changed between the first and second boiling (parboiling). When this detoxification technique is not followed, as in preparation of poke salad or pokeroot tea, violent GI effects can ensue 0.5â€“6 hours after ingestion. Nausea, vomiting, abdominal cramping, diarrhea, hemorrhagic gastritis, and death may occur. In addition, bradycardia and hypotension, perhaps induced by an increase in vagal tone, may be associated with nausea and vomiting.[159,297] More often than not, toxicity is limited to the GI tract. The mitogen produces a lymphocytosis 2â€“4 days after ingestion that may take up to 10 days to clear, but this is without clinical consequence.[16]

Mistletoe berries, both American and European, can produce severe gastroenteritis, especially when delivered as teas or extracts, or particularly as parenteral antineoplastic medicinal agents in Europe.[95] As festive holiday plants they become seasonally available for children. Poison Center data suggest that ingestion of 3â€“5 berries or 1â€“5 leaves of the American species may not cause toxicity, but these suggestions are based on limited evidence. (See Chap. 130.)[214] Despite single reports of seizure, ataxia, hepatotoxicity, and death,[156,327] most authors performing such retrospective examinations[155,219,327] conclude that mistletoe exposures are not a highly consequential risk.

Hypoglycin A (Î²-methylene cyclopropyl-L-Î±-aminopropionic acid) and *hypoglycin B* (dipeptide of hypoglycin A and glutamic acid) are found in the unripe ackee fruit and seeds of *Blighia sapida* (Euphorbiaceae). (See ILBLIGHIASAPIDA in the Image Library at http://www.goldfrankstoxicology.com.) The tree is native to Africa but was imported to Jamaica in 1778 by the botanist Thomas Clarke. The scientific name of the plant derives from Captain William Bligh, the British explorer.[32] The tree is also naturalized in Central America, southern California, and Florida. Epidemics of illness (Jamaican vomiting sickness) associated with consumption of the unripe ackee fruit (raw and cooked) occur in Africa but are more common in Jamaica, where ackee is the national dish.[50,246] The most toxic part is the yellow oily aril of the fruit, which contains three large shiny black seeds.[53] Cases in the United States usually are associated with canned fruit.[245] Hypoglycin A is metabolized to methylene cyclopropyl acetic acid, which competitively inhibits the carnitineâ€“acyl coenzyme (CoA) transferase system.[1,31,32] This prevents importation of long-chain fatty acids into the mitochondria, preventing their Î²-oxidation to precursors of gluconeogenesis. Î²-Oxidation and gluconeogenesis are further arrested by inhibition of various enzymes,[31,101] such as glutaryl CoA dehydrogenase, which blocks the malate shunt (Chap. 13). In addition, increased concentrations of glutaric acid may

inhibit glutamic acid decarboxylase, which produces GABA from glutamic acid. This not only depletes GABA but also increases concentrations of excitatory glutamate to produce seizures.[1,193] Insulin concentrations remain unaffected by hypoglycin and metabolites.[253] Carboxylic and other organic acid substrates build up in the urine and serum as a

result of these metabolic perturbations. Detection of these acids can help corroborate the diagnosis.[143]

Jamaican vomiting sickness is characterized by epigastric discomfort and the onset of vomiting starting 2â€“6 hours after ingestion. Convulsions, coma, and death can ensue, with death occurring approximately 12 hours following consumption. Laboratory findings are notable for profound hepatic aminotransferase and bilirubin abnormalities, and aciduria and acidemia without ketonemia. Cholestatic hepatitis can occur and is reported with chronic use.[219] Autopsy reveals fatty degeneration of liver, particularly microvesicular steatosis, and other organs with depletion of glycogen stores.[170] Left untreated, patient mortality reaches 80%, with 85% of the fatal cases suffering seizures. Treatment with glucose and fluid replacement is essential. Benzodiazepines can control seizures, perhaps directly if the seizures are related to depletion of GABA. L-Carnitine therapy may exert a theoretical therapeutic role similar to that noted with valproic acid toxicity,[104,223] whereas glycine therapy shows some beneficial effects in rats (Chap. 47).[319]

The *lathyrins* Î²-*N*-oxalylamino-L-alanine (BOAA) and Î²-aminopropionitrile (BAPN) are peptides from the grass pea *(Lathyrus* sativus) found in the seeds and leaves, respectively. BOAA produces neurolathyrism (seeds) and BAPN produces osteolathyrism (leaves) in individuals with a dietary dependence on this plant. Neurolathyrism is clinically indistinguishable from spastic paresis associated with consumption of improperly prepared cassava (see Cyanogenic Glycosides: *(S)*-Sambunigrin,

Amygdalin, Linamarin, and Cyacasin). Thiol oxidation with depletion of nicotinamide adenine dinucleotide (NADH) dehydrogenase at the level of neuronal mitochondria (ie, excitatory AMPA receptors) may be the common etiology.[246,273,326] Epidemics occur in Bangladesh, Ethiopia, Israel, and India.[137,226] Exposure to BOAA results in degeneration of corresponding corticospinal pathways that becomes irreversible if consumption of undetoxified grass peas is not stopped early. BOAA stimulates the AMPA class of glutamate receptors to provide constant neuronal stimulation, eventual degeneration, and hence spasticity. BAPN affects bone matrix and leads to bone pain and skeletal deformities that develop in adulthood.[163] These diseases occur in areas where the plants are endemic, the food is consumed for two months or more, and when diets are otherwise poor in protein and possibly in zinc.[214]

Microcystins are found in several cyanobacteria (blue-green algae) belonging to various species of the genera *Microcystis, Anabaena*, *Nodularia*, *Nostoc*, and *Oscillatoria*. [42] They elaborate a series of peptide xenobiotics called microcystins and nodularins *(Nodularia spumigena).* These xenobiotics produce hepatotoxicity by causing deterioration of the microfilament function in hepatocytes, leading to cell shrinkage and bleeding into the hepatic sinusoids. Evidence indicates that these peptides are carcinogenic to humans.[90] Although most cases of untoward effects from blue-green algae occur in animals, the potential for harm was demonstrated by use of microcystin-contaminated water in a dialysis unit in Brazil.[184] Unfiltered water was identified as the risk factor for liver disease in 100 patients who attended the dialysis center (Chap. 10). Fifty of these patients died of acute liver failure following early signs of nausea, vomiting, and visual disturbances. The concern for poisoning is heightened because certain species of *Cyanobacteria* are harvested and consumed as health foods[43,142,191] or may be consumed secondarily in fish.[231] In addition to the sodium channel and acetylcholinesterase effects, ingestion of the genus *Microcystis*

produces photosensitivity.[119]

Phenols and Phenylpropanoids: Coumarins, Capsaicin, Karwinskia Toxins, Naringenin and Bergamottin, Asarin, Nordihydroguaiaretic Acid, Podophyllin, Psoralen, and Esculoside

Phenols and phenylpropanoids represent one of the largest groups of secondary metabolites.[107,296] Coumarins and their isomers are phenylpropanoids that are discussed in Chap. 57. Some coumarins are warfarinlike in their activity and are capable of producing a bleeding diathesis when plants are consumed in sufficiently large quantities.[174,216] Lignans are formed when phenylpropanoid side chains react to form bisphenylpropanoid derivatives. Lignins are high-molecular-weight polymers of phenylpropanoids that bind to cellulose and provide strength to cell walls of stem and bark. Tannins are polymers that bind to proteins and divide into 2 groups: hydrolyzable and condensed (called *proanthocyanidins*, eg, karwinol).

Capsaicin is derived from *Capsicum annuum* or other species of chile or cayenne peppers. It is a simple phenylpropanoid that causes release of the neuropeptide substance P from sensory C-type nerve fibers. The immediate response to capsaicin is intense local pain and is the rationale for its use in pepper spray. Eventual depletion of substance P prevents local transmission of pain impulses from these receptors to the spinal cord, blocking perception of pain by the brain, explaining its use in postherpetic neuralgia.[364]

Painful exposures to capsaicin-containing peppers are among the most common plant-related exposures presented to poison centers. They cause burning or stinging pain to the skin. If

ingested in large amounts by adults or small amounts by children, they can produce nausea, vomiting, abdominal pain, and burning diarrhea.[89,364] Eye exposures produce intense tearing, pain, conjunctivitis, and blepharospasm.[344]

Skin irrigation, dermal aloe gel, analgesics, and oral antacids are therapeutic agents that may be helpful as appropriate, but patients can be reassured that the effects are transitory and produce no long-term damage. Irritated eyes can be treated with irrigation and local analgesia, but generally resolve without sequelae within 24 hours.[185]

Karwinskia toxins from plants commonly named Buckthorn, coyotillo, tullidora, wild cherry, or capulincillo *(Karwinskia humboldtiana)*. These xenobiotics are identified by their molecular weights (T-514, T-496, T-516, T-544). Toxicity has been known for more than 200 years. In 1920, an epidemic of deaths was reported after 20% of 106 Mexican soldiers died following ingestion of foraged *Karwinskia* fruits.[196,234] The fruits are attractive to children; epidemic poisonings have been reported in Central America[11] and are possible wherever the shrub is found (in semidesert areas throughout the southwestern United States and Caribbean, Mexico, and Central America). Recently, poisonings from this plant in Mexico have increased from a total of 72 cases reported between 1990 and 1994 to 40 cases per year currently reported in northern Mexico.[234,264] Uncoupling of oxidative phosphorylation or dysfunction of peroxisome assembly and integrity is described for Schwann cells.[353,368] Each xenobiotic exhibits similar cytotoxic effects at the cellular level, but with trophism for different organs in animal models.[234]

Within a few days of ingestion, a symmetric motor neuropathy ascends from the lower extremities to produce a bulbar paralysis that may lead to death. Deep-tendon reflexes are abolished in affected areas, but cranial nerve findings are absent. Distinction of this demyelinating motor neuropathy from Guillain-BarrÃ©

syndrome,

poliomyelitis, solvent, and other polyneuropathies is best assisted by detection of T-514 in the blood of affected patients.[29,196,234] The other recognized toxins are not detected in blood. Occasionally, axonal damage is observed, but demyelination is the predominant finding on biopsy. Nerve conduction studies always demonstrate loss or abolition of function in fast-conducting axons. Cerebrospinal fluid demonstrates normal protein, glucose, and cytology. Treatment is supportive, with mechanical ventilation as needed, and recovery typically is slow.

Naringenin and *bergamottin* are phenylpropanoids derived from grapefruit that inhibit CYP3A4 in gut and liver.[128] Grapefruit juice consumption can increase circulating concentrations of drugs reliant on 3A4 for metabolic elimination, including terfenadine, carbamazepine, and felodipine. These effects are maximally achieved by a single glass of grapefruit juice.[228]

Hyperforin is another phenylpropanoid found in St. John's wort *(Hypericum perforatum)* and is associated with plantâ€“drug interactions.

Asarin is found in the sweet flag plant tuber *(Acorus calamus).* Putative euphoric and hallucinogenic effects that motivate ingestion are in contrast to confirmed reports of unpleasant GI effects.[352]

Nordihydroguaiaretic acid (NDGA) is associated with hepatotoxicity after ingestions of chaparral *(Larrea tridentata)*.[317] Podophyllin and psoralens are phenylpropanoids discussed in Antimitotic Alkaloids and Resins and in Plant-Induced Dermatitis, respectively.

Esculoside (also called *esculin* or *aesculin)* has triterpene saponin side chains and is believed to be the toxic component in horse chestnut *(Aesculus hippocastanum).* Horse chestnut extracts are used medicinally in patients with venous insufficiency. Its

therapeutic use at high doses (>340 Âµg/kg) is associated with renal failure or a lupuslike syndrome.[151,168] Leaves, twigs, or horse chestnuts ingested by children or infused as teas result in a syndrome that resembles nicotine intoxication. The syndrome consists of vomiting, diarrhea, muscle twitching, weakness, lack of coordination, dilated pupils, paralysis, and stupor.[262] The mechanism of toxicity is not defined, but ingestion of chestnut approximately 1% of a child's weight is suggested to be poisonous to a child.

Carboxylic Acids: Oxalic Acid and Oxalate Raphides

Oxalic acid is the strongest acid among the carboxylic acids found in living organisms. It forms poorly soluble chelates with calcium and other divalent cations. Higher plants have varying ability to accumulate these products of metabolism. Oxalates are mainly found in certain plant families, such as the Araceae, Chenopodiaceae, Polygonaceae, Amaranthaceae, and several of the grass families. Human dietary sources include rhubarb, spinach, strawberries, chocolate, tea, and nuts.[236] Human consumption of soluble oxalate-rich foods correlates with kidney stone formation.[169]

The insoluble calcium oxalate raphides that are present in certain plants, usually in the Araceae family, are found in conjunction with a protein toxin that increases the painful irritation to skin or mucous membranes. This special manifestation is discussed in greater detail in Plant-Induced Dermatitis.

Alcohols: Cicutoxin

Cicutoxin, a diacetylenic diol, is found in the water hemlock *(Cicuta maculata)* and other *Cicuta* spp. Ingestion of any part of the plant constitutes the most common form of lethal plant ingestion in the

United States. In a series of 83 ingestions from 1900â€“1975, the case fatality rate was 30%, and it dominated plant-related fatalities among the most recent 10-year reviews of the Toxic Exposure Surveillance System (TESS) and Centers for Disease Control (CDC) plant-poisoning records (Chap. 130).[213,252] In contrast to most plant exposures in humans (which tend to involve children), these ingestions usually involve adults who incorrectly identify the plant as wild parsnip, turnip, parsley, or ginseng. All plant parts are poisonous at all times, but the tuber is especially toxic, and more so during the winter and early spring.[145,252] Absorption of cicutoxin is rapid and occurs through the skin as well as through the gut.[200] Ingestion of as little as a 2-cm section of the sweet-tasting root of *Cicuta* can produce fatal status epilepticus, the mechanism of which remains unclear.[25,41,165,270,335]

Symptoms of mild or early poisonings consist of GI symptoms (nausea, vomiting, epigastric discomfort) and begin as early as 15 minutes after ingestion. Emesis may diminish the toxic load in the gut. Diaphoresis, flushing, dizziness, excessive salivation, bradycardia, hypotension, bronchial secretions with respiratory distress, and cyanosis occur and rapidly progress to violent seizures. Complications include rhabdomyolysis with renal failure and severe acidemia.[41] Immediate gastric evacuation should be performed, and benzodiazepines should be administered for seizures. Case reports recommend diverse treatments such as hemodialysis, anticholinergic therapy, and sodium thiopentone infusion as potential lifesaving measures.[205,270,294,330]

Unidentified Toxins

Consistent with the inherent complexity of plants and the relatively early stage of the science, identification of the active ingredient(s) involved in poisoning is not always possible. An epidemic of the irreversible lung disease bronchiolitis obliterans developed in

1994. It involved more than 200 dieters who had been eating *Sauropus androgynous* as a weight-loss vegetable. The effects were dose related (usually~100 g/d) and manifested by month 7 after approximately 10 weeks of use.[176] The cases were associated with at least 4 deaths and, in addition to pulmonary disease, included 3 cases of torsade de pointes.[54,227] This last complication is consistent with the plant's high concentration of papaverine, a toxin that produces dysrhythmias in animals, but papaverine does not cause the lung disease.[375] Steroid and bronchodilator therapy consistently failed to improve pulmonary symptoms, and lung transplantation remains the only effective treatment for advanced cases.[227]

Milk sickness is an historic poisoning described by pioneer farmers. It was caused by transmission of the nontoxic ketone tremetone to humans via milk of animals grazing on white snakeroot plants *(Eupatorium rugosum)*.[242,318] Tremetone is transformed into an unknown, unstable toxin by hepatic microsomal enzymes.[19,20] Toxicity is cumulative. Milk sickness can be fatal in 1â€“21 days or is associated with a slow recovery marked by weakness for months or years, relapsing sometimes to death. A delay in the lactating animal's symptoms provided a lag time when xenobiotic-laden milk was taken from presymptomatic animals and thereby transmitted to humans before the problem was detected. Reports in animals but not humans may be found in the literature.

Breynia officinalis,[224] black cohosh *(Actaea racemosa)*,[341] and the yam *(Dioscorea bulbifera)*[338] are implicated as agents producing hepatotoxicity. Unidentified components of the plant

Achyranthes aspera are associated with production of hypotension and bradycardia.[161] Additional studies are needed to verify these effects.

Consumption of the food star fruit *(Averrhoa carambola)* and preexisting renal insufficiency are associated with development of

intractable hiccups, vomiting, motor disabilities, paresthesias, confusion, seizures, and death unless patients receive supportive care and hemodialysis.[61,266,348] The unidentified toxin appears to be neuroexcitatory and active in the thalamus and right temporooccipital cortex.[57]

Effects Shared Among Different Classes of Xenobiotics

Plantâ€“Drug Interactions

By increasing the metabolic rate of CYP enzymes,[302] hyperforin in St. John's wort *(H. perforatum)* decreases concentrations of (1) cyclosporin, (2) digoxin, (3)warfarin, (4) theophylline, (5) oral contraceptives, and (6) indivir. Activity of some of these 6 drugs and others (eg, amitriptyline and theophylline) may be reduced by flavonoids in St. John's wort, which increases drug elimination by increasing the activity of P-glycoprotein.[181] On the other hand, bergamottin and naringenin from grapefruit reduce activity of the CYP system enzymes and increase drug concentrations. Other *Citrus* species also appear to increase drug concentrations.[175]

Additive effects may be responsible for serotonin excess or mild serotonin syndrome when St. John's wort is used concurrently with tryptophan or serotonin reuptake inhibitors. Additive effects also appear to be responsible for increased prothrombin time in patients taking *Ginkgo biloba* and various dugs to affect coagulation (eg, warfarin or aspirin) because the ginkgolides have antiplatelet activity.[79,127,181,251] Hawthorn (*Crataegus* spp), used medicinally for cardiac disorders, may produce an additive effect when taken concomitantly with digoxin, producing bradycardia.[173] Excessive intake of broccoli provides enough vitamin K to competitively inhibit the negative effects of warfarin on vitamin K activation.[79]

Sodium Channel Effects: Aconitine, Veratridine, Zygacine, Taxine, and Grayanotoxins

Several unrelated plants produce xenobiotics that affect the flow of sodium at the sodium channel. For instance, aconitine and veratrum alkaloids tend to open the channels to influx of sodium, whereas others (eg, taxine) tend to block the flow, and grayanotoxins both increase and block sodium flow. The sodium channel opener aconitine from *Aconitum* spp or.(See ILACONITUMRAPELLUS in the Image Library at http://www.goldfrankstoxicology.com) *Delphinium* spp has the most persistent toxicity and the lowest therapeutic index among the many active alkaloid ingredients of the toxin called aconite. Some of these related alkaloids are controlled medicinal substances in the People's Republic of China and Taiwan.[88] Aconite has been abused for its psychoactive â€œout of bodyâ€• effects[110,343] and for suicide and homicide.[101,106] Properly processed aconite is supposedly less cardiotoxic than unprocessed material, because processing results in production of the less toxic dehydroaconitine. This xenobiotic should be suspected in potentially poisoned patients who manifest cardiac toxicity, paresthesias, and seizures.[60,110,256]

The mechanism of action depends on the individual alkaloid. Some compounds block and others activate sodium channels.[6,313] Aconitine itself opens the voltage-dependent sodium channel at binding site 2 of the Î±-subunit, initially increasing cellular excitability.[6] By prolonging sodium current influx, neuronal and cardiac repolarization eventually slows. It also has calcium channel-opening effects. Asian prescription medicines use the alkaloids to treat dysrhythmias and pain by reducing the excitability of the cardiac conducting system and sensory neurons, respectively. Enhanced activity of the vagus nerve results in

bradycardia, which is treated successfully by atropine.[197,283] Approximately one teaspoon (2â€“5 mg) of the root may cause death by paralyzing the respiratory center or cardiac muscle.

The aconitine alkaloids are rapidly absorbed from the GI tract. Cardiovascular symptoms typically progress from bradycardia and hypotension to tachydysrhythmias and cardiac arrest. CNS symptoms typically progress from paresthesias to CNS depression, respiratory muscle depression, paralysis, and seizures.[6] Nausea, vomiting, diarrhea, and abdominal cramping occur.[56,110,206,269,378] Cardiac toxicity resembles that caused by cardioactive steroids, with atrioventricular conduction blockade and increased ventricular automaticity resulting in a variety of rapid ventricular rates, from multifocal premature ventricular contractions to ventricular fibrillation and torsade de pointes. A history of paresthesias may be useful in differentiating aconitine toxicity from that caused by a cardioactive steroids, but empiric use of digoxin-specific antibody fragments should not be delayed if there is any doubt. These antibodies, however, are ineffectual against aconitine. Orogastric lavage, activated charcoal, and preparation for cardiac pacing, bypass, or balloon pump assist are warranted given the potential for rapid cardiovascular deterioration.[118,271] Success with amiodarone is reported.

Ingestion of veratridine and other veratrum alkaloids (from *Veratrum viride* and other *Veratrum* spp) generally results from foraging errors where the root appears similar to leeks *(Allium porrum)* and above-ground parts appear similar to gentian *(Gentiana lutea)* used for teas and wines in Europe.[40,115,120,125,287] The mechanism of action is like that of aconitine (sodium channel opening) but with shorter duration.[247,350] Although severe toxicity is reported, management is supportive with fluids, atropine, and pressors. Deaths are rare.[75,183,232]

Zygacine from *Zigadenus* spp (death camus) and other members of

the lily family produces the same toxic effects as veratridine alkaloids (vomiting, hypotension, and bradycardia). Symptoms begin 1â€“2 hours after ingestion[167,328] and usually result from errors while foraging for onions because of the plant's look-alike bulb. Treatment options are the same as above with Veratrum alkaloids. Fatalities among Native Americans in the western United States caused by *Zigadenus* were recorded after interviews conducted in the 19th century.

Taxine is another alkaloid mixture of sodium channel effectors that tend to close the channel.[340,373] It is derived from the yew (*Taxus baccata* [see ILTAXUS spp in the Image Library at http://www.goldfrankstoxicology.com]). Suicide using leaves is reported despite the large number of leaves required.[112,261,331,366,371] Toxic alkaloid is contained within the hard central seed but not in the surrounding fleshy red aril, which partly explains the low rate of toxicity in reported cases.[363]

Paclitaxel (Taxol) is an alkaloid component of the relatively rare Pacific yew *(Taxus brevifolia)* that is used as an antitumor chemotherapeutic agent because of its ability to promote the assembly of microtubules and to inhibit the tubulin disassembly

process in mitotic cells. Within 1 hour after ingestion, toxicity progresses from nausea, abdominal pain, bradycardia, and cardiac conduction delays to wide-complex ventricular dysrhythmias, paresthesias, ataxia, and mental status changes.[111,269] Four prisoners who drank an extract of yew experienced profound hypokalemia, and 2 died of cardiac arrest.[111,269] Animal models indicate that bradycardia is responsive to atropine,[289] but wide-complex tachydysrhythmia is unresponsive to sodium bicarbonate.[305]

Grayanotoxins (formerly termed *andromedotoxins*) are a series of 18 toxic diterpenoids present in leaves of various species of *Rhododendron*, *Azalea*, *Kalmia* (see ILKALMIA sp Image Library at

http://www.goldfrankstoxicology.com), and *Leucothoe* (Ericaceae). They exert their toxic effects via sodium channels, which they open or close, depending on the toxin.[263] Grayanotoxin I increases membrane permeability to sodium and affected calcium channels in a manner similar to that of veratridine (and batrachotoxin).[92,131,198] Grayanotoxins become concentrated in honey made from the plants, mainly in the Mediterranean. Accounts of poisoning by honey date back to at least 401 B.C., when Xenophon's troops were incapacitated after they consumed honey made from nectar of *Rhododendron luteum.* These accounts are echoed by modern accounts of toxic honey in the same region.[22,289,376] Bradycardia, hypotension, GI manifestations, mental status changes (â€œmad honeyâ€•), and seizures are described in patients or animals suffering grayanotoxin toxicity.[23,201,217,288,289,332,376]

Antimitotic Alkaloids and Resins: Colchicine, Vincristine, and Podophyllum

Consumption of colchicine from plant sources such as autumn crocus *(Colchicum autumnale)* produces a spectrum of symptoms, including nausea, vomiting, watery diarrhea, hypotension, bradycardia, electrocardiographic abnormalities, diaphoresis, alopecia, bone marrow depression, renal failure, hepatic necrosis, hemorrhagic acute lung injury, convulsions, and death.[130,147,202,249]

Colchicine-induced deaths from ingestion of *Gloriosa superba* are among the most common plant-associated fatalities in Sri Lanka.[114] Confusion of the bulbs or leaves of this plant with those of wild onions or garlic occur as a foraging error. Unintentional consumption by children, or ingestion with suicidal intent, accounts for the other cases involving morbidity or mortality.[3] The

mechanism of toxicity is disruption of microtubule formation in mitotic cells.

Vincristine and vinblastine are two other indole alkaloids that are used as antineoplastics and are both isolated from the Madagascar periwinkle *(Catharanthus roseus).* No reports of poisoning by these alkaloids following ingestion of the plant could be found (Chap. 52).

Podophyllum resin is the dry, alcoholic extract of the rhizomes and roots of mayapple (*Podophyllum peltatum* [see ILPODOPHYLLUMPELTATUM in the Image Library at http://www.goldfrankstoxicology.com]). The dry resin consists of up to 20% podophyllotoxin, Î±- and Î²-peltatin, desoxypodophyllotoxin, and dehydropodophyllotoxin. These xenobiotics are originally present in the plant as Î²-D-glucosides. Podophyllum resin containing podophyllin is available by prescription for topical treatment of venereal warts. Its medicinal derivatives (eg, etoposide) are used for a range of neoplastic diseases. It is used as a popular traditional Chinese medicine and may produce toxicity even in â€œtherapeuticâ€• doses.[191] Podophyllotoxins make up 20% of the resin from the roots of mayapple *(P. peltatum).* As a group, they disrupt tubulin formation, producing multisystem organ failure. Poisonings are caused by misidentification and adulteration, possibly because the list of common names by which it is known includes mayapple, as well as mandrake, wild mandrake, American mandrake, and European mandrake.[37,124] Catharsis is prominent after ingestion, but onset of symptoms may be delayed (10 hours in a fatal ingestion[44]). Acute severe sensorimotor neuropathy and bone marrow suppression following transient leukocytosis can occur even after one-time acute exposures and may be directly related to inhibition of microtubule assembly. Lethargy, confusion, encephalopathy, autonomic instability, sensory ataxia, and death are described following large exposures,[268] but poisoning also can occur after â€œtherapeuticâ€• doses of a popular traditional

Chinese medicine.[191] Glutamic acid has been used to prevent vincristine-induced peripheral neuropathy and would be a reasonable therapy following podophyllin ingestion.[182]

Plant-Induced Dermatitis

A large number of plants result in undesirable dermal, mucous membrane, and ocular effects (Chap. 29), the most common adverse effects reported to US poison centers and occupational health centers. Plant-induced dermal disorders can be categorized[106,254,310,334] into 4 mechanistic groups, that is, dermatis that results from (1) mechanical injury, (2) irritant molecules that penetrate the skin, (3) allergy, or (4) photosensitivity (direct and hepatogenous).

There is much overlap between these categories (some plants can produce all types). Clinicians may have difficulty distinguishing between plant-induced dermatitis and skin disorders[237,239] or between plant-induced dermatitis and pseudophytodermatitides caused by arthropods, pesticides, or wax (used in fruit and vegetable packaging).[334] Agents that cause adverse skin reactions can also cause eye and local gastric mucosal irritation.

Dermatitis from *mechanical injury* often is combined with primary or allergic contact dermatitis. Stinging nettles *(Urtica dioica* and other species) have a specialized apparatus in the form of an elongated silicious cell (glandular trichome) that acts like a hypodermic syringe to deliver irritant chemicals into the skin. Contact with these stinging hairs shears off the tip of the hair, producing micromechanical injury and releasing irritant contents: acetylcholine, histamine, and 5-hydroxytryptamine.[272] The proteinase mucunain is released from the barbed trichomes of *Mucuna* spp (cowhage),[105] and workers who handpick pineapples are subject to fissuring and loss of fingerprints after bromelain is introduced following dermal abrasion by raphides.[204]

Exposures to commonly available household plants such as dumbcane (*Dieffenbachia* spp), *Philodendron* spp,[241] and *Narcissus* bulbs can lead to mechanical injury and painful microtrauma produced by bundles of tiny needlelike calcium oxalate crystals called *raphides.* Packages of hundreds of raphides called *idioblasts* contain proteolytic enzymes. *Dieffenbachia* (>30 species [see ILDIFFENBACHIA sp. in the Image Library at http://www.goldfrankstoxicology.com]) exposures are commonly reported household or malicious plant exposures.[10,285] These exposures are rarely serious.[280] When the leaves are chewed, immediate oropharyngeal pain and swelling occur. Severe oral exposures can be excruciating and progress to profuse salivation, dysphagia, and loss of speech. Soothing liquids, ice, parenteral opioids, corticosteroids, and airway protection may be indicated, but antihistamines provide little relief. The edema and pain typically begin to subside after 4â€“8 days.[241] Ocular exposure to the sap may produce chemical conjunctivitis, corneal abrasions, and, rarely, permanent corneal opacifications.

Similar exposures to oxalate raphide-containing household plants in the same family *(Philodendron, Brassaia, Epipremnum aureum, Spathiphyllum*, and *Scheflera* spp) are not as painful as to dumbcane, presumably because the crystals are packaged differently and do not simultaneously deliver proteolytic enzymes.[204,260] One exception to their lower severity is a report of death in an 11-month-old following complications arising from esophageal lesions induced by philodendron.

Irritant dermatitis results from low-molecular-weight xenobiotics such as phorbol esters (Euphorbiaceae) that directly penetrate the skin without antecedent mechanical injury. Similar penetrance is achieved by products of glycoside hydrolysis. For instance, hydrolysis of ranunculin gives rise to anemonin in Ranunculaceae, the buttercup family, and hydrolysis of sinigrin in plants in the mustard family Brassicaceae yields allyl isothiocyanate. Although

one death is attributed to prolonged contact with sinigrin in mustard plaster,[254] exposures to primary irritants in Brassicaceae and Ranuculaceae usually are mild. Alternatively, dermatitis can occur without contact, as in cases of airborne contact dermatitis, in which typically exposed sites are the upper eyelids, neck, uncovered extremities, including antecubital fossae, and other skin folds[63,310] (Chap. 29).

Phorbol esters found in spurges (Euphorbiaceae) are contained in milky sap that is capable of producing erythema, desquamation, and bullae. The saps of some species are more irritating than others.[100] For instance, the manchineel tree *(Hippomane mancinella)*, found in the Caribbean and Florida, once was planted on graves to deter grave robbers, and juice from the tree has been used to brand animals and to blind people.[254] In addition to dermal and ocular injury, ingestion of some spurges can induce severe GI injury. Poinsettia *(Euphorbia pulcherrima)*, crown of thorns *(E. splendens)*, candelabra cactus *(E. lacteal)*, and pencil tree *(E. tirucalli)* are spurges found in the home as holiday or other ornamentation that rarely produce serious injury, despite reputations to the contrary. The poinsettia plant, for instance, gained a reputation of significant toxicity based on a single, inadequately documented case report from Hawaii in 1919, involving the death of a 2-year-old child. In a subsequent case, an 8-month-old child developed oral mucosal burns after chewing poinsettia.[99] Contact dermatitis, irritation of mucous membranes, and GI complaints (eg, nausea, vomiting, and abdominal pain)[78,99] are rare findings among the many reported exposures to poinsettia.[212]

Allergic contact dermatitis results from type IV hypersensitivity response and, unlike irritant dermatitis, requires repeat exposures to the agent before symptoms manifest. The most infamous of these xenobiotics are the urushiol oleoresins derived from catechols that are found in *G. biloba* (Ginkgoaceae) and members of the Proteaceae (eg, *Macadamia integrifolia*) and the

Anacardaceae.[105] The latter family is notable for inclusion of poison ivy *(Toxicodendron radicans)*, poison oak *(T. toxicarium, T. diversilobum)*, and poison sumac *(T. vernix)*,[67,116,117,233,339] as well as mango *(Mangifera indica)*, pistachio *(Pistacia vera)*, cashew *(Anacardium occidentale)*, and Indian marking nut â€œBhilawanolâ€• *(Semecarpus anacardium)*.[144] Upon first exposure, urushiol resins penetrate the skin and react with proteins to form antigens to which the body forms antibodies. Upon reexposure to urushiol resins, inflammatory mediators are released, leading to urticaria, itching, swelling, and pain. In extreme cases, these reactions can progress to type I hypersensitivity, as demonstrated by a 6% rate of anaphylaxis to mango among 580 patients who previously had mango-induced contact dermatitis.[8] Cross-reactivity between allergens is possible, and particular vigilance is required in sensitive individuals.[113,160,230] Prevention by removal of exposed objects that act as fomites for the oils and use of protective ointments are appropriate.[233,356] Therapy includes washing with soap and water and corticosteroid creams and, for those frequently exposed, desensitization (Chap. 29).[115,257]

Allergic contact dermatitis is the most common plant-induced occupational injury. In the United States, 33% of 462 floral shops surveyed reported that at least one employee had developed contact dermatitis.[310] Reactions are reported following exposure to tulips, *Narcissus*, Peruvian lily (*Alstroemeria* spp), and primroses (*Primula* spp). Exposure to the glycoside tuliposide A results in â€œtulip fingers,â€• the dry, painfully fissured hyperkeratosis of fingers observed in horticultural workers who chronically handle tulips.[172] Upon hydrolysis, this compound yields Î±-methylene-butyrolactone, the true allergen. Cross-reactivity is possible among some of these xenobiotics. *Alstroemeria* spp, a common ornamental called *Peruvian lily*, contain tuliposide A and thus can cross-react with antigens in those persons already allergic to tulips, producing an allergic contact dermatitis. Primin (2-methoxy-

6-*n*-pentyl-*p*-benzoquinone) from members of the Primulaceae[62,225] was responsible for the most frequently reported allergic plant dermatitis in northern Europe until workers refused to stock primroses. The â€œwood cutters dermatitisâ€• of loggers occurs with development of sensitivity to compounds in liverwort (*Frullania* spp), which is cross-reactive to ursinic acid in lichens and mosses found on the wood.[358] Cross-reactivity with common weeds such as ragweed (*Ambrosia* spp) or dandelion (*Taraxacum* spp) initiate the risk of hypersensitivity from members of the Composite family. A myriad of other types of plants are involved in producing occupational dermatitides.[134,189,190,279,308]

Sensitivity to Compositae (daisy family) involves more than 600 sesquiterpene lactones in at least 200 of the 25,000 species in the family and is as ubiquitous as the distribution of species. *Chrysanthemum* allergy is a common occupational hazard in Europe,[153,334]

Direct photosensitivity dermatitis is produced when compounds such as psoralen or other linear furocoumarins come into direct contact with the skin or is digested and becomes bloodborne to dermal capillary beds, where it interacts with sunlight.[65] These photosensitizing agents are activated by ultraviolet A (320â€“400 nm), producing singlet oxygen and DNA adducts. In addition to severe sunburnlike symptoms (erythema, epidermal bullae), hyperpigmentation lasting for several months may result from exposure to these compounds. The mechanism by which this reaction is produced is unknown, but depletion of glutathione is postulated to indirectly stimulate melanogenesis by disinhibiting the normally suppressant tyrosinase.[87,310] More than 200 of these xenobiotics have been identified in at least 15 plant families, including food sources, such as Apiaceae (anise, caraway, carrot, celery, chervil, dill, fennel, parsley, and parsnip), Rutaceae (grapefruit, lemon, lime, bergamot, and orange), Solanaceae (potato), and Moraceae (figs) family.[229,310] A 45-year-old woman died of complications of severe burns received in a tanning salon

following exposure to psoralen,[87] but most other human reactions are sequelae to handling crop plants or retail produce. Humans using St. John's wort *(H. perforatum)* may be susceptible to this syndrome.[93,139,202]

Hepatogenous photosensitivity is produced when a xenobiotic that normally is harmlessly ingested, absorbed, and hepatically excreted gains access to the peripheral circulation through failure of a liver excretion or detoxification mechanism. An example is

the photosensitivity that occurs when phylloerythrin, a product of chlorophyll digestion normally eliminated in the bile, accumulates in the blood as a result of liver dysfunction. The cyanobacterium *Microcystis aeruginosa*, as well as the plants *Lantana camara*, *Tribulus terrestris*, and *Agave lecheuilla*, reportedly cause this type of photosensitization in animals.[119]

Summary

Plant xenobiotics, as well as therapeutic ingredients, can be organized using a pharmacognosy approach. Examples are provided in which the toxin has therapeutic use (colchicine, taxine, physostigmine, pilocarpine, and others). Some xenobiotics act directly or are metabolized to toxic principals (tremetone), whereas others are toxic through secondary contact in animal meat or milk (coniine, tremetone, nitrates, pyrollizidine alkaloids, and ptaquiloside).[192,277,323]

This analysis should not lead to the false conclusion that all toxic plants, all xenobiotics in plants, or all toxic mechanisms are known. Some reassurance can be achieved by excluding exposure to most life-threatening plants and plant xenobiotics or ascertaining whether a common exposure is toxic. This determination can be aided by basic taxonomy while awaiting expert input. Management should balance the relative risks of using invasive gastric emptying and use of activated charcoal if the

plant induces sedation or vomiting or is nontoxic. Potentially fatal ingestions warrant gastric emptying in addition to standard decontamination with activated charcoal and supportive measures. Xenobiotics from sodium channel effectors, cicutoxin, or high-dose belladonna alkaloids necessitate expert toxicologic care and consultation for cardiac support devices and hemodialysis, respectively. Physostigmine should be at hand for serious anticholinergic toxicity. Seizures can be controlled with benzodiazepines, with knowledge that some plants may require pyridoxine (Ginkgo seeds) or possibly thiamine (ginkgolides, ptaquilosides). Hepatotoxicity should be treated empirically with *N*-acetylcysteine. Other xenobiotic-specific measures are noted throughout this chapter, but most patients require supportive management, the intensity of which is dictated by the patient's condition and plant identification. Laboratory diagnostic assays are published for many plant xenobiotics but in most cases are impractical to perform.

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Chapter 115
Arthropods

In-Hei Hahn

Neal A. Lewin

A 24-year-old man presented to the emergency department (ED) with a chief complaint of a â€œbiteâ€• on his right hand that occurred several hours earlier. He was unpacking a crate of vegetables in his grocery store when he initially felt the bite on his hand and noted several small brown spiders in the bottom of the empty crates. Within 2 hours, the bite became painful and blistered. His vital signs were: blood pressure, 130/80 mm Hg; pulse, 74 beats/min; respiratory rate, 12 breaths/min; temperature, 100Â°F (37.2Â°C). The only remarkable finding was a painful blister surrounded by erythema on the dorsal aspect of his right thumb. The lesion was cleansed with soap and water. Two hours later, the wound became slightly ulcerated and painful. Based on the history and physical findings, the presumptive diagnosis was a cutaneous reaction to a brown recluse spider bite. The patient was shown a picture of the suspected spider, and he identified the brown recluse as his presumed attacker. Dapsone and erythromycin were administered, and the patient was discharged for followup with a dermatologist. He was told to return if systemic

symptoms developed.

The majority of arthropods are benign and environmentally beneficial. Some clinicians regard bites and stings as inconsequential and more of a nuisance than a threat to life. However, some spiders and ticks produce toxic venoms that can produce dangerous painful lesions or significant systemic effects. Important clinical syndromes are produced by bites or stings from the phylum Arthropoda, specifically the classes Arachnida (spiders, scorpions, and ticks) and Insecta (bees, wasps, hornets, and ants) (Table 115-1). Infectious diseases transmitted by arthropods, such as the various encephalitides, Rocky Mountain spotted fever, human ehrlichiosis, babesiosis, and Lyme disease, are not discussed in this chapter.

Arthropoda is the largest phylum in the animal kingdom. At least 1.5 million species are identified, and half a million are yet to be classified. It includes more species than all other phyla combined (Figure 115-1).[2] Arthropoda means â€œjoint-footedâ€• in Latin and describes their jointed bodies and legs connected to a chitinous exoskelelton.[2] Araneism or arachnidism results from the envenomation caused by a spider bite. â€œBitesâ€• are different from â€œstings.â€• Bites are defined as purposeful biting from the oral pole by species for either catching prey or blood feeding, and not inadvertent biting by plant-feeding species.[76,170] â€œStingsâ€• occur from a modified ovipositor at the aboral pole that is no longer able to function in egg laying. Stinging behavior typically is used for defense. Most spiders are venomous, and the venom enables them to secure, neutralize, and digest their prey. They are not aggressive toward humans unless they are provoked. The chelicerae (jaws) of many species are too short to penetrate human skin.

Spiders can be divided into categories based upon whether they pursue their prey as hunters or trappers. Trappers snare their prey by spinning webs, feed, and enshrine excess victims in a cocoon for a later feast. Although capable of producing silk, hunters do not spin such intricate webs; rather, they forage or lie in wait for their insect

prey.

The order of spiders (Araneae) differs from other members of the class because of various anatomic differences best assessed by an entomologist. Simplistically, the arachnids have 4 pairs of joined legs whereas insects have 3 pairs. The arachnid's body is divided into cephalothorax, pedicle, unsegmented abdomen, and 3 or 4 pairs of spinnerets from which silk is spun. Two pedipalps are attached anteriorly on the cephalothorax on either side of their chelicerae and are used for sensation. Spiders have 8 eyes but are quite myopic. Prey is localized by touch as they land in the spider's web. Most spiders are venomous (except for the family Uloboridae) and use their venom to kill or immobilize their prey. The remaining species of medical importance in the United States include the widow spiders (*Latrodectus* spp), the violin spiders (*Loxosceles* spp), and the hobo spider (*Tegenaria agrestis*). In Australia, the funnel web spider (*Atrax robustus*) can cause serious illness and death. In South America, the Brazilian Huntsmen (*Phoneutria fera*) and Arantia Armedeira (*Phoneutria nigriventer*) are threats to humans.

Most information on the clinical presentation of spider bites continues to be unreliable, based on case reports and case series. Frequently the cases do not have any expert confirmation of the actual spider involved, which can lead to propagation of misinformation about different spiders, particularly with necrotic arachnidism. For example, the white tail spider (*Lampona* spp) was suspected for more than 20 years to cause necrotic lesions. Only recently has a prospective study of confirmed spider bites refuted this myth by reporting more than 700 confirmed spider bites in Australia.[103,104] Because most arthropod-focused research involves characterizing the structure of spider toxins rather than verifying clinical presentations, it is important to focus on clinical studies that have definite bites confirmed by the actual presence of the spider and are defined by an expert to avoid spreading these myths. Definite spider bites or stings are defined as the following:[100] (1) evidence of a bite or sting soon after the incident or the creature

can be seen to bite or sting, (2) collection of the particular creature, either alive or dead, and (3) identification of the creature by an expert biologist/taxonomist in the field relating to the creature. Prospective studies using rigorous standards such as confirmed bites and stings, collection of the creature, complete data collection, recruitment of sufficient cases, and followup can only enhance the promotion of accurate information and expose the myths of necrotic arachnidism.

TABLE 115-1. Insects and Other Arthropods that Bite, Sting, or Nettle Humans

Arthropod	Description
Honeybee (*Apis mellifera*)	Hairy, yellowish brown with black markings
Bumblebee and carpenter bee (*Bombus* spp and *Xylocopa* spp)	Hair, but larger than honeybees and colored black and yellow
Vespids (yellow jackets, hornets, paper wasps)	Short-waisted, robust black and yellow or white combination
Schecoids (thread-waisted wasps)	Threadlike waist
Nettling caterpillars (browntail, Io, hag, and buck moths, saddleback and	Caterpillar shaped

puss caterpillars)	
Southern fire ant (*Solenopsis* spp)	Ant-shaped
Spiders (*Arachnida*) black widow, brown recluse	Body with 2 regions, cephalothorax, and abdomen; 8 legs
Scorpions (*Centruroides*)	Eight-legged, crablike, stinger at the tip of the abdomen; pedipalps (pincers) highly developed (not a true insect)
Centipedes (*Chilopoda*)	Elongated, wormlike, with many jointed segments and legs; 1 pair of poison fangs behind head

History and Epidemiology

Since the time of Aristotle, spiders and their webs were used for medicinal purposes. Special preparations were concocted to cure a fantastic array of ailments, including earache, running of the eyes, â€œwounds in the joints,â€• warts, gout, asthma, â€œspasmodic complaints of females,â€• chronic hysteria, cough, rheumatic afflictions for the head, and stopping blood flow.[201]

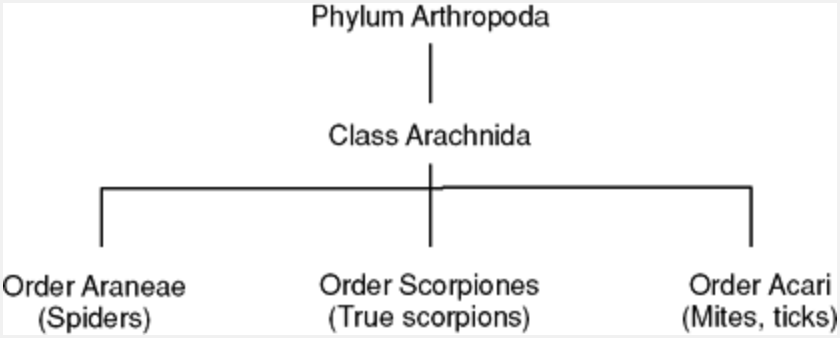

Figure 115-1. Taxonomy of the phylum Arthropoda.

The *Latrodectus* species has an infamous history of medical concern, hence the name *mactans*, which means â€œmurdererâ€• in Latin.[160] Hysteria regarding spider bites peaked during the 17th century in the Taranto region of Italy. The syndrome tarantism, which is characterized by lethargy, stupor, and a restless compulsion to walk or dance, was blamed on *Lycosa tarantula*, a spider that pounces on its prey like a wolf. Deaths were associated with these outbreaks. Dancing the rapid tarantella to music was the presumed remedy. The real culprit in this epidemic was *Latrodectus tredecimguttatus*.[160] Other epidemics of arachnidism occurred in Spain in 1833 and 1841.[133] In North America, there was a rise of spider exposures during the late 1920s, Rome reported large numbers in 1953, and Yugoslavia reported a large number of cases between 1948 and 1953.[28,133] These epidemics may be related to actual reporting biases as well as climactic variations.[160] Spider bites are more numerous in warmer months, presumably because both spiders and humans are more active during that season.

Approximately 200 species of spiders are associated with envenomations.[169,171] Eighteen genera of North America spiders produce poisonings that require clinical intervention (Table 115-2). In

one series of 600 suspected spider bites, 80% were determined to result from arthropods other than spiders, such as ticks, bugs, mites, fleas, *Lepidoptera* insects, flies, beetles, water bugs, and *Hymenoptera.* Ten percent of the presumed bites actually were manifestations of other nonarthropod disorders.[169,171]

From 1995â€“2003, an annual average of 22,000 spider exposures and 50,000 insect exposures were reported to US poison centers. No more than 4 fatalities were reported per year. In 2003, deaths resulted from *Hymenoptera, Solenopsis*, and *Loxosceles* exposures and a tick exposure[214] (Chap. 130). Arachnophobia by the public and by physicians is a perceived danger that far exceeds the actual risk. Often the misdiagnosis of spider bites results from the wide presentation of dermatologic conditions. For example, cutaneous anthrax can be mistaken for a cutaneous necrotic spider bite. In most cases, mortality is rare if supportive care is available and the healthcare provider addresses

the severe pain and associated catecholamine release that may affect the very young, the elderly, and those with underlying cardiopulmonary disease.

TABLE 115-2. North American Spiders of Medical Importance

Genus	Common Name
Araneus spp	Orb weaver
Argiope aurantia	Orange argiope
Bothriocyrtum spp	Trap door spider

Chiracanthium spp	Running spider
Drassodes spp	Gnaphosid spider
Heteropoda spp	Huntsman spider
Latrodectus spp	Widow spider
Liocranoides spp	Running spider
Loxosceles spp	Brown, violin, or recluse spider
Lycosa spp	Wolf spider
Misumenoides spp	Crab spider
Neoscona spp	Orb weaver
Peucetia viridans	Green lynx spider
Phiddipus spp	Jumping spider
Rheostica (*Aphonopelma*) spp	Tarantula
Steatoda grossa	False black widow spider
Tegenaria agrestis	Hobo spider

Ummidia spp	Trap door spider

Black Widow Spider (*Latrodectus Mactans;* Hourglass Spider)

Five species of widow spiders are found in the United States: *Latrodectus mactans* (black widow) (see ILLATRODECTUSMACTANS in the Image Library at http://www.goldfrankstoxicology.com), *Latrodectus hesperus* (Western black widow), *Latrodectus variolus* (found in New England, Canada, south to Florida and west to eastern Texas, Oklahoma, and Kansas), *Latrodectus bishopi* (brown widow of the South), and *Latrodectus geometricus* (brown widow or brown button spider) (see ILLACTRODECTUSGEOMETRICUS in the Image Library). Dangerous widow spiders in other parts of the world include *L. geometricus* and *L. mactans tredecimquttatus* (European widow spider found in southern Europe), *L. mactans hasselti* (red-back widow spider found in Australia, Japan, and India) (see ILLATRODECTUSHASSELTI in the Image Library), and *L. mactans cinctus* (found in South Africa). These spiders live in temperate and tropical latitudes in stone walls, crevices, wood piles, outhouses, barns, stables, and rubbish piles. They molt multiple times and as a result can change colors. The ventral markings on the abdomen are species specific, and the classic red hourglass-shaped marking is noted in only *L. mactans.* Other species may have variations on their ventral surface, such as triangles and spots. The female *L. mactans* typically is shiny, jet-black, and large (8â€“10 mm), with a rounded abdomen and a red hourglass mark on its ventral surface. Her larger size and ability to penetrate human skin with her fangs make her more venomous and toxic than the male spider, who is smaller, lighter in color, and has a more elongated abdomen and fangs that usually are too short to envenomate humans (Table 115-3). Black widow females are trappers and inhabit large untidy irregularly shaped webs. Webs are placed in or

close to the ground and in secluded, dimly lit areas that can trap flying insects, such as outdoor privies, barns, sheds, and garages.[2]

Pathophysiology

The venom is more potent on a volume-per-volume basis than the venom of a pit viper and contains 6 active components with molecular weights of 5000â€“130,000 daltons.[2] The 6 components are Î±-latrotoxin (Î±-LTX), 5 latroinsectotoxins (Î±-, Î²-, Î³-, Î´-, Îµ-LITs) affecting insects, and latrocrustatoxin (Î±-LCT) active only for crustaceans.[84] Î±-Latrotoxin binds, with nanomolar affinity, to the specific presynaptic receptors neurexin I-Î± and Ca^{2+}-independent receptor for Î±-latrotoxin (CIRL), otherwise known as *latrophilin*.[25,90,99] The binding triggers a cascade of events: conformational change allowing pore formation by tethering the toxin to the plasma membrane, Ca^{2+} ionophore formation, and translocation of the N-terminal domain of Î±-LTX into the presynaptic intracellular space, and intracellular activation of exocytosis from dense and clear vesicles containing norepinephrine, dopamine, neuropeptides, and acetylcholine, glutamate, and Î³-aminobutyric acid (GABA) respectively.[2,147,151] Neurexin I-Î± receptors, otherwise known as type I or calcium-dependent receptors, are from a family of neuron-specific cell membrane proteins with one transmembrane domain neuron-specific cell-adhesion molecule.[129,151] Neurexin I-Î± is not required for the excitotoxic action of Î±-LTX. Neurexin I-Î±â€“deficient mice were created and still were susceptible to Î±-LTX via stimulation of the CIRL receptor, or the type II receptor.[73] CIRL is a neuronal receptor that belongs to the family of 7-transmembrane domain G-proteinâ€“coupled receptors. Type II receptors bind to Î±-LTX independently of Ca^{2+} in the extracellular media. CIRL is thought to be coupled to phospholipase C, resulting in subsequent phosphoinositide metabolism that couples the function to secretion.[25,118] CIRL-1 and CIRL-3 are high-affinity neuronal receptors. CIRL-2 has 14 times less affinity to Î±-LTX than CIRL-1 but is expressed ubiquitously, specifically by placenta, kidney, spleen, ovary, heart, lung, and

brain.[99] The nervous system is the primary target for Î±-LTX, but cells from other tissues also are susceptible to the Î±-LTX because of the presence of CIRL-2.[99]

Clinical Manifestations

Widow spiders are shy and nocturnal. They usually bite when their web is disturbed or upon inadvertent exposure in shoes and clothing, although one patient developed latrodectism following the intentional intravenous injection of a crushed whole black widow spider.[34] A sharp pain typically described as a pinprick occurs as the victim is bitten. A pair of red spots may evolve at the site, although the bite is commonly unnoticed.[39,132] The venom is primarily a neurotoxin and does not usually cause a significant local reaction. The bite mark itself tends to be limited to a small puncture wound or wheal and flare reaction that often is associated with a halo (Table 115-3). However, the bite from *L. mactans* may produce *latrodectism*, a constellation of signs and symptoms resulting from systemic toxicity. Some cases do not progress; others may show severe neuromuscular symptoms within 30â€“60 minutes. The effects from the bite spread contiguously. For example, if a person is bitten on the hand, the pain progresses up the arm to the elbow, shoulder, and then toward the trunk during systemic poisoning. Typically, a brief time to symptom onset denotes severe envenomation. Several signs and symptoms are described with the bite of the female black widow spider. Adult male black widow spiders are half the size of the female and are considered harmless.

Hypertoxic myopathic syndrome of latrodectism involves muscle cramps that typically present 15 minutes to 1 hour after the bite. The muscle cramps initially occur at the site of the bite but later may involve rigidity of other skeletal muscles, particularly muscles of the chest, abdomen, and face. The pain increases over time and occurs in waves that may cause the patient to writhe. Large muscle groups are affected first. Classically, severe abdominal wall spasm occurs and may be confused with a surgical abdomen, especially in children who cannot

relate the history with the initial bite.[34] Muscle pain often subsides within a few hours but may recur for several days. Transient muscle weakness and spasms may persist for weeks to months.

Additional clinical findings include â€œ*facies latrodectismica*,â€• which consists of sweating, contorted, grimaced face associated with blepharitis, conjunctivitis, rhinitis, cheilitis, and trismus of the masseters.[133] A fear of death, *pavor mortis*, is described.[133] The following symptoms also are reported: nausea, vomiting, sweating, tachycardia, hypertension, muscle cramping, restlessness, and rarely priapism and compartment syndrome at the site of the bite.[2,47,95,189] Extreme restlessness occurs. Recovery usually ensues

within 24â€“48 hours, but symptoms may last several days with more severe envenomations.

TABLE 115-3. Brown Recluse and Black Widow Spiders: Comparative Characteristics

	Brown Recluse (*Loxosceles*)	Black Widow (*Latrodectus*)
Description	Female brown, 6â€“20 mm, violin-shaped mark on dorsum of cephalothorax; female greater toxicity than male	Female jet black, 8â€“10 mm, red hourglass mark on ventral surface, female greater toxicity than male
Major venom component	Sphingomyelinase D	Î±-Latrotoxin

Pathophysiology of envenomation	Vascular injury, dermonecrosis, hemolysis	Lymphatic, hematogenous spread neurotoxicity
Epidemiology	Bites more common in warmer months North America (southern and western states): *L. reclusa* South America: *L. laeta, L. gaucho* Europe: *L. rufescens* Africa (southern): *L. parrami, L. spiniceps, L. pilosa, L. bergeri* Asia/Australia: Rare	Bites more common in warmer months in subtropical and temperate areas; perennial in topics North America: *L. mactans, L. Hesperus, L. geometricus* Europe: *L. tredecimguttatus* Africa (southern): *L. indistinctus* Australia: *L. hasselti* Asia/South America: Rare
Clinical effects	Cutaneous	Cutaneous
	Initial (0â€“2 h after bite): painless, erythema, edema 2â€“8 h: Hemorrhagic, ulcerates, painful 1 week: Eschar Months: Healing	Initial (5 minâ€“1 h after bite): local pain 1â€“2 h: Puncture marks hours: Regional lymph nodes swollen, central blanching at bite site with

			surrounding erythema CVS: Initial tachycardia followed by bradycardia, dysrhythmias, initial hypotension followed by hypertension GI: Nausea, vomiting, mimic acute abdomen
		Hematologic Methemoglobinemia, hemolysis, thrombocytopenia, DIC	Hematologic: Leukocytosis Metabolic Hyperglycemia (transient) Musculoskeletal: Hypertonia, abdominal rigidity, â€œfacies latrodectismicaâ€• Neurologic CNS: Psychosis, hallucinations, visual disturbance, seizures PNS: Pain at the site ANS: Increase in all secretions; sweating, salivation,

		lacrimation, diarrhea, bronchorrhea, mydriasis, miosis, priapism, ejaculation
	Renal: Renal failure, secondary to hemolysis	Renal: Glomerulonephritis, oliguria, anuria Respiratory: Bronchoconstriction, acute lung injury
Treatment	Analgesia	Analgesia
	Wound care	Muscle relaxants
	Dapsone (?) Hyperbaric oxygen (?) Antivenom (?) not available universally Corticosteroids	Antivenom

Life-threatening complications include severe hypertension, respiratory distress, cardiovascular failure, and gangrene.[34,46,47,142,155,159] In the past 20 years, more than 40,000 presumed black widow spider bites have been reported to American Association of Poison Control Centers since its first publication in 1983. Death is rarely reported. There have been 2 fatalities in Madagascar from envenomation of the *Latrodectus geometricus*, one from cardiovascular failure and the other from

gangrene of the foot.[159] The most recent fatality reported from Greece resulted from toxic myocarditis secondary to envenomation of *L. mactans tredecimguttatus*,[155] confirmed by a local veterinarian. The patient developed severe dyspnea, hypoxemia, cyanosis, cardiomyopathy, and global hypokinesis of the left ventricle confirmed by echocardiography followed by death 36 hours later; antivenom was not available; on autopsy, diffuse interstitial and alveolar edema, with mononuclear infiltrate of the myocardium and degenerative changes, were noted and on toxicologic analysis for xenobiotics, as well as all blood, urine, bronchial, and serologic viral cultures, were negative. The paucity of mortalities is presumed to result from the improvement in medical care, the availability of antivenom, or the limited toxicity of the spider.

Diagnostic Testing

Laboratory data generally are not helpful in management or predicting outcome. According to one study, the most common findings include leukocytosis and increased creatine phosphokinase and lactate dehydrogenase concentrations.[46] Currently no specific laboratory assay is capable of confirming latrodectism.

Management

Treatment involves establishing an airway and supporting respiration and circulation, if indicated. Wound evaluation and local wound care, including tetanus prophylaxis, are essential.[213] The routine use of antibiotics is not recommended.

Pain management is a substantial component of patient care and depends on the degree of symptomatology. One grading system divides the severity of the envenomation into 3 categories.[46] Grade 1 envenomations range from no symptoms to local pain at the envenomation site with normal vital signs. Grade 2 envenomations

involve muscular pain at the site with migration of the pain to the trunk, diaphoresis at the bite site, and normal vital signs. Grade 3 envenomations include the grade 2 symptoms with abnormal vital signs, diaphoresis distant from the bite site, generalized myalgias to back, chest, and abdomen, nausea, vomiting, and headache. Using this grading system, grade 1 envenomations may require only cold packs and orally administered nonsteroidal antiinflammatory agents. Grade 2 and 3 envenomations probably require intravenous opioids and benzodiazepines to control pain and muscle spasm. Traditionally, 10 mL 10% calcium gluconate solution was given intravenously (IV) to decrease cramping. It was infused over 10 minutes and repeated at 30 minutes. A retrospective chart review of 163 patients envenomated by the black widow concluded that calcium gluconate was ineffective for pain relief compared with a combination of IV opioids (morphine sulfate or meperidine) and benzodiazepines (diazepam or lorazepam).[46,114] Another study found greater neurotransmitter release when extracellular calcium concentrations were increased, suggesting that administration of calcium is irrational in patients suffering from latrodectism.[167] The mechanism of action of calcium remains unknown and its efficacy anecdotal; therefore we do not recommend calcium administration for pain management. Although often recommended, methocarbamol (a centrally acting muscle relaxant) and dantrolene also are ineffective for treatment of latrodectism.[114,172] A benzodiazepine, such as diazepam, is more effective for controlling muscle spasms and achieves sedation, anxiolysis, and amnesia. Management should primarily emphasize supportive care, with opioids and benzodiazepines for controlling pain and muscle spasms, because the use of antivenom risks anaphylaxis and serum sickness.

Latrodectus antivenom is rapidly effective and curative. In the United States, the antivenom formulation is effective for all species but is available as a crude hyperimmune horse serum that may cause anaphylaxis and serum sickness. The morbidity of latrodectism is high, with pain, cramping, and autonomic disturbances, but mortality is low.

Hence controversy exists over when to administer the black widow antivenom. The antivenom can be administered for severe reactions (eg, hypertensive crisis or intractable pain), to high-risk patients (eg, pregnant women suffering from a threatened abortion), or for treatment of priapism.[95,160] Use of antivenom probably should not be considered for patients unless systemic symptoms otherwise designated as grade 3 are present because of the risk for anaphylaxis or anaphylactoid reactions.[46] The usual dose is 1â€“2 vials diluted in 50â€“100 mL 5% dextrose or 0.9% sodium chloride solution, with the combination infused over 1 hour (Antidotes in Depth: Scorpion and Spider Antivenoms). Skin testing may identify a highly allergic individual but does not eliminate the occurrence of hypersensitivity reactions; therefore we do not recommend skin testing. Pretreatment with histamine H_1- or H_2 -blockers and epinephrine may be beneficial in preventing histamine release and/or anaphylaxis, but their efficacy is unproven. Patients with allergies to horse serum products and those who have received antivenom or horse serum products are at risk for immunoglobulin IgE-mediated hypersensitivity reactions. Prevention consists of destroying the spider and taking precautions in areas inhabited by the spiders. When working in high-risk areas, gloves, heavy garments buttoned at the wrists and collars, and shoes should be worn.

In Australia, a purified equine-derived IgG-F(ab)$_2$ fragment antivenom for the red-back spider *Latrodectus hasselti* (RBS-AV) is available. A study showed that RBS-AV prevents latrodectism in mice envenomated with other widow spider venoms from the United States and Europe.[83] Inadvertent use of RBS-AV successfully treated envenomations from the comb-footed spider (*Steatoda* spp).[101] Hence RBS-AV may have a future role in treating black widow spider envenomations in the United States. The RBS-AV (CSL, Melbourne, Australia) is administered intramuscularly and given as first-line therapy to patients presenting with systemic signs or symptoms in Australia. Since its introduction in 1956, there have been no deaths, and the incidence of mild allergic reactions to RBS-AV is reported as 0.54% in 2144 uses.[198] However, a

prospective cohort study of confirmed red-back spider bites failed to show that intramuscular antivenom was better than no treatment when all patients were followed up over one week.[102] This study lacked the power to definitely demonstrate no difference between intramuscular treatment and no treatment, but the study found that only 17% of patients were pain-free at 24 hours with treatment. Therefore, intramuscular antivenom appears to be less effective than previously thought, and the route of administration requires review.

Brown Recluse Spider (*Loxosceles Reclusa*; Violin or Fiddleback Spider)

Loxosceles reclusa was confirmed to cause necrotic arachnidism in 1957, although reports of systemic symptoms following brown spider bites have appeared since 1872.[6] This spider has a brown violin-shaped mark on the dorsum of the cephalothorax, 3 pairs of eyes arranged in a semicircle on top of the head, and legs that are 5 times as long as the body. It is small (6â€“20 mm long), gray to orange or reddish brown (see ILLOXSCELESRECLUSA in the Image Library). *Loxosceles* spiders weave irregular white, flocculent adhesive webs that line their retreats.[71] Spiders in the genus *Loxosceles* have a worldwide distribution. In the United States, other species of this genus, which include *L. rufescens, L. deserta, L devia*, and *L. arizonica*, are prominent in the Southeast and Southwest.[4] They are hunter spiders that live in dark areas (wood piles, rocks, basements), and their foraging is nocturnal. They are not aggressive but will bite if antagonized (Table 115-3). These spiders live up to 2 years. They are resilient and can survive up to 6 months without water or food and tolerate temperatures from 46.4Â°Fâ€“109.4 Â°F (8Â°Câ€“43Â°C).[76] Like the black widow spider, the female is more dangerous than the male and bites only when provoked. *Loxosceles* venom has variable toxicity, depending on the species, with *L. intermedia* venom causing more severe clinical effects in humans.[11]

Pathophysiology

The venom is cytotoxic. Purification techniques have identified 8 subcomponents, including various enzymes, such as hyaluronidase, deoxyribonuclease, ribonuclease, alkaline phosphatase, lipase, and sphingomyelinase-D.[122] The two main constituents of the venom are sphingomyelinase-D and hyaluronidase. Hyaluronidase is a spreading factor that facilitates the ability of the venom to penetrate tissue but does not induce lesion development.[122] Sphingomyelinase-D, with a molecular weight of 32,000 daltons, is the primary constituent of the venom that causes necrosis and hemolysis. Sphingomyelinase-D causes human platelets to release serotonin and red blood cells to release hemoglobin.[122] Sphingomyelinase also reacts with sphingomyelin in the red blood cell membrane to release choline and *N*-acylsphingosine phosphate, which triggers a chain reaction releasing inflammatory mediators, such as thromboxanes, leukotrienes, prostaglandins, and neutrophils, leading to vessel thrombosis, tissue ischemia, and skin loss.[122] The rest of the constituents in the venom contain alkaline phosphatase, proteases, collagenase, esterase, ribonuclease, and deoxyribonuclease.[54,207]

An early study in experimental animals describes the pathogenesis of the skin lesion requiring polymorphonuclear leukocytes and complement infiltration of blood vessels at the bite site with resultant blood vessel injury as the pathologic basis for skin loss.[181] They demonstrated early perivascular collections of polymorphonuclear leukocytes with hemorrhage and edema progressing to intravascular clotting. Coagulation and vascular occlusion of the microcirculation occur, ultimately leading to necrosis.

Clinical Manifestations

The peak time for envenomation is from spring to autumn. Most victims are bitten in the morning. The clinical spectrum of loxoscelism can be divided into 3 major categories. The first category includes

bites in which very little, if any venom, injected. A small erythematous papule may be present that becomes firm before healing and is associated with a localized urticarial response. In the second category, the bite undergoes a cytotoxic reaction. The bite initially may be painless or have a stinging sensation but then blisters and bleeds, and ulcerates 2â€“8 hours later (Table 115-3). The lesion may increase in diameter, with demarcation of central hemorrhagic vesiculation, then ulcerate, and develop violaceous necrosis, surrounded by ischemic blanching of skin and outer erythema and induration over 1â€“3 days: This is also known as the â€œred, white, and blueâ€• reaction (see ILLOXOSCELESEVENOMATION in the Image Library).[115,217] Necrosis of the central blister occurs in 3â€“4 days, with eschar formation between 5 and 7 days. After 7â€“14 days, the wound becomes indurated and the eschar falls off, leaving an ulceration that heals by secondary intention. Local necrosis is more extensive over fatty areas (thighs, buttocks, and abdomen).[121] The size of the ulcer determines the time for healing. Large lesions up to 30 cm may require 4 months or more to heal.

The third category consists of systemic loxoscelism, which is not predicted by the extent of cutaneous reaction, and occurs 24â€“72 hours after the bite. The young are particularly susceptible.[94,173] The clinical manifestations of loxoscelism include fever, chills, weakness, edema, nausea, vomiting, arthralgias, petechial eruptions, rhabdomyolysis, disseminated intravascular coagulation, hemolysis that can lead to hemoglobinemia, hemoglobinuria, renal failure, and death.[22,36,68,131,177,216] Another extremely unusual presentation of loxoscelism is upper airway obstruction. This life-threatening complication was reported in a child who was bitten on his neck and subsequently developed progressive cervical soft tissue edema with airway obstruction and dermonecrosis 40 hours later.[80] There has been one other report of stridor and respiratory distress following a brown recluse envenomation of the ear. Although the presentation is rare, respiratory compromise should be considered when an envenomation occurs near the airway.[75] In North American, the incidence of systemic

illness is rare and mortality is low.[5]

Diagnostic Testing

Bites from other spiders, such as *Chiracanthium* (sac spider), *Phidippus* (jumping spider), *Argiope* (orb weaver), and *Tegenaria* (northwester brown spider), can become necrotic wounds. These spiders are often the actual culprits when the brown recluse is mistakenly blamed. Definitive diagnosis is achieved only when the biting spider is positively identified. No routine laboratory test for loxoscelism is available for clinical application, but several techniques are presently used for research purposes. The lymphocyte transformation test measures lymphocytes that have undergone blast transformation up to 1 month after exposure to *Loxosceles* venom. The lymphocytes incorporate thymidine into the nucleoprotein, providing a quantitative response.[3] A passive hemagglutination inhibition test (PHAI) has been developed in guinea pigs. The PHAI assay is based on the property of certain brown recluse spider venom components to spontaneously adsorb to formalin-treated erythrocyte membranes and the ability of the BRS venom to inhibit antiserum-induced agglutination of venom-coated red blood cells.[13] The test is 90% sensitive and 100% specific for 3 days postenvenomation and may prove useful for early diagnosis of brown recluse spider envenomation.[13] An enzyme-linked immunoassay (ELISA) specific for *Loxosceles* venom in biopsied tissue can confirm the presence of venom for 4 days postenvenomation.[13] The drawbacks of using a skin biopsy are the invasive nature of the procedure, which can result in further scarring with an increased potential for infection, and the lack of proof that skin biopsy can diagnose early envenomations prior to the development of dermatonecrosis. Another ELISA for detection of venom antigens has been developed that correctly discriminates the mice inoculated with antigens *Loxosceles intermidia* venom. The ELISA immunoassay, and antivenom may become useful early diagnostic tools if envenomation can be proved early, especially prior to the development of the purplish discoloration and blister formation that usually progresses to

cutaneous gangrene.[44] A venom-specific enzyme immunoassay that uses hair, skin biopsies, or aspirated tissue near a suspected lesion to detect the presence of venom up to 7 days after injury is under investigation.[120,137] In Brazil, ELISA is used to detect the venom of *L. reclusa* in wounds and patient sera, but the technique is not in widespread clinical use.[40]

Laboratory data may be remarkable for hemolysis, hemoglobinuria, and hematuria. Coagulopathy may be present, with laboratory data significant for elevated fibrin split products, decreased fibrinogen levels, and a positive D-dimer assay. Other tests may show increased prothrombin time (PT) and partial thromboplastin time (PTT), leukocytosis (up to 20,000â€“30,000 cells/mm^3),

spherocytosis, Coombs-positive hemolytic anemia, thrombocytopenia, or abnormal renal and liver function tests.[2,7,71,169,170 and 171,213]

Treatment

Optimal local treatment of the lesion is controversial. The most prudent management of the dermatonecrotic lesion is wound care, immobilization, tetanus prophylaxis, analgesics, and antipruritics as warranted (Table 115-4).[2,71,208,213] Early excision or intralesional injection of corticosteroids appears unwarranted.[164] Corrective surgery can be performed several weeks after adequate tissue demarcation has occurred. One case series used curettage of the lesion to remove necrotic and indurated tissue from the lesion, thus eliminating any continuing action of the lytic enzymes on the surrounding tissue with positive results.[93] These patients had wound healing without further necrosis and minimal scarring. Electric shock delivered via stun guns was not found to be useful in a guinea pig envenomation model.[13] Cyproheptadine, a serotonin antagonist, was not beneficial in a rabbit model.[153] A randomized control study evaluating the efficacy of topical nitroglycerin for envenomated rabbits showed no difference in preventing skin necrosis and suggested the possibility of increased

systemic toxicity.[127] Antibiotics should be used to treat cutaneous or systemic infection, but should not be used prophylactically.

Early use of dapsone in patients who develop a central purplish bleb or vesicle within the first 6â€“8 hours may inhibit local infiltration of the wound by polymorphonuclear leukocytes.[115] The dosage recommended is 100 mg twice daily for 2 weeks.[164] However, prospective trials with large numbers of patients are lacking. One study compared erythromycin and dapsone therapy, erythromycin and antivenom therapy, and erythromycin, dapsone, and antivenom therapy.[163] Although the treatment groups were very small, all groups showed wound healing at approximately 20 days. Use of dapsone in the management of a local lesion should be considered experimental until its use is validated by controlled randomized clinical trials. Hepatitis,[166] methemoglobinemia, and hemolysis (Chap. 122) are associated with dapsone use. If dapsone therapy is used, a baseline glucose-6-phosphate dehydrogenase and weekly complete blood counts should be performed.

TABLE 115-4. Management of Brown Recluse Spider Bite

General Wound Care
Clean
Tetanus prophylaxis as indicated
Immobilize and elevate bitten extremity
Apply cool compresses; avoid local heat
Local Wound Care
Serial observations
Natural healing by granulation
Delayed primary closure
Delayed secondary closure with skin graft
Gauze packing, if applicable
Systemic

Antipruritic/antianxiety and/or analgesic agents
Antibiotics for secondary bacterial infection
(?) Polymorphonuclear white blood cell inhibitors: dapsone, colchicine
Antivenom (experimental)
(?) Hyperbaric oxygen

An animal study evaluated the effects on the size of skin lesions induced by *Loxosceles* envenomation by treatment with hyperbaric oxygen therapy, dapsone, and combined hyperbaric oxygen therapy and dapsone.[91] However, the study design was limited and could find only a 100% difference in treatment groups. The study concluded that there was no clinically significant change in necrosis or induration by these treatment modalities. Further evaluation of these interventions remains appropriate. Another study using hyperbaric oxygen for treatment of *Loxosceles*-induced necrotic lesions in rabbits revealed no clinical improvement in the size of the lesion; however, the histology of the lesions improved. Whether this finding is of value in humans has not been determined.[191] Use of 1.2 mg colchicine, a leukocyte inhibitor, followed at 2-hour intervals with 0.6 mg for 2 days, then 0.6 mg every 4 hours for 2 additional days is sometimes recommended, but this treatment has substantial potential toxicity.[169,171]

Rabbit-derived intradermal anti-*Loxosceles* Fab (Î±-Loxd) fragments attenuated the dermatonecrotic inflammation of rabbits injected with *L. deserta* venom in a time-dependent fashion.[78] At time 0 after envenomation, lesion development was blocked. At 1 and 4 hours after envenomation, the Î±-Loxd Fab antivenom continued to suppress the lesion areas, although the longer the delay in treatment, the smaller the difference in treatment and control lesion areas. At 8 and 12 hours, there was no difference in lesion size. The typical 24-hour delay in lesion development makes the diagnosis difficult, and the antivenom would be useless if administered so late in the clinical course. Use of antivenom would be facilitated if the spider were caught and positively

identified or another test could be used to positively identify *Loxosceles* envenomation. Currently this antivenom is not available for commercial use. Patients manifesting systemic loxoscelism or those with expanding necrotic lesions should be admitted to the hospital. All patients should be monitored for evidence of hemolysis, renal failure, or coagulopathy. If hemoglobinuria ensues, increased IV fluids and urinary alkalinization an be used in an attempt to prevent acute renal failure. Hemolysis, if significant, can be treated with transfusions. Patients with a coagulopathy should be monitored with serial complete blood cell count, platelet count, PT, PTT, fibrin split products, and fibrinogen. Disseminated intravascular coagulopathy may require treatment, based on severity.

Hobo Spider (Tegenaria Agrestis, Northwestern Brown Spider, Walckenaer Spider)

The hobo spider is native to Europe and was introduced to the northwestern United States (Washington, Oregon, Idaho) in the 1920s or 1930s.[209] These spiders build funnel-shaped webs within wood piles, crawl spaces, basements, and moist areas close to the ground. They are brown with gray markings and 7â€“14 mm long. They are most abundant in the midsummer through the fall. They bite if provoked or threatened, but otherwise are reticent to bite and retreat quickly with disturbance.[18] The medical literature is sparse in reported hobo spider bites that are verified by a specialist. There is only one confirmed Hobo spider bite resulting in a necrotic lesion.[42] The case describes a 42-year-old woman with a history of phlebitis who felt

a burning sensation on her ankle, rolled her pants, and found a crushed brown spider, later confirmed to be *T. agrestis.* She complained of persistent pain, nausea, and dizziness, and a vesicular lesion developed within several hours. The vesicle ruptured and ulcerated the next day. The lesion initially was 2 mm, but over the

next 10 weeks enlarged to 30 mm in diameter and was circumscribed with a black lesion, at which time she sought medical advice. She was given a course of antibiotics, which did not limit the progression of this ulcer. Subsequently, the patient was unable to walk, and she was found to have a deep venous thrombosis. The other cases implicating Hobo spiders as a cause for dermatonecrotic injuries are based on proximity of the Hobo spider or other large brown spiders that are unidentified and on a rabbit model bioassay.[209,210] The Hobo spider from Europe is considered benign. When analyzing the venom from the European Hobo spiders and US Hobo spiders using liquid chromatography, little variability was found to account for the necrotic effects, which suggests that the Hobo spider toxicity syndrome needs to be revisited. New evidence suggests that Hobo spiders may have been falsely accused.[23] More investigation using large prospective studies must include verification of the spider by an expert arachnologist or definitive identification of an envenomed patient. *Tegenaria* spp is difficult to identify reliably, unless the arachnid's genitalia is examined microscopically.[211] These standards will allow for a more evidence-based approach rather than encouraging anecdotal information as a substitution for fact.

Pathophysiology

The toxin has been fractionated, with 3 peptides identified as having potent insecticidal activity, and no discernible effects in mammalian in vivo assays.[108] The peptide toxins TaITX-1, TaITX-2, and TaITX-3 exhibit potent insecticidal properties by acting directly in the insect central nervous system, and not at the neuromuscular junction.[108] Insects envenomated with *T. agrestis* venom and the insecticidal toxins purified from the venom developed a slowly evolving spastic paralysis. Currently, little is known about the toxin and its mechanism of action in humans.

Clinical Manifestations

The toxicity of Hobo spider venom is questionable; however, it occasionally causes necrosis secondary to infection. Other causes of dermatonecrotic lesions should be considered. The most common symptom associated with the spider bite is a headache that may persist for 1 week.[42] Other symptoms, including nausea, vomiting, fatigue, memory loss, visual impairment, weakness, and lethargy, are reported.[42,210]

Diagnostic Testing

No specific laboratory assay confirms envenomation with *T. agrestis* spider.

Treatment

Treatment emphasizes local wound care and tetanus prophylaxis, although systemic corticosteroids for hematologic complications may be of value. Surgical graft repair for severe ulcerative lesions may be warranted when there is no additional progression of necrosis.[42,157]

Tarantulas

Tarantulas, ancestors to the true spider, belong to the family Theraphosidae, a subgroup of Mygalomorphs (Greek word *mygale* for field mouse).[45,175] There are more than 1500 species, with approximately 40 species found in the deserts of western United States. Because of their great size and reputation, tarantulas are often feared. They are the largest and hairiest spiders, popular as pets, and can be found throughout the United States as well as tropical and subtropical areas (see ILAPHONOPELMASMITHI1 in the Image Library). The lifespan of the female can exceed 15â€“20 years. They have poor eyesight and detect their victims by vibrations. Their defense lies in either their painful bite with erect fangs or by spraying their victim with barbed urticating hairs that are released on provocation.[45]

Tarantulas bite when provoked or roughly handled. Based on the few

case reports, their venom has relatively minor effects in humans but can be deadly for canines and other small animals, such as rats, mice, cats, and birds.[33,105] A study from Australia covering a 25-year span reported only nine confirmed bites by theraphosid spiders in humans and seven confirmed bites in canines and two of which the spider then bit the human.[105] Four genera of tarantulas (*Lasiodora, Grammostola, Acanthoscurria*, and *Brachypelma*) possess urticating hairs that are released in self-defense when the tarantulas rub their hind legs against their abdomen rapidly to create a small cloud (see ILAPHONOPELMASMITHI2 in the Image Library).[76] There are 4 different types of hairs. Type 1 hairs are found on tarantulas in the United States and are the only hairs that do not penetrate human skin. Type 2 hairs are incorporated into the silk web retreat but are not thrown off by the spider. Type 3 hairs can penetrate up to 2 mm into human skin. Type 4 hairs belong to the South American *Grammostola* spider and cause severe respiratory inflammation. Tarantula hairs cause intense inflammation that may remain pruritic for weeks.

Pathophysiology

Tarantula venom, specifically the venoms of *Dugesiella henzi* (Arkansas tarantula) and members of the genus *Aphonopelma* (Arizona tarantula), contains hyaluronidase, nucleotides (adenosine triphosphate [ATP], adenosine diphosphate, and adenosine monophosphate), and polyamines (spermine, spermidine, putrescine, and cadaverine) that are used for digesting their prey from the inside out.[35,113,175] The role of spermine is unclear, but hyaluronidase is a spreading factor that allows more rapid entrance of venom toxin by destruction of connective tissue and intercellular matrix. ATP potentiates death in mice exposed to the *D. hentzi* venom and lowers the LD_{50} in comparison to venom without ATP.[43] Both venoms cause skeletal muscle necrosis when injected intraperitoneally into mice.[150] The primary injury results in rupture of the plasma membrane, followed by the inability of mitochondria and sarcoplasmic reticulum to maintain normal levels of calcium in the cytoplasm leading to cell

death. *Aphonopelma* venom is similar to scorpion venom in composition and clinical effects. Novel toxins have been discovered in the venom that can act on potassium channels, calcium channels, and the recently discovered

acid-sensing ion channels that may elucidate the molecular mechanism of voltage-dependent channel gating and their respective physiologic roles.[63,64]

Clinical Manifestations

Although relatively infrequent in occurrence, bites may or may not present with puncture or fang marks. They range from being painless to a deep throbbing pain that may last several hours without any inflammatory component.[105] Fever has been associated even in the absence of infection, suggesting a direct pyrexic action of the venom. Rarely, bites create a local histamine response with resultant itching, and hypersensitive individuals could have a more severe reaction and less commonly mild systemic effects such as nausea and vomiting.[76,105] Contact reactions from the hairs are more likely to be the health hazard than is the spider bite. The urticating hairs provoke local histamine reactions in humans and are especially irritating to the eyes, skin, and respiratory tract. Inflammation can occur at all levels from conjunctiva to retina. An allergic rhinitis can develop if the hairs are inhaled.[113] Tarantula hairs resemble sensory setae of caterpillars, both are type 3 that can migrate relentlessly and cause multiple foci of inflammation at all levels of the eye.[97] Ophthalmia nodosa, a granulomatous nodular reaction to vegetable or insect hairs, is reported with casual handling of tarantulas.[17,21] Other eye findings include spines in the corneal stroma, anterior chamber inflammation, migration into the retina, and secondary glaucoma and cataracts.[26]

Treatment

Treatment is largely supportive. Cool compresses and analgesics

should be given as needed. All bites should receive local wound care, including tetanus prophylaxis if necessary. If the hairs are barbed, as in some species, they can be removed by using adhesive or cellophane tape followed by compresses or irrigation with 0.9% sodium chloride solution. If the hairs are located in the eye, then surgical removal may be required, followed by medical management of inflammation. Urticarial reactions should be treated with oral antihistamines and topical or systemic corticosteroids.

Funnel Web Spiders

Australian funnel web spiders are a group of large mygalomorphs that can cause a severe neurotoxic envenomation syndrome in humans. The fang positions of funnel web spiders are vertical relative to their body, which requires the spider to rear back and lift the body to attack. The length of fangs can reach up to 5 mm. This spider can bite tenaciously and may require extraction from the victim.[139] The *Atrax* and *Hadronyche* species have been found along the eastern seaboard of Australia. *Atrax robustus*, also called the Sydney funnel web spider, is the best known and is located around the center of Sydney, Australia.[139] Funnel web spiders tend to prefer moist, temperate environments.[139] They are primarily ground dwellers and live in burrows, crevices in rocks, around foundations of houses. They build tubular or funnel-shaped webs.[76] At night, the spiders ascend the tubular web and wait for their prey. The Sydney funnel web spider is considered one of the most poisonous spiders. It was responsible for 14 deaths between 1927 and 1980, at which time the antivenom was introduced.[193]

Pathophysiology

Robustotoxin (atracotoxin or atraxin) is a protein with a molecular weight of 4854 daltons. It contains 42 amino acids and is the lethal component of *A. robustus* venom.[139] Robustotoxin produces an autonomic storm, releasing acetylcholine, noradrenaline, and

adrenaline. A 5 Âµg/kg intravenous infusion dose of robustotoxin from male *A. robustus* spiders causes dyspnea, blood pressure fluctuations leading to severe hypotension, lacrimation, salivation, skeletal muscle fasciculation, and death within 3â€“4 hours when administered to monkeys.[145] Versutoxin, a toxin from the Blue Mountain funnel web spider, is closely related to robustotoxin and has demonstrated voltage-dependent slowing of sodium channel inactivation.[148]

Clinical Manifestations

A biphasic envenomation syndrome associated with *A. robustus* is described in humans and monkeys.[195,196] Phase 1 consists of localized pain at the bite site, perioral tingling, piloerection, and regional fasciculations (most prominent in the face, tongue, and intercostals). Fasciculations may progress to more overt muscle spasm; masseter and laryngeal involvement may threaten the airway.[196] Other features include tachycardia, hypertension, cardiac dysrhythmias, nausea, vomiting, abdominal pain, diaphoresis, lacrimation, salivation, and acute lung injury, which often is the cause of death in phase 1.[215] Phase 2 consists of resolution of the overt cholinergic and adrenergic crisis; secretions dry up, and fasciculations, spasms, and hypertension resolve. The apparent improvement can be followed by the gradual onset of refractory hypotension, apnea, and cardiac arrest.[196]

Treatment

Pressure immobilization using the crepe bandage to limit lymphatic flow and immobilization of the bitten extremity may inactivate the venom and should be applied if symptoms of envenomation are present. Funnel web venom is one of the few animal toxins known to undergo local inactivation.[193,194] The patient should be transferred to the nearest hospital with the bandage in place. Monkey studies and a human case report suggest the utility of pressure immobilization.[81,197] Pressure immobilization should be removed when the patient is located at a facility that can administer antivenom. A purified IgG antivenom

protective against *Atrax* envenomations was developed in rabbits by Sutherland.[193] One ampule of the antivenom contains 100 mg purified rabbit IgG or 125 units of neutralizing capacity per ampule.[215] It has been effective for more than 40 humans bitten by the *Atrax* species.[194] The starting dose is 2 ampules if systemic signs of envenomations are present, and 4 ampules if the patient develops pulmonary edema or decreased mental status. Doses are repeated every 15 minutes until clinical improvement is seen.[215] Up to 8 ampules is common in a severe envenomation. Anaphylaxis has not been reported.[194] The manufacturer no longer recommends premedication. Even serum sickness seems to be rare after funnel web antivenom administration. There has been 1 case after the patient received 5 ampules of antivenom for an *A. robustus* envenomation.[138]

Scorpions

Scorpions are invertebrate arthropods that have existed for more than 400 million years.[48] Of the 650 known living species, most of the lethal species are in the *Buthidae* family (Table 115-7). The genera of the family *Buthidae* include *Centruroides, Tityus, Leuirus, Androctonus, Buthus*, and *Parabuthus*.[48] Unlike most spiders, scorpions envenomate humans by stinging rather than biting. Their 5-segmented tail contains a bulbous segment called the *telson* that contains the venom apparatus (see ILTITYUSSERRULATUS in the Image Library). More than 100,000 medically significant stings likely occur annually worldwide, predominantly in the tropics and North Africa.[1,20,56,85,106,119] According to American Association of Poison Control Centers data from 1995â€“2003, approximately 11,000â€“14,000 scorpion annual exposures occurred in the United States, mostly in the southwestern region, but no deaths have been reported. These members of the class *Arachnida* rarely cause mortality in victims older than 6 years.[165] The poisonous scorpions in the United States are *Centruroides gertschii.* The most important is *Centruroides exilicauda*, previously called *Centruroides sculpturatus Ewing* (bark scorpion; Table 115-5).

Pathophysiology

Components of scorpion venom are complex and species specific. Scorpions from the family Buthidae are the most harmful to humans.[88,158,165] The venom is thermostable and consists of phospholipase, acetylcholinesterase, hyaluronidase, serotonin, and neurotoxins. Components of *C. exilicauda* venoms are primarily neurotoxic. Four neurotoxins designated toxins Iâ€“IV have been isolated from *C. exilicauda*. Some of the toxins target excitable membranes, especially at the neuromuscular junction, by opening sodium channels. The results are repetitive depolarization of nerves in both sympathetic and parasympathetic nervous systems causing acetylcholine and catecholamine release, increased neurotransmitter release, catecholamine release from the adrenal gland, catecholamine-induced cardiac hypoxia, and action at the juxtaglomerular apparatus, causing increased renin secretion.[52,165] *Tityus* scorpion sting is related to elevated concentrations of interleukin (IL)-1Î², IL-6, IL-8, IL-10, and tumor necrosis factor (TNF)-Î±, which correlate with the severity of envenomation and hyperamylasemia.[62,70] The kinin system seems to participate in the pathogenesis of human *Tityus* envenomation.[69]

TABLE 115-5. Scorpions of Toxicologic Importance[85,105]

USA: *Centroides exilicauda*
Brazil, South America: *Tityus serrulatus*
Mexico: *Centroides sufusus*
India: *Buthus tamulus*
Spain: *Buthus occitanus*
Saudi Arabia: *Leirus quinquestriatus, Androctonus crassicauda*
Middle East: *Leirus quinquestriatus, Buthus minax, Androctonus* spp
North Africa: *Androctonus Australis, Buthus occitanus, Leirus* spp
South Africa: *Androctonus crassicauda*
Persian Gulf: *Androctonus crassicauda*
Australia: *Lychas marmoreus, Lychas* spp, *Isometrus* spp, *Cercophonius squama, Urodacus* spp

Clinical Manifestations

Scorpion stings produce a local reaction consisting of intense local pain, erythema, tingling or burning, and occasionally discoloration and necrosis without tissue sloughing (Table 115-7). Depending on the scorpion species involved, systemic effects may occur, including autonomic storm consisting of cholinergic and adrenergic effects. Cardiotoxic effects include myocarditis, dysrhythmias, and myocardial infarction.[55,66,86,87,135,174] ECG abnormalities may persist for several days and include sinus tachycardia, sinus bradycardia, bizarre broad notched biphasic T-wave changes with additional ST elevation or depression in the limb and precordial leads, appearance of tiny Q waves in the limb leads consistent with an acute myocardial infarction pattern, occasional electrical alternans, and prolonged QTc interval.[87,89] Other reported effects include pancreatitis, coagulation disorders, acute lung injury (ALI), massive hemoptysis, cerebral infarctions in children, seizures, and a shock syndrome that may precede but usually follows the hypertensive

phase.[19,59,66,86,87,174,184]

In the United States, *C. exilicauda* stings produce local paresthesias and pain that can be accentuated by tapping over the envenomated area (tap test) without local skin evidence of envenomation.[51,165] Symptoms begin immediately after envenomation, progress to maximum severity in 5 hours, and may persist for up to 30 hours.[48,165] Autonomic symptoms include hypertension, tachycardia, diaphoresis, emesis, and bronchoconstriction. The somatic motor symptoms reported include ataxia, muscular fasciculations, restlessness, thrashing, and opsoclonus; rarely, children require respiratory support[52,158] (Table 115-6).

Treatment

Because most envenomations do not produce severe effects, local wound care, including tetanus prophylaxis and pain management, usually is all that is warranted. In young children or patients who manifest severe toxicity, hospitalization may be required. Treatment

emphasizes support of the airway, breathing, and circulation. Corticosteroids, antihistamines, and calcium have been administered without any known benefit.[51]

TABLE 115-6. Envenomation Gradation for *Centruroides Exilicauda* (Bark Scorpion)

Grade	Signs and Symptoms
I	Site of envenomation Pain and/or paresthesias Positive tap test (severe pain increase with touch or percussion)
II	Grade I plus Pain and paresthesias remote from sting site (eg, paresthesias moving up an extremity, perioral â€œnumbnessâ€•)
III	One of the following: Somatic skeletal neuromuscular dysfunction: jerking of extremity(s), restlessness, severe involuntary shaking and jerking, which may be mistaken for seizures Cranial nerve dysfunction: Blurred vision, wandering eye movements, hypersalivation, trouble swallowing, tongue fasciculation, upper airway dysfunction, slurred speech
IV	Both cranial nerve dysfunction and somatic skeletal neuromuscular dysfunction

Modified with permission from Curry SC, Vance MV, Ryan PJ, et al: Envenomation by the scorpion Centruroides sculpturatus. J Toxicol Clin Toxicol 1983â€“1984;21: 417â€“448; Allen C: Arachnid Envenomations. Emerg Med Clin North Am 1992;10:276.

The severity of envenomation dictates the need to use antivenom.

Continuous intravenous midazolam infusion has been used for *C. exilicauda* scorpion envenomation until resolution of the abnormal motor activity and agitation occurs.[74] Atropine has been used to reverse the excessive oral secretions in *C. exilicauda* scorpion envenomation, with some success in healthy children.[192] Routine use is not recommended and should be limited to species whose envenomations cause a prominent cholinergic crisis, such as *Parabuthus transvaalicus* in southern Africa.[192] The possibility of potentiating the adrenergic effects and causing cardiopulmonary toxicity is reported, so routine use of atropine is not recommended.[15] Atropine use to reverse the effects of stings from scorpions from India, South America, the Middle East, and Asia is contraindicated, because these scorpions cause an â€œautonomic stormâ€• with transient cholinergic stimulation followed by sustained adrenergic hyperactivity.[14,192]

One grading system suggests using antivenom for severe grade III and grade IV envenomations, which include somatic and/or cranial nerve dysfunction (Table 115-6).[51] A goat serum-derived anti-*Centruroides* antivenom is no longer available in Arizona, but was used successfully in a limited number of severe cases.[29] This approach is not universally accepted. Proponents believe antivenom may resolve symptoms sooner, whereas opponents cite serum sickness as a substantial concern (Antidotes in Depth: Scorpion and Spider Antivenoms).[29] A retrospective chart review of children younger than 10 years who experienced severe *Centruroides* scorpion envenomation found that anti-*Centruroides* antivenom resulted in rapid resolution of all symptoms in all 12 patients treated.[29] Of the patients treated with antivenom, 3% developed immediate hypersensitivity reactions and 58% had a delayed rash or serum sickness.[126] An equine-derived $F(ab)_2$ product called Alacramyn, developed in Mexico against the *Centruroides limpidus* venom, can be used to treat *C. exilicauda* bites, but US use of this foreign pharmaceutical is controversial.[16,183]

Scorpion envenomation can be prevented by wearing shoes when walking, particularly at night, because of the nocturnal nature of

scorpions. Shoes, sleeping bag, and tents should be shaken out prior to use. Cracks and crevices should be filled, wood piles and rubbish piles eliminated, and insecticides used in infested areas. The bark scorpion (*C. exilicauda*), which is fluorescent, can be demonstrated in the dark using a Woods lamp.

Ticks

In 1912, Todd[203] described a progressive ascending flaccid paralysis after bites from ticks. Three families of ticks are recognized: (1) *Ixodidae* (hard ticks), (2) *Argasidae* (soft ticks), and (3) *Nuttalliellidae* (a group that has characteristics of both hard and soft ticks). The terms *hard* and *soft* refer to a dorsal scutum or â€œplateâ€• that is present in the *Ixodidae* but absent in the *Argasidae.* Both types are characteristically soft and leathery, and both have clinical importance. *Ixodidae* females are capable of enormous expansion up to 50 times their weight in fluid and blood.[72] Ticks have 4 stages in their life cycle: egg, larva, nymph, and adult. The paralytic syndrome can occur during the larva, nymph, and adult stages and is related to the tick obtaining a blood meal. The following discussion focuses only on tick paralysis or tick toxicosis, and not on any of the infectious diseases associated with tick bites.

Most of the major tick-borne diseases in North America are transmitted by Ixodid ticks, except for relapsing fever, which is spread by the soft tick of the genus *Ornithodorus* or the louse. In North America, *Dermacentor andersoni* (North American wood tick) and *Dermacentor variabilis* are the most commonly implicated causes of tick paralysis.[79,204] While in Australia, the *Ixodes holocyclus* or Australian marsupial tick is the most common offender.[79,204]

Pathophysiology

Venom secreted from the salivary glands during the blood meal is absorbed by the host and systemically distributed. Paralysis results

from the neurotoxin â€œixovotoxin,â€•[1] which inhibits the release of acetylcholine at the neuromuscular junction and autonomic ganglia, very similar to botulinum toxin.[82,144] Both demonstrate temperature dependence in rat models and shows increased muscular twitching activity as the temperature is reduced.[49,128]

Clinical Manifestations

Usually the tick must remain on the person for 5â€“6 days in order to cause systemic symptoms. Several days must pass before tick salivary glands begin to secrete significant quantities of toxin. Once secreted, the toxin does not act immediately and may undergo binding and internalization, in a similar sequence to botulinum toxin.[49,110] Ticks typically attach to the scalp but can be found on any part of the body, including the ear canals and anus. Children, particularly girls, and adult men in tick-infested areas are predominantly affected. One large series of 305 cases in Canada reported that 21% were adults older than 16 years.[178] Among the children, 67% were girls; in adults 83% were male. The distribution was attributed to the difficulty of detecting ticks in long hair and the possible greater exposure of adult men to tick-infested environments. Children may appear listless, weak, ataxic, and irritable for several days before they develop an ascending paralysis that begins in the lower limbs. Fever usually is absent. Other manifestations include sensory symptoms such as paresthesias, numbness, and mild diarrhea. These symptoms are followed by absent or decreased deep-tendon reflexes and an ascending generalized weakness that can progress to bulbar structures involving speech, swallowing, and facial expression within 24â€“48 hours, as well as fixed dilated pupils and disturbances of extraocular movements.[82,178] If the tick is not removed, respiratory weakness can lead to hypoventilation, lethargy, coma, and death. Unlike the *Dermacentor* spp of North America, removal of the *I. holocyclus* tick does not result in dramatic improvement for several days to weeks. The maximal weakness may not be reached until 48 hours after the tick has been removed or drops off.[82] It is imperative to closely observe patients for

possible deterioration. The differential diagnosis includes Guillain-BarrÃ© syndrome (GBS), poliomyelitis, botulism, transverse myelitis, and spinal cord lesions. The cerebrospinal fluid remains normal and the rate of progression is rapid, unlike GBS and poliomyelitis.[65,176] The edrophonium test is negative. Nerve conduction studies in patients with tick paralysis may resemble those of patients with early stages of GBS: findings in both conditions include prolonged latency of the distal motor nerves, diminished nerve conduction velocity, and reduction in the amplitudes of muscle and sensory-nerve action potentials.[65]

Treatment

The most important aspect of treatment is considering tick paralysis in the differential diagnosis of any patient with ascending paralysis. Other than removal of the entire tick, which is curative, treatment is entirely supportive. The *I. holocyclus* of Australia is considerably more toxic and patients are more likely to deteriorate before they improve, so they must be closely observed for several days until improvement is certain.[82] Antitoxin, a hyperimmune serum prepared from dogs, is the usual treatment for paralyzed animals, and has been used sparingly in severely ill humans because of the risk of acute reactions and serum sickness.[82]

Prevention of tick bites includes wearing protective clothing and spraying clothes with insect repellant. Diethyltoluamide (DEET) repels ticks, but does not kill them. Permanone is a new tick aerosol spray repellant for use on clothing. It contains permethrin, which kills ticks on contact.[117] According to one study, permethrin in concentrations of 0.036â€“2.276 mg/m^2 induces 90â€“100% tick mortality, with 100% effectiveness for 1 month, and a decrease in effectiveness to 52% after the first washing.[117] Close inspection of all body parts and especially the scalp is important. Proper removal of the tick is very important, otherwise infection or incomplete tick removal may occur. The tick should be grasped as close to the skin surface as possible with

blunt curved forceps, tweezers, or gloved hands. Steady pressure without crushing the body should be used, otherwise expressed fluid may infect the patient. After tick removal, the site should be disinfected. Traditional methods of tick removal using petroleum jelly, topical lidocaine, fingernail polish, isopropyl alcohol, or a hot match head are ineffective and/or may induce the tick to salivate or regurgitate into the wound.[146]

Hymenoptera: Bees, Wasps, Hornets, Yellow Jackets, and Ants

Within the order *Hymenoptera* are three families of clinical significance: *Apidae* (honeybees and bumblebees), *Vespidae* (yellow jackets, hornets, and wasps), and *Formicidae* (fire ants). Insects of this subclass (Figure 115-2) are of great medical importance because their stings are the most commonly reported and can cause acute toxic and fatal allergic reactions (Table 115-7). An estimated 40 deaths per year are attributed to anaphylaxis secondary to hymenoptera stings.[12,182]

Apis Mellifera and *Bombus* species (honeybees and bumblebees) build nests away from humans and are passive unless disturbed. Apids can only sting once because their stinger is a modified ovipositor that resides in the abdomen. The structure is barbed and has a venom sac attached. Once the stinger embeds into the skin, the stinger disembowels the bee. Vespids, on the other hand, are more aggressive and build nests in trees and under awnings; yellow jackets inhabit the ground. They have smaller barbs that can be extracted from human skin and are able to sting multiple times.[76] The introduction of the Africanized honeybee in Brazil (because originally they were thought to be a more efficient honey producer) has caused significant economic and health issues. The bees have migrated toward the southern border of the United States, are less productive as a honey producer, and pose a greater threat to humans. African bees are characterized by large

populations, can make nonstop flights of at least 20 km, and have a tendency toward mass attack with little provocation.[140]

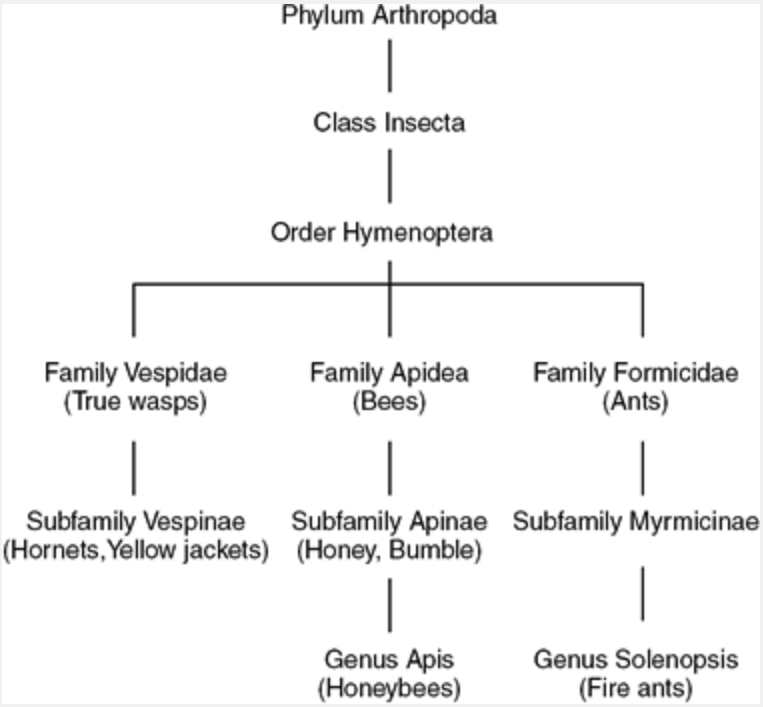

Figure 115-2. Taxonomy of the order Hymenoptera.

TABLE 115-7. Classification of Reactions to Hymenoptera Sting

Reaction	Clinical Presentation
Local	
Minimal	Localized pain, pruritus, swelling

	Lesion <5 cm Duration several hours
Large	Localized pain and pruritus Contiguous swelling and erythema Lesion >5 cm Duration 1â€“3 days
Systemic	
Minimal	Localized pain, pruritus, swelling Distant and diffuse urticaria, angioedema, pruritusand/or erythema, conjunctivitis Abdominal pain, nausea, diarrhea
Severe	Dermatologic Local: Pain, pruritus, and swelling Distant: Urticaria, angioedema, pruritus, and/or erythema Gastrointestinal Nausea, abdominal pain, diarrhea Respiratory Nasal congestion, rhinorrhea, hoarseness, bronchospasm, stridor, tachypnea, cough, wheezing Cardiovascular Tachycardia, hypotension, dysrhythmias, myocardial infarction Miscellaneous Seizures, feeling of impending doom, uterine contractions

Reprinted with permission from Sinkinson CA, French RS, Graft

DF, eds: Individualizing therapy for Hymenoptera stings. Emerg Med Rep 1990;11:134.

TABLE 115-8. Composition of Hymenoptera Venom

Vespid (wasps, hornets, yellow jackets)
Biogenic amines (diverse)
Phospholipase A, phospholipase B
Hyaluronidase
Antigen 5
Acid phosphatase
Mast cell degranulating peptide
Kinin
Apids (honeybees)
Biogenic amines (diverse)
Phospholipase A, phospholipase B (?)
Hyaluronidase
Acid phosphatase
Minimine
Mellitin
Apamin
Mast cell degranulating peptide
Formicids (fire ants)
Biogenic amines (diverse)
Phospholipase A
Hyaluronidase
Unidentified others
Piperidines

Modified with permission from Sinkinson CA, French RS, Graft DF, eds: Individualizing therapy for Hymenoptera stings. Emerg

Med Rep 1990;11:134; King TP, Valentine MD: Allergens of hymenptera venoms. Clin Rev Allergy 1987;5:137 Stablein JJ, Lockey RF: Adverse reactions to ant stings. Clin Rev Allergy 1987;5:161.

Pathophysiology

Several allergens (Table 115-8) and pharmacologically active compounds are found in honeybee venom. The three major venom proteins for the honeybee are melittin, phospholipase A_2, and hyaluronidase.[125] Other proteins include apamin, acid phosphatase, and other unidentified proteins. Phospholipase A_2 is the major antigen/allergen in bee venom.[27]

Melittin is the principal component of honeybee venom. It acts as a detergent to disrupt the cell membrane and liberate potassium and biogenic amines.[10] Histamine release by bee venom appears to be largely mediated by mast cell degranulation peptide. Apamin is a neurotoxin that acts on the spinal cord. Adolapin inhibits prostaglandin synthase and has antiinflammatory properties that may account for its use in arthritic therapy.[179] Phospholipase A_2 and hyaluronidase are the chief enzymes in bee venom.

Vespid venoms contain 3 major proteins that serve as allergens and a wide array of vasoactive peptides and amines.[125] The intense pain following by vespid stings is largely caused by serotonin, acetylcholine, and wasp kinins. Antigen 5 is the major allergen in vespid venom.[141] Its biologic function is unknown. Mastoparans have action similar to mast cell degranulation peptide, but weaker.[10] One study found that phospholipase A_2 may be responsible for inducing coagulation abnormalities.[152]

Clinical Manifestations

Normally, the honeybee sting is manifested as immediate pain, a

wheal-and-flare reaction, and localized edema without a systemic reaction. Vomiting, diarrhea, and syncope can occur with a higher dose of venom resulting from multiple stings.[30] Rarely, a sting in the oropharynx produces airway compromise.[182] Toxic reactions occur with multiple stings (>500 stings are described as possibly fatal)[76] and include GI symptoms, headache, fever, syncope and, rarely, rhabdomyolysis, renal failure, and seizures.[30] Bronchospasm and urticaria are typically absent. This type of toxic reaction is different from the hypersensitivity reactions or anaphylactic reactions because it is not an IgE-mediated response, but rather a direct effect from the venom itself.

Hypersensitivity reactions, including anaphylaxis, occur to hymenoptera stings. These reactions are IgE mediated. The IgE antibodies attach to tissue mast cells and basophils in individuals who have been previously sensitized to the venom. These cells are activated, allowing for progression of the cascade reaction of increased vasoactive substances, such as leukotrienes, eosinophil chemotactic factor-A, and histamine. An anaphylactic reaction is not dependent on the number of stings. Patients who are allergic to hymenoptera venom develop a wheal-and-flare reaction at the site of the inoculum. The shorter the interval between the sting and symptom onset, the more likely the reaction will be severe. Fatalities can occur within several minutes; even initially mild symptoms may be followed by a fulminant course. Generalized urticaria, throat and chest tightness, stridor, fever, chills, and cardiovascular collapse can ensue.

Treatment

Application of ice at the site usually is sufficient to halt discomfort. The stinger should be removed by scraping with a credit card or scalpel, as opposed to pulling, which may release additional retained venom. Topical aspirin preparations or paste have not been proven to be effective in reducing swelling or pain with bee or wasp stings, and they significantly increased the duration of redness.[9] Therapy is aimed at

supportive care.

Prevention, especially in the allergic person, includes avoiding bright clothing, flowers, scented deodorants and shampoos, perfumes, and barefoot walks outdoors. An emergency kit containing a prefilled spring-loaded epinephrine syringe (EpiPen delivers 0.3 mg, EpiPen Jr. delivers 0.15 mg) with careful instructions from a physician, an antihistamine (diphenhydramine), and an emergency alert card or tag should be carried or worn by the sensitized individual. Individuals with a clear history of anaphylaxis should followup with an allergist for skin testing and venom immunotherapy for positive results. Immunotherapy significantly reduces the potential risk of anaphylaxis with subsequent stings.[77,98] Commercial preparations of venom from the honeybee, yellow jacket, white-faced hornet, yellow hornet, and wasp can be used for diagnosis and immunotherapy for patients with life-threatening reactions to stings. Several authors have discussed the indications and safety of immunotherapy.[125,218]

Fire Ants

There are native fire ants in the United States, but the imported fire ants *Solenopsis invicta* and *Solenopsis richteri* are the significant pests and have no natural enemies. They are native to Brazil, Paraguay, Uruguay, and Argentina, but were introduced into Alabama in the 1930s. They have spread rapidly throughout the southern United States, damaging crops, reducing biologic diversity, and inflicting severe stings to humans.[199] *Solenopsis*

invicta, the most aggressive species, now infests 13 southern states and has been introduced into Australia.[185,187] Allergic reactions to ant stings were limited to the jumper ant (*Myrmecia pilosula*, other *Myrmecia* spp) and the greenhead ant (*Rhytidoponera metallica; Odontomachs, Cerapachys*, and *Brachyponera* spp) in Australia until February 2001, when the red imported fire ant was identified at two sites in Brisbane.[185] The mode of introduction is unknown but may

have originated from the transport of infested sea cargo. The incursion is estimated to be 5 years old. Fire ants range from 2â€“6 mm in size and live in grassy areas and garden sites near still and flowing water. The nests are largely subterranean and have large, conspicuous, dome-shaped above ground mounds (up to 45 cm above the ground), with many openings for traffic. The mounds can contain 80,000â€“250,000 workers and one or more queens that live for 2â€“6 years and produce 1500 eggs daily.[212] Fire ants are named for the burning pain inflicted after exposure that can result in necrosis at the site. The imported fire ant attacks with little warning. By firmly grasping the skin with its mandibles, both the fire ant and the jumper ant can repeatedly inject venom from a retractile stinger at the end of the abdomen. Pivoting at the head, the fire ant injects an average of 7 or 8 stings in a circular pattern.[187] In the United States, residents of healthcare facilities who are immobile or cognitively impaired are at risk for fire ant attacks, especially when the facility lacks pest control techniques for fire ants.[58] Healthcare personnel often are unaware of the behavior of these insects, and the special measures required for their control.

Pathophysiology

The clinical sequelae from fire ant stings are related to the biologic activity of the venom. The venom inhibits sodium and potassium adenosine triphosphatases, reduces mitochondrial respiration, uncouples oxidative phosphorylation, adversely affects neutrophil and platelet function, inhibits nitric oxide synthetase, and perhaps activates coagulation.[107,109] Unlike the venoms of wasps, bees, and hornets that contain mostly aqueous containing proteins, the imported fire ant venom is 95% alkaloid, with a small aqueous fraction that contains soluble proteins.[130] Of the alkaloids, 99% is a 2,6-disubstituted piperidine that has hemolytic, antibacterial, insecticidal, and cytoxic properties.[57] These alkaloids do not cause allergic reactions, but produce a pustule and pain. The aqueous portion of the venom contains the allergenic activity of fire ant venom, *Sol i* I-

IV.[92,187] The proteins identified in the venom include a phospholipase, a hyaluronidase, and the enzyme *N*-acetyl-Î²-glucosaminidase.[57,187]

Clinical Manifestations

Three categories are suggested based on the reactions to the imported fire ant: local, large local, and systemic.[188] *Local reactions* occur in nonallergenic individuals. *Large local reactions* are defined as painful, pruritic swelling at least 5 cm in diameter and contiguous with the sting site. *Systemic reactions* involve signs and symptoms remote from the sting site. The sting initially forms a wheal that is described as a burning itch at the site, followed by the development of sterile pustules. In 24 hours, the pustules umbilicate on an erythematous base. Pustules may last 1â€“2 weeks.[76] Late cutaneous allergic reactions can occur in some persons who experience indurated pruritic lumps at the site of subsequent stings.[57] Large reactions may lead to tissue edema sufficient to compromise blood flow to an extremity. Anaphylaxis occurs in 0.6â€“6% of persons who have been stung.[187] Often, healing occurs with scarring in 10â€“14 days.

Diagnosis

Clinical clues such as pustule development at the sting site after 24 hours, species identification, and history may help to identify fire ant exposure. No laboratory assays to determine exposure are available. Fire ant allergy can be determined by correlating the clinical manifestation of fire ant sting reactions with imported fire antâ€“specific IgE determined by skin testing or radioallergosorbent test.

Treatment

Local reactions require cold compresses and cleansing with soap and water. Some authors recommend topical or injected lidocaine with or without 1:100,000 epinephrine and topical vinegar and salt mixtures to

decrease pain at the site of the bite and sting.[96,134] Topical application of aluminum sulfate and papain is not effective for reducing pain or pruritus.[32,168] Large local reactions can be treated with oral corticosteroids, antihistamines, and analgesics. Secondary infections should be treated with antibiotics. Systemic reactions should be treated with subcutaneous or intravenous epinephrine.

Butterflies, Moths, and Caterpillars

Butterflies and moths are insects of the order *Lepidoptera.* Several moth and butterfly families have species whose caterpillars are clinically important, that is, they contain spines or urticating hairs that secrete a poison that is irritating to humans on contact. *Lepidopterism* is a general term that describes the adverse effects to humans when they are exposed to moths and butterflies.[143] Caterpillar, which means *hairy cat* in Latin, is the larval stage for moths and butterflies. In the United States, several significant stinging caterpillars are of note. The puss caterpillar (*Megalopyge opercularis*) often is considered one of the most important and toxic of the caterpillars in the United States because it has been reported to be such a nuisance, especially in Texas.[190] Other names for the puss caterpillar are woolly/hairy worm, wooly slug, opossum bug, tree asp, Italian asp, and little perrito in Spanish.[190] The caterpillars look furry and are covered in silky tan to brownish hairs that hide short spines containing an urticarial toxin. The spines are yellowish with black tips, and the hairs vary in colors ranging from pale yellow and gray to brown.[24] Other significant stinging caterpillars in the United States are the flannel moth caterpillar (*Megalopyge crispata*), the Io moth (*Automeris io*), the saddleback caterpillar (*Sibine stimulata*), and the hickory tussock caterpillar (*Lophocampa caryae*).[123] In South America, especially Brazil, *Lonomia obliqua* caterpillars are notorious for causing severe pain and a hemorrhagic syndrome.[38,53] In Australia several caterpillars are of medical importance: mistletoe brown tail moth (*Euproctis edwardsi*), processionary caterpillars (*Ochrogaster lunifer*), cup moths (*Doratifera* spp), and the white-stemmed gum moth (*Chelepteryx*

collesi).[8] Pine processionary caterpillars (*Thaumetopoea pityocampa*) are the most important defoliator of pine forests in the Mediterranean and central European countries, with significant consequential economic and occupational repercussions for workers who frequent these pine forests.[205]

Pathophysiology

Little is known about the composition of the venom, which probably varies according to the different caterpillar species. Some toxins contain proteins that cause histamine release, such as thaumetopoien isolated from *Thaumetopoien pityocampa* or pine processionary caterpillar.[205,206] Another protein isolated from the *L. obliqua* caterpillar causes coagulopathy; its mechanism of action is not fully known but it somehow activates factors X and II.[61,112] The venom and hair structure of *Lagoa crispata*, which has often been confused with the southern Texas puss caterpillar, has been characterized.[124] The venom is stored at the base of the hollow setae (spines) where the poison sac and nervous tissue are located. Upon contact with these spines, the toxin is released. The toxin may be a protein or a substance that conjugates with proteins.[67] The varying differences of caterpillar venom and their clinical effects emphasize the importance of positive identification of caterpillars.

Clinical Manifestations

The clinical effects of caterpillar exposure can generally be separated into 2 typesâ€”stinging reaction and pruritic reactionâ€”although overlap may occur. Stinging caterpillars, such as *Megalopyge opercularis*, envenomate by contact with their hollow spines containing venom. The reaction is characterized as a painful, burning sensation with local effects and, less commonly, systemic effects. The area may become erythematous and swollen, and papules and vesicles may appear. The classic gridlike pattern develops within 2â€“3 hours of

contact. Reported symptoms include nausea, vomiting, fever, headache, restlessness, tachycardia, hypotension, urticaria, seizures, and even radiating lymphadenitis and regional adenopathy.[154] Another stinging caterpillar previously mentioned is the *L. obliqua* caterpillar, which causes the hemorrhagic syndrome that presents as a disseminating intravascular coagulopathy and as secondary fibrinolysis with skin, mucosal, and visceral bleeding, acute renal failure, and intracerebral hemorrhage.[38,112] Pruritic reactions occur upon exposure to the itchy caterpillars that have nonvenomous urticating hairs, which can produce a mechanical irritation, allergic reaction, or a granulomatous reaction from the chronic presence of the hairs. Several species that cause allergic reactions are the white-stemmed moth (*Chelepteryx collesi*), Douglas fir tussock moth (*Orgyria pseudotsugata*), and gypsy moth caterpillar (*Lymantria dispar*).[143] Caterpillar hairs can cause ocular trauma, otherwise known as *ophthalmia nodosa*.[186] The range of ocular pathology depends on the penetration factor and the effect of the released urticating toxins.[37] The ocular spectrum has been classified into 5 types by Cadera et al:[37]

- *Type 1:* Brief exposure time of 15 minutes. Symptoms of chemosis, inflammation, epiphora, and foreign body sensation may last for weeks.
- *Type 2:* Chronic mechanical keratoconjunctivitis (hairs in bulbar/palpebral conjunctivitis). Foreign body sensation is relieved by removal of hairs. Cornea abrasions may be present.
- *Type 3:* Gray-yellow nodules or asymptomatic granulomas.
- *Type 4:* Severe iritis with or without iritis nodules. Hairs in the anterior chamber and possible intralenticular foreign body.
- *Type 5:* Vitreoretinal involvement. Hairs may enter through the anterior chamber or iris lens or by transscleral migration. May cause vitreitis, cystoid macular edema, papillitis, or endophthalmitis.

Treatment

Treatment of ocular lesions depends upon the exposure classification. Most patients can be classified as type 1 or 2. Irrigation with saline should be followed by meticulous removal of setae, followed by topical steroids and antibiotics. Type 3 requires surgical excision of the nodules. Type 4 requires topical steroids with or without iridectomy for nodules or operative removal of setae. Type 5 requires local treatment with or without systemic steroids. Resistant cases may require vitrectomy with removal of setae. Treatment for dermal contact should be immediate, with removal of the embedded spines using cellophane tape and application of ice. Opioids may be necessary, if minor analgesics do not provide relief. If muscle cramps develop, benzodiazepines should be administered. One study recommended use of 10 mL 10% calcium gluconate administered intravenously, which provided pain relief.[136] Topical corticosteroids can be used to decrease local inflammation. Antihistamines such as diphenhydramine (25â€“50 mg for adults and 1 mg/kg, maximum 50 mg, in children) can be used to relieve pruritus and urticaria.[136,154] Nebulized Î²-agonists and epinephrine administered subcutaneously may be required for more severe respiratory symptoms and anaphylactoid/anaphylactic-type reactions. For hemorrhagic syndrome resulting from exposure to *L. obliqua* caterpillar, an antidote called the antilonomic serum (SALon) is available and is used for treatment of the hemorrhagic syndrome in Brazil.[60]

Blister Beetles

Blister beetles are plant-eating insects that exude a blistering agent for protection. They can be found in the eastern United States, southern Europe, Africa, and Asia. Most are from the order Coleoptera, family Meloidae. *Epicauta vittata* is the most common of more than 200 blister beetles identified in the United States.[111] When the beetles sense danger, they exude cantharidin by filling their breathing tubes with air, closing their breathing pores, and building up body fluid

pressure until fluid is pushed out through one or more leg joints.[76] Cantharidin is a potent blistering agent found throughout all 10 stages of life of the blister beetle.[41] Cantharidin is produced only by the male blister beetle and is stored until mating. The female loses most of her reserves as she matures. In the wild, the female repeatedly acquires cantharidin as copulatory gifts from her mates.[41] Cantharidin, also known popularly as *Spanish fly*, takes its name from the Mediterranean beetle *Cantharis vesicatoria.* It has been used as a sexual stimulant for millennia. The aphrodisiac properties are related to the ability of cantharidin to cause vascular engorgement and inflammation of the genitourinary tract, hence the reports of priapism and pelvic organ engorgement.[202] Cantharidin has been used for treatment of bladder and kidney infections, stones, stranguria (bladder spasm), and various venereal diseases.[111] In the last century, cantharidin was commonly used for treatment of pleurisy, pneumonia, arthritis, neuralgias, and various dermatitides. A topical 1% commercial preparation can be used for removal of warts and molluscum contagiosum.[50,180] Cantharidin poisoning has been reported by cutaneous exposure,[31] unintentional inoculation,[156] and inadvertent ingestion of the beetle itself.[200] Fewer than 30 cases of Spanish fly poisoning have been reported since 1900.[111]

Pathophysiology

Cantharidin is a natural defensive toxicant produced by blister beetles and shares a structural similarity with the herbicide Endothall.

Although the mechanism of action has not been elucidated, one mechanism based on an in vitro study suggests that cantharidin inhibits the activity of protein phosphatases type 1 and 2A. This inhibition alters endothelial permeability by enhancing the phosphorylation state of endothelial regulatory proteins and results in elevated albumin flux and dysfunction of the barrier.[116] Enhanced permeability of albumin may be responsible for the systemic effects of cantharidin, which lead to diffuse injury of the vascular endothelium

and resultant blistering, hemorrhage, and inflammation.

Clinical Manifestations

The clinical effects can mostly be attributed to the irritative effects on the exposed organ systems. The secretions cause an urticarial dermatitis that is manifested several hours later by burns, blisters, or vesiculobullae.[31] Symptoms may be immediate or delayed over several hours. In addition to the local effects, cantharidin can be absorbed through the lipid bilayer of the epidermis and cause systemic toxicity, with diaphoresis, tachycardia, hematuria, and oliguria from extensive dermal exposure.[202] If the periorbital region is contaminated, edema and blistering can evolve. Ocular findings from direct contact with the beetle or hand contamination include decreased vision, pain, lacrimation, corneal ulcerations, filamentary keratitis, and anterior uveitis.[156] When cantharidin is ingested, severe GI disturbances and hematuria can occur, described primarily as cantharidin toxicosis in horses.[161] Initial patient complaints may include burning of the oropharynx, dysphagia, abdominal cramping, vomiting, hematemesis followed by lower GI tract hematochezia, and tenesmus.[149] Although equids develop cantharidin toxicosis from their diet, there is one case of inadvertent blister beetle ingestion by a child who thought it was the edible *Eulepida mashona* or white grub; the child developed hematuria and abdominal cramping.[200] Genitourinary effects include dysuria, urinary frequency, hematuria, proteinuria, and renal impairment. Most symptoms resolved over several weeks. However, death from renal failure with acute tubular necrosis has been reported.[202] Most human exposures involve inadvertent contact with the beetle or its secretions, resulting in dermatitis, keratoconjunctivitis, and periorbital edema secondary to handâ€“eye involvement, also called the *Nairobi eye*.[156]

Diagnostic Testing

Cantharidin toxicosis has been identified for equine and ruminant

exposures by screening urine and gastric contents with high-performance liquid chromatography and gas chromatography-mass spectrometry.[161,162] This method has not been used in clinical practice.

Treatment

Treatment is largely supportive. Wound care and tetanus status should be assessed. For keratoconjunctivitis, an ophthalmologist should be consulted early in the clinical course and the patient treated with topical corticosteroids (prednisolone 0.125%), mydriatics (cyclopentolate 1%), and antibiotics (ciprofloxacin 0.3%).

Summary

Healthcare providers should have an extensive knowledge regarding bites and stings by arthropods and arachnids so that they can recognize the local and systemic reactions. Treatment of arthropod-borne disease rarely entails use of antivenoms. Proper hygiene to prevent secondary infections, avoiding contact with arthropods, decreasing the arthropod population mechanically and/or chemically, and use of repellents are important measures to decrease morbidity from arthropods. The patient should bring the arthropod to the hospital, if possible, to facilitate identification, and every attempt should be made to describe the evolution of the bite to assist in the differential diagnosis.

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Antidotes in Depth

Antivenom (Scorpion and Spider)

Jeffrey N. Bernstein

The terms *antivenom* and *antivenin* often are used interchangeably. Wyeth, the maker of Crotaline and *Micrurus* antivenom, and Merck and Co., the makers of *Latrodectus* antivenom, adopted *antivenin* in the brand names for their products. Brand name recognition has largely been responsible for the use of the term *antivenin* in place of *antivenom.* Except where it refers to a specific brand name, the term *antivenom* is used in this Antidotes in Depth and throughout this textbook.

Antivenom for spiders and scorpions is prepared by immunizing animals with venom and then collecting the immune serum for administration.[4,37] Monkeys, horses, goats, sheep, chicken, camels, and rabbits have been used as sources of antivenom.[41] The animals are placed on an immunization schedule to allow production of immunoglobulins, mostly specific immunoglobulin IgG. Optimal antibody production typically takes approximately 6 weeks. The choice of animal used to make an immune serum is more often dictated by the availability of a species, financial considerations, and tradition than by scientific modeling. Horses are used

by the majority of antivenom producers. Horses are easy to maintain, and large volumes of serum can be obtained at one time without harming the animals. Although manufacturers may state that a specific animal gives a less immunogenic product, no studies have compared immune sera of different animals for human compatibility or tolerance. Varying efforts by the manufacturer are made to remove animal proteins such as albumin. The antidotal fraction of an antivenom exists as either whole IgG, or Fab, or $F(ab)_2$. Digestion of disulfide bonds of an IgG molecule with papain yields a mixture of Fab and Fc. The Fab component then can be isolated with affinity chromatography, and the highly antigenic Fc portion is discarded. Similarly, digestion of the IgG molecule with pepsin yields a mixture of $F(ab)_2$ and Fc. Although Fab and $F(ab)_2$ are more expensive to produce than their whole immunoglobin counterparts, they are generally regarded as less allergenic and therefore safer to use.

IgG is the easiest and most inexpensive to produce. It has a molecular weight of 150 kDa, the largest of the three antivenom types. Because of its size, it is less filterable at the glomerulus and has the smallest volume of distribution. IgG has a longer elimination half-life than either Fab or $F(ab)_2$.[27]

$F(ab)_2$ has an intermediate size (100 kDa) and elimination half-life. Because it lacks the Fc fragment of the IgG molecule, it has less potential to initiate anaphylaxis. The advantage of $F(ab)_2$ is that much of the allosteric configuration of the original IgG molecule is retained compared to Fab. This configuration theoretically allows for tighter binding to venom.

Fab is the smallest (50 kDa) in size and is eliminated renally. It has the largest volume of distribution and a greater ability to reach intracellular compartments. The pharmacokinetic properties of the venom have been suggested to define the development and characteristics of an antivenom.[27] Arachnid venoms with effects on the central nervous system tend to have low molecular weights and large volumes of distribution. Fab- and $F(ab)_2$ -based antivenoms with their larger volumes of distribution may be more suitable for binding these low-molecular-weight

centrally acting components of arachnid venom.[27]

Immunoglobulin-based antivenoms can be given by the intramuscular, intravenous, or subcutaneous route. Intravenous antivenom therapy is preferred for its ability to achieve rapid peak serum concentrations and the ability to withdraw the offending antivenom in the event of an allergic reaction.[28] Intramuscular injection has been used in instances where intravenous access is unobtainable. In a rabbit model, the elimination half-life of *Buthus occitanus* venom is reduced faster when antivenom is given by the intravenous route than are comparable doses given intramuscularly. Pharmacokinetic comparisons of venom and antivenom suggest that the lower-molecular-weight components of scorpion venom are absorbed and distributed faster than antivenom, when administered intramuscularly or given subcutaneously. Therefore intravenous antivenom is the preferred route for neutralization of venom.[30, 34, 35]

The unavailability of specific antivenoms necessitates symptomatic treatment or use of a comparable foreign antivenom. In the United States the specific goat-derived antivenom for *Centruroides* envenomation is no longer being produced. Clinical trials are underway for the use of Mexican equine $F(ab)_2$ for treatment of severe envenomation. In a study of 72 moderate scorpion stings in Para, Brazil, 32.7% who met criteria for antivenom administration did not receive treatment because of unavailability of the antivenom.[46] *Latrodectus* antivenom has been in short supply in the past, leading to the observation that *Latrodectus mactans* and *Latrodectus hesperus* could be neutralized by *Latrodectus hasseltii* antivenom.[18, 19, 39]

The exact identity of the species of arachnid is rarely known in the clinical setting. The spider or scorpion specimen usually is not available. The species usually is inferred more from the geographic region where the injury occurred than from the clinical presentation. For example, black widow envenomations that occur in southern Arizona are presumed to result from *L. hesperus* rather than *L. mactans*. Occasionally, stings or bites result from scorpions or spiders in imported foreign rugs and fruit. The clinician must also be aware that professional and amateur

entomologists may be exposed to bites or stings from exotic species. However, in these instances, the exact genus and species, or at least the common name, usually are known.

Centruroides Species

Centruroides exilicauda (formerly known as *Centruroides sculpturatus*) is the only scorpion of medical importance in the United States. It is indigenous to the deserts of Arizona but reportedly exists in Texas, New Mexico, California, and Nevada.[17] Occasionally, envenomations occur in nonindigenous areas of the country from â€œstowawayâ€• scorpions in the luggage of travelers.[59]

The two poison centers in Arizona receive between 8000 and 10,000 calls annually for scorpion exposures (Chap. 130).[40] In the past, the mortality from scorpion envenomation in the

United States was twice as high as that of all other venomous animals combined.[48] Although the incidence of envenomation remains high, no deaths associated with the toxic effects of scorpion venom have occurred for more than 40 years. However, the recent death of a 62-year-old woman likely was secondary to an anaphylactic reaction to scorpion venom.[10] The low incidence of fatalities most likely is attributable to better methods of supportive care, the use of antivenom, and the development of pediatric intensive care units.[32]

Antivenom for the *Centruroides* spp was produced in horses in Mexico as early as the 1930s.[17] In 1947, antivenom was produced from rabbits and cats immunized with *C. sculpturatus* and *Centruroides gertschi* .[52] The Antivenom Production Laboratory at Arizona State University (APL-ASU) began producing antivenom to *C. sculpturatus* in goats in 1965. This antivenom was used for treatment of scorpion stings in Arizona until November 2004. Production of the APL-ASU antivenom has ceased. All stockpiles have expired; however, several hospitals retain vials of antivenom in their inventory.[40] No FDA approval was ever granted for thi product; its use was restricted to the state of Arizona, where it was

supplied free of charge to hospitals for compassionate use. Transport across state lines was prohibited.

In view of the limited mortality from envenomation and the risk of seriou immediate hypersensitivity or serum sickness from administration of antivenom, there is rarely, if ever, an absolute indication for administration of *Centruroides* scorpion antivenom. Administration of antivenom, therefore, was reserved for patients with the most severe envenomations, typically in children younger than 6 years. A 4-level severity grading of scorpion envenomation is given in Table 115-7 .[17] Administration of antivenom is recommended for patients with grade III o IV systemic toxicity. However, these same symptoms also can be successfully managed in an intensive care setting with aggressive airway management, monitoring, and benzodiazepine infusions.

In Mexico, two antivenoms are primarily directed toward neutralizing the venom of *Centruroides* spp. The Mexico-Pharma Polyvalent Scorpion Antivenom may also be effective against North American *Centruroides* stings; however, there is no known reliable repository of this antivenom i the United States.[3] Although antibody fragments (Fab) were developed from immune goat serum for treatment of *Centruroides* envenomation, they are not commercially available.[8] In June 2000, Silanes Laboratory received orphan drug status for Alacramyn, an equine-derived $F(ab)_2$ fror *Centruroides limpidus* , *Centruroides noxius, Centruroides suffusus suffusus, and Centruroides meisei* (formerly known as *Centruroides elegans*). Currently, clinical trials of $F(ab)_2$ use in envenomed children are underway, stimulated by the absence of the ASU-APL product. One vi of Alacramyn contains sufficient $F(ab)_2$ to neutralize 150 mouse LD_{50} of *Centruroides* venom.[42] It is administered by slow IV infusion, 1 vial at a time with observation for 30 to 60 minutes before repeating. Dosing is similar in children and adults. It efficacy is documented in both animals and humans.[1 , 11 , 25] A prospective evaluation of serum venom concentrations in 14 clinically envenomed children was performed using enzyme-linked immunosorbent assay. After administration of antivenom, serum venom concentrations fell from 1000 to 4000 pg/mL to less than 200 pg/mL within 30 minutes and were unmeasurable within 2 hours.[25]

In a rabbit model, the total serum concentration of venom increased afte administration of $F(ab)_2$, suggesting that $F(ab)_2$ is capable of pulling venom from its site of action into serum.[11]

Cross-neutralization of the venom of 8 different species of *Centruroides* , including *C. exilicauda* , has been documented in vitro.[22]

The incidence of allergic reactions to Alacramyn is reported to be 2.7%, similar to the 3.4% reported for the APL-ASU goat serum.[9 , 38] The average duration of symptoms in treated patients was 1.4 hours. In a study of 15 children, the 12 patients who receive APL-ASU antivenom hac resolution of neurologic, respiratory, and cardiovascular symptoms within 3 hours of initiating therapy. In the 3 patients who did not receive antivenom therapy, symptoms lasted 15 to 24 hours.[9] If the current clinical trials of $F(ab)_2$ reveal the product to be safe and effective, the threshold to treat scorpion envenomation may be lowered by many clinicians. Alacramyn is tentatively set to be marketed under the name Anascorp in the United States.

Leiurus Species

The *Leiurus quinquestriatus* scorpion is indigenous to Africa, Asia, and th Middle East, including Egypt, Israel, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Syria, and Turkey. Antivenom to *L. quinquestriatus* i made in France, Israel, and Turkey. The clinical effects of this scorpion are relatively resistant to treatment with antivenom. The manufacturer of Turkey antiscorpion antivenom recommends a dose of 1 mL antivenom fo treatment of envenomation. The usual dose for control of symptoms is 5 to 20 mL antivenom given intravenously.

In observational studies, an intravenous infusion of 5 to 20 mL was needed to control venom effects, and only patients given antivenom withi the first several hours demonstrated significant benefit.[2 , 31] The rate of allergic reactions for the Turkey antiscorpion antivenom is reported to be 1.6% to 6.6%.[31] The recommended dose of the Israeli *L. quinquestriatus* antivenom is 5 to 15 mL for intravenous use. Several authors report lack

of clinical efficacy of this antivenom.[6,26,53]

Leiurus quinquestriatus antivenom was successfully used to treat a 2-year-old boy with envenomation by *Androctonus crassicauda*. Symptoms resolved 2 hours after antivenom administration.[47]

Tityus Species

Tityus species of scorpions are endemic to South America, particularly Brazil. An $F(ab)_2$ for *Tityus serrulatus* antivenom is available from FundaÃ§Ã£o Ezequiel Dias (FUNED), in Belo Horizonte, Brazil. The usual dose of the antivenom is 20 mL as an intravenous infusion.[20]

In a series of 18 patients with *T. serrulatus* envenomation treated with antivenom, vomiting and local pain decreased within 1 hour, and cardiorespiratory manifestations disappeared within 6 to 24 hours in all patients except the 2 who presented with acute lung injury.[20] Sixteen patients recovered completely by 24 hours. Additionally, the Instituto Buntantan in Brazil produces Soro antiarachnidico and Soro antiscorpionico for treatment of *Tityus* spp.[44]

Androctonus Species

Scorpion antivenom in South Africa is an equine-derived antivenom available from the South African Vaccine Producers, formerly South African Institute for Medical Research (SAIMR), Johannesburg, South Africa.

Scorpifav, produced by Aventis Pasteur, is produced for treatment of *Androctonus* spp, *B. occitanus*, and *L. quinquestriatus*.

Buthus tamulus monovalent red scorpion antivenom serum produced by Central Research Institute of India is an equine-derived lyophilized antivenom for the venom of *Mesobuthus tamulus*. Although the manufacturer recommends a dosage of 1 vial, a dose of 5 vials reduced the mortality significantly in one study.[36,54]

In Pakistan, the treatment of scorpion stings was modified in 1991 to include the administration of 5 vials of antivenom. A retrospective case series of 950 patients treated with and without antivenom was compared to 968 cases after the 5-vial protocol was initiated. A statistically significant decrease in mortality occurred. The last recorded death resulting from a scorpion sting occurred in 1991 in a patient who did not receive antivenom.[54]

Parabuthus spp antivenom from South African Vaccine Producers is an equine-derived antivenom to *Parabuthus* spp. In one study antivenom became unavailable, allowing for a unique design of matched pairing of patients. Patients who received antivenom had a significant decrease in hospital stay after receiving 1 (5-mL) vial of antivenom. Pain, hypersalivation, fasciculation, tremor, and bladder distension responded best to serotherapy. Antivenom therapy did not significantly improve dysphagia, ptosis, or local swelling.[7]

Latrodectus Species (*L. Mactans, L. Hesperus, Latrodectus Bishopi, Latrodectus Geometricus, Latrodectus Indistinctus*)

Administration of the black widow spider antivenom is controversial. Although black widow envenomation is associated with severe muscle pain, cramping, and autonomic disturbances,[12 , 13 , 33] mortality is low. Symptomatic treatment almost always can be accomplished with muscle relaxants and opioids individually or in combination. Some authors believ that antivenom has too high a risk-to-benefit ratio to justify its use.[50] In selected patients, however, use of antivenom may reduce pain and suffering, shorten the course of envenomation, and reduce or eliminate the need for hospitalization.[45 , 55] We believe that indications for antivenom administration include severe muscle cramping, hypertension, diaphoresis, nausea, vomiting, and respiratory difficulty that is unresponsive to other therapy (Chap. 115). Pregnancy is suggested as a possible indication for antivenom administration.[5 , 51]

Antivenoms for a number of *Latrodectus* spiders are available worldwide (Table A32-1). *Latrodectus mactans* antivenom is produced by Merck and Co. in North America. The Australian red-back spider *L. hasseltii* antivenom is manufactured in horses by CSL Ltd. South Africa (SAFR) produces antivenom for both the black widow *(Latrodectus indistinctus)* and the brown widow *Latrodectus geometricus* . Aracmyn, a polyvalent $F(ab)_2$, is an equine-derived antivenom created for *L. mactans* in both Argentina and Mexico and for *Loxosceles* spp.

In North America Antivenin (Merck and Co.) for black widow venom (*L. mactans*) is made by immunizing horses. Each vial of antivenin contains 6000 antivenin units standardized by biologic assay in mice. Because the venoms of Latrodectus species are virtually identical by immunologic and electrophoretic mechanisms, antivenom created for *L. mactans* is presumed to be effective in other species of Latrodectus as well.[39] A recent shortage of antivenin (Merck and Co.) prompted the discovery that antivenom against *L. hasseltii* , the Australian red-back spider, also neutralizes venom of *L. mactans* in a mouse model.[19] In a review of 163 cases of presumed *L. hesperus* , envenomations antivenom reduced the duration of symptoms from a mean of 22 hours to a mean of 9 hours. Symptoms usually subsided within 1-3 hours of administration of the antivenom. Hospital admission rate fell from 52% in those who were managed with opioids and muscle relaxants to 12% in those patients receiving antivenom.[12] Administration of antivenom was also effective, even when given as late as 90 hours after envenomation.[45 , 55]

Dosage of antivenin (Merck and Co.) is usually one vial (2.5 mL) diluted in 50 mL of saline for intravenous administration. Black widow spider antivenom can also be given IM; however, this route carries the disadvantage of slower, more erratic absorption, less control over the rate of administration, and the inability to stop administration of the drug should an allergic reaction occur. For these reasons, the intramuscular route is not recommended.

Despite the apparent efficacy of antivenom, the decision to give horse serum for a disease with limited mortality is of great concern. Death from

bronchospasm and anaphylaxis is reported as a complication of antivenor administration, as is serum sickness.[13] Black widow antivenom is listed a a Pregnancy Category C agent.

In Australia, antivenom to the red-back spider (*L. hasseltii* , CSL Ltd.) is made by immunizing horses for production of $F(ab)_2$. Horse-derived $F(ab)_2$ has a lower reported incidence of allergic reactions, with early anaphylactoid reactions as low as 0.5% to 0.8%. The incidence of serum sickness is reported at less than 5%.[56 , 57]

In a report covering 1995 to 1996, only 20% of patients with *L. hasseltii* (red-back spider) bites required antivenom administration.[60] When treatment was given, 1 ampule was used in 76% of cases, 2 ampules wer used in 18% of cases, and 3 ampules were administered in only 6% of cases.[60] Three patients who required 6 to 8 vials of antivenom after failing to respond to the usual 1 to 2 vials are reported.[29] No antihistamine or epinephrine pretreatment was given, and no allergic or serum sickness complications occurred.

European widow spider *(Latrodectus tredecimguttatus)* antivenom is no longer produced.[29]

Funnel-Web Spider (Atrax and Hadronyche) Envenomation

A rabbit IgG-based funnel-web spider antivenom is available in Australia. Since the introduction of the antivenom, no deaths have been reported.[29] The initial dose should be 2 ampules in patients with any signs of envenomation. Patients with evidence of acute lung injury or decreased consciousness should receive 4 ampules.[43] The dosage for children is the same as for adults.[16]

In severe envenomations, the following protocol should be used.[43] Two ampules (each 5 mL of 2.0% [100-mg]) rabbit IgG) antivenom should be administered very slowly intravenously (adult or child). The dose can be repeated in 15 minutes if no improvement is seen. The dose should be

doubled for severe cases. A rapid response should occur. Administration o antivenom should be repeated until symptoms are completely reversed.[21] Not uncommonly, *Atrax robustus* envenomations require more than 3 ampules of antivenom.

Scorpions

Androctonus aenas

France: Antiscorpion Venom Serum, Pasteur Merieux

Androctonus amorexi

France: Antiscorpion Venom Serum, Pasteur Merieux

Androctonus australis

Algeria: Antiscorpion

France: Scorpifav, Aventis Pasteur

Germany: Scorpion Antivenom, Twyford

Androctonus crassicauda

Iran: Scorpion Antivenom

Turkey: Anti-Scorpion

Androctonus mauritanicus

France: Antiscorpion Venom Serum, Pasteur Merieux

Morocco: Serum antiscorpionique

Androctonus *species*

France: Antiscorpion Venom Serum, Pasteur Merieux

Buthotus saulcyi

Iran: Scorpion Antivenom

Buthus occitanus

France: Antiscorpion Venom Serum, Pasteur Merieux

France: Scorpifav, Aventis Pasteur

Germany: Scorpion Antivenom, Twyford

Buthus gibbosusbrulla

Turkey: Anti-Scorpion

Buthus tamulus

India: Anti-Scorpion Venom Serum (AScVS), Haffkine

Centruroides species (*elegans, gertschi, limpidus, suffuses, noxius, exilicauda*)

Mexico: Alacramyn, Bioclon

Mexico: GGBR Polivalent Scorpion Antivenom

Euscorpius carpathicus, italicus

Turkey: Anti-Scorpion

Leiurus quinquestriatus

France: Antiscorpion Venom Serum, Pasteur Merieux

France: Scorpifav, Aventis Pasteur

Germany: Scorpion Antivenom, Twyford

Israel: *Leiurus quinquestriatus*

Turkey: Anti-Scorpion

Mesobuthus eupeus

Iran: Scorpion Antivenom

Mesobuthus tamulus concanesis

India: Anti-Scorpion Venom Serum (AScVS), Haffkine

Odontobuthus doriae

Iran: Scorpion Antivenom

Palamnaeus species

India: Monovalent Red Scorpion Antivenom Serum

Parabuthus species

South Africa: Scorpion Antivenom, SAIMR

Scorpio maurus

France: Scorpion Antivenom Serum, Aventis Pasteur

Iran: Scorpion Antivenom

Turkey: Anti-Scorpion (subspecies fuscus)

Tityus bahiensis

Brazil: Soro Antiescorpionico, Instituto Butantan

Tityus serrulatus

Brazil: Anti Arachnidic Serum, Instituto Butantan

Brazil: Soro Antiescorpionico, Instituto Butantan

Spiders

Atrax species

Australia: Funnel-Web Spider Antivenom

Hadronyche species

Australia: Funnel Web Spider Antivenom, CSL Ltd.

Latrodectus mactans (Black widow spider)

Australia: Red-backed spider Antivenom
USA: Antivenin, Merck
Latrodectus hasselti
Redback Spider Antivenoms, CSL Ltd.
Latrodectus indistinctus
South Africa: Spider Antivenoms, SAIMR
Laitrodectus species
Mexico: Aracmyn, Bioclon
Loxosceles *species*
Mexico: Aracmyn, Bioclon
Loxosceles (*reclusa, rufescens*)
Brasil: Anti Arachnidic Serum
Loxosceles (*laeta, rufipes*)
Peru: Antiloxoscelico

TABLE A32-1. Worldwide Availability of Scorpion and Spider Antivenom [14, 16, 44, 58]

Loxosceles Species (*Loxosceles Reclusa, Loxosceles Laeta, Loxosceles Rufescens, Loxosceles Arizonica, Loxosceles Unicolor*)

Envenomation by the brown recluse spider *Loxosceles reclusa* , is associated with low, but significant, morbidity, particularly in the southeast United States. Anti-*Loxosceles* Fab blocks dermonecrosis in a rabbit model, but only if it is given within 24 to 48 hours of envenomatio in one study or as late as 48 hours in another study.[24, 49] However, comparisons do not reveal significant differences between dapsone- and antivenom-treated animals and suggest that a combination may be the best therapy.[15, 49] No commercially available antivenom exists in North America for treatment of *Loxosceles* envenomation. The late presentation of patients with necrotic lesions from a spider bite and the uncertainty of

the genus of the arthropod vector make antivenom use for *Loxosceles* difficult to study. The Instituto Butantan in Brasil has produced an antivenom for *L. reclusa* and *L. rufescens.*

Summary

The indications for antivenom administration in both spider and scorpion envenomations are controversial. The decision to use antivenom should b individualized to the patient, weighing the risk of giving a foreign immune serum, the level of available supportive care, the cost of supportive care, and the cost of obtaining or importing antivenom. The preferred route of administration is intravenous. One to two vials is the recommended dose for most antivenoms; higher doses may be needed to alleviate symptoms

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Chapter 116
Marine Envenomations

D. Eric Brush

A 28-year-old man was stung on the lateral surface of his right hand by a lionfish when he reached into his tropical fish aquarium to adjust the aerator. Within seconds he experienced severe pain and swelling of his hand. En route to the hospital the patient applied an ice pack. In the emergency department he was awake, alert, and in considerable distress. His vital signs were: blood pressure, 150/90 mm Hg; pulse, 110 beats/min; respiratory rate, 18 breaths/min; oral temperature, 98.6Â°F (37Â°C).

Three small linear puncture marks, approximately 8 mm apart, were located on the lateral surface of the patient's right hand. The hand was swollen and erythematous. Neurovascular examination of the hand was normal. (See ILLIONFISH in the Image Library at http://www.goldfrankstoxicology.com.)

The hand was immersed in water that had been heated to 110Â°F (43.3Â°C). The immersion resulted in pain relief within 5 minutes. However, the pain recurred when the water cooled to room temperature. The patient received a diphtheria-tetanus toxoid

vaccination and was discharged 4 hours after arrival to the emergency department. No systemic signs had developed, and his pain was significantly relieved. He was instructed to take ibuprofen 400 mg every 6 hours, for pain and to have his hand examined by his private physician the next day.

Human encounters with venomous marine creatures are commonplace and may result in serious clinical effects. Injuries may arise from direct toxin effects and from mechanical destruction from the stinging apparatus. Significant morbidity and documented deaths have occurred following envenomation with spiny fish, cone snails, octopi, sea snakes, and several species of jellyfish. Despite significant advances in basic science research regarding the biochemical nature of marine toxins and their mechanisms of action, our knowledge of clinical effects in humans, and the optimal therapies for human envenomation, remain limited. Evidence for effective treatment is primarily derived from in vitro and in vivo animal research without the benefit of controlled human trials. However, current research in toxinology (the study of toxic proteins from microbial, plant, and animal origin) coupled with clinical observations provides information that can translate into reduced morbidity and mortality associated with these injuries.

Invertebrates

Cnidaria

The phylum *Cnidaria* (formerly *Coelenterata*) includes more than 9000 species, of which approximately 100 are known to cause injury in humans. They are commonly referred to as *jellyfish;* however, their phylogenetic designations separate â€œtrue jellyfishâ€• and other organisms into distinct classes (Table 116-1) (see ILJELLYFISH in the Image Library). All species possess microscopic cnidae (Greek knide = nettle), which are highly

specialized organelles consisting of an encapsulated hollow barbed thread bathed in venom. Thousands of these stinging organelles, called *nematocysts* (or *cnidoblasts*), are distributed along tentacles. A trigger mechanism called a *cnidocil* regulates nematocyst discharge. Pressure from contact with a victim's skin, or chemical triggers such as osmotic changes, stimulates discharge of the thread and toxin from its casing. Penetration of flesh leads to hypodermic venom delivery. Nematocysts of most *Cnidaria* are incapable of penetrating human skin, rendering them harmless. *Cnidaria* causing human envenomation, such as the box jellyfish, discharge threads capable of penetrating into the papillary dermis of human skin.[132]

Cubozoa

Members of the class *Cubozoa* are not true jellyfish. Animals in the *Cubomedusae* order have a cube-shaped bell with 4 corners, each of which supports between 1 and 15 tentacles. Species from this order produce the greatest morbidity and mortality of all *Cnidaria*. The order has two main families of toxicologic importance: *Chirodropidae* and *Carybdeidae*.

The *Chirodropidae* family is well known for the box jellyfish *Chironex fleckeri* (Greek cheiro = hand, Latin nex = murderer, is known as â€œassassin's handâ€•). The species was named in honor of Dr. Hugo Flecker, a physician from Cairns, Australia.[128] When full grown, its bell measures 25 to 30 cm in diameter, and 15 tentacles are attached at each corner of the bell. These tentacles may extend up to 3 m in length. Another member of this family is *Chiropsalmus quadrigatus*, the sea wasp. Its pale blue color makes detection in water nearly impossible.

The *Carybdeidae* family is most notable for *Carukia barnesi*, the Irukandji jellyfish. It is named in honor of Dr. Jack Barnes, who identified the species as the cause of a severe systemic syndrome following stings among a tribe of Aboriginal people (the Irukandji)

in the Cairns region of northern Australia.[59] Its small size, with a bell diameter of 2.5 cm, makes detection in the water difficult.

Hydrozoa

The *Hydrozoa* class, like the *Cubozoa*, are not true jellyfish; however, they are capable of inflicting considerable pain and even death in humans. The order *Siphonophora* (*Physaliidae* family) includes two unusual creatures of toxicologic concern:

Physalia physalis, the Portuguese man-of-war, and its smaller counterpart, *Physalia utriculus*, the bluebottle. They are pelagic (floating) colonial *Hydrozoa*, meaning they exist as a colony of multiple hydroids (*Cnidaria* is a polyp as the dominant life phase) in a formed mass. The easily recognizable blue sail that floats above the surface of the water is filled with nitrogen and carbon monoxide. Tentacles of *P. physalis* may reach lengths in excess of 100 ft and contain more than 750,000 nematocysts in each of its numerous tentacles (up to 40). *Physalia utriculus* has only one tentacle, which measures up to 15 m.

TABLE 116-1. Cnidaria

Latin Name	Common Name	Habitat[b]
Cubozoa class		
Chironex fleckeri[a]	Box jellyfish	Tropical Pacific Ocean, Indian Ocean, Gulf of Oman

Carukia barnesi[a]	Irukandji jellyfish	North Australian coast
Chiropsalmus spp[a]	Sea wasp or fire medusa	North Australian coast, Philippines, Japan, Indian
C. quadrigatus *C. quadrumanus*		Ocean, Gulf of Mexico, Caribbean, and Puerto Rico
Carybdea alata	Hawaiian box jelly	Hawaii
Carybdea rastoni	Jimble	Australia
Hydrozoa class		
Physalia physalis[a]	Portuguese man-of-war	Eastern US Coast from Florida to North Carolina, Gulf of Mexico, Australian coastal waters (rare reports)
Physalia utriculus	Bluebottle	Tropical Pacific Ocean, particularly Australia

Millepora alcicornis	Fire coral	Wide spread in tropical waters, including Caribbean
Scyphozoa class		
Chrysaora quinquecirrha	Sea nettle	Chesapeake Bay, widely distributed in temperate and tropical waters
Stomolophus meleagris	Cabbage head or cannonball jelly	Gulf of Mexico, Caribbean
Stomolophus nomura[a]		Yellow Sea between China and South Korea
Cyanea capillata	Lion's mane or hair jelly	Northwest US coast up to Arctic Sea, Norwegian and British coastlines
Pelagia noctiluca	Mauve stinger or purple-striped jelly	Caribbean

Linuche unguiculata	Thimble jelly	Florida, Mexico, and Caribbean
Anthozo[a] class		
Anemonia sulcata	European stinging anemone	Eastern Atlantic, Mediterranean, Adriatic Sea
Actinodendron plumosum	Hell's fire anemone	South Pacific
Actinia equina	Beadlet anemone	Great Britain, Ireland
[a]Well-documented human fatalities [b]Represents most common areas where stings are reported.		

The *Milleporina* order is well known for the sessile *Millepora alcicornis*, fire coral, which also exists as a colony of hydroids. It appears much like true coral and has a white to yellow-green lime carbonate exoskeleton. Small tentacles protrude through minute surface gastropores. The overall structure ranges from 10 cm to 2 m.

Scyphozoa

True jellyfish belong to the class *Scyphozoa* and are extremely diverse in size, shape, and color. Common varieties known to envenomate humans are *Cyanea capillata* (lion's mane or hair jelly), *Chrysaora quinquecirrha* (sea nettle), and *Pelagia noctiluca*

(mauve stinger). The mauve stinger is easily recognized; it appears pink in daylight and phosphorescent at night. Larvae of certain *Linuche linguiculata* cause sea bather's eruption (SBE). The larvae are pin-head sized and are seen only when they are grouped in large numbers near the surface of the water.

Anthozoa

The *Anthozoa* class has a diverse membership, including true corals, soft corals, and anemones. Only the anemones are of toxicologic concern. They are common inhabitants of reefs and tide pools and attach themselves to rock or coral. Armed with modified nematocysts known as *sporocysts* located on their tentacles, they can produce stings similar to those of organisms from other *Cnidaria* classes.

History and Epidemiology

Stings from *Cnidaria* represent the overwhelming majority of marine envenomations. In Australia, approximately 10,000 stings per year are recorded from *Physalia* spp alone.[54] Most *Cnidaria* stings occur during the warmer months of the year. Stings occur with greatest frequency on hotter-than-average days with low winds, particularly during times of low precipitation. â€œStinger netsâ€• are used in high-risk areas of the Australian coastline; however, one study reported that 63% of stings requiring medical attention occurred within netted waters.[84] Each stinger season, the Royal Darwin Hospital in Australia treats approximately 40 patients with stings.[40] A prospective evaluation of stings presenting to that hospital during a 12-month period from 1999â€“2000 revealed that 70% resulted from the box jellyfish. The remaining 30% involved other *Cubozoa* such as *C. barnesi*.[103] Although this finding may indicate a predominance of box jellyfish as the cause of stings, it also suggests that stings from box jellyfish are more severe and require medical attention with

greater frequently than stings from other *Cubozoa.*

Cases of sea bathers eruption (SBE) a stinging rash from *Cnidaria* larvae, occur in clusters. They display variation in intensity and frequency from year to year, as exemplified by a 25-year hiatus during which no cases were reported in Florida.[138] In 1992, more than 10,000 cases of SBE were seen in south Florida, with similar peaks in the 1940s and 1960s. Cases of SBE also are reported in Cuba, Mexico, the Caribbean, and occasionally in Long Island, New York.

Cnidaria common to the United States include the Portuguese man-of-war and sea nettle. Other species are widely distributed throughout the tropical and temperate waters of the globe (Table 116-1). Locations with documented deaths include the United States (Florida, North Carolina, Texas), Australia, the Indo-Pacific region (Malaysia, Langkawi Islands, Philippines, Solomon Islands, Papua New Guinea), and the coast of China. Since 1884 the estimated number of deaths in Australia attributed to *C. fleckeri* is approximately 70.[54,83] An estimated 2â€“3 deaths per year occur in Malaysia from an unknown species.[54] Approximately 20â€“40 deaths are reported yearly in the Philippines from an unidentified species of the *Chirodropidae* family.[54] Three deaths are well documented from *P. physalis* in the United States (Florida, North Carolina).[22,54,131] One death from *Chiropsalmus quadrumanus* occurred along the coast of Texas.[12] Eight fatalities in the Bohai waters of China (Yellow Sea) have been reported from *Stomolophus nomurai*.[54,151] Although *Chirodropidae* are found off the western coast of Africa, no fatalities in that region are documented.

Pathophysiology

Cnidaria venoms contain a variety of components that may induce dermanecrosis, myonecrosis, hemolysis, or cardiotoxicity,

depending on the particular species. In rats, *C. fleckeri* venom evokes transient blood pressure elevation, followed by hypotension and cardiovascular collapse within minutes.[107,109] Other effects in animals include decreased inotropy, cardiac conduction delay, ventricular tachycardia, and decreased coronary artery flow.[40] However, experiments using the most pure venom extracts without contamination from tentacle material demonstrate cardiovascular collapse without electrocardiographic changes.[109] *Chironex fleckeri* venom also possesses dermanecrotic and hemolytic fractions, although hemolysis in humans is not documented.[9] Two myotoxins from *C. fleckeri* cause powerful sustained muscle contractions in isolated muscle fibers.[44] Isolated heart models using *C. fleckeri* venom suggest its mechanism of action is nonspecific enhancement of cation conductance leading to increased Na^+ and Ca^{2+} entry into cells.[99] Other in vitro work confirms increased Na^+ permeability in cardiac tissue.[61]

Carukia barnesi, the Irukandji jelly, likely induces its dramatic vasopressor effects via catecholamine release. In rats the venom produces a pressor response that is blocked by $Î±_1$-adrenoreceptor antagonism.[108] The pressor response is not dose dependent; therefore, catecholamines in the venom would not explain this effect. No electrocardiographic abnormalities occurred in envenomated rats.

Venom from *Physalia* spp blocks neural impulses in isolated frog sciatic nerve[80] and produces ventricular ectopy, cardiovascular collapse, hyperkalemia, and hemolysis in dogs.[70] *Physalia* spp venom inhibits Ca^{2+} entry into the sarcoplasmic reticulum.[80] Similar mechanisms are proposed for *Chrysaora, Chiropsalmus*, and *Stomolophus. Chrysaora quinquecirrha* venom contains a 150-kDa polypeptide that induces atrioventricular block[18] and produces myocardial ischemia, hypertension, dysrhythmias, and nerve conduction block,[23,24] as well as hepatic and renal necrosis.[98] *Chrysaora quinquecirrha*â€“induced hepatotoxicity is believed to be a direct toxin effect not mediated by pore formation or Ca^{2+}

channel effects.[72] Equinatoxin II (EqtII), found in the venom of the anemone *Actinia equina*, induces pore formation in cell membranes, causing hemolysis.[1] This protein belongs to a group of anemone lysins, known as *actinoporins*, which bind to cell membranes and form pores via oligimerization.[88]

Symptoms resulting from stings may be partly immune mediated. Elevated serum antiâ€“sea-nettle immunoglobulin IgM, IgG, and IgE may persist for years in patients with exaggerated reactions to stings compared to controls.[19] A direct correlation between titers against *Chrysaora* and *Physalia* and severity of a visible skin reaction to envenomation, strongly suggests an allergic component.[120] Elevated IgG titers were demonstrated in one death from *P. physalis*.[131] Dermatonecrosis from *C. fleckeri* may involve the release of leukotrienes and other arachidonic acid derivatives and direct cell damage.[41] Postenvenomation syndromes may result from an exaggerated, prolonged, aberrant T-cell response.[25,26] Erythema nodosum has been reported following a sting from *P. physalis*, lending further support to a immunologic component to symptoms.[5] SBE displays a characteristic delay in onset of symptoms and can be effectively treated with steroids, suggesting a primary immune-mediated process for this entity. This is further supported by histopathology which shows the presence of perivascular and interstitial infiltrates with lymphocytes, neutrophils, and eosinophils.[148]

Clinical Manifestations

Most patients with stings are treated beachside and never require hospital treatment. The vast majority of patients with stings who seek medical care have severe pain, but are not systemically poisoned.[40] However, severe systemic manifestations may develop following stings from *C. fleckeri*, *C. barnesi*, *P. physalis*, and a few other *Cnidaria.*

Envenomation by *C. fleckeri* causes the most severe pain and is

frequently associated with systemic toxicity. Common symptoms include immediate severe pain, followed by an erythematous whiplike linear rash with a â€œfrosted ladderâ€• appearance. The pain often is excruciating and may require parenteral analgesia. Systemic symptoms include nausea, vomiting, muscle spasms, headache, malaise, fever, and chills. Pain generally abates over several hours, although the rash may persist for days. In a prospective series of *C. fleckeri* stings, 58% manifested delayed hypersensitivity reactions in the form of an itchy maculopapular rash at 7â€“14 days.[103] Most resolved spontaneously; some were treated with antihistamines and topical corticosteroids.

Some estimates cite a fatality rate following *C. fleckeri* envenomation of 15%â€“20%.[115] This likely represents a gross overestimation, given the low number of documented fatalities in the context of the extraordinary number of yearly stings. A prospective study of stings from *Cubozoa* over one year in Australia revealed no dysrhythmias, pulmonary edema, or death.[103] No patient received antivenom, and analgesia was the only pharmacotherapy implemented. Hospital admission was not required for any victim. Although most victims suffer only local severe pain, serious systemic toxicity occurs occasionally, and may include vertigo, ataxia, paralysis, delirium, syncope, and respiratory distress. Hypotension, dysrhythmia, pulmonary edema, hemolysis, and acute renal failure characterize the clinical findings. The last 10 reported deaths from *C. fleckeri* occurred in children, suggesting vulnerability due to lower body mass.[40] Fatality is documented following as little as 4 m of tentacle markings.[132] Death, when it occurs, typically is rapid leaving, many victims unable to reach shore. Cardiac arrest and pulmonary edema may develop in young healthy patients without prior cardiopulmonary disease.[76,87,147] Survival is possible with immediate cardiopulmonary resuscitation (CPR).[146] *Chiropsalmus quadrumanus*, a close relative of the box jellyfish, induces symptoms that parallel *C. fleckeri* stings, including pulmonary

edema and death.[12]

Irukandji syndrome is a particularly severe form of envenomation following *Cubozoa* stings. The causative species was isolated with brave self-experimentation by Dr. Jack Barnes using the *Cubomedusae* named *Carukia barnesi* in his honor. His conclusion that *C. barnesi* causes Irukandji was confirmed in a retrospective review of 50 cases, 39 of which had skin scrapings consistent with *C. barnesi*.[73] However, one patient who died had nematocysts that could not be identified, suggesting the possible existence of another causative species. This syndrome was thought to be isolated to Australia; however, three recent cases of Irukandjilike syndrome stemming from an unidentified organism were reported in the Florida Keys.[67]

Individuals afflicted with Irukandji syndrome often notice a mild sting while they are in the water; however, skin findings typically are absent. Severe systemic symptoms develop within 30 minutes and mimic a catecholamine surge: tachycardia, palpitations, hyperpnea, headache, pallor, restlessness, apprehension, sweating, and a sense of impending doom. A prominent feature is severe whole-body muscle spasms that come in waves and preferentially affect the back. Spasms are described as unbearable and frequently require parenteral analgesia. Symptoms generally abate over several hours. Admission rates in patients presenting to medical care can exceed 50%.[84] Hypertension is universal and may be severe, with systolic blood pressures well over 200 mm Hg. Two fatalities are described involving severe hypertension (systolic 280/150 mm Hg and 230/90 mm Hg) resulting in intracranial hemorrhage.[50,73] Hypotension frequently follows, requiring vasopressor support. Pulmonary edema results from myocardial dysfunction and is a potentially severe complication that can develop within 2 hours or be delayed several hours. Echocardiograms consistently reveal global ventricular dysfunction,[84,86,90] although focal hypokinesis may be present.[73]

Normal cardiac function typically returns after several days.[85] In a retrospective review of 116 cases presenting to Cairns Base Hospital, 22% of patients had elevated troponin I measurements,[73] although some reviews cite a frequency as high as 78%.[86] Nonspecific electrocardiographic changes were frequently noted in those reviews.

Physalia physalis envenomation typically causes severe pain, bullae, and skin necrosis (see ILJELLYFISH in the Image Library). Systemic symptoms include weakness, numbness, anxiety, headache, abdominal and back spasms, lacrimation, nasal discharge, diaphoresis, vertigo, hemolysis, cyanosis, renal failure, shock, and rarely death. Some patients experience local numbness and paralysis of the affected extremity that resolves spontaneously.[74] As with serious *C. fleckeri* stings, cardiovascular collapse and death occur within minutes of envenomation.[22] However, fatalities can be delayed several days following envenomation and may stem from complications such as myocardial infarction and aspiration pneumonia.[131] An unusual presentation is reported of a 4-year-old child who was stung along the North Carolina coast and developed massive hemolysis requiring red blood cell transfusions, followed by renal failure necessitating temporary dialysis.[68] In contrast to *P. physalis, P. utriculus* stings typically are mild and relieved with ice, although systemic toxicity occasionally develops.[56]

Millepora alcicornis (fire coral) is a common cause of stings in southern US and Caribbean waters. Although it belongs to the same phylogenetic class as *P. physalis*, it produces far less significant injuries. It is a nuisance to divers who touch what they perceive to be harmless coral and then suffer moderate burning pain for hours. Untreated pain generally lessens within 90 minutes, with skin wheals flattening at 24 hours and resolving within 1 week. Hyperpigmentation may persist up to 8 weeks.[15] The feather hydroid is the most numerous of the *Hydrozoa* and produces only mild stings.[92]

True jellyfish typically are less harmful to humans than *Cubozoa* or *Hydrozoa*. However, systemic toxicity and occasional deaths are reported from certain species such as *S. nomurai*, *C. capillata*, *C. quinquecirrha*, and *P. noctiluca*. *Stomolophus meleagris* is a common cause of stings; however, its weak venom produces only minor injury.[4]

Larvae of *Linuche unguiculata* are the primary cause of a pruritic papular eruption on the skin of sea bathers in Florida, occurring mostly in areas covered by a bathing suit as a result of larvae trapped under the garments. Cases were first noted in 1949 and referred to as SBE.[121] The larvae appear as pin-sized brown to green-brown spheres in the upper 2 inches of the water and typically go unnoticed. In a retrospective review, 50% of people reported a stinging sensation while they were in the water, and 25% reported itching upon exiting the water.[148] The remainder of patients developed symptoms within 11 hours. Skin lesions develop within hours of itching and appear as discrete, closely spaced papules, with pustules, vesicles, and urticaria. Most lesions occur in areas covered by the bathing suit; however, folds of skin such as the axilla, breasts, and neck may be affected. Itching often is severe and prevents sleep. New lesions may continue to develop over 72 hours. The average duration of symptoms is just under 2 weeks, and a small percentage of patients experience a recurrence of lesions several days later. Systemic symptoms such as chills, headache, nausea, vomiting, and malaise may occur. (See ILSEABATHERS in the Image Library.)

Following stings from sea anemones, victims may develop immediate or delayed pain. Skin findings range from mild erythema and itching to ulceration. A review of 55 stings from *Anemonia sulcata* presenting to a hospital in Yugoslavia (Adriatic Sea) revealed that, in addition to the local skin findings, many patients suffered nausea, vomiting, muscle aches, and dizziness.[89] Larvae of the anemone *Edwardsiella lineata* also cause SBE among

ocean swimmers in Long Island, New York. The hell's fire anemone *Actinodendron plumosum* is native to the South Pacific and causes significant local pain. One death occurred in the Virgin Islands following envenomation from an unknown species described as a â€œwhite anemone with blue tips.â€• The onset of hepatic and renal failure was rapid and required transplantation, after which the patient died.[63] Nonfatal elevation of hepatic enzyme concentrations following anemone sting also is reported.[16]

Diagnostic Testing

Laboratory evaluation may be warranted in patients suffering systemic toxicity following *Cnidaria* envenomation. Serial measurement of serum cardiac markers should be obtained from victims of Irukandji stings or others with consequential cardiovascular toxicity. Following severe stings from a variety of *Cnidaria*, urinalysis, hematocrit, and serum creatinine should be considered to detect the presence of hemolysis and subsequent renal injury. Chest radiography is indicated for complaints of dyspnea or abnormalities in oxygenation. Venom assays are not available, and serum antibody titers are not clinically useful.

Management

Initial interventions after *Cnidaria* envenomation should follow standard management strategies. Secondary measures are directed toward the prevention of further nematocyst discharge, which could intensify pain and enhance toxicity. Many topical agents have been used for this purpose, including

sea water, vinegar, Stingose, methylated spirits, ethanol, isopropyl alcohol, dilute ammonium hydroxide, urine, sodium bicarbonate, papain, shaving cream, and sand.

Vinegar is a common first-line treatment for topical application following *Cnidaria* stings. In vitro trials with *C. fleckeri* tentacles

demonstrate complete irreversible inhibition of nematocyst discharge following a 30-second application.[69] Additional study findings include massive nematocyst discharge with application of urine or ethanol, and no effect on discharge with use of sodium bicarbonate. Followup in vivo experiments demonstrate that vinegar is effective for other *Cubozoa*, including Morbakka (large *Cubozoan* in Australia),[49] *Carybdea rastoni*,[52] and *C. barnesi*.[53] Although massive nematocyst discharge occurs when vinegar is applied to *C. capillata* tentacles in vitro clinical exacerbation following this treatment is not reported in humans.[48] Massive discharge also occurs with *C. quinquecirrha*.[28] A smaller degree of discharge (30%) occurs with *P. physalis*,[56] whereas nematocysts of *P. utriculus* are unaffected by application of vinegar.[69]

Stingose is a commercially available product designed to counteract venom of insects, bees, stinging plants, and marine stingers. It is an aqueous solution of 20% aluminum sulfate and 1.1% surfactant. Its proposed mechanism of action is denaturing of proteins and long-chain polysaccharides via interaction with the Al^{3+} ion, as well as osmotic removal of venom. A human volunteer trial involving stings from live tentacles of *C. fleckeri* demonstrated pain relief within 5 seconds of Stingose application.[71] Similar results were achieved following treatment of stings from *C. quinquecirrha*. A field trial that included 17 *C. fleckeri* and 150 *P. utriculus* sting victims who were treated with Stingose immediately following injury was conducted. All victims reported rapid relief. However, placebo or alternative therapies were not used in this case series. The efficacy of treatment with vinegar, Stingose, methylated spirits, and salt water was measured in human volunteers following forearm application of *P. physalis* tentacles.[141] Vinegar demonstrated superior pain control compared to Stingose, whereas methylated spirits increased pain. The study assessed pain relief only and did not investigate the effects of the treatments on nematocyst discharge or systemic toxicity.

In many cases the identity of the â€œjellyfishâ€• causing injury is unknown. In those cases, therapy must be guided by geographic location. In the United States, where *P. physalis* and *C. quinquecirrha* are of greatest consequence, sea water should be used to aid in tentacle removal given that vinegar enhances nematocyst discharge. In the Indo-Pacific region, where *C. fleckeri* and *C. barnesi* are of greatest concern, vinegar should be the primary agent used. Following a 30-second application, adherent tentacles must be carefully removed. This can be accomplished with a gloved or towel-covered hand, or with sand and gentle scraping with a credit card or other blunt straight-edged tool.

In a nonrandomized trial, ice packs provided rapid effective relief for patients with mild-to-moderate pain from *Cnidaria* stings.[45] Patients with severe pain were less likely to benefit from ice packs. The venom of *C. fleckeri* and *C. quinquecirrha* is heat stable; therefore, hot water is ineffective for venom neutralization and may increase pain.[17]

Pressure immobilization bandaging is a technique that applies sufficient pressure to a wound to impede lymphatic drainage and prevent the entrance of toxin into systemic circulation. It typically has been used for snake bites, and its use following *Cnidaria* stings has sparked controversy. Given the rapid onset of symptoms, the utility of a technique that impedes lymphatic drainage is unlikely to provide benefit. Although the technique would be used only after tentacle removal, some microscopic nematocysts remain adherent to the skin after visible tentacle are removed. In vitro data investigating the effect of pressure on discharged nematocysts demonstrate not only that discharged nematocysts still contain venom, but that applying pressure forces more venom down the hollow tube.[105] This finding is correlated clinically as patients can deteriorate following pressure immobilization bandaging.[55] Given the lack of evidence suggesting benefit, coupled with clear, in vitro, evidence of increased venom delivery with this technique, it should not be used for treatment of

Cnidaria stings.

Box jellyfish antivenom is sheep-derived whole IgG raised against the â€œmilkedâ€• venom of *C. fleckeri.* It has been available in Australia since 1970. Combining *C. fleckeri* venom with box jellyfish antivenom prior to injection into pigs prevents all toxicity.[137] An isolated chick muscle experiment demonstrates that box jellyfish antivenom prevents the neurotoxicity and myotoxicity from *C. fleckeri* following pretreatment; however, there is no â€œrescue effect.â€•[106] Given that antivenom in humans is always used as a rescue therapy, this research raises concerns regarding efficacy in the clinical setting. Pretreatment of rats with box jellyfish antivenom prevented cardiovascular collapse in 40%, but did not blunt the initial hypertensive effect.[107] In vitro data demonstrate that box jellyfish antivenom neutralizes the dermonecrotic, hemolytic, and lethal fractions of venom from *Chiropsalmus* spp; however, the venom of *P. physalis* and *C. quinquecirrha* were not neutralized.[10] Other in vitro and in vivo data demonstrate incomplete neutralization of *Chiropsalmus* spp venom.[10,106]

There are no controlled studies in humans evaluating the efficacy of box jellyfish antivenom in the treatment of *C. fleckeri* envenomations, nor is there convincing evidence that its use has saved human lives. Despite the frequency of hospital visits for stings from *C. fleckeri* in Australia, the use of box jellyfish antivenom is rare.[40] Evidence for its efficacy stems from case reports suggesting that pain abates rapidly after administration.[14,147] Although box jellyfish antivenom may improve pain control, patients still may require parenteral narcotics for analgesia following antivenom administration.[11] Significant morbidity and mortality still occur despite antivenom use.[39,87,132] Case reports of box jellyfish antivenom use for *C. barnesi* stings demonstrate no apparent benefit.[47]

Many serious stings occur in the Northern Territory of Australia,

where stinger nets are not commonly used. Distance from medical care limits the ability to obtain antivenom in a timely fashion.[40] Although box jellyfish antivenom can be administered by paramedics via intramuscular (IM) injection,[55] poor IM absorption and incomplete venom neutralization with antivenoms, as well as delayed peak serum concentrations, limit the utility of this approach.[114] The amount of antivenom required to neutralize twice the lethal dose in humans, is estimated to be 12 vials.[40] The manufacturer recommends treating initially with 1 ampule intravenously (IV) diluted 1:10 with saline or 3 undiluted ampules (1.5â€“4 mL each) IM at 3 separate sites, if IV access is unavailable. Some authors who have treated multiple patients with antivenom suggest treating coma, dysrhythmia, or respiratory depression with 1 ampule IV, titrating up to 3 ampules with continuation of CPR in patients with refractory dysrhythmia until a total of 6 ampules have been administered.[103] For less serious envenomations, patients can be given 1 ampule if ice packs and parenteral analgesia prove ineffective.[103] Serious adverse events or delayed sequelae following the use of IV antivenom are uncommon, although allergic reactions are a consideration.[133]

Verapamil was considered a treatment for *C. fleckeri* stings based on evidence that calcium entry into cells is an important mechanism of toxicity. One animal model demonstrated synergy with use of verapamil in combination with box jellyfish antivenom,[27] whereas another showed verapamil pretreatment as well as rescue prolonged survival.[20] This is in contrast to other models demonstrating that verapamil negates the benefits of antivenom[107] and increases mortality.[137] Verapamil also has been tested in animals with *C. quinquecirrha* envenomation but demonstrated no benefit.[98] Interestingly, addition of magnesium to antivenom for treatment of *C. fleckeri* envenomation in rats prevented cardiovascular collapse in 100%, suggesting that magnesium may have a role in the treatment of stings from this

species.[107] Given that animal data are inconsistent with regard to verapamil and that hypotension may develop with severe envenomation, use of calcium channel blockers is not recommended for treatment of *C. fleckeri* stings.

Treatment for Irukandji syndrome should focus on analgesia and blood pressure control. Several modalities for control of severe hypertension have been suggested and include phentolamine, IV magnesium, and nitroglycerin.[38,51] No single therapy demonstrates superior efficacy, although titratable agents are preferred because hypotension may occur in later stages of toxicity.

Mollusca

The phylum *Mollusca* (Latin mollis = soft) includes the classes *Cephalopoda* (octopus, squid, and cuttlefish) and *Gastropoda* (cone snails). Of the cephalopods, only the blue-ringed octopus *Hapalochlaena maculosa* and the greater blue-ringed octopus *Hapalochlaena lunulata* are of toxicologic concern. Of the 400 species of cone snails that belong to the genus *Conus*, 18 are implicated in human envenomations.

History and Epidemiology

The blue-ringed octopus normally is yellow-brown in color, but it develops iridescent blue rings when it is threatened. It is not aggressive and only causes envenomation in humans when it is handled. A 1983 review of reported octopus envenomations uncovered a total of 14 cases, all of which occurred in Australia.[142] There were 2 deaths[60,130] and 4 serious envenomations. Other reviews suggest up to 7 deaths may have occurred prior to 1969, some outside Australia.[43] The blue-ringed and greater blue-ringed octopus are found in the Indo-Pacific region, primarily in Australian waters. (See ILBLUERING in the Image Library.)

Estimates of reported cone snail envenomations suggest only 15 deaths have occurred worldwide.[46] *Conus geographicus* (fish hunting cone) is the most common species implicated, although *Conus textile* may also cause death in humans. Cone snails are found predominantly in the Indo-Pacific, including all parts of Australia, New Guinea, Solomon Islands, and Philippines. Two deaths from *C. geographicus* occurred in Guam.[82]

Pathophysiology

The octopus salivary gland secretes a toxin that previously was called *maculotoxin.* The structure was later identified as tetrodotoxin.[125] The beak of the octopus creates small punctures in human skin through which venom is introduced. Tetrodotoxin blocks Na^+ conductance in neurons, leading to paralysis. Venom also contains 5-hydroxytryptamine (5-HT), hyaluronidase, tyramine, histamine, tryptamine, octopine, taurine, acetylcholine, and dopamine.[134] Rabbits subjected to bites develop rapid flaccid paralysis without cardiotoxicity and die from asphyxia.[134] Other animal models using venom gland extract demonstrate rapid onset of respiratory muscle paralysis and severe hypotension.[58] Death occurs despite artificial respiration and results from hypotension.

TABLE 116-2. Conus Peptide Targets

Receptor Type	Peptide	Mechanism
Ligand-gated ion channels		
Nicotinic	Î±-Conotoxin M1 M2	Competitive antagonism neuromuscular junction neuronal receptors

5-HT_3	Î±-Conotoxin	Noncompetitive antagonism
NMDA	Conantokins	Inhibits conductance
Voltage-gated ion channels		
Ca^{2+}	Ï‰-Conotoxin	Channel blockade
Na+	Âµ-Conotoxin	Channel blockade
	Î´-Conotoxin	Delayed channel activation
K+	Îº-Conotoxin	Channel blockade
G-protein linked		
Vasopressin receptor	Conopressin-G	Receptor agonism
Neurotensin receptor	Contulakin-G	Receptor agonism

Cone snails have a hollow proboscis that contains a tooth bathed in venom. Envenomation occurs when the shells are handled. The proboscis can extend the length of its shell, thereby envenomating

the hand of someone touching the opposite end of the shell. Any *Conus* species contains approximately 100 peptides or *conotoxins* in its venom. Targets include voltage- and ligand-gated ion channels as well as G-proteinâ€“linked receptors (Table 116-2).[102] Many of these peptides have been used extensively in laboratory research for their ability to selectively target a variety of specific calcium channel subtypes. *Conus imperialis* (worm hunter) has venom that contains a substantial amount of 5-HT, which is not found in any other *Conus* venom tested thus far.[94] This species also contains a vasopressinlike peptide.[100] *Conus* peptides with antinociceptive properties are being used in human trials of chronic pain. Ziconotide (Prialt, Elan Pharmaceuticals) has completed phase III human trials for control of chronic pain via intrathecal infusion pump.[93] Clinical trials with other peptides for treatment of chronic pain are underway.[136]

Clinical Manifestations

The blue-ringed octopus creates 1 or 2 puncture wounds with its chitinous jaws, causing only a small amount of discomfort. A wheal may develop with erythema, tenderness, and pruritus. Tetrodotoxin exerts a curareform effect that causes paralysis while retains normal mental status. Symptoms include perioral and intraoral paresthesias, diplopia, aphonia, dysphagia, ataxia, weakness, nausea, vomiting, flaccid muscle paralysis, respiratory failure, and death. Detailed case reports demonstrate rapid onset of symptoms.[142] Complete paralysis requiring intubation with findings of fixed and dilated pupils is followed within 24 to 48 hours by near-complete recovery of neuromuscular function.[142] In one reported death, a young man placed the octopus on his shoulder. He subsequently noted a small puncture wound, developed dry mouth, dyspnea, inability to swallow, and became apneic. He developed asystole 30 minutes after arrival at the hospital despite artificial ventilation.[60] Another similar bite resulted in symptom onset at 10 minutes, followed by

death at 90 minutes, despite bystander CPR.[134] With less severe envenomations, cerebellar signs may be present without paralysis. Near-total paralysis with intact mentation resolving over 24 hours is described in humans.[134]

Envenomation from cone snails occurs with careless handling or from rummaging through sand. Cone snails are nocturnal feeders, so they may present more of a hazard to night divers. Symptoms range from a slight sting to excruciating pain. Local symptoms include tissue ischemia, cyanosis, and numbness. Systemic symptoms include weakness, diaphoresis, diplopia, blurred vision, aphonia, dysphagia, generalized muscle paralysis, respiratory failure, cardiovascular collapse, and coma. Death is rapid and occurs within 2 hours. Based on military medical records of more than 30 cases predating 1970, the mortality rate approaches 25%, with *C. geographicus* being the most lethal.[82] Other estimates suggest that, without medical care, mortality may reach 70%.[150] Given the rarity of severe human envenomation from cone snails, it is unclear if death results purely from respiratory insufficiency, or if cardiovascular toxicity plays a significant role.

Diagnostic Testing

Laboratory testing following envenomation from octopi or cone snails should be directed by clinical findings. Coma, respiratory failure, and hypotension merit evaluation of serum metabolic parameters, chest radiography, and electrocardiogram. Tetrodotoxin can be detected in the urine or serum using high-performance liquid chromatography with subsequent fluorescence detection, but this assay is not readily available.[101]

Management

Primary interventions include, maintenance of airway, breathing, and circulation. Some authors recommend hot water

(45Â°â€“50Â°C, 113Â°â€“122Â°F) following cone snail stings for pain relief.[82] Unlike *Cnidaria* envenomations, where nematocysts full of venom can persist on the skin and lead to continued venom delivery, stings from the octopus and cone snail mirror those of snake bites, where venom delivery is an immediate and finite event. Therefore, pressure immobilization bandaging may help following octopus or cone stings by decreasing lymphatic spread of toxin without concern for worsening the envenomation.[46] Other measures include local wound care and tetanus prophylaxis. Antivenom is not available for octopus or cone snail venoms.

Echinodermata, Annelida, and Porifera

The *Echinodermata* phylum includes starfish, brittle stars, sea urchins, sand dollars, and sea cucumbers. *Annelida* are segmented worms that include the *Polychaetae* family of bristle worms. Sponges are classified in the *Porifera* phylum. One feature that all three phyla share is the passive envenomation of people who mistakenly handle or step on the animals. Most stings from these creatures are mild.

History and Epidemiology

Echinoderms, annelids, and sponges are ubiquitous ocean inhabitants. The crown-of-thorns starfish *Acanthaster planci* is found in the warmest waters of Polynesia to the Red Sea and is a particularly venomous species because of its sharp spines, which easily puncture human skin. Sea urchins are found in all oceans of the world. Bristle worms such as *Hermodice carunculata* typically are found in tropical waters such as those of Florida and the Caribbean. However, some species live in the frigid waters of Antarctica. The fire sponge *Tedania ignis* is a brilliant yellow-orange sponge found in large numbers in Hawaii and the Florida Keys. Other common American sponges are *Neofibularia nolitangere* (poison-bun sponge or touch-me-not sponge) and

Microciona prolifera (red sponge). *Neofibularia mordens* (Australian stinging sponge) is a common Southern Australian variety. In the Mediterranean, sponges are often colonized with sea anemones, which may be the cause of severe stings.[15]

Pathophysiology

Sea urchins are covered in spines and pedicellariae. The pedicellariae are pincerlike appendages used for feeding, cleaning, and defense. They generally contain more venom than the spines and are more difficult to remove from wounds. Urchins laden with pedicellariae can evoke more severe stings than urchins with less pedicellariae. Venom contained within the spines consists of steroid glycosides, 5-HT, hemolysin, protease, and acetylcholinelike substances. Some species harbor neurotoxins. The most venomous are species of *Diadema*, *Echinothrix*, and *Asthenosoma.* Starfish are less noxious because they generally have short, blunt spiny projections. The crown-of-thorns is the exception, with its longer sharp spines containing toxic saponins with hemolytic and anticoagulant effects as well as histaminelike substances.[135] Sea cucumbers excrete holothurin, a sulfated triterpenoid oligoglycoside, from the anus (organs of Cuvier) as a defense. The toxin inhibits neural conduction in fish, leading to paralysis. Some cucumbers eat *Cnidaria* and subsequently secrete their venom.

Bristle worms have many parapodia that have the appearance, but not the function, of legs. Several bristles extend from each parapodium, which gives the family *(Polychaeta)* its name (poly = many, chaetae = bristles). The bristles may penetrate human skin, leading to envenomation with an unknown substance.

Sponges have an elastic skeleton with spicules of silicon dioxide or calcium carbonate. They attach to the sea floor or coral beds. Toxins include halitoxin, odadaic acid, and subcritine, the nature of which is uncertain.[21] Dried sponges are nontoxic; however, on

rewetting they may cause toxicity even after several years.[129]

Clinical Manifestations

Most injuries from sea urchins are caused by inadvertently stepping on the spines or attempting to handle the animal. An intense burning with local tissue reaction occurs, including edema and erythema. Rarely, with multiple punctures, light-headedness, numbness, paralysis, bronchospasm, and hypotension may occur, although this is not documented in the medical literature.[3] Reports of death are not substantiated with evidence. The Pacific urchin *Tripneustes* has a neurotoxin with a predilection for cranial nerves.[15] Mild elevations of hepatic enzymes are reported in one patient with foot cellulitis from an urchin sting.[149] Small cuts on the skin from handling starfish may allow venom to penetrate, leading to contact dermatitis. The crown-of-thorns may cause severe pain, nausea, vomiting, and muscular paralysis.[92] Handling sea cucumbers leads to contact dermatitis, intense corneal inflammation, and even blindness. Bristle worms are covered in irritating bristles that can cause a reddened urticarial rash. Symptoms typically are mild and resolve over several hours to days.

Contact with the fire sponge, poison-bun sponge, or red-moss sponge causes erythema, papules, vesicles, and bullae, which generally subside within 3â€“7 days. Victims may develop fever, chills, and muscle cramps. Skin desquamation occurs at 10 days to 2 months,[4] with chronic skin changes lasting months.[21] Erythema multiforme and anaphylaxis are uncommon complications but may occur with *Neofibularia* spp.[15] Colonization of sponges with

Cnidaria can lead to dermatitis with skin necrosis, referred to as *sponge diver's disease.*

Management

The primary objective following envenomation from sea urchins and crown-of-thorns starfish is analgesia. Submersion of the affected extremity in hot water (105Â°Fâ€“115Â°F, 40.6Â°C â€“46.1Â°C) is commonly used and administration of oral analgesics generally are sufficient.[46,92] Puncture wounds require radiographic evaluation to locate potential foreign bodies. Spines frequently crumble when extraction is attempted. Intraarticular spines should be surgically removed. Decisions regarding spines in other locations should be influenced by ease of removal, presence of infection, and persistent pain. Tetanus prophylaxis should be addressed. Consideration of antibiotic prophylaxis should be based on degree of injury and patient factors such as diabetes or other immunocompromise. Although most infections likely are secondary to human skin flora, marine flora such as *Mycobacterium marinum* and *Vibrio parahaemolyticus* should be considered potential wound contaminants. Treatment of sponge exposures usually requires only removal of spicules using adhesive tape or the edge of a credit card. Use of antihistamines and topical steroids often provides no relief from stinging sponges.[21]

Vertebrates

Snakes

Sea snakes are members of the class *Reptilia* and are divided into 2 subfamilies: *Hydrophiinae* and *Laticaudinae*. They are close relatives of the cobra and krait. They are generally less than 1 m in length, have a flattened tail, and often are brightly colored. Distinction from eels is made by the presence of scales and the absence of fins and gills. There are 52 species of sea snakes, all of which are venomous. At least 6 species are implicated in human fatalities. The most common species cited in human envenomation is *Enhydrina schistosa*, the beaked sea snake. *Pelamis platurus*, the yellow-bellied sea snake, also is frequently implicated.

History and Epidemiology

The true incidence of sea snake envenomation is unknown because many bites go unreported. Worldwide the number of deaths per year may approach 150, with an overall mortality rate estimated at 3%.[46] In a review of 120 documented bites, 51.7% of victims were fisherman handling nets.[111] The remainder of victims were wading or swimming along the coast line. In another review of 101 bites occurring from 1957â€“1964 in North West Malaysia, more than 50% of bites were from the beaked sea snake, including 7 of the 8 fatal bites in that series, bringing the mortality to 8% prior to the availability of antivenom.[113] However, 31 â€œdry bitesâ€• were excluded, suggesting that the overall mortality is somewhat lower. Of the 20% of patients in that series suffering â€œserious envenomation,â€• half died despite supportive care.[113] A followup series of patients after the introduction of antivenom described 2 deaths out of 11 â€œserious envenomations,â€• suggesting a decreased mortality resulting from this intervention. These were all retrospective reviews of published or personally communicated cases, thereby limiting interpretation.

Sea snakes are common to the tropical and temperate Indian and Pacific Oceans, but also are found along the eastern Pacific Coast of Central and South America and the Gulf of California. In this eastern Pacific region, the yellow-bellied sea snake is the only species known. There are no sea snakes in the Atlantic Ocean. The majority of envenomations occur along the coasts of South East Asia, the Persian Gulf, and the Malay Archipelago (Malaysia). Snakes tend to inhabit the turbid coast lines and deeper reefs of these regions.

Pathophysiology

All sea snakes have small front fangs. Their venom is neurotoxic, myotoxic, nephrotoxic, and hemolytic. Known components of the venom include acetylcholinesterase, hyaluronidase, leucine

aminopeptidase, 5â€²-nucleotidase, phosphodiesterase, and phospholipase A. The neurotoxin is a highly stable 6000- to 8000-dalton protein similar to that of the cobra and krait. In mice, beaked sea snake venom is 4â€“5 times more potent than cobra venom based on a microgram/kilogram ratio; however, cobra venom yield is greater.[31] Venom homology exists across many species.[75] The neurotoxin acts postsynaptically via acetylcholine (ACh) receptor blockade at the neuromuscular junction and presynaptically causes initial release, followed by inhibition of ACh release.[97,116,143] In vitro cell research shows direct nephrotoxicity of crude venom, which may partially account for the nephrotoxicity seen clinically.[124] Renal failure likely is a combination of rhabdomyolysis and direct venom effects on the kidneys.

Clinical Manifestations

Sea snakes generally are docile, except when they are provoked, or during the mating season. Bites typically are painless or inflict minimal discomfort. Between 1 and 4 fang marks are common; however, up to 20 fang marks are possible as a result of multiple bites. The diagnosis can be obscured, because victims may not associate the slight prick following the bite with later onset of ascending paralysis. Symptom onset may occur within minutes, although a delay of up to 6 hours is possible. Although paralysis results from the neurotoxic fraction of the venom, muscle destruction stemming from myotoxic fractions causes painful, stiff muscle movements and myoglobinuria, which are hallmarks of sea snake myotoxicity. Myoglobinuria develops between 30 minutes and 8 hours after the bite. Other classic symptoms include ascending flaccid paralysis, dysphagia, trismus, ptosis, aphonia, nausea, vomiting, fasciculations, and ultimately respiratory insufficiency, seizures, and coma. Morbidity and mortality stem from respiratory paralysis, aspiration, rhabdomyolysis, and renal failure.

Diagnostic Testing

Laboratory diagnostics are directed toward identifying hemolysis, myonecrosis, hyperkalemia, and renal failure. Serum electrolytes, creatinine, and creatine phosphokinase, as well as hematocrit and urinalysis, should be obtained. Elevated concentrations of hepatic enzymes may indicate severe envenomation. Serial measurement of these parameters is recommended.

Management

Prehospital management of sea snake bites mirrors treatment of terrestrial snake bites and includes immobilization of the extremity and consideration of a pressure immobilization bandage to impede lymphatic drainage. Currently no data regarding the efficacy of this technique for sea snake envenomations are available. Tourniquets that impede venous or arterial flow are not recommended and may be detrimental. Airway and respiratory effort should be closely monitored because paralysis can develop rapidly.

The most commonly used antivenoms for sea snakes are equine IgG Fab fragments derived from the beaked sea snake (*E. schistosa*) or terrestrial tiger snake (*Notechis scutatus*) (Table 116-3). In vitro experiments demonstrate that sea snake antivenom is effective for neutralizing all species of sea snakes tested (*Praescutata*

viperina in Thailand, *Pelamis platurus* in Central America, *Laticauda semifasciata* in the Philippines, *Laticauda laticaudata* in Japan, *Hydrophis cyanocinctus*, *Lapemis hardwickii*).[140] Optimal neutralization occurs within the subfamily *Hydrophiinaem*, which contains *E. schistosa*; however, effective neutralization is demonstrated within the subfamily *Laticaudinae*. Terrestrial tiger snake antivenom also can neutralize sea snake venom in vitro. Based on the volume of antivenom required, tiger snake

antivenom was more effective for neutralization of all sea snake venoms tested except that of the beaked sea snake, for which sea snake antivenom was more effective.[7] This finding is expected because the beaked sea snake venom is the antigen used for producing sea snake antivenom. Based on units required, sea snake antivenom was more effective for all venoms tested. Another in vitro study comparing tiger snake and sea snake antivenom against venom *E. schistosa* demonstrated tiger snake antivenom was 10 times more effective in terms of milligram of venom neutralized per milliliter antivenom.[96] In the same study, the use of 17 different types of elapid antivenom resulted in poor neutralization of beaked sea snake venom.

TABLE 116-3. Antivenoms

Organism	Manufacturer	Derivation	Concentration
Box jellyfish			
C. fleckeri	CSL	Ovine, whole IgG	20,000 units/ampule
Sea snake			
E. schistosa (beaked sea snake)	CSL	Equine, IgG Fab	1000 units/ampule
N. scutatus	CSL	Equine, IgG Fab	3000 units/ampule

(terrestrial tiger snake)			
Stonefish			
S. trachynis	CSL	Equine, IgG Fab	2000 units/ampule
CSL = Commonwealth Serum Laboratories, Melbourne, Australia.			

In rescue experiments with mice using 11 different sea snake venoms and 4 different antivenoms (*E. schistosa*, *E. schistosa-N. scutatus*, *N. scutatus*, and polyvalent sea snake *Lapemis hardwickii, Laticauda semifasciata, Hydrophis cyanocinctus*), tiger snake antivenom was superior to all others with respect to volume amount required to prevent death.[8] The experiment compared effective dose 50 (ED_{50}) in milliliter amount of antivenom; however, the numbers of stated units per milliliter of antivenoms were not equivalent. One milliliter of tiger snake antivenom used in the experiments contained 380 units, which is 14 times the amount contained per milliliter of monovalent sea snake antivenom (27.3 units/mL). Another finding of the study was improved efficacy with early administration of antivenom.

No controlled human trials have evaluated the efficacy of sea snake antivenom, although case reports suggest improved outcomes and more rapid recovery with its use.[95,113] There are also well-documented cases of successful use of tiger snake antivenom.[2,62] Anecdotal experience in Malaysia using sea snake antivenom suggests slow recovery from myalgias and weakness over 48 hours, compared to resolution over 2 weeks without

antivenom (2 cases, 1 control).[112]

Based on in vitro and in vivo research, the optimal antivenom for treatment of sea snake bites is unclear. Both sea snake and tiger snake antivenom are effective in neutralizing a wide variety of sea snake venoms. Therefore, the most readily available antivenom should be used when needed. Commonwealth Serum Laboratories manufactures both monovalent sea snake and tiger snake antivenom for use in Australia. However, limited distribution to aquariums and zoos outside Australia does occur. The manufacturer's guidelines for use of monovalent sea snake antivenom recommend administration of 1 ampule (1,000 units) for systemic symptoms. However, because symptoms may be delayed and early administration is more likely to result in venom neutralization, any evidence of envenomation should prompt the administration of antivenom. The antivenom should be diluted 1:10 with 0.9% sodium chloride solution and administered IV over 30 minutes. A 1:5 dilution can be used for small children. Skin testing is not recommended. Epinephrine and antihistamines should be readily available. No upper limit is suggested for the number of vials to administer, although larger amounts are more likely to result in serum sickness. Patients have received up to 7000 units without adverse effect directly attributable to the antivenom.[95] One ampule (3000 units) of tiger snake antivenom can be used as an alternative, if sea snake antivenom is unavailable. Other treatments should focus on wound care, tetanus prophylaxis, analgesia, and fluid administration to minimize nephrotoxicity from myoglobinuria.

Fish

Stingrays are members of the class *Chondrichthyes* (Order *Rajiformes:* skates and rays). Families include *Dasyatidae* (whip ray or sting ray), *Urolophidae* (round ray), *Myliobatidae* (batfish or eagle ray), *Gymnuridae* (butterfly ray), and *Potamotrygonidae*

(river ray, freshwater). The order of toxicity is butterfly ray <eagle ray <stingray, and whip ray <round rays.[4]

The family *Scorpaenidae* is composed of a variety of venomous spiny fish (Table 116-4). Fish in the genus *Pterois* are commonly called *lionfish* (*P. volitans* and *P. lunulata*). Stonefish are grouped under the genus *Synanceja* and include *S. trachynis* (Australian estuarine stonefish), *S. horrida* (Indian stonefish), and *S. verrucosa* (reef stonefish). They are unattractively disguised to blend in with the rocky sea bottom. (See ILSTONEFISH1 and ILSTONEFISH2 in the Image Library.) Scorpionfish have a similar appearance and belong to the genus *Scorpaena* (eg, *S. guttata:* California sculpin). Other *Scorpaenidae* include *Notesthes robusta* (bullrout) and *Gymnapistes marmoratus* (cobbler). The European weeverfish causes toxicity similar to members of *Scorpaenidae* and is classified under the family *Trachinidae*. This includes *Trachinus vipera* (lesser weever) and *T. draco* (greater weever, aka adderpike, stingfish, seacat). These bottom dwellers are smaller and have fewer spines than *Scorpaenidae* and are much less ghoulish in appearance. Another cause of venomous fish stings is catfish. Although most live in freshwater, marine catfish such as *Plotosus lineatus* can cause human envenomation. Other venomous spiny fish include rabbitfish, stargazers, toadfish, ratfish, and even some sharks that have spines on their dorsal fins (Port Jackson shark, dogfish shark).

History and Epidemiology

Some estimates suggest 1500â€“2000 stingray injuries occur yearly in the United States. Most envenomations occur when the animal is inadvertently stepped on. In a review, a total of 17 fatalities resulting from trunk wounds, hemorrhage, or tetanus, were identified worldwide.[46] In a review of 603 cases of stingray injuries, only 2 deaths occurred, both as a result of intraabdominal trauma.[118] No deaths stemming solely from venom are recorded.

There are 11 different species of sting rays in

US costal waters (7 in the Atlantic, 4 in the Pacific). In the southeastern United States, *Dasyatis americana* is a common inhabitant. *Urolophus halleri* is the most common species on the western coast of the United States.

TABLE 116-4. Spiny Fish

Latin Name	Common Name	Habitat
Scorpaenidae family		
Pterois		
P. volitans	Lionfish (also zebrafish, turkeyfish, or red firefish)	Indo-Pacific region, coast of Florida to North Carolina (nonnative to US coast)
P. lunulata	Lionfish or butterfly cod	
Synanceja		
S. trachynis	Australian estuarine stonefish	Indo-Pacific region

S. horrida	Indian stonefish	
S. verrucosa	Reef stonefish	
Scorpaena		
S. cardinalis	Red rockcod, scorpionfish	Coast of Australia
S. guttata	California sculpin, scorpionfish	Coast of California
Notesthes robusta	Bullrout	Coast of Australia
Gymnapistes marmoratus	Cobbler	
Trachinidae family		
Trachinus		Coasts of Great Britain to Northwest Africa, throughout
T. vipera	Lesser weeverfish	Mediterranean and Black Seas

T. draco	Greater weeverfish (also adderpike, stingfish, or seacat)	

Three populations are at highest risk for spiny fish envenomation: fishermen sorting the catch from nets, waders, and aquarium enthusiasts. Only 5 deaths from *Scorpaenidae* have been reported; all resulted from stonefish and are poorly documented.[46] One death in 1915 occurred days after envenomation and likely resulted from infection.[37] No deaths from stonefish are reported in Australia, a country where they are commonly found in coastal waters.[40] The incidence of weeverfish stings is unknown, but they are a common occurrence in the summertime among Italian coastal towns.[30] A review of reported weeverfish stings between 1955 and 1962 identified approximately 12 cases per year resulting in â€œserious illness.â€•[127] Approximately 10 stings per year are reported in Denmark.[29]

Scorpaenidae are found throughout the tropical and temperate oceans. They exist as far north as the Gulf of Oman and Southern Japan and extend south beyond New Zealand. In the United States, *Scorpaenidae* stings occur in the Florida Keys, the Gulf of Mexico, off the coast of California, and Hawaii. Lionfish (genus *Pterois*) are common to home aquariums and account for most poison center calls involving spiny fish envenomation in the United States. The bullrout inhabits the eastern coast of Australia, along with the cobbler, which is found only in Australia. Weeverfish live in the shallow temperate waters with sandy or muddy bottoms in the eastern Atlantic and Mediterranean, including the European Coast extending to the southern tip of Norway. The marine catfish lives in the tropical Indo-Pacific waters.

Pathophysiology

Stingray tails possess tapered, bilaterally retroserrated spines covered by an integumentary sheath. The ventrolateral groove contains venom glands that saturate the spine with venom and mucus. The venom contains several amino acids, 5-HT, 5â€²-nucleotidase, and phosphodiesterase.[4] In animal models venom induces local vasoconstriction, bradydysrhythmias, atrioventricular nodal block, subendocardial ischemia, seizures, coma, cardiovascular collapse, and death.[3,118] A rabbit model demonstrates initial vasodilation followed by vasoconstriction and cardiac standstill suggesting a direct cardiac effect.[119] Wound specimens reveal necrotic muscle and neutrophilic infiltrates.[6] Other reports show central hemorrhagic necrosis with surrounding lymphoid and eosinophilic infiltrates indicating an immune-mediated cause of delayed wound healing.[65]

Scorpaenidae have 12â€“13 dorsal, 2 pelvic, and 3 anal spines that are covered with an integumentary sheath (see ILLIONFISH in the Image Library). Glands at the base contain 5 to 10 mg of venom each. Ornate pectoral fins are not venomous. Venom can remain stable for 24â€“48 hours after the fish dies.[91] Three main toxins have been isolated from various species of stonefish: stonustoxin (SNTX), verrucotoxin (VTX), and trachynilysin (TLY). SNTX, from *S. horrida*,[66] has 2 subunits, Î± and Î² (71,000 and 79,000 daltons, respectively). It induces formation of hydrophilic pores in cell membranes.[32] Toxicity in animals includes hemolysis, local edema, vascular permeability, platelet aggregation, endothelium-dependent vasodilation, and hypotension. Decreased myocardial contractility occurs in rabbits.[122] VTX, isolated from *S. verrucosa*, has homology to SNTX. It blocks cardiac Ca^{2+} channels.[64] TLY, isolated from *S. trachynis*, is a 159-kDa protein that forms pores in cell membranes. It allows Ca^{2+} entry and causes Ca^{2+}-dependent release of ACh from nerve endings at motor endplates and increased catecholamine release.[79,104,123]

Synanceja trachynis venom causes endothelium-dependent vasodilation and cardiovascular collapse in rats, which appears to be mediated by muscarinic and adrenergic receptors.[33] Hemolysis is demonstrated in animals but does not occur in human erythrocytes.[78] Other venoms of *Scorpaenidae* include hyaluronidase, proteinase, phosphodiesterase, alkaline phosphomonoesterase, arginine esterase, arginine amidinase, 5â€²-nucleotidase, acetylcholinesterase, and biogenic amines. Crude venom from *G. marmoratus*, *P. volitans*, and *S. trachynis* leads to increased intracellular Ca^{2+} and muscle contracture in vivo.[36] Toxins from other spiny fish include dracotoxin (*T. draco*), trachinine (*T. vipera*), and nocitoxin (*N. robusta*).[35] Effects mirror those of *Scorpaenidae* toxins.[126]

Clinical Manifestations

Stepping on the body of a stingray causes a reflexive whip of the tail leading to wounds in the lower extremity. Intense pain out of proportion to the appearance of the wound is characteristic. Symptoms peak 30â€“90 minutes after injury and may persist for 48 hours. Local edema, cyanosis, erythema, and petechiae may follow rapidly and may lead to necrosis and ulceration. Systemic symptoms include weakness, nausea, vomiting, diarrhea, vertigo, headache, syncope, seizures, muscle cramps, fasciculations, hypotension, and dysrhythmias. Chest and abdominal wounds, as well as tetanus, have caused death.[57,110,118]

Stings from stonefish produce immediate severe pain with rapid wound cyanosis and edema that may progress up the injured extremity. Pain reaches a maximum after 30â€“90 minutes and usually resolves over 6â€“12 hours, although pain may persist for days. Wound healing may require months. Systemic symptoms following stonefish envenomation may include headache, vomiting, abdominal pain, delirium, seizures, limb paralysis, hypertension,

respiratory distress, dysrhythmia, congestive heart failure, and hypotension. In one case report, a healthy male received 6 punctures to the foot and developed rapid pulmonary edema requiring intubation.[81] The patient received 3 ampules of stonefish antivenom and recovered in 24 hours.

A Poison Control Center (PCC) case series from 1979â€“1988 identified 23 cases of *P. volitans* envenomation.[139] Reported symptoms included pain, swelling, nausea, numbness, joint pain, anxiety, headache, dizziness, and cellulitis. Another PCC series identified 51 *Scorpaenidae* stings (45 *P. pterois*, 6 *S. guttata*).[77] Intense pain was reported in 98%, extension of pain to the limb in 22%, swelling in 58%, and systemic signs (nausea, diaphoresis, dyspnea, chest pain, abdominal pain, weakness, hypotension, and syncope) in 13%. Thirteen percent of patients in the series developed wound infection; one patient's wound healing was delayed several weeks. Stings from weeverfish are similar to *Scorpaenidae* envenomation. One fatal sting occurred on the coast of Spain.[13] The victim developed syncope and cardiopulmonary arrest within 1 hour of envenomation. Autopsy revealed the puncture wound traversed the greater saphenous vein, suggesting direct IV injection of venom. Catfish stings invoke injuries similar to those of other stinging fish.[42]

Management

Wounds caused by stingrays and spiny fish should be carefully examined for imbedded foreign material. Radiographs may uncover occult spines left behind in the wound. Sting ray wounds can be extensive and require surgical attention for vascular or tendonous disruption. Tetanus prophylaxis should be addressed. As discussed for sea urchin stings, treatment with antibiotics may be appropriate for some injuries. Heating stonefish venom to 122Â°F (50Â°C) for 5 minutes prevents wound necrosis and hypotensive effects in animal models.[144] In a series of 51 stings from *P.*

pterois and *S. guttata*, 80% of patients had complete relief with hot water.[77] Success with using hot water also is reported with weeverfish stings.[117] In a human volunteer study in which subjects received a subcutaneous injection of stingray venom, severe pain developed immediately, and was alleviated with water heated to 122Â°F (50Â°C).[118] Pain increased with application of cold water. If relief is not sufficient, local lidocaine injection can alleviate pain.[57] Oral or parenteral analgesia may be required.

Stonefish antivenom is equine-derived IgG Fab fragment and is raised against the venom of *S. trachynis*. Each ampule contains 2000 units and neutralizes 20 mg venom. Between 1965 and 1981, antivenom was used in at least 267 cases.[40] Anecdotal reports suggest it provides effective relief from pain.[40,145] In a review of 26 documented cases in Australia where antivenom was administered IM, no acute adverse effects were identified.[133] Eight patients required 2 ampules. Two of 15 patients who had followup visits suffered serum sickness. Rash may develop several days postinjection.[145] In vitro and in vivo research with the antivenom demonstrates neutralization of venom from *G. marmoratus*[34] and *P. volitans*;[35] however, the application for human therapy is untested.

The manufacturer recommends IM administration, although IV administration may be considered. Administration is indicated for systemic toxicity or pain not controlled with hot water and other analgesics. Dosing is guided by the number of puncture wounds sustained: 1 vial for 1â€“2 punctures, 2 vials for 3â€“4 punctures, and 3 vials for 5 or more punctures. Epinephrine and diphenhydramine should be readily available for treatment of anaphylactic reactions.

Summary

Fatalities from marine envenomations are rare. However, significant morbidity may result from bites and stings, including

severe pain, retained foreign bodies, infection, respiratory compromise, hypotension, and cardiac dysrhythmias. Interventions should focus on patient comfort and recognition of potential complications. A thorough understanding of the mechanisms of toxicity and expected clinical course following envenomations from marine creatures will provide clinicians with the ability to manage these injuries effectively.

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Chapter 117
Snakes and Other Reptiles

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Case 1 A 25-year-old man exploring the mountains of Virginia was bitten toe by an unidentified snake when he was rock climbing in bare feet. He hear a rattle and only caught a glimpse of a copper-colored snake as it c away. Within 10 minutes he noted mild swelling and discomfort around a puncture wound on the top of the fourth toe.

Within 1 hour the man developed moderate throbbing pain in the entire f associated with paresthesias. At 2 hours a hemorrhagic blister developed bite site. The swelling had progressed to the dorsum of the ankle, but he systemic symptoms. A friend drove him to a local hospital. No specific firs was administered. The swelling did not progress past the ankle, and the did not report nausea, vomiting, diaphoresis, dizziness, or systemic weak The vital signs, complete blood cell count, and coagulation profile were r The patient reported only mild pain of the foot.

Because of progression of local symptoms and lack of definitive identifica the snake, the patient was admitted to the hospital. Antivenom was obta but not administered. The patient had moderate pain and stiffness of his Edema reached the lower leg at 24 hours but did not progress further. No systemic symptoms developed, and the laboratory profile remained norm Minor surgical debridement of a small area of skin slough on the toe was required. The patient was discharged after 48 hours to continue extremity elevation, and outpatient physical therapy was arranged. After 10 days of progressive decrease in swelling, the patient had full use of the foot with minor stiffness. Within 3 weeks, the stiffness had disappeared completely

Case 2 A 40-year-old utility worker was bitten on the right hand by a sna while he was working on an electrical box. He had immediate onset of pai the bite site. Coworkers who were familiar with snakes native to the area identified the snake as a western diamondback rattlesnake (*Crotalus atro* intravenous line was established and fluids administered en route to the hospital.

The patient arrived to the emergency department approximately 45 minu after the bite. He complained of worsening pain in his right arm, nausea, dizziness. His presenting vital signs were: blood pressure, 90/45 mm Hg; 118 beats/min; respiratory rate, 24 breaths/min; temperature 97Â°F (36 Two puncture wounds were identified on his right thumb, as were surrou ecchymosis and a small amount of blood oozing from the wounds. Swellin extended from his right hand to just beyond his elbow, and his forearm compartments were soft. No other bleeding was noted, and the remainder physical examination was unremarkable.

A second large-bore intravenous line was placed, and 0.9% sodium chlori solution administered while the patient's blood was sent for analysis. The pharmacy was asked to prepare 6 vials of crotalidae polyvalent immune F (ovine) in 250 mL 0.9% sodium chloride solution. In the meantime, the right arm was splinted in near-complete extension and elevated above the of his heart. While awaiting the reconstituted antivenom, the patient's blo work returned: hemoglobin, 15.1 mg/dL; platelets 90,000/mm^3 ; prothro time, >100 seconds; fibrinogen, 55 Âµg/mL. Following administration of 3

0.9% NaCl, the patient's systolic blood pressure increased to 110 mm Hg his pulse decreased to 95 beats/min. Intravenous fentanyl was given for infusion of 6 vials of crotalidae polyvalent immune Fab (ovine) was initia

After a dose of 6 vials of antivenom was administered, local tissue injury reassessed and repeat laboratory studies obtained. Despite elevation of t arm, the patient developed increased swelling in his hand that progressed shoulder. Repeat blood work demonstrated hemoglobin, 13.2 mg/dL; pla 76,000/mm^3 ; prothrombin time, >100 seconds; fibrinogen, 55 Âµg/mL. dose of 6 vials of antivenom was administered based on worsening labora results and local swelling. At the conclusion of the second dose of antiver the upper extremity swelling, while not resolved, did not appear to be progressing further. Results of hematologic studies performed at the con of the second antivenom dose were improved from the previous results: platelets, 100,000/mm^3 ; prothrombin time, 45 seconds; fibrinogen, 105 Âµg/mL.

The patient was admitted to the intensive care unit, where maintenance infusions of crotalidae polyvalent immune Fab (ovine) were initiated at 2 every 6 hours for a total of 3 additional doses. Hourly measurements of l forearm, and arm circumferences during crotalidae polyvalent immune Fa (ovine) maintenance infusions were unchanged. After all antivenom doses administered, the patient's pain was controlled with oral analgesics. His f laboratory findings were hemoglobin, 13.5 mg/dL; platelets, 175,000/mm prothrombin time, 12 seconds; fibrinogen 240 Âµg/mL. After a 48-hour h stay, he was discharged home with analgesics and strict instructions to a any activity that could result in trauma for 3 weeks. He was informed tha coagulopathy and thrombocytopenia could recur despite the treatment wi antivenom.

At follow-up examination 48 hours after hospital discharge, the patient's swelling had increased slightly, but he stated that he had not kept the ha adequately elevated. He was feeling well but had not returned to work be of the inability to use his dominant hand. Repeat blood work demonstrate platelet count, 100,000/mm^3 ; prothrombin time, 25.2 seconds; fibrinoge

concentration, 75 Âµg/mL. He was reminded that he was at risk for bleed told to return for repeat laboratory studies in 48 hours.

The patient was reevaluated every 2â€“3 days with repeat hematologic s Multiple laboratory studies over the subsequent week demonstrated a sta thrombocytopenia and coagulopathy. Tissue swelling continued to decreas hematologic parameters normalized 2 weeks after the envenomation. The patient had no bleeding episodes or other ill effects.

Epidemiology

Incidence of Venomous Snakebites in the United States

Venomous snakes are found throughout the United States, except Maine, and Hawaii. They are common in the Appalachian states, the south, and t west; they are rare in New England and the northern states. Approximate 6000 to 8000 venomous snakebites occur per year, and many thousands snakebites occur from nonvenomous species. Mortality from snakebites is considered rare in the United States; estimates range from 5â€“15 deaths year.[32 , 51] Exact statistics are lacking, but mortality rates can be signifi higher in other countries. As many as 27,000 rattlesnake bites and 100 occur per year in Mexico,[15] and thousands of deaths per year occur in so developing countries in Asia and Africa.

Because snakes hibernate in the winter, most bites in the United States o between May and October. Snakes may bite at night, but the most comm for envenomation is between 2 and 6 PM.[81] Coral snakes are particularly for their nocturnal habits. The majority of bites occur to the extremities, bites to the face and tongue occur when snakes are purposefully held nea body. The striking range of a snake is approximately half its length.

Children, intoxicated individuals (mostly men), snake handlers, and colle are frequent victims. More than half of the reported bites occur while the individual is purposely handling a known venomous snake. There is a sig market for many illegal and dangerous reptiles, and a surprising number

individuals keep and sell venomous snakes as pets. Many specimens are and highly toxic species from other countries. Some religious groups in th and southeastern states handle poisonous snakes (usually rattlesnakes) a routine ceremonial practice, and envenomation is common.

Identification of a Venomous Snake

There are 120 species of snakes native to North America, including approximately 30 venomous species (Table 117-1). Most of these venom snakes are members of the family Viperidae (subfamily Crotalinae), which include the rattlesnakes (*Crotalus and Sistrurus*) and the copperheads ar water moccasins (*Agkistrodon*) (see ILAGKISTRODONCONTOTRIX1 and ILCROTALUSATROX in the Image Library at http://www.goldfrankstoxicology.com). Snakes of the subfamily Crotalina also called *pit vipers* because of the presence of a pitlike depression of th behind the nostril that contains a heat-sensing organ. The other family of venomous snakes native to the United States is the Elapidae, which inclu coral snakes. The vast majority of venomous snakebites in the United Sta from pit vipers, with approximately 60% of bites from rattlesnakes and th remainder from copperheads and water moccasins.[74] Fewer than 1% of venomous bites are from the docile coral snake.[61 , 69]

Crotalinae (Pit Vipers)
Rattlesnakes
Crotalus adamanteus
Eastern diamondback
Crotalus atrox
Western diamondback
Crotalus cerastes cerastes
Mojave Desert sidewinder
Crotalus cerastes cercobombus
Sonoran Desert sidewinder
Crotalus horridus horridus
Timber
Crotalus horridus atricaudatus

Canebrake

Crotalus molossus molossus

Northern blacktail

Crotalus ruber ruber

Red diamond

Crotalus scutulatus scutulatus

Mojave

Crotalus viridis cerberus

Arizona black

Crotalus viridis helleri

Southern Pacific

Crotalus viridis lutosus

Great Basin

Crotalus viridis oreganus

Northern Pacific

Crotalus viridis viridis

Prairie

Sistrurus catenatus catenatus

Eastern massasauga

Sistrurus catenatus edwardsi

Desert massasauga

Sistrurus catenatus tergeminus

Western massasauga

Sistrurus millarius millarius

Carolina pigmy

Other Pit Vipers

Agkistrodon contortrix contortrix

Southern copperhead

Agkistrodon contortrix laticinctus

Broad-banded copperhead

Agkistrodon contortrix mokason

Northern copperhead

Agkistrodon piscivorus conanti

Florida cottonmouth

Agkistrodon piscivorus piscivorus
Eastern cottonmouth
Agkistrodon piscivorus leucostoma
Western cottonmouth
Bothrops lanceolatus
Fer-de-lance
Elapidae (Coral Snakes)
Micruroides euryxanthus
Sonoran coral snake
Micrurus fulvius fulvius
Eastern coral snake
Micrurus fulvius tenere
Texas coral snake

Scientific Name Common Name

TABLE 117-1. Scientific and Common Names of Medically Impor
Venomous Snakes of North America

Pit Vipers

The venomous Crotalinae in the United States have a triangular-shaped h vertically elliptical pupils, and easily identifiable fangs (Figure 117-1). Th fangs are paired, needlelike structures that inject venom and can retract hingelike mechanism into the roof of the mouth. Rattlesnakes have the lo fangs, reaching 3 to 4 cm. In addition to fangs, venomous snakes have ro small teeth. An adult snake usually has 2 fangs, but the fangs may be sin multiple. The undersurface of pit vipers has a single row of plates or scal opposed to the double row found on nonvenomous varieties. Depending o maturity, rattlesnakes may or may not have rattles, which occasionally a heard before a strike. Water moccasins are semiaquatic and have a distin white mouth suggesting their common name (cottonmouths). They repor are quite aggressive and capable of underwater bites. Copperheads are k for their reddish-brown (copper) heads and hourglass markings on their

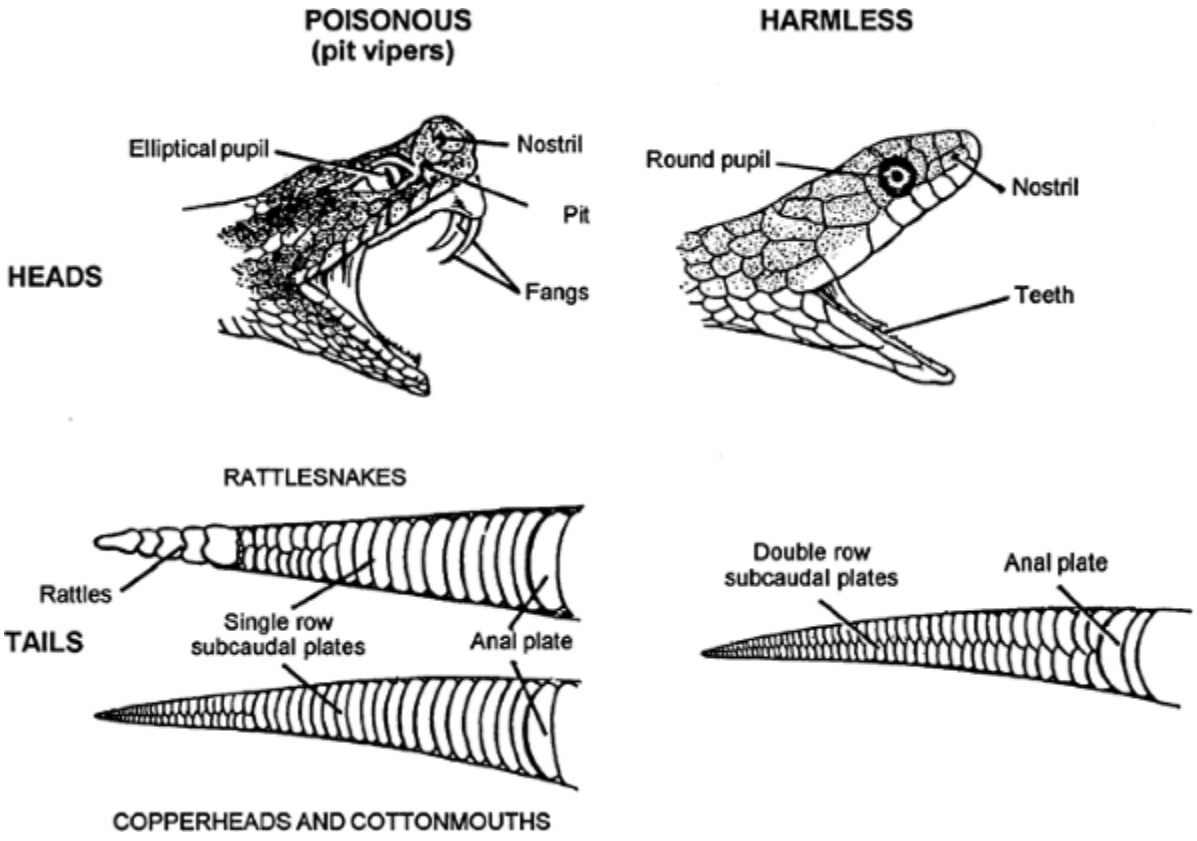

Figure 117-1. Features of pit vipers and harmless snakes. (Modified and reprinted with permission from Parrish HM, Carr CA: Bites by copperheads United States. JAMA 1967;8:201:927.)

Elapidae

The coral snakes (*Micruroides* and *Micrurus* spp) are the brightly colored Elapids, which have easily identifiable red, yellow, and black bands along length of their body. Coral snakes and the similarly colored nonpoisonous scarlet king snake often are confused. In a report of 39 victims of coral s bites, 9 patients were envenomated because they erroneously believed th were dealing with the nonpoisonous scarlet king snake.[48] The coral and k snakes can be distinguished by the spacing of their colored rings and the of the head. Coral snakes have black snouts, whereas king snakes have r snouts. Both species have red, yellow, and black rings, but in different

sequences. The red and yellow rings touch in the coral snake but are sep by black rings in king snakes (â€œRed on yellow kills a fellow, red on bla venom lackâ€•).

The fangs of coral snakes are much smaller (1â€“3 mm) than those of the rattlesnakes, and discrete fang marks may not be obvious after envenom Coral snakes appear to have the curious propensity of hanging onto a vic â€œchewingâ€• for a few seconds, and a history of this activity may hel identify a coral snakebite when the offending reptile cannot be located. Removing a coral snake from the skin has been likened to separating piec hook and loop closure (Velcro).

Exact identification of a snake often is not possible unless the victim brin offending reptile to the hospital. This usually is impossible and poses an additional threat to the victim or prehospital personnel and is discourage Because of the excitement generated by the bite, the victim's identificatio the snake may not be accurate. Identifying a snake by its color or markin difficult for the novice. Knowledge of the indigenous venomous snakes oft helpful to medical personnel. Snake handlers and owners of pet snakes u know the exact species responsible for their bite, but some are reluctant specific information out of fear of prosecution or confiscation of the illega by authorities.

Characteristics of a Venomous Snakebite

The severity and clinical manifestations of envenomation depend on a nur factors, including number of strikes, depth of envenomation, size of the s potency and amount of venom injected, size and underlying health of the and location of the bite (Figure 117-2).[52, 64] Larger snakes generally in more venom, but the potency is species variable. Children and small adul well as those with underlying medical conditions (diabetes, cardiovascula disease) may be more seriously affected by envenomation.[62] Envenomati usually occurs in subcutaneous tissues and less commonly in muscle. Sys absorption occurs via lymphatic and venous drainage of the envenomated Intravenous envenomation may occur and result in the rapid development life-threatening complications.[22] Airway obstruction necessitating trachea

intubation has been reported after a rattlesnake bite to the face and tong
Individuals may be envenomated by rattlesnakes thought to be dead, ever

60 minutes after decapitation, because of persistent reflexes in the venor
apparatus.[75]

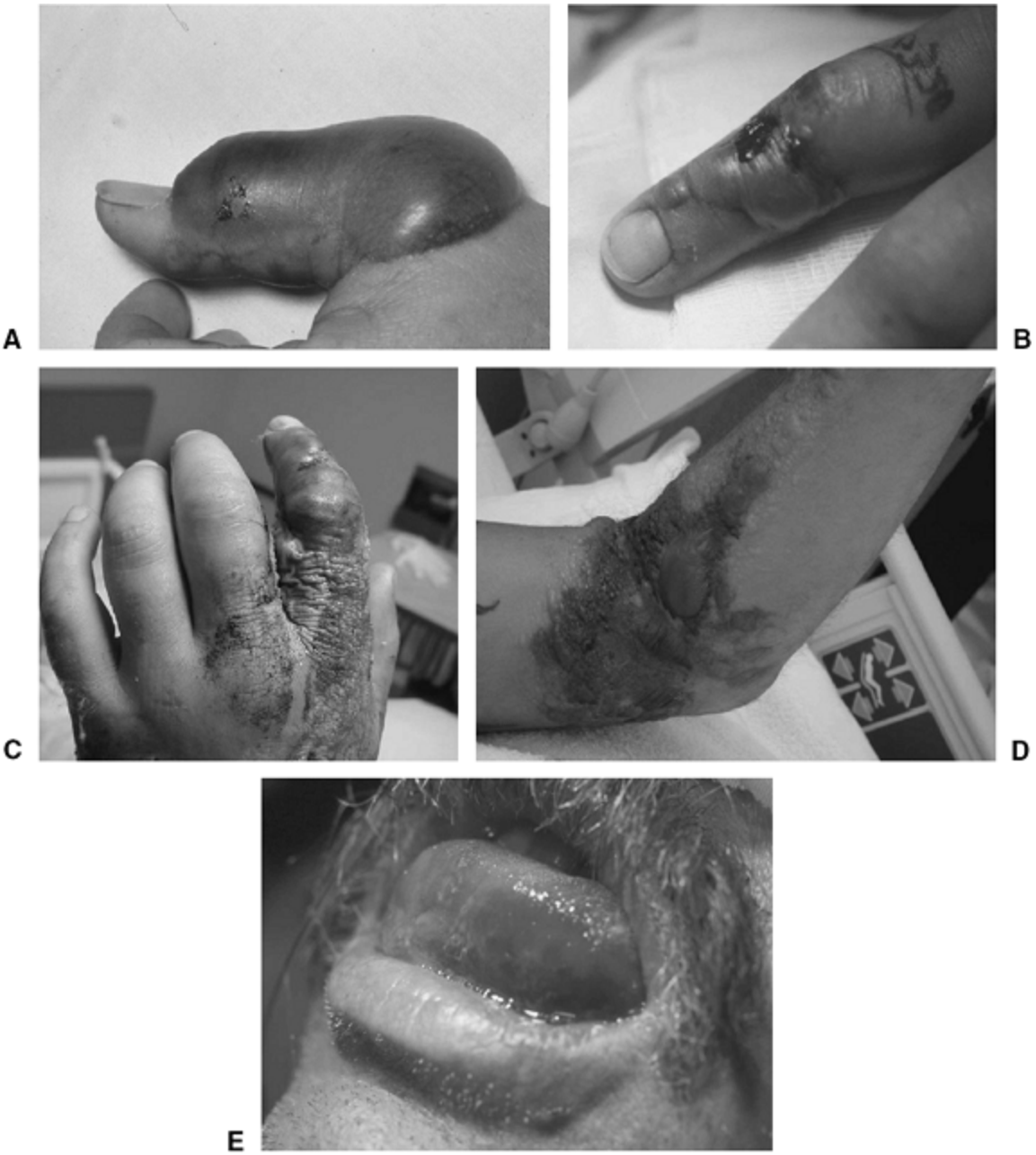

Figure 117-2. A, B: Hemorrhagic bullae approximately 24 hours followin

by *Crotalus atrox* . C: Swelling and hemorrhagic bullae 36 hours following by unknown rattlesnake. D: Antecubital hemorrhagic bullae and skin necr following bite by unknown rattlesnake. E: Tongue swelling 24 hours follov bite to tongue by *Crotalus atrox.* (Copyright Â© 2002, Department of Toxicology. Good Samaritan Regional Medical Center.)

Pit vipers produce a characteristic bite when they strike, and distinct fang usually can be identified (see ILDIAMONDBACK1 in the Image Library at http://www.goldfrankstoxicology.com). The small delicate fangs of coral may not produce easily identifiable fang marks. Fang marks may be singl double, and occasionally multiple. Although most snakes have two fangs, exact number of fang marks may vary because of glancing blows and/or strikes. Protection by clothing or shoes can alter these findings. The bites rodents, lizards, and even thorn or cactus injuries can be misdiagnosed a poisonous snakebites.

Pharmacology of Venom

It is difficult to attribute specific pathology or pathophysiology to particu components of snake venom. Crotaline venom is a complex heterogeneou solution and suspension of various proteins, peptides, lipids, carbohydrate enzymes, including ribonuclease and deoxyribonuclease, kinins, leukotrie histamine, phospholipase, serotonin, hyaluronidase, acetylcholinesterase, collagenase, and metallic ions.[44 , 45] It has been referred to as a â€œmo antigens.â€• Numerous unidentified proteolytic enzymes, procoagulants anticoagulants, cardiotoxins, hemotoxins, and neurotoxins abound in cro venom, making it very complex to analyze.

Crotalinae venom can simultaneously damage tissue directly, affect blood vessels and cellular elements of blood, and alter the myoneural junction nerve transmission. Toxic components of snake venom exhibit their patho varying times, and some of the variation in clinical manifestations of envenomation result not only from the specific properties of the venom b differences in absorption rates and ability to permeate membranes and t In addition, the content and potency of venom in any given snake vary w

size, age, diet, climate, time of year, and possible cross-breeding among different species. Venom is present in the circulation and fixed to tissues Circulating venom is more readily neutralized by antivenom, whereas the of tissue-fixed venom are more difficult to counteract. This may partly ex the clinical observation that antivenom corrects systemic dysfunction and coagulopathy but does little to reverse local pathology. Antivenom may h progression of further edema, hemorrhage, and soft-tissue swelling, but these conditions are present, antivenom likely will not rapidly reverse pa at the site of envenomation.

Coral snake venom consists of a number of unidentified neurotoxins with curarelike effects that produce systemic neurotoxicity, as opposed to loca tissue injury.

Pathophysiology and Clinical Manifestation

Crotaline Envenomation

Local Reactions

Crotaline (pit viper) venom usually is injected only into the subcutaneous although deeper, intramuscular (subfascial) envenomation rarely occur. N every bite from a venomous snake results in release of venom into the v so-called â€œdry bitesâ€• occur in up to 20% of strikes.[49] Repeat strikes result in additional envenomation because the snake's entire supply of ve usually was not exhausted with the first attack. Approximately 25â€“75% stored venom is discharged following a rattlesnake bite, and the entire su replenished in 3â€“4 weeks.[69]

Symptoms may range from mild to severe, but the initial benign presenta a pit viper bite may be very misleading[43] (Table 117-2). Generally, withi minutes after significant envenomation from a pit viper, the area around bite becomes swollen and painful. Within minutes to hours, ecchymosis, blistering, and signs of tissue necrosis may be evident both proximal and

to the bite. The patient may describe paresthesias or other neurologic symptoms around the bite. Edema may progress to involve an entire extr within a few hours, and systemic symptoms may develop. The local reacti pit viper envenomation results from altered blood vessel permeability and necrosis of the tissue caused by the venom. Additional tissue damage can from the effects of ischemia, swelling, and rarely secondary infection. In addition to local myonecrosis, generalized severe rhabdomyolysis may occ the absence of impressive muscular swelling. This finding is considered characteristic following envenomation of the canebrake rattlesnake (*Crota horridus atricaudatus*) found in the Gulf Atlantic states.[12] (See ILMASSASAUGA1, ILMASSASAUGA2, and ILRATTLER1 in the Image Librar

Compared with the venom of rattlesnakes, the venom of water moccasins (cottonmouths) produces less severe local and systemic pathology, and envenomation from copperheads tends to be less severe than that of eith rattlesnakes or water moccasins. Although the soft-tissue swelling from a copperhead bite may be significant, envenomation from this snake usually not cause coagulopathy, systemic symptoms, or extensive tissue destruc Copperhead envenomation often results in only minimal edema and pain usually requires only conservative local treatment.[80] (See ILCOPPERHEAD and ILCOPPERHEADTOE in the Image Library). Lethality is so rare that it considered reportable.

None (â€œdry biteâ€•)
Fang marks may be seen, but no local or systemic symptoms after 8â€“12
None
Local wound care
Tetanus prophylaxis
Discharge after 8â€“12 hours of observation
Minimal
Minor local swelling and discomfort only, with no systemic symptoms or hematologic abnormalities
None
Local wound care
Tetanus prophylaxis

			Admit to monitored unit for 24-hour observation	
Moderate	Progression of swelling beyond area of bite, with local tissue destruction, hematologic abnormalities, or systemic symptoms	Yes	IV fluids Cardiac monitoring Analgesics Follow laboratory values Tetanus prophylaxis Admit to ICU	
Severe	Marked progressive swelling and pain, with blisters, bruising, and necrosi systemic symptoms such as vomiting, fasciculations, weakness, tachycar hypotension, and severe coagulopathy	Yes	IV fluids Cardiac monitoring Analgesics Follow laboratory values Oxygen Vasopressors PRN Tetanus prophylaxis Admit to ICU	

[a] See Antidotes in Depth: Crotaline and Elapid Antivenoms , for dosing recommendations.

Extent of Envenomation	Clinical Observations	Antivenom Recommendation[a]	Other Treatment	Dispo

TABLE 117-2. Evaluation and Treatment of Crotaline Envenomatio

Envenomation is a dynamic and ever-changing process that can rapidly o

unpredictably progress to serious local or systemic involvement. The full of envenomation may not become evident for a number of hours. On rare occasions symptoms appear to be resolving, only to return minutes to ho later with greater intensity. If local symptomatology initially is ameliorate arrested by antivenom therapy, the swelling may recur when antivenom concentrations drop hours later. As a general rule, however, it may be as that envenomation from a North American pit viper has not occurred (dry if no symptoms develop within 8â€“12 hours from the time of the bite.

Systemic Signs

Most bites from pit vipers that occur on the extremities are limited to loca regional pathology; however, systemic symptoms and life-threatening to may develop. When venom is injected subcutaneously, it travels by lymp and superficial venous channels and spreads slowly to the general circula Generally, subcutaneous envenomation produces systemic symptoms withi number of hours, but this timetable is variable. Occasionally, symptoms rapidly even with subcutaneous envenomation. Intravascular envenomati produces significant systemic symptoms in minutes.[22] Direct intravenous envenomation probably is rare, but this occurrence, in addition to the un case of overt anaphylaxis, may account for the majority of fatalities. Rar respiratory compromise from airway obstruction or bronchospasm is a dir consequence of crotaline envenomation.[28]

Systemic signs of pit viper envenomation vary, and some symptoms resul fear, pain, or anxiety alone. In mild cases, the patient may manifest non weakness, malaise, nausea, and restlessness. More severe envenomation produces confusion, abdominal pain, vomiting, diarrhea, sweating, dyspn tachycardia, hypotension, blurred vision, salivation, and a metallic taste i

mouth. Rarely, patients exhibit disseminated intravascular coagulation (D with spontaneous bleeding, significant hypotension, and multiorgan syste failure.[18 , 29] Although crotaline venom may be directly nephrotoxic, rena failure probably is secondary to hemoglobinuria, myoglobinuria, or cardiovascular collapse.

Local tissue destruction dominates Crotalinae envenomations, but neurot effects also occur with certain species of snakes. The Mojave rattlesnake (*Crotalus scutulatus scutulatus*) produces the neurotoxic Mojave toxin, w can cause lethargy, cranial nerve dysfunction, and respiratory paralysis.[4] acts at presynaptic terminals of the neuromuscular junction by inhibiting acetylcholine release. Mojave toxin is formed by a heterodimer protein composed of an acidic subunit and a basic subunit, both of which are req for a functional neurotoxin. Interestingly, production of Mojave toxin appe be geographically distributed. A western population in California produces functional Mojave toxin A with neurotoxic effects, but little or no tissue destruction. More eastern populations lack the acidic subunit and do not functional Mojave toxin, but do express metalloproteases that lead to tiss necrosis. Mojave rattlesnakes in an intergrade zone (Arizona and New Me between these two populations produce both neurotoxic and tissue destr toxins.[30 , 83] Bites from Mojave rattlesnakes in this zone often look ident bites from other local rattlesnake species, with local tissue effects and hematologic toxicity, but an absence of clinical neurotoxicity. Mojave toxi also been found in the venom of the Southern Pacific rattlesnake (*Crotalu halleri*) found in southern California, with envenomations leading to neu symptoms.[13 , 26] The Timber rattlesnake (*Crotalus horridus horridus*) commonly causes myokymia, particularly of the facial muscles.[7 , 53] Crot a neurotoxic protein found in the venom of the South American rattlesnal (*Crotalus durissus terrificus*), typically produces analgesia at the bite loc and possesses potent opioid activity.[6]

Hematologic

Significant crotaline envenomation may produce complex and dramatic hematologic abnormalities secondary to the effects of the venom on the coagulation pathways, endothelial cells, and platelets[3 , 9 , 68 , 73] (Figure). An initial drop in fibrinogen concentrations (to near zero) and platelet (in the 10,000â€“50,000/mm^3 range), in addition to immeasurably high prothrombin time (PT) and partial thromboplastin time (PTT), frequently after moderate-to-severe crotaline envenomation. Regardless of which sr caused the envenomation, the majority of patients have no clinical bleedi

even with severe coagulopathies and thrombocytopenias. A routine coagu profile and platelet count should be obtained following envenomation by a crotaline and repeated in 4â€“6 hours. Significant coagulopathy and/or thrombocytopenia may be present, but other systemic effects may be spa Coagulopathy is attributed to a complex variety of anticoagulants, procoagulants, fibrinolysin, and hemorrhagins in crotaline venom (Table). Some portions of snake venom may actually have therapeutic uses as anticoagulants or platelet receptor (GPIIb-IIIa) antagonists. Overall, crot venom has a thrombinlike effect, but specific hematologic effects are spe dependent. No single venom contains all of the identified hemostatically components. Thrombocytopenia (<150,000/mm^3) is a common finding f envenomation from most species of rattlesnakes and can occur in the abs elevated PT or PTT.[3] Thrombocytopenia appears to be especially common, often severe, following the bite of the timber rattlesnake (*Crotalus horrid horridus*), which inhabits the Appalachian mountains of the eastern Unite States.[3] The protein crotalocytin, which is found in timber rattlesnake ve causes platelet aggregation and is thought to be at least partially respon for thrombocytopenia. Following the trends in laboratory parameters is an important way to assess the progression or reversal of envenomation.

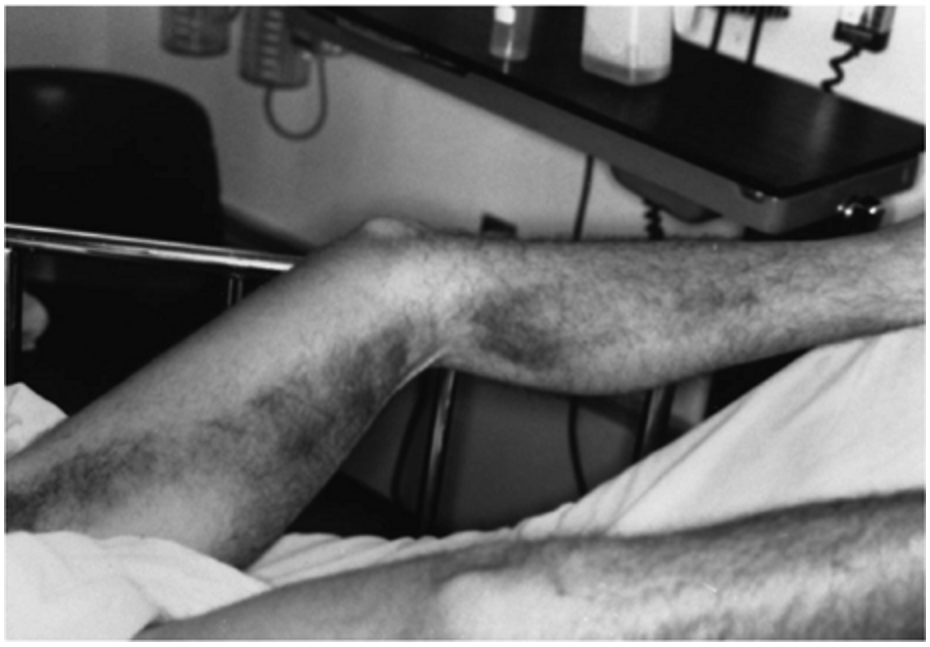

Figure 117-3. Ascending subcutaneous hemorrhagic ecchymosis develop

within 8 hours of a copperhead bite to the foot. The ecchymosis follows t course of lymphatic or venous drainage. Only minor discomfort was noted There was no systemic coagulopathy. The actual cause is unknown, but th is an example of the hemorrhagic diatheses produced by crotaline envenomation. (Reproduced with permission from Roberts JR, Greenberg Ascending hemorrhagic signs after a bite from a copperhead. N Engl J Me 1997;336:1262â€“1263.)

A major difficulty in objectively grading the severity of crotaline envenor and following its progress is that no scoring system readily fits the vagari envenomation. Most patients exhibit only a subset of all of the possible consequences, so all, some, or none of the anticipated signs and symptor develop in any given individual. In addition, some of the characteristics o envenomation (nausea, tachycardia, restlessness, and tachypnea) may be related to fear and not to envenomation. A validated severity score for c assessment of crotaline envenomation has

been developed for research purposes and holds promise as a standardiz tool for clinical evaluation.[21]

Enzymes that clot fibrinogen
Enzymes that degrade fibrinogen
Plasminogen activators
Prothrombin activators
Factor V activators
Factor X activators
Anticoagulant activities including inhibitors of prothrombinase complex formation, inhibitors of thrombin, phospholipases, and protein C activator
Enzymes with hemorrhagic activity
Enzymes that degrade plasma serine proteinase inhibitors
Platelet aggregation inducers including direct-acting enzymes, direct-acti nonenzymatic components, and agents that require a cofactor
Platelet aggregation inhibitors including Î±-fibrinogenases, 5â€²-nucleot phospholipases, and disintegrins

From Markland FS: Snake venoms and the hemostatic system. Toxicon 1998;36:1749â€“1800.

TABLE 117-3. General Hemostatic Characteristics of Snake Venom

Anaphylaxis

Rarely, patients bitten by crotalines experience classic anaphylaxis from venom itself. This reaction can complicate evaluation, or mimic a severe systemic reaction to venom. In one report, a man developed pruritus and shortness of breath accompanied by hypotension, generalized urticaria, a wheezing immediately following a rattlesnake bite.[40] The symptoms quick responded to standard treatment for anaphylaxis (epinephrine, antihistar and corticosteroids). The patient was bitten previously and may have bee sensitized at that time. Snake handlers may be sensitized through inhalat skin contact and develop IgE antibodies to venom. Antivenom is not indic for treatment of anaphylaxis, but differentiating anaphylaxis from envene often is clinically difficult. The presence of pruritus and urticaria or whee which is uncommon with envenomation, suggests anaphylaxis.[12]

Elapid Envenomation

The severe local reaction to crotaline envenomation contrasts with the us minor pain and clinically unimpressive local reactions that occur with a co snake bite. However, lack of local symptoms does not signify that serious envenomation has not occurred. Initially judging which patients bitten by snakes will develop symptoms is difficult. In general, less than 40% of p bitten by a coral snake are subsequently determined to have been envenomated; rates for envenomations from the eastern coral snake spe possibly are higher.[48] Coral snake envenomation may be manifested by s systemic reactions with little symptomatology at the actual site of envenomation, even after an asymptomatic period of up to 12 hours. The of the eastern coral snake (*Micrurus fulvius*) and Texas coral snake (*Micr tenere*) are more potent than that of the Sonoran coral snake (*Micruroid*

euryoxanthus). In fact, no cases are reported of serious toxicity followin bite of the Sonoran coral snake, which is found primarily in Arizona and New Mexico.

Systemic Effects

The systemic effects of elapid envenomation (Table 117-4) are characteristically delayed for a number of hours. One report described a who had an asymptomatic period of 13 hours followed by a sudden and precipitous deterioration severe enough to require ventilatory support.[49] neurologic abnormalities noted included slurred speech, paresthesias, pt diplopia, dysphagia, stridor, muscle weakness, fasciculations, and respira paralysis.[49] The major immediate cause of death from coral snake envenomations is respiratory arrest secondary to neuromuscular weakne cardiovascular effects are less common than in crotaline envenomation. can develop total-body paralysis that may last 3â€“5 days and take week resolve completely. With respiratory support, however, the paralysis is completely reversible. Pulmonary aspiration is a common sequela in the subacute phase.

Fang marks
85
Local swelling
40
Paresthesias
35
Nausea
30
Vomiting
25
Euphoria
15
Weakness
15
Dizziness

10
Diplopia
10
Dyspnea
10
Diaphoresis
10
Muscle tenderness
10
Fasciculations
5
Confusion
5
Reprinted, with permission, from Kitchens CS, Van Mierop LHS: Envenom by the eastern coral snake (Micrurus fulvius): A study of 39 victims. JAM 1987;258:1615.

Sign or Symptom Percent

TABLE 117-4. Signs and Symptoms of Envenomation by the Eas Coral Snake (*Micrurus Fulvius*) (N = 20)

Management

Objectives for Treatment

The specific treatment of a patient with a snakebite is controversial, and literature contains confusing and contradictory recommendations. Folklore home remedies abound. The benign natural history of many bites undoub has accounted for many apparent cures from â€œtherapeuticâ€• interve such as ethanol, electric shocks, carbolic acid, strychnine, cauterization, cryotherapy. Many accepted treatment plans are based on anecdotal or b information, with conclusions drawn from animal studies or uncontrolled reports. There are no universally accepted standards of care for many as

of treatment.[81] Many authors tend to be staunch advocates of their parti regimens and are unwilling to accept a less rigid approach. The initial ob are to determine the presence or absence of envenomation, to provide ba supportive therapy, to treat the local and systemic effects of envenomatio to limit or repair tissue loss and/or functional disability (Table 117-2).

A combination of medical therapy including supportive care, antivenom w warranted, and conservative surgical treatment using debridement of de tissue when indicated, individualized for each patient, likely will provide appropriate results. In general, the more rapidly treatment is instituted, better the final outcome.

Observation of Asymptomatic Patients

All patients who report a history of snakebite from North American crotal should be observed for 8â€“12 hours after the bite, if the skin is broken a offending snake cannot be positively identified as nonpoisonous. The initi presentation of pit viper bites may be misleading. Significant worsening o seemingly benign bite may occur as long as 24 hours after presentation,[4] such cases are unusual. Restlessness, anxiety, abdominal pain, nausea, a tachycardia are nonspecific symptoms, but could signal systemic enveno and they should not be routinely dismissed as resulting from fear or anxi Fang marks may be subtle and easily mistaken for scratches or teeth mar prudent approach is to observe all victims of possible crotaline bites for a 8â€“12 hours after the bite, and admit patients with any evidence of envenomation. If the patient was bitten by an exotic or nonnative snake, period of observation should be extended to 12â€“24 hours.

Eastern coral snake bites can be misleading because of the absence of ea symptomatology. Serious delayed neurologic and respiratory symptoms h been specifically noted, so patients bitten by these snakes should be obs for 24 hours regardless of initial presenting symptoms and treatment.

Initial Treatment

No first aid measures or specific field treatment is proven to positively at the outcome of a crotaline envenomation. Undue importance is placed on immediate prehospital care of patients with snakebites, and some therapi could be detrimental. When the patient is not in extremis and medical at is available within a few hours, the prudent approach is a conservative or excitement or hysteria generated by a possible poisonous snakebite comp some caregivers to intervene quickly, often irrationally, and with unprove harmful procedures. It is common to confuse treatment priorities and cre additional morbidity with hurried or ill-conceived attempts to stop or limi â€œcertain deathâ€• or subsequent amputation. In reality, both death a amputation are rare if proper medical attention is available within a few Most morbidity stems from delayed treatment, either because of inaction patient, often related to alcohol intoxication, or because of inaccessibility medical care. Prehospital care generally should be limited to immobilizatio the patient's affected limb and rapid transport to a medical facility. Physi activity, such as walking, should be avoided because this action may hast systemic absorption of venom. Prehospital personnel should follow standa advanced cardiac life support protocols for the rare unstable snakebite v

Pressure Immobilization

In the past, various methods have been advocated to prevent systemic absorption of venom following snakebites. The traditional tourniquet that occludes venous and arterial flow is contraindicated and may compound t initial insult by increasing edema and aggravating ischemia. (See ILTOURINQUET in the Image Library). Evidence indicates that a broad, fi constrictive wrap (elastic bandage) placed over the bitten area and encir the entire immobilized limb will slow the systemic absorption of venom. In human volunteer study simulating intradermal and subcutaneous enveno using labeled radiotracer, immediately wrapping an entire extremity with rolled elastic bandage to a pressure of 50â€“70 mm Hg significantly dela transit time from periphery to the systemic circulation.[42] This wrapping procedure (the Sutherland wrap) is intended to collapse lymphatics and superficial veins to retard venom uptake. A reasonable guide is to wrap t bandage as tightly as a compression bandage would be applied for a spra

ankle. A constriction band is not a true tourniquet. When a constriction b is applied properly, a finger can be easily placed between the band and t

The pressure immobilization technique has been used for treatment of nonnecrotizing elapid snakebites in Australia where systemic toxicity is th major concern and transit times can be prolonged.[82] The benefit of this technique for the more necrotizing bite of North American pit vipers is les clear. A randomized controlled study using a porcine model with intramu injection of a lethal dose of *C. atrox* (western diamondback) venom follow pressure immobilization versus observation was performed. The results demonstrated prolonged time to death in the pressure immobilization gro also markedly increased compartment pressures. With local tissue necros death, the major morbidity associated with North American pit viper envenomations, the authors concluded that pressure immobilization with compression bandage cannot be suggested as a routine field procedure.[10] not recommend pressure immobilization for management of North Americ viper envenomations.

Venom Removal

Incision and suction, whether by mouth or a commercially available devic cannot be recommended as standard first aid in the field. Incision may le damage of underlying structures such as nerves and tendons, and mouth is unproven and can introduce bacteria into the wound. A commercially a plunger-type suction device (The Extractor, Sawyer Products, Long Beach can generate up to 1 ATA negative pressure when placed over nonincised puncture wounds for extraction of venom.[4] Animal models addressing this intervention give conflicting results. In human models, no benefit of nega pressure venom extraction was found, and additional injury resulting from of the device was possible. Venom extractors currently are unproved the and are not recommended.[1 , 11 , 27] Simple suction cups supplied in first kits are worthless.

It should be stressed that compression dressings and vacuum extraction not be considered if the patient can rapidly reach a hospital. Minor pain c swelling is not an indication for aggressive field treatment. Furthermore,

treatments are never a substitute for rapid transport, in-hospital evaluati antivenom therapy. The bitten area should not be placed in ice, because cryotherapy is not effective in neutralizing venom, and may compound th injury.[56]

Immediate In-Hospital Therapy

The initial in-hospital approach to a victim of a poisonous snakebite follo standard accepted guidelines for stabilization and assessment of any pati with a potentially serious medical problem.[57] A complete medical history, including current tetanus immunization status and known allergies, should obtained. A careful description of the bite and the extent of the local pat should be documented, including measuring the diameter of the extremity noting the extent of edema by marking the skin with a pen to help recogn progression of the envenomation. This evaluation should be repeated as required by the clinical condition. A comprehensive physical examination be performed, with emphasis on vital signs, cardiorespiratory and neurol status, neurovascular status of the extremity, and evaluation for evidence melena, hematuria, and gingival bleeding. A baseline complete blood coun and platelet count), electrolytes, urinalysis, blood urea nitrogen (BUN), g PT, PTT, and fibrinogen concentration should be obtained initially and rep in 4 to 6 hours.

Pain and anxiety should be treated with analgesics and anxiolytics as clin warranted. Tetanus prophylaxis should be addressed. The extremity shoul immobilized in a well-padded splint in near-full extension and elevated to prevent dependent edema. The patient should be reassessed frequently w serial vital signs and repeat physical examinations, specifically noting any progression of swelling. This can be accomplished by taking measurement the circumference of the involved extremity at multiple points proximal to wound.

Victims of proven copperhead bites should be observed for 8 hours and evaluated for signs of systemic involvement, development of coagulation abnormalities, or progression of local pathology. In many instances, the care of a patient with a minimal copperhead envenomation can be accom

in the emergency department, but a conservative approach is advised. H admission for further observation is warranted if follow up cannot be assu if the identification of the snake or progression of symptoms is questiona

Antivenom Therapy

For Crotaline envenomations, antivenom should be considered as first-lin therapy for patients with moderate-to-severe envenomations (Table 117- Each clinical case must be individualized, but in the vast majority of pati who have a significant envenomation, the benefits of antivenom therapy outweigh the risks. Antivenom given in a timely manner can reverse the coagulopathy and halt progression of local symptoms.

The most common currently available antivenom for treatment of North American pit viper envenomation is Crotalidae polyvalent immune Fab Cr Protherics, Savage Laboratories). It is an ovine-derived Fab fragment an developed from commonly encountered North American pit vipers. It has replaced the traditional Antivenin Crotalidae Polyvalent (Wyeth-Ayerst). It has produced far fewer hypersensitivity reactions than reported with administration of the equine-derived whole immunoglobulin product. It is infused intravenously in 4â€“6 vials doses reconstituted in 0.9% sodium solution. The infusions are initiated at a slow rate. If no signs of anaphyl reaction develop (hives, wheezing), the rate is increased to complete the infusion over 1 hour. The patient is reassessed at the end of the infusion evidence of progressive swelling or worsening thrombocytopenia or coagulopathy. If these conditions are present, a repeat dose of 4â€“6 vial infused. This process is repeated until symptoms are controlled. Once co has been gained, maintenance doses are given as 2 vials every 6 hours fo total of 3 maintenance doses. Antivenom therapy is discussed in detail in Antidotes in Depth: Antivenom (Crotaline and Elapid) .

Surgical Therapy

Envenomation may mimic a compartment syndrome by producing distal

paresthesias, tense soft-tissue swelling, pain on passive stretch of muscl within a compartment, and muscular weakness. However, because subfas envenomation is uncommon, much of the impressive edema produced by envenomation does not occur in compartmentalized areas. Using noninva vascular arterial studies and skin temperature determinations in patients rattlesnake envenomation, a report demonstrated that pulsatile arterial b flow to an envenomated extremity actually increased after envenomation, distal to the site of envenomation.[17] A compartment syndrome cannot be reliably diagnosed in envenomated extremities without directly measuring compartment pressures. Although there is little doubt that some crotaline eventually may require some surgical debridement or even skin grafting, initial routine use of tissue excision, fasciotomy, or â€œexploration and debridementâ€• is not recommended.[36 , 76] Excising tissue likely will not significantly halt the envenomation process. Indications for fasciotomy ar and only based on objective data of measured compartment pressures. Following crotaline envenomation, successful treatment of documented e compartment pressure with antivenom and mannitol alone is reported.[33] ILCOMPARTMENT1 and ILCOMPARTMENT2 in the Image Library).

Surgical debridement of necrotic tissue and hemorrhagic blebs and bliste usually is performed between 3 and 6 days after envenomation. Physical should be instituted early to ameliorate joint stiffness and decrease swel

Surgery is not a concern in the treatment of coral snakebites. Similarly, copperhead and water moccasin bites rarely require surgical intervention except for delayed local debridement.

Blood Products

Alterations in platelet count, PT/PTT, fibrin split products, and fibrinogen concentration are commonly encountered with crotaline envenomations. A victims should be evaluated for a coagulopathy, even in the absence of symptoms.[22 , 62] Surprisingly abnormal laboratory results, such as immeasurably low fibrinogen concentrations, PT >100 seconds, and plate count <20,000 are routinely encountered, and such abnormal laboratory alone should not prompt the clinician to treat with blood products in the

of major clinical bleeding. The circulating crotaline venom responsible for initial hematologic changes still is present and likely will inactivate any component transfusions. For this reason, the mainstay of treatment for c envenomation-induced coagulopathy is antivenom, not blood products. Correction of laboratory coagulation abnormalities and bleeding frequentl be achieved with antivenom. Monitoring trends in the coagulation profile i objective way to assess the seriousness of envenomation and the respons antivenom therapy.

Rarely, antivenom alone does not correct a significant coagulopathy, in w case fresh-frozen plasma, cryoprecipitate, packed red blood cells, or plat transfusions are required. The criteria for use of blood products appears t arbitrary in clinical practice, but in general, blood products should be administered along with antivenom only if the patient is actively bleeding

Thrombocytopenia following rattlesnake envenomation may be difficult, o impossible, to totally correct with platelet transfusions or large amounts antivenom. The initial elevation of platelet counts following platelet trans or antivenom administration tends to be transient (lasting only 12â€“24 and thrombocytopenia may persist for days to weeks after normalization other coagulation parameters. The significance of prolonged thrombocyto in the absence of bleeding complications is uncertain. In the absence of bleeding, thrombocytopenia may be a benign self-limiting disorder that is tolerated and closely followed in lieu of repeated platelet transfusions or additional antivenom administration.[67] Persistent thrombocytopenia, as a isolated finding, does not require aggressive threatment.[67] Hypofibrinoge alone generally is not associated with clinically significant bleeding and m require correction. Coral snake venom does not alter coagulation, so no bleeding diathesis is expected.

Treatment of Coral Snake Envenomation

The benign local effects of coral snake envenomation can be misleading a mistakenly equated with a dry bite.[60] Because initially judging which pat are envenomated is impossible, any patient with confirmed coral snake e who have fang marks or other evidence of skin penetration should receiv

antivenom therapy, even in the absence of symptoms. A more conservati approach in the patient with a less likely coral snake envenomation still at least 24 hours of observation. Clinical deterioration may be totally unexpected and progress rapidly. Eastern coral snake envenomation can fatal, but patients usually recover completely with supportive care and antivenom therapy. In one series, 6 of 39 patients required intubation an ventilation, but none died or suffered tissue loss or permanent neurologic sequelae.[49]

Other Considerations

Tetanus prophylaxis should be administered and hyperimmune tetanus a given if primary immunization is inadequate or the history is uncertain.

Prophylactic antibiotics are not indicated, as studies show extremely low (0â€“3%) rates of wound infections.[54] There is no rationale for use of corticosteroids or antihistamines in the routine treatment of patients with snakebites, but they are used to combat the rare cases of anaphylaxis fr exposure to venom or the more common acute and delayed allergic react antivenom. Corticosteroids may be detrimental to local tissue in the early of envenomation.[16] Cardiovascular collapse is a life-threatening conseque severe systemic envenomation and should be treated aggressively with la amounts of antivenom, invasive monitoring, and standard intensive care techniques.[18] Vasopressors may be required, and respiratory compromise should be anticipated in severe cases. Because of sudden and unpredicta respiratory paralysis associated with coral snake envenomation, tracheal intubation should be considered at the first sign of bulbar paralysis. Any given antivenom or who has significant envenomation should be observed intensive care unit.

Multiple treatments with hyperbaric oxygen suggest that enhanced healing myonecrosis may occur in mice injected with *C. atrox* venom. No effect o edema associated with envenomation was observed in one study, and the beneficial effect was dose dependent, with up to 10 treatments (1â€“1.5 at 2â€“2.75 ATA) given.[47] The mechanism of action is not known but is

speculated to be related to enhanced tissue oxygenation. The effects of hyperbaric oxygen therapy for poisonous snakebites in humans is unknow use should be considered experimental at this time.

Recurrence Phenomena of Crotaline Envenomation

Data detailing the natural history of crotaline envenomation following init treatment with traditional Antivenin Crotalidae Polyvalent are sparse. Ho studies assessing the efficacy and safety of ovine Fab antivenom have sh interesting light on the clinical course of victims of crotaline envenomatic treated with this newer antivenom. Definite recurrent local and coagulop effects, in the form of worsening of symptoms after initial clinical improv are described following antivenom.[5 , 72] Recurrence phenomena are attri to the interrelated kinetics and dynamics of venom and antivenom. Simpl stated, Fab antivenom has a clinical half-life shorter than that of venom. tissue injury and coagulation deficits have been halted or corrected, tissu injury and coagulopathies may worsen, unless additional antivenom is administered. This may result in greater tissue injury and a risk of hemo Complicating matters, recurrence of coagulopathy may manifest days afte hospital discharge. The exact clinical significance of this observation and for clinical intervention are uncertain and may be predominately theoreti Currently, the most reasonable way to address possible delayed recurren effects of crotaline envenomation, especially coagulopathy, is careful foll after hospital discharge. This concern has not been extended to coral sna envenomation [see discussion in Antidotes in Depth: Antivenom (Crotalid Elapid)].

Nonvenomous Snakebites

Approximately 50,000 snakebites occur annually in the United States, and (90â€“95%) are from nonvenomous snakes.[32] Most snakes in the United are nonvenomous, and the majority are of the Colubrid family, which are generally considered harmless to humans. However, several authors have

reported toxic secretions from Duverney glands in many common species including the hognose snake, garter snake, parrot snake, banded water s and ringneck snake.[35, 58, 78] Although no deaths have been reported, s victims developed coagulopathies and local edema and hemorrhage that be confused with early crotaline envenomation.[56] No antivenom is availab treatment of bites from these snakes, and serious complications from nonvenomous snakebites are extremely rare.

Although Colubrids do not possess true fangs, some species, such as the common wandering garter snake (*Thamnophis* spp), have elongated and grooved posterior maxillary teeth (a primitive rear fang) that can penetra skin and deliver irritating saliva into the victim via a chewing motion. Son clinicians believe that the presence of teeth marks at the bite excludes th possibility that the bite was made by a venomous snake. Although it is tr fang marks are absent following nonvenomous snakebites, venomous snak have teeth, and abrasions or teeth marks may occur in conjunction with a venomous bite. This fact, along with the possibility that snakes heretofor considered nonvenomous may be dangerous, should make the clinician m cautious in diagnosing a nonvenomous bite based entirely on the presence teeth marks.

When no sign of envenomation is present after an appropriate period of observation following a suspected nonpoisonous snakebite, attention shou focused on the basic principles of wound care. The wound should be clea any foreign material removed, and an appropriate dressing applied. Certa large snakes of the Boidae family (not seen in the United States, except a or in zoologic gardens), including boas, pythons, and anacondas, may pre special problem because the force of contraction of their jaws may be gre enough to cause severe tissue contusion or fractures and retained teeth (117-4). These reptiles also have numerous large, brittle teeth that comm break off and lodge in the wound when the bitten part is forcibly extricate the snake's mouth.

Usually radiographs of the bitten area are required to exclude fracture or foreign body.

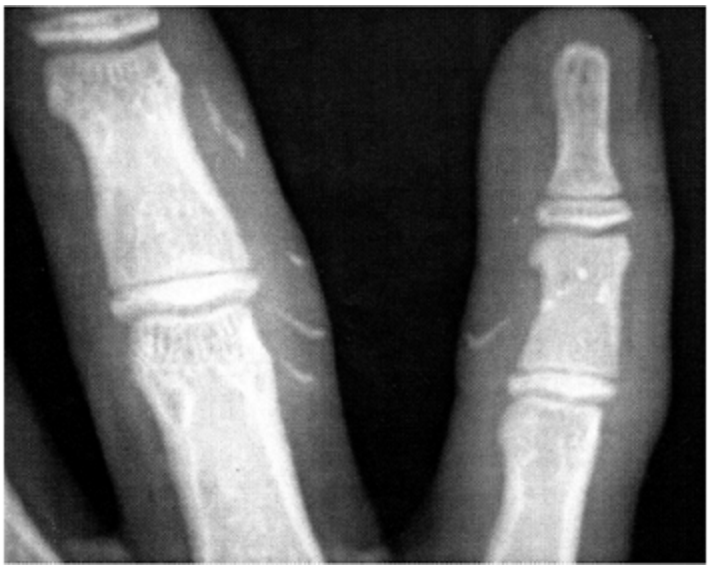

Figure 117-4. Significant local morbidity can result from the bite of nonvenomous snakes. This 10-year-old boy was bitten on the hand by a albino python. After the snake was removed, the boy complained of pers pain, redness, and swelling. The radiograph shows retained teeth in the s tissues. Following a short hospitalization for intravenous antibiotics, the recovered without sequelae. (Courtesy of the Toxicology Fellowship of the York City Poison Center.

The morbidity associated with a nonvenomous snakebite results from the case of bony injury and wound infection. Some authors recommend antib for nonvenomous snakebites, but their routine use cannot be supported. report, no infections followed nonpoisonous snakebites in 72 patients bitte variety of nonpoisonous snakes indigenous to New England and imported constrictors and pythons.[79] Although *Clostridium tetani* has not been isol from the mouths of snakes, the ubiquitous nature of this organism requir prophylaxis following the recommended approach for a contaminated wou cogent argument can be made for administering prophylactic antibiotics i nonvenomous snakebites if tooth fragments are retained or soft-tissue c is significant. A first-generation cephalosporin or antistaphylococcal peni given for 7â€“10 days should be adequate. Outpatient therapy is appropr the patient should be instructed on wound care and told to seek medical signs of infection occur. Minor abrasions from nonvenomous snakes requi

local wound care and tetanus prophylaxis. Delayed infection should prompt investigation for a retained foreign body, especially a tooth fragment.[38]

Special Considerations for Management of Pregnant Patients with Snakebites

Scant information on the effects of poisonous snakebites during pregnancy available. Case series show that maternal death is rare, but fetal loss may high as 43%.[24] The mechanism of injury to the fetus from envenomation includes uterine artery hypotension and subsequent hypoxia, hemorrhagic complications such as abruptio placentae, or uterine contractions initiated venom.[63]

Intracranial hemorrhage and death in an infant born at 34 weeks of gesta was reported in a woman envenomated by a copperhead during week 28 pregnancy.[25] At the time of the bite, she was given antivenom and devel anaphylaxis and hypotension, which was treated with large doses of epinephrine. It is suggested that the Î±-adrenergic effects of epinephrine uterine artery, coupled with maternal hypotension, contributed more to th demise than the direct effects of venom. As in each case of snakebite, it prudent to evaluate the need for antivenom carefully during pregnancy ar administer antivenom only when envenomation is significant and the bene antivenom outweigh the possible risks from allergic reactions. Fetal mon should be routine following poisonous snakebite.

Repeated Exposure to Snake Venom

Handlers and collectors are at risk for multiple bites over their careers, a questions have been raised about possible immunity. In a report of 14 pa with two or more bites, evidence that immunity develops as a result of re envenomation was not established.[64] Victims of repeat bites actually may greater risk for anaphylaxis because of a prior sensitization and the development of IgE antibodies to venom.

Exotic Snakebites (See ILNAGANAGA2 in th Image Library)

Approximately 3% of poisonous snakebites in the United States are from nonnative species.[2,8,34] Many such snakes are owned by collectors, ill imported, or stolen from zoos or pet stores. However, private individuals easily purchase a plethora of vipers, cobras, and adders by mail or at rep shows. There is surprisingly little regulation of the sale or ownership of e snakes in the United States. Exotic venomous snakes pose a particularly problem for both diagnosis and management. Many victims are collectors researchers who can identify the offending snake. However, because of fe legal retribution, some owners of exotic snakes can be quite vague about circumstances or origin of their envenomation. If they cannot provide identification, the local zoo, regional poison center, or herpetology society be helpful. Once the snake is identified, the antivenom must be obtained. always a formidable task and often impossible, but local zoos, poison cen collectors may have the antivenom. Some poison centers, some zoos, and American Association of Zoological Parks and Aquariums (301-562-0777) maintain the Antivenom Index, a listing of available antivenoms for exotic snakes, but these resources have limited ability to deliver many antivenc Bites from many nonnative Elapidae snakes, such as mambas, kraits, cob and several Australian species, are associated with high morbidity and m rates. Approximately one-third of bites from the king cobra are fatal.[34] B from these snakes may not display early local or systemic signs (Table 1. therefore, the grading system developed for North American pit vipers is helpful. Although local tissue destruction and edema may develop, classic the neurologic signs, such as ptosis, dysphagia, muscular weakness, pare ophthalmoplegia, and respiratory failure, are noted, often at a delayed or advanced stage. Cobra envenomation usually produces significant local t and these snakes are the only elapids whose venom possesses hemorrha activity. Enzyme-linked immunosorbent assay techniques can be used to specific venom antigens in suspected exotic snakebites. This technique c is not available in the United States but is used in Africa, Asia, and Austr (See ILMALAYSIANCOBRA1 in the Image Library).

Guidelines for the administration of antivenom for exotic snakes are vagu empiric. In addition, there is little standardization of the antivenoms for same snake among the different manufacturers. Exotic snakes generally quite poisonous, so if fang marks are present, envenomation is strongly suspected, the snake is identified, and the specific antivenom is obtained physicians believe it is logical to proceed with antivenom administration empirically. Antivenom is administered according to the package insert. Generally, 4â€“5 vials are administered under the same guidelines given crotaline antivenom. If the antivenom cannot be obtained, then supportiv and close in-hospital observation may be all that is possible. Local incisio suction are best avoided. Compression immobilization of an entire extren with an elastic bandage (the Sutherland wrap) for the bite of some elapid sea snakes, kraits, cobras, and brown snakes) experimentally decreases movement of elapid snake venom from the bite site to the systemic circu and may be useful when antivenom is not available. This intervention, wh does not delay transport to medical care, has been recommended for bite exotic elapids.[82] Crotalinae Polyvalent Antivenom (Wyeth) is ineffective fo bites of elapid snakes, but is active against venom of South American pit such as the bushmaster (*Lachesis muta*) and fer-de-lance (*Bothrops*). W Crotalidae polyvalent immune Fab (Protherics) is effective for South Ame pit viper envenomations is unknown. Coral snake antivenom is active only against the North American eastern coral snake and is not effective

against the western, Mexican, or South American species. It is prudent, b often difficult, to obtain expert assistance with managing any exotic snal

One report documents dramatic reversal of the neurotoxic effects of a monocellate cobra (*Naja kaouthia*) bite following intravenous administrat the anticholinesterase neostigmine methyl sulfate (0.5 mg every 20 minu 4 doses).[31] The major neurotoxin from this snake is believed to resemble curare, causing a postsynaptic blockade of nicotinic neuromuscular recep sites. The neurotoxicity from sea snakes and other elapids has also been experimentally reversed with neostigmine.[71] Edrophonium chloride (10 m administered intravenously with 0.5 mg of atropine) has also been sugge

Other Poisonous Reptiles in the United Sta

In North America there are 2 indigenous species of venomous lizards that belong to the order Squamata, the same order as venomous snakes: the monster (*Heloderma suspectum*) and the beaded lizard (*Heloderma horr* These lizards are found primarily in the desert areas of Arizona, southwe Utah, southern Nevada, New Mexico, California, and Mexico. They are lar slow-moving, nocturnal thick-bodied lizards that are prized by collectors hobbyists. Adults are 30â€“40 cm long. In general, they are shy creature bites are relatively rare, usually unintentional or secondary to handling. monsters are known for their forceful bite. They have a propensity to han tenaciously during a bite and may be difficult to disengage. Some rather innovative anecdotal techniques have been developed to remove a Gila m from an extremity, including the use of chisels, screwdrivers, and crowba pouring gasoline or ammonia into the lizard's mouth, or holding a flame t animals jaw. Teeth may break off in the wound.

Gila monster venom is complex, containing components similar to those o snake venoms, including numerous enzymes, hyaluronidase, phospholipas kallikrein, and serotonin.[37 , 70 , 77] Helothermine is the suspected toxin. venom delivery systems are not as efficient as those of poisonous snakes consist of venom glands and grooved teeth rather than fangs. Dry bites o occur because of the ineffective mechanism of delivery. Following skin pu and venom release, the victim experiences local tenderness and soft tissu swelling, pain, and edema. Anaphylactoid reactions, hypotension, angioed lip, tongue, and throat, respiratory depression, coagulopathy, and myoca infarction are reported occasionally.[65 , 66] Significant tissue destruction i unusual, but maceration may occur, and a cyanosis or blue discoloration noted about the wound. No antivenom against lizard venom is available. Treatment consists of avoiding overaggressive local treatment and provid supportive care and wound care. Serious morbidity from lizard bites is un The characteristics of the beaded lizard are similar, but their bites are les commonly confronted clinically.

Other Venomous or Poisonous Animals

It was generally believed that there are poisonous or venomous members classes of animals except birds. However, discoveries in New Guinea have birds to the list.[23, 41] Three avian Pitohui species have been found to co homobatrachotoxin, a poison very similar to that in poison dart frogs of S America. Like the frogs, the Pitohui birds are conspicuous and brightly co Little information on the toxicity of these birds is available.

Several species of mammals contain venomous members. For example, th Australian duckbilled platypus (*Ornithorhynchus anatinus*) has a hollow s that can inject venom. The Cuban insectivore (*Solendon paradoxes*) and American short-tailed shrew both secrete venom from the maxillary gland bite with the lower incisors. Envenomations from mammals are rare, and known about the specific clinical toxicity from these creatures.

Several species of amphibians, frogs, toads (*Anura*), newts, and salaman (*Urodela*) can secrete toxins through their skins, which may be a defens repellant or alarm mechanism.[6, 14, 19, 20, 39] These creatures are not venomous because they have no specific mechanism for delivering the xenobiotic. Most cases of toxicity involve children or pets ingesting the a The best-known examples are the Colombian poison dart frogs (*Phyllobat Atelopus*), which secrete the toxins zetekitoxin, tetrodotoxin, and batrachotoxin.[59] Batrachotoxin irreversibly activates (depolarizes) the so channel and is 250 times more toxic than curare in mice. Newts of the ge *Taricha* contain the irreversible sodium channel-blocking agent tetrodotox their skin and internal organs. Their toxicity is expected to be similar to occurring with puffer fish (fugu) poisoning (Chap. 45). Ingestion of a ne potential adverse consequences. Treatment is supportive. The East Coast species is less toxic than the West Coast variety, the Oregon rough-skinn newt (*Taricha granulosa*). Salamanders of the genus *Salamandra* contain very potent CNS toxin salamanderin. Large exposures theoretically could produce neurotoxicity.

Toad species of the genus *Bufo* have been abused by a curious technique licking their skin, which contains a number of toxic substances, including biogenic amines (serotonin), steroids, and polypeptides. A lysergic acid diethylamide (LSD)-like high is reported, but there is considerable folklore

confusion on the exact effects.[55] Toxicity is reported following toad lickin mouthing, toad ingestion, and toad soup consumption. Salivation, seizure cardiac dysrhythmias have been reported with ingestion of toxin from *Bu alvarius* , the Colorado River toad. The cane toad (*Bufo marinus*) is less Bufotalin, a cardioactive steroid toxin (bufadienolide) derived from this t has a chemical structure very similar to that of digoxin[50] (further details Chap. 62).

Summary

The physician faces numerous critical decisions when treating a patient w possibly has been bitten by a poisonous snake. The most basic questions address are whether or not the patient actually was bitten by a snake and whether envenomation has occurred. Careful history and examination, al with judicious use of laboratory data and observation, should answer thes questions. For patients with significant envenomations, supportive care a early use of antivenom are the mainstays of treatment.

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Antidotes in Depth

Antivenom (Crotaline and Elapid)

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For decades, Wyeth Laboratories (Marietta, PA) has manufactured a crotaline antivenom for treatment of snakebites in the United States. It is a whole immunoglobulin product derived from horse serum. Wyeth temporarily stopped production of this antivenom but has resumed manufacturing the product; however, supplies are available on a limited basis. In October 2000, the US Food and Drug Administration approved the use of another crotaline antivenom. It is a refined crotaline antivenom (crotalidae polyvalent immune Fab (ovine), Protherics, Savage Laboratories), derived from sheep serum and formulated more specifically for the crotalines found in the United States. Crotalidae polyvalent immune Fab (ovine) is an

effective and less allergenic alternative to the horse serum products.[7,11,19] Thus, crotalidae polyvalent immune Fab (ovine) has become the most practical antivenom option currently available, and the most widely used snake antivenom in the United States. A comparison of available crotaline antivenoms is given in Table A33-1.

Wyeth also produces a coral snake antivenom effective against the eastern and Texas coral snakes. Numerous other antivenoms exist for bites from exotic or foreign snakes, but they are of limited availability, are difficult to obtain, and are rarely used. Poison control centers or local zoos may have information regarding access to these antivenoms.

Crotaline antivenom is given to ameliorate the effects of local and systemic envenomation by pit vipers, and it is considered lifesaving by some clinicians.[10] Animal studies document decreased mortality when antivenom is given immediately after envenomation.[8] A delay in treatment of even a few hours lessens the beneficial effects of antivenom in animal models.[12] Case reports, anecdotal evidence, and now prospective studies support the concept that antivenom will halt the progression of local tissue swelling and at least temporarily reverse systemic effects, including most coagulation and platelet defects.[4,9,10,15]

When indicated, antivenom should be given as soon as possible to neutralize circulating venom. However, it is impossible to define the exact benefit at any specific time, and the value of late administration is impossible to quantify. Delay of antivenom administration for a few hours likely will not significantly change morbidity or mortality in the majority of cases. However, crotaline antivenom should not be given â€œprophylacticallyâ€• to patients with minimal symptoms, or those with no evidence of envenomation. Envenomation following a rattlesnake bite often progresses such that antivenom is required, whereas envenomation following a copperhead bite is less likely to require antivenom administration. The severity of envenomation by water moccasins is somewhere between that of the

relatively benign copperhead and the more tissue-destructive rattlesnake. In contrast, coral snake antivenom should be administered in cases where a coral snake bite is assumed or proven, even in the absence of symptoms.

Indications for crotaline antivenom treatment must be individualized for each patient's condition. Because antivenoms can cause life-threatening allergic reactions and delayed serum sickness, the risks and benefits must be weighed prior to treatment initiation. The major indications for crotaline antivenom therapy are (1) rapid progression of swelling, (2) significant coagulopathy or thrombocytopenia, (3) neuromuscular toxicity, or (4) hemodynamic compromise. Patients with previous life-threatening reactions to specific antivenoms still can receive those antivenoms in the absence of an effective alternative antivenom, but only if the envenomation is suspected to result in severe morbidity or mortality. Precautions must be taken to prevent and treat anaphylaxis prior to initiating antivenom therapy. Patients who are sensitized or have a known allergy to horse-derived antivenoms should receive the newer ovine-derived antivenom for crotaline envenomation.

Patients with only mild local tissue swelling following crotaline envenomation should not be given antivenom. There is no justification for infusions of 1 or 2 vials in minor cases. Standard doses for each antivenom are described. No dosing adjustment is required for children or small adults because the amount of venom requiring neutralization is not dependent upon the patient's weight. The initial dose of antivenom should be given as soon as possible but administered cautiously to limit anaphylactoid reactions from rapid infusion. Anecdotally, antivenom may reverse some of the venom-induced coagulopathy even if the antivenom is given more than 24 hours after the bite. Once symptoms begin to progress rapidly, they usually continue and antivenom is warranted. Early treatment likely will be more effective than late administration. All patients who receive antivenom should be hospitalized for at least 24 hours.

Both the equine- and ovine-derived antivenoms can cause anaphylactic and anaphylactoid reactions, as well as serum sickness.[1] Even though the refined crotaline antivenom is a purified immune Fab product, allergic reactions are reported. The true incidence of these allergic reactions is unknown, but premarketing and postmarketing data report rates much lower than for the equine-derived whole immunoglobulin products.[9,19] Because of the potential for life-threatening reactions, antivenom should be administered only in areas where resuscitation efforts can occur. Epinephrine infusion, H_1 and H_2 antihistamine receptor blockers, and corticosteroids should be available at the patient's bedside before therapy is initiated.

Discharged patients should have telephone followup for 3 weeks after antivenom treatment to permit evaluation for signs of serum sickness. Although the incidence of serum sickness is much lower for the Fab product than for the equine-derived antivenoms, serum sickness from all snake antivenoms is reported.

In addition to evaluation for serum sickness after Fab treatment, repeat outpatient laboratory studies are necessary, following hospital discharge. Crotalidae polyvalent immune Fab (ovine) use has led to the creation of a new term in antivenom treatment called *recurrence.* After crotalidae polyvalent immune Fab (ovine) stops the progression of tissue swelling and reverses coagulopathy and thrombocytopenia, a significant number of patients demonstrate recurrence of either local tissue edema and/or hematologic abnormalities. Several theories have been suggested, but the likely explanation for this phenomenon is an apparent mismatch between effective duration of

Fab antivenom and venom-induced local and systemic pathology.[19] Patients who initially have significant coagulopathy or thrombocytopenia appear to be at greater risk for recurrence of these venom effects, although the significance of these findings, or the need for treatment, is unknown. The appropriate management of recurrence is still debated.

TABLE A33-1. Comparison of Available Crotaline Antivenom

	Crotaline Polyvalent Immune Fab Antivenom (Savage Laboratories)	Antivenom Crotalidae Polyvalent (Wyeth Laboratories)
Animal source	Sheep	Horse
Venom component	*Crotalus atrox*	*Crotalus atrox*
	Crotalus adamanteus	*Crotalus adamanteus*
	Crotalus scutulatus	*Crotalus durissus terrificus*
	Agkistrodon piscivorus	*Bothrops atrox*
Immunoglobulin	IgG Fab	IgG (whole)
Hypersensitivity reactions		
Acute	14.3%	23â€“56%
Delayed	16%	75â€“86%

Recurrence[a]	Common	Rare
Dose	4â€“6 vials repeated as needed for control,[b] then 2 vials every 6 hours for 3 doses	10 vials repeated as needed for control[b]

[a]Recurrence of local tissue swelling or hematologic abnormality anytime after completion of treatment.
[b]Control = arrest of local tissue manifestations and clear improvement in coagulopathy and thrombocytopenia.

Crotaline Polyvalent Immune Fab Antivenom (Ovine Origin)

Polyvalent ovine-derived antivenom is obtained by inoculating sheep with the venom of the eastern diamondback rattlesnake (*Crotalus adamanteus*), western diamondback rattlesnake (*Crotalus atrox*), cottonmouth (*Agkistrodon piscivorus*), and Mojave rattlesnake (*Crotalus scutulatus*). This process results in an antivenom that is more specific to snakes found in the United States than the traditional Wyeth product. One report anecdotally suggests that the Fab antivenom has superior activity against the neurotoxicity of the Mojave rattlesnake.[7] The manufacturing process includes papain digestion of isolated IgG antibodies to eliminate the Fc portion of the immunoglobulin and to isolate specific antibody fragments (Fab and $F(ab)_2$), as well as affinity purification and lyophilization. The Fab fragments have a smaller molecular weight, are less immunogenic, and may have increased tissue penetration compared to whole IgG. In preliminary studies, the number of severe acute and chronic

hypersensitivity reactions associated with the Fab use was significantly reduced compared with horse serum products, but clinical experience is limited.[9] Few clinical trials have evaluated the safety of antivenom, but a study reported a 14.3% incidence of acute and 16% incidence of delayed hypersensitivity reactions.[10] Despite the uncertainty, antivenom has been safely administered to children as young as 14 months.[17] Urticaria, rash, bronchospasm, pruritus, angioedema, delayed serum sickness, and anaphylaxis all are associated with use of this product.[9,19] The same cautions that have been used with whole immunoglobulin antivenoms should be practiced with the Fab product.

The pharmacokinetics and pharmacodynamics of Fab antivenom differ from those of other antivenoms, and there is an apparent mismatch between effective duration of Fab antivenom and venom-induced local and systemic pathology.[19] The duration of action of the Fab antivenom appears to be less than that of traditional equine-derived polyvalent antivenom. The elimination half-life of 12â€“23 hours is less than that of the venom itself, so periodic or repeat dosing of Fab antivenom is required to prevent or treat recurrent symptoms.[4]

Prospective data on patients who have been treated with Fab antivenom have generated important information on the clinical utility of antivenom. The use of a clinical severity-of-illness scale has demonstrated that antivenom will correct coagulopathies and thrombocytopenia associated with envenomation from snakes native to the United States.[10] In an animal lethality model, the new ovine-derived antivenom was 5 times more potent than traditional equine-derived antivenom against 14 different crotaline snake venoms.[8] However, the progression of local tissue injury was ameliorated but not significantly reversed, suggesting that once ecchymosis, edema, and local cell injury secondary to crotaline venom develop, they are essentially irreversible. Initial experience with the Fab antivenom has been promising, and the antivenom appears to be effective in halting progression of many aspects of crotaline envenomation while minimizing allergic reactions.

Technique of Administration

A thorough history regarding asthma, atopy, concurrent use of Î²-adrenergic antagonists, allergy to papaya or papain, and previous use of antivenoms should be obtained. According to the manufacturer, the only absolute contraindication to the Fab antivenom use is allergy to papaya or papain, which is a contaminant left after the Fab portion of the immunoglobulin is cleaved from the Fc portion. A history of asthma, atopy, or use of Î²-adrenergic antagonists should be carefully considered when weighing the risks and benefits of antivenom for a particular patient. These conditions should not exclude the use of antivenom if the patient is suffering from moderate-to-severe envenomation. In cases of mild envenomation, the risk of allergic reaction to antivenom or inability to effectively treat an allergic reaction in a patient receiving Î²-adrenergic antagonists might outweigh any benefit in this patient population. Because the Fab antivenom is ovine derived, reactions from previous use of equine-derived antivenoms should not preclude use of this product.

Our practice has been to prepare for administration of the Fab antivenom in the same manner as for administration of the whole immunoglobulin antivenoms. Prior to drug infusion, an intravenous epinephrine infusion (250 mL D_5W mixed with 1 mg epinephrine), 1â€“2 mg/kg methylprednisolone, 0.5â€“1 mg/kg diphenhydramine, and an H_2 antihistamine receptor blocker are placed at the patient's bedside. Antivenom is always administered in a monitored unit where resuscitation can be performed and airway supplies can be quickly accessed.

Each vial of the Fab antivenom must be reconstituted in 10 mL sterile 0.9% sodium chloride solution prior to use. A continuous gentle swirl or rolling method is used to expedite the reconstitution. To prevent foaming, shaking and other vigorous methods should not be used. Four to 6 vials of the reconstituted antivenom are mixed in 250 mL

0.9% sodium chloride solution and administered over 1 hour. The exact concentration of antivenom is not critical. For children, the total volume of fluid in which the antivenom is diluted can be decreased when necessary. The antivenom is infused at an initial rate of 10 mL/h while the patient is observed for evidence

of hypersensitivity reactions. The rate is doubled every few minutes as tolerated by the patient. If no adverse reactions are witnessed, the remaining dose can be given over 1 hour. If the patient tolerates the initial dose without adverse effects, subsequent doses can be given over 1 hour without slowly increasing the rate.

When antivenom is administered too rapidly, mast cells release histamine and produce nonimmunogenically mediated anaphylactoid reactions. In general, patients appear to tolerate 4â€“6 vials per hour without developing anaphylactoid reactions. If the patient requires rapid administration of antivenom because of the severity of the envenomation, H_1 and H_2 antihistamine receptor blockers may be needed in addition to an epinephrine infusion. Clinically differentiating between anaphylactoid and anaphylactic reactions may be difficult, especially when antivenom is administered rapidly.

For acute anaphylactic reactions (which often occur shortly following initiation of even low doses of antivenom), the antivenom should be stopped, and intravenous steroids, H_1 and H_2 antihistamine receptor blockers, and epinephrine given. Epinephrine 2â€“4 Âµg/min (0.03â€“0.06 Âµg/kg/min for children) can be initiated and then titrated to effect. After the symptoms of hypersensitivity resolve, the antivenom should be restarted only in patients at high risk for significant morbidity or mortality from snake envenomation. In such cases, the antivenom infusion is restarted at 1â€“2 mL/h, while the epinephrine infusion is continued. The antivenom infusion rate can be slowly increased as the patient tolerates. If anaphylaxis recurs, the antivenom should be stopped and the epinephrine infusion increased until symptoms resolve. Antivenom then can be restarted while epinephrine is continued at the higher rate. With constant monitoring

of patients at the bedside and titrating epinephrine and antivenom infusions, patients with life-threatening envenomation should tolerate the full antivenom dose. Patients have safely received subsequent doses of crotalidae polyvalent immune Fab (ovine) after an acute life-threatening reaction.[6]

After two preclinical trials studied crotalidae polyvalent immune Fab (ovine), the therapeutic regimen was empirically determined to include repeat doses of 4â€“6 vials until â€œcontrolâ€• is obtained, followed by regularly scheduled maintenance infusions. The manufacturer defines *control* as arrest of local tissue manifestations and return of coagulation parameters, platelet counts, and systemic signs to normal. However, select patients develop coagulopathy and thrombocytopenia that is resistant to antivenom treatment.[19] Some authors advocate control to mean clear improvement in hematologic parameters rather than complete normalization.[19] This definition may be more realistic for the subset of patients with difficult-to-treat coagulopathy and thrombocytopenia. After each dose of 4â€“6 vials, prothrombin time, fibrinogen, and platelet counts are determined, and the patient's local injury is reexamined. Multiple doses may be required to achieve control. The optimal dose has not yet been determined. After achieving control, a maintenance dose of 2 vials every 6 hours is given, for a total of 3 doses. Again, the 2 vials are added to 250 mL 0.9% sodium chloride solution and administered over 1 hour. Because the duration of action of antivenom is not as prolonged as that of the venom, the maintenance doses are an attempt to prevent recurrence of local manifestations, thrombocytopenia, and coagulopathy. An algorithm for crotalidae polyvalent immune Fab (ovine) antivenom administration for treatment of significant crotaline envenomation is shown in Figure A33-1.

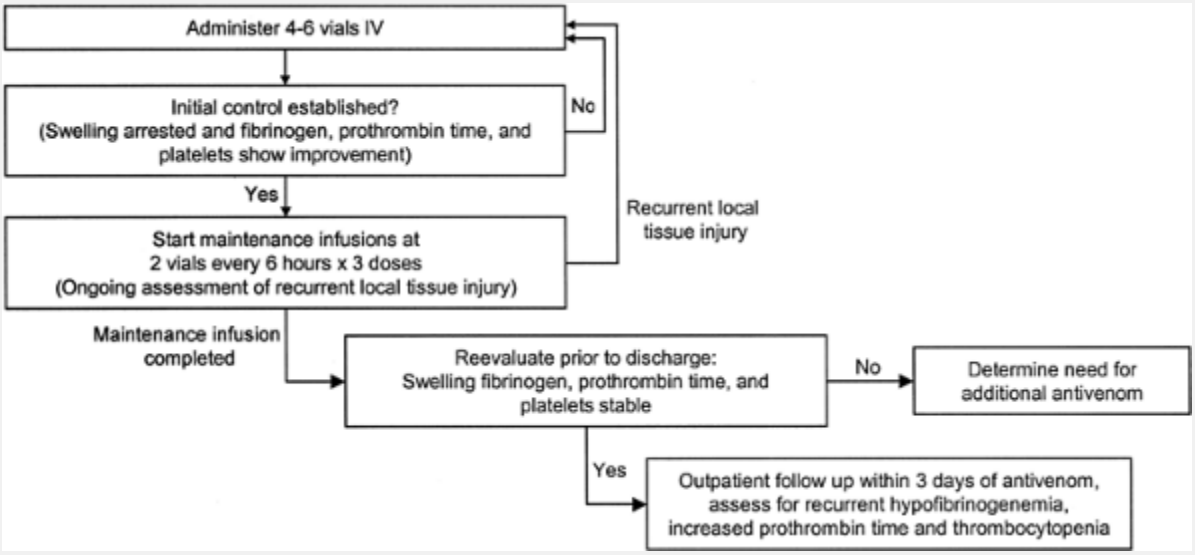

Figure A33-1. Algorithm for crotaline polyvalent immune Fab antivenom administration for treatment of significant crotaline envenomation.

At the time of discharge, the patient should be informed of the possibility of recurrence and told to refrain from activities associated with high risk for trauma and to avoid any surgical procedures for 3 weeks. The patient should receive instructions to watch for signs of bleeding, which may be associated with coagulopathy or thrombocytopenia. Followup prothrombin time, fibrinogen level, and platelet count should be obtained within 3â€“5 days of antivenom completion in all patients. In most patients who develop recurrence, the decrease in platelets or increase in prothrombin time usually is evident within 3 days of last antivenom therapy. Recurrence occurs in approximately 25â€“50% of patients with rattlesnake envenomation who receive crotalidae polyvalent immune Fab (ovine).[3,19] Early administration of antivenom may have masked the findings in patients who initially did not demonstrate

coagulopathy or thrombocytopenia, and these patients still may develop these effects within days of completing antivenom treatment. Treatment recommendations for recurrence of venom effects vary. Clinical experience demonstrates that recurrence may be resistant to additional antivenom,[19] so the benefits of re-treatment in the absence of active bleeding are unclear. No specific dosing regimen for re-treatment is known at this time. In our practice, where we frequently encounter recurrence, our approach is to re-treat patients who develop (1) isolated thrombocytopenia with platelet count <10,000â€“20,000/mm^3, (2) platelet count <30,000/mm^3 and prothrombin time >20 seconds or fibrinogen <150 mg/dL, or (3) active bleeding. A more conservative approach can be used for patients with additional risk factors for bleeding, such as high risk for trauma or use of warfarin (Coumadin). Other patients with less severe recurrence, or isolated coagulopathy without thrombocytopenia, usually can be managed at home with close followup and repeat laboratory tests every few days. Increased local tissue swelling at the time of followup usually is not an indication for redosing antivenom and most often is the result of dependent edema from inadequate extremity elevation. In the absence of any recurrence phenomenon, patients should have regular telephone followup for 3 weeks to check for signs of serum sickness.

Mild cases of serum sickness consist of urticaria, pruritus, and mild systemic symptoms, such as malaise. Occasionally arthralgias, lymphadenopathy, and fever develop. Immune-complex glomerulonephritis, neuritis, vasculitis, and myocarditis occur rarely. The syndrome of serum sickness after antivenom use has not been well characterized or studied, but usually it is neither serious nor associated with chronic sequelae.[13] Most patients respond favorably to antihistamines and systemic corticosteroids. Immediately after onset of symptoms, 2 mg/kg prednisone divided into twice daily dosing are given for 1 week. Oral antihistamines can be used for symptomatic treatment as well. After 1 week of corticosteroid therapy, the dose is slowly tapered over the following week. If

symptoms recur during the taper, the dose is increased for 3 days before the taper is reinstated. The vast majority of patients can be managed as outpatients.

As experience with the Fab antivenom expands, alternate dosing regimens may reduce the number of patients who develop recurrence. In the meantime, all patients should be considered at risk for delayed coagulopathy or thrombocytopenia. Furthermore, acute and delayed allergic reactions are less common than those reported with use of whole immunoglobulin antivenoms, but do occur. The same precautions used when administering other antivenoms should be used with the Fab antivenom.

Crotaline Polyvalent Antivenom (Equine Origin)

Crotaline polyvalent antivenom (Antivenin Crotalidae Polyvalent, Wyeth-Ayerst) is active against the venom of rattlesnakes (*Crotalus*, *Sistrurus*), water moccasins, copperheads (*Agkistrodon*), some South American pit vipers, and some Asian snakes. It is not effective for bites of exotic snakes, such as cobras and other Elapidae. This antivenom is a refined and concentrated preparation of equine serum immunoglobulins (IgG) formulated into a freeze-dried powder that is reconstituted before use. It is a suspension of various venom-neutralizing antibodies prepared from the serum of horses that are gradually hyperimmunized against the venom of a specific cadre of pit vipers found in the western hemisphere: eastern diamondback rattlesnake (*C. adamanteus*), western diamondback rattlesnake (*C. atrox*), tropical rattlesnake (*C. durrisus terrificus*), and fer-de-lance (*Bothrops atrox*). These crotalines share many of the common antigens found in pit viper venom throughout the world, so the polyvalent antivenom is presumed effective against a number of species, including all pit vipers found in the United States. Even though the polyvalent antivenom is not derived from copperheads or other crotalines, such as the Mojave rattlesnake, Pacific rattlesnake,

and timber rattlesnake, it is commonly administered following severe envenomation from these species.[2] The antivenom may be less effective against these snakes, and the neurotoxicity from the Mojave rattlesnake has been suggested to be resistant to crotaline polyvalent antivenom.[5]

Because this antivenom is a whole immunoglobulin product, its use entails a significant incidence of immediate and delayed hypersensitivity reactions,[13] including minor cutaneous hypersensitivity (urticaria), anaphylaxis, anaphylactoid reactions, and serum sickness. As the dose or rapidity of administration of antivenom is increased, the incidence of immediate and delayed hypersensitivity reactions also increases. Because the ammonium sulfate precipitation process currently used to prepare this antivenom is inefficient, the serum contains unwanted contaminants in the form of extraneous heterologous proteins such as albumin, Î±- and Î²-globulins, and IgM, in addition to the venom-specific IgG. These contaminants are largely responsible for the allergic properties of the antivenom.

Anaphylactic reactions result from the presence of circulating IgE antibodies to horse protein in the recipient's blood leading to degranulation and histamine release from mast cells or basophils. Serum sickness is caused by delayed production of antibodies by the recipient following infusion of a relatively large dose of foreign protein (antigen excess reaction). Serum sickness develops a few days to weeks after administration of horse serum-derived antivenom in the majority of patients who receive this therapy. Fortunately, serum sickness generally is mild, easily treated, and not associated with significant chronic sequelae, although rarely immune-complex vasculitis, myocarditis, neuritis, and glomerulonephritis are noted. Few data on the exact incidence of allergic reactions are available, but some form of acute hypersensitivity reportedly occurs in nearly 25% and delayed serum sickness in 50% of patients receiving antivenom.[14] Moreover, more than 80% of patients develop serum sickness if more than 8 vials of antivenom are administered.[14] The

majority of patients given antivenom experience urticaria as the only acute adverse reaction.

Technique of Administration

Before antivenom is administered, the patient should be asked about a history of asthma, atopy, current use of Î²-adrenergic antagonists, and previous horse serum-derived antivenom exposure. If any of these conditions are present, efforts should be made to obtain crotaline polyvalent immune Fab antivenom. Use of skin testing for sensitivity to horse serum is controversial, and we do not recommend its use before antivenom administration. Skin testing is an unreliable predictor of either immediate or delayed hypersensitivity reactions. Both false-positive (~50%) and false-negative (~20%) skin tests are encountered. A 1-mL vial of horse serum is included in the Wyeth Crotalidae antivenom kit with instructions for skin testing use. In life-threatening situations, and if the Fab antivenom is not available, administration of antivenom to patients with a positive skin test or known allergy to horse serum is warranted.[16,18] Antivenom administration can be continued in selected

cases of serious envenomation even in the presence of an allergic reaction. In such cases, where the skin test is positive or a reaction develops during administration of antivenom, prophylactic or concomitant use of corticosteroids, epinephrine, and antihistamines has alleviated most of the allergic symptoms. Treatment should entail use of both H_1 and H_2 antihistamine receptor blockers. In a study, the cutaneous and systemic signs and symptoms of immediate hypersensitivity were all effectively treated with antihistamines and epinephrine, with no adverse sequelae.[14] Slowing the rate of infusion of antivenom or increasing the dilution frequently lessens the severity of the allergic reaction (Chap. 117). There is no practical way to desensitize patients to horse serum. However, the Fab antivenom is a safe alternative available for horse-serum allergic patients.

The same procedure used in reconstitution of the Fab antivenom can be used for the equine product. A diluent is included in the Wyeth antivenom kit, but the diluent offers no benefit to sterile 0.9% sodium chloride solution and actually may prolong reconstitution because the diluent volume is inadequate to completely fill each antivenom vial. The same technique is described for administration of both products. It is essential that intravenous corticosteroids, H_1 and H_2 antihistamine receptor blockers, and intravenous epinephrine infusion (1 mg epinephrine mixed in 250 mL D_5W) be available at the patient's bedside. Antivenom treatment should never be initiated without close access to resuscitation equipment. Dosing differs for these two products. Ten to 20 vials are given as an initial dose, and no maintenance doses are used. After the initial dose, prothrombin time, fibrinogen level, and platelet counts are drawn, and the patient's local injury is reexamined. Repeat antivenom doses of 10 vials are given as needed to control coagulopathy, thrombocytopenia, and worsening tissue injury. On average, 30 vials are often required for adequate treatment of rattlesnake envenomation.

Followup care for patients receiving equine antivenom usually does not require repeat hematologic studies, unless patients develop signs of bleeding, because recurrence is rarely reported. Although recurrence of coagulopathy and thrombocytopenia is less frequent than with the Fab antivenom patients can have delayed bleeding, if they are not closely monitored. Long-term followup is important following administration of the equine antivenom. There is an approximately 80% chance of developing serum sickness within 3â€“20 days of antivenom administration, especially if more than 8 vials are administered.[14] The frequency of serum sickness is directly related to the number of vials of antivenom administered. The full description of serum sickness treatment is discussed in the Technique of Administration for the Fab antivenom.

Elapid Antivenom (Equine Origin)

Antivenom of equine origin is available in limited supplies from Wyeth for treatment of envenomation by the eastern coral snake (*Micrurus fulvius fulvius*) and Texas coral snake (*Micrurus fulvius tenere*). Toxicity requiring treatment with antivenom has not been reported following bites from the less virulent Arizona (Sonoran, *Micruroides euryoxanthus*) coral snake. The coral snake antivenom does not treat envenomation from coral snakes found in Mexico, Central America, or South America. In contrast to the recommendation to withhold crotaline polyvalent antivenom unless signs of significant envenomation are evident, prophylactic use of coral snake antivenom is recommended in any asymptomatic cases where a coral snake bit is assumed or proven.[15] Limited supplies of this antivenom may make adherence to this recommendation difficult. For a number of hours following the bite of a coral snake, little objective evidence suggests envenomation, but systemic symptoms can develop insidiously. Therefore, at least 3â€“5 vials of coral snake antivenom are given initially and repeated on the basis of the clinical condition. The caveats for administration of crotaline antivenom (skin testing, rate of infusion, treatment of reactions) apply to coral snake antivenom, except less antivenom usually is required for coral snakes. Up to 10 vials can be administered, but dosing recommendations are vague.

Conclusion

In the past, equine crotaline polyvalent antivenom was the only antivenom available for treatment of crotaline envenomation. It is an effective therapy, but carries a significant risk of life-threatening immediate and delayed hypersensitivity reactions. Some hospital pharmacies still maintain supplies of the antivenom, and Wyeth will provide it on an â€œas neededâ€• basis. In recent years, ovine crotaline polyvalent immune Fab antivenom (CroFab) has become the more commonly available treatment for crotaline envenomation. Although treatment with the Fab antivenom requires maintenance doses and often leads to recurrence of envenomation effects, it is

clearly a safer alternative to the equine product. One aspect of crotaline therapy that has not yet been fully evaluated is a cost-to-benefit analysis comparing the two antivenoms. As experience with the Fab antivenom grows, the cost of drug administration, followup care with repeated laboratory examinations, and possible rehospitalization for recurrence may become more evident. Regardless, most physicians are restricted to the Fab antivenom use merely because supplies are more easily secured, thus making any cost-to-benefit analysis less meaningful.

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Chapter 118

Industrial Poisoning: Information and Control

Peter H. Wald

Three workers engaged in the production of mercuric acetate were admitted to hospital within 22 calendar days of each other, 30, 48, and 5 days, respectively, after their last working day. The workers served the same reactor in which elemental mercury was oxidized by peroxide to mercuric oxide, and mercuric acetate was formed by the reaction of mercuric oxide with acetic acid. They all presented with neurologic findings including ataxia, dysarthria, tremor, deteriorating vision, and cerebellar signs. The first two had rapidly progressive downhill courses to coma that ended in death. The diagnosis of mercury vapor intoxication of the first two patients was established 21 and 16 days after their admission, when the third patient was admitted and hospitals were informed about their exposure. Blood mercury levels in all three patients were approximately 2000 Âµg/L with low urine mercury levels. All patients were chelated with penicillamine without any noticeable

effect.

Organic mercury probably was formed as an unintended byproduct of this reaction. In this reaction, methyl mercury acetate, which is 5.4 times more volatile than mercury vapor, could have been formed. The incorrect diagnosis of mercury vapor exposure in these cases was established despite the facts that (1) the observed signs of a rapid irreversible clinical course, ataxia, dysarthria, and constriction of visual fields are rarely present in mercury vapor poisoning and are characteristic of organic mercury poisoning; (2) the degree of deterioration after removal from exposure further implicated organic mercury, not mercury vapor; (3) blood mercury concentrations were in the range associated with severe poisoning in the Iraq methyl mercury epidemic; (4) patients had little response to treatment with penicillamine, the opposite of what is expected with mercury vapor; and (5) the blood-to-urinary mercury concentration ratios were high, whereas this ratio usually is <0.5 in mercury vapor toxicity or in workers exposed to mercury vapor.

The other important facet of these cases is the public health implications of this sentinel health event. Three employees in this workplace were affected by this exposure. Were there any others?

These cases illustrate three important problems associated with the diagnosis and treatment of occupational or environmentally caused diseases: (1) the ability to establish the diagnosis correctly, (2) the ability to treat the condition correctly, and (3) the ability to act correctly on any public health issues related to the exposure. The following discussion instructs the clinician on how to assemble adequate information to achieve the appropriate diagnosis and treatment.

Taking an Occupational History

Because time spent at work is a large percentage of many people's

day, the occupational health history should be a routine part of any medical history. This is especially true of patients who present to a physician with potential chemical exposures at work or unusual symptoms. The history should include several brief survey questions. Positive responses then lead to a more detailed occupational and environmental history, which is composed of three elements: present work, past work, and nonoccupational exposures.

The Brief Occupational Survey

The following three questions should be incorporated into the occupational survey:

- Exactly what kind of work do you do?
- Are you exposed to any physical (radiation, noise, extremes of temperature or pressure), chemical (liquids, fumes, vapors, dusts, or mists), or biologic hazards at work (Table 118-1)?
- Are your symptoms related in any way to starting or being away from work? For example, do the symptoms start when you arrive at work at the beginning of the day or week or when you work at a specific location, or during a specific process at work?

TABLE 118-1. Hazard Classes, Hazard Types, and Several Common Examples Found in the Workplace

Hazard Class	Hazard Type	Examples
Physical hazards	Manâ€“machine interfaces	Repetitive motion Lifting

		Vibration Mechanical trauma, electric shock
	Physical environment	Temperature Pressure Long/rotating shifts
	Energy	Ionizing radiation: x-ray, ultraviolet Nonionizing radiation: infrared, microwave, magnetic fields Lasers Noise
Chemical hazards	Solvents	Aliphatics, aromatics, alcohols, ketones, ethers, aldehydes, acetates, peroxides, halogenated compounds
	Metals	Lead, mercury, cadmium
	Gases	Combustion products, irritants, simple and chemical asphyxiants
	Dusts	Organic (wood) and inorganic (asbestos/silica)

	Pesticides	Organic chlorine, organic phosphorus, carbamate
	Epoxy resins and polymer systems	Toluene diisocyanate, systems phthalates
Biologic hazards	Bacteria	*Bacillus anthracis, Legionella pneumophila, Borrelia burgdorferi*
	Viruses	Hepatitis, human immunodeficiency virus, hantavirus
	Mycobacteria	*Mycobacterium tuberculosis*
	Rickettsia and *Chlamydia*	*Chlamydia psittaci, Coxiella brunetti*
	Fungi	*Histoplasma capsulatum, Coccidioides immitis*
	Parasites	*Echinococcus* spp, *Plasmodium* spp
	Envenomations	Arthropod, marine, snake
	Allergens	Enzymes, animals, dusts, insects, latex, plant pollen dusts

Present Work

Collected data on a person's present job reveals what his or her present exposures may be, which can help formulate the differential diagnosis for the employee's complaints. These data can be systematically collected by focusing on four areas: specifics of the job, hazardous exposures, health effects, and control measures (Table 118-2).

Specifics of the Job

It is not sufficient simply to inquire what the patient does for a living. Like healthcare professionals, workers in other industries have their own jargon. When asked for a job title, a patient may respond with a title that has meaning only in his or her trade. Even if the job title is recognizable, it may not provide any useful information and, in fact, may be misleading. A secretary working in a small plastics manufacturing plant may have occupational exposures quite different from the secretary who works for a law firm.

The important specific information requested should include name of employer, type of industry, duration and location of employment, hours and shift changes, process description including unusual occasional activities, and adjacent processes. The employer may be able to provide information about materials used at the plant. However, clinicians should always obtain the patient's permission before calling the employer. A patient may be fired or otherwise discriminated against (despite legal protections) for suggesting that health problems are work related.

It is important to learn actually what happens in the patient's immediate work environment because nearby work processes may

contribute other exposures. If possible, the patient should be asked for a diagram of the work area. The patient also should be questioned

about job process changes. A previously safe job may have been changed to a potentially dangerous job without a change in the patient's job title.

TABLE 118-2. Components of an Occupational Health History

Current work history
  Specifics of the job
    Employer's name
    Type of industry
    Duration of employment
    Employment location, hours, and shift changes
    Description of work process
    Unusual activities of the job that are occasional (maintenance)
    Adjacent work processes
  Hazardous exposures (Table 118-1)
  Possible health effects
    Suspicious health problems
    Temporality of symptoms
    Specific distribution of symptoms (rash, paresthesias)
    Affected coworkers
    Presence or absence of known risk factors (smoking, alcohol)
  Workplace sampling and monitoring
    Individual and/or area air monitoring
    Surface sampling
    Biologic monitoring

- Medical surveillance records
- Exposure controls
  - Administrative controls
  - Process engineering controls
    - Enclosure
    - Shielding
    - Ventilation
    - Electrical and mechanically controlled interlocks
  - Personal protective equipment
    - Respirators
    - Protective clothing
    - Earplugs, glasses, gloves, face shields, head and foot protection
- Past work history
  - Review current work history for all past employment
- Nonoccupational exposures
  - Secondary employment
  - Hobbies
  - Outdoor activities
  - Residential exposures
  - Community contamination
  - Habits

The patient should describe exactly what he or she does on any given day and for how long. Unusual and nonroutine tasks, such as those performed during overtime, maintenance, or in an emergency, should be described. The primary job may not involve chemicals, but the patient may nevertheless perform tasks that entail unprotected exposure to a toxic chemical.

Hazardous Exposures

The names and/or types of all chemicals or substances to which the patient may be exposed are important in determining potential

adverse effects and any relationship to the patient's complaints. It is important to elicit any recent changes in suppliers of these products, as even a slight change in the formulation of a chemical may cause adverse effects in an individual who previously had no problems working with that compound. This information may be obtained from the material safety data sheet (MSDS), an important but not universally reliable source of information about the chemical. In addition to adverse health effects, the MSDS contains information on chemical reactivity, safety precautions, and other data. As an initial step, the MSDS should be requested and reviewed; however, information provided on health effects should be confirmed using other resources. Four major concerns result from relying solely on the MSDS: (1) some MSDS forms are excellent, but others are incomplete and inadequate; (2) components of a product that are regarded as â€œtrade secretsâ€• do not have to be revealed; (3) components that have important health effects (eg, solvent or solid carriers of the â€œactive ingredientsâ€•) often may be grouped together under â€œinert ingredientsâ€• without being specifically named; and (4) process intermediates or unintended byproducts of a manufacturing process may not be identified. However, if a chemical is believed to be related to a health effect, manufacturers are required to release to a physician all information, including trade secrets and inert components.

Exposures to physical and biologic xenobiotics can be elicited during the review of job processes. Most patients know what they are, or have been, exposed to, even if they do not know the exact name of the xenobiotics or its medical effects.

Health Effects

Significant occupational exposures usually cause medical effects, although some do so only after a substantial latency period. Key areas of interest include suspicious health problems, temporality

of symptoms, and affected coworkers. These data, combined with workplace monitoring and sampling data, can help in determining whether the patient is suffering a work-related illness (Table 118-3). Patients may suspect that their illness or complaint is work related, especially when symptoms occur at the workplace and improve or disappear over the weekend or during a vacation. Specific distribution of findings, such as a rash in a bilateral glove pattern, is supportive of an occupational etiology. Coworkers with similar complaints (not necessarily of the same severity) should raise suspicion that a workplace exposure is responsible for a particular symptom complex. Finally, diseases such as lung cancer or hepatitis, which occur in the absence of known risk factors such as smoking and alcohol, are important.

TABLE 118-3. Evidence Supporting Work-Relatedness of Occupational Disease

Known or documented exposure to a causative agent
Symptoms consistent with suspected workplace exposure
Suggested or diagnostic physical signs
Similar problems in coworkers or workers in related occupations
Temporal relationship of complaints related to work
Confirmatory environmental or biologic monitoring data
Scientific biologic plausibility
Absence of a nonoccupational etiology
Resistance to maximum medical treatment because employee continues to be exposed at work

Workplace Sampling, Monitoring, and

Control

Control of workplace hazards begins with an industrial hygiene monitoring program. Employers are required to give results of both area and individual sampling to employees. A medical surveillance program that includes periodic spirometry and respiratory questionnaires usually indicates that the patient works with a potential respiratory toxin. A medical surveillance program that includes biologic monitoring for a specific substance also may provide an immediate clue to what may be causing the patient's complaints. Finally, if the patient knows exactly what he or she is working with, the physician usually can quickly determine whether any of the substances are compatible with the patient's complaints. Many companies do not perform routine industrial hygiene monitoring or medical surveillance. Individuals who became sick or ill at work often are sent to local emergency departments. In such situations, emergency physicians must be prepared to develop the type of time-consuming, detailed occupational history outlined here or be able to consult or refer immediately to appropriate individuals or clinics.

Portions of Table 118-2 and the following section on Evaluation and Control of Workplace Hazards detail the types of controls usually used in workplaces. It is important to determine whether the workplace uses any control measures, engineering controls, work practice protocols, administrative controls, and personal protective equipment. The existence of control measures usually indicates that the employer recognizes and has attempted to deal with a hazardous exposure.

Past Work

It is important not to limit the occupational history to the patient's current workplace and job. Many occupational diseases have long latency periods between exposure to a toxic agent(s) and initial development of clinical symptoms. In addition, patients may have

been exposed to xenobiotics at work that make them more sensitive to other environmental agents. For example, someone who developed asthma secondary to a previous workplace exposure may suffer asthma attacks upon exposure to simple irritants in the current workplace. When taking an in-depth occupational history, explore issues relevant to the current work history for each previous job.

Nonoccupational Exposures

Workers may be exposed to toxic xenobiotics in the course of pursuing secondary employment, hobbies, or outdoor activities in contaminated or industrial areas. Residential exposures, such as those from gas and wood stoves, chemically treated furniture and fabrics, and pest control, may be relevant. It is important to ask patients about these potential exposures before focusing entirely on exposures in their primary place of employment. This obviously includes relevant issues from the social history, such as tobacco, alcohol, and licit and illicit drug use.

Evaluation and Control of Workplace Hazards

Initial Workplace Evaluation

The Occupational Safety and Health Act places legal responsibility for providing a safe and healthy workplace on the employer. The rationale for this placement of responsibility is that the employer is in the best position to make any modifications necessary to prevent additional work-related illness and injury. The physician may wish to initiate a dialogue with a patient's employer to promote preventive action but should do so only with the patient's informed consent. The initial treating physician may also refer to

an occupational medicine specialist, who is specifically trained to manage work-related exposures and diseases and initiate prevention programs.

Because the initial contact may influence subsequent events, it is important to identify an individual with an appropriate administrative role, such as someone in the company medical department, the patient's supervisor, the plant's safety officer, or the shop manager. If management is willing to examine the hazardous conditions, a plant walk-through inspection can provide unique insight and information usually unavailable in an office setting. A walk-through by an occupational medicine specialist makes it easier to understand the work environment, identify safety and health hazards, assess control measures, and recognize opportunities for prevention. It also facilitates a good working relationship with key personnel in management and labor. The physician who cares for a number of patients who work in the plant or who provides health services to the workers through the company or labor union may wish to be involved in the walk-through. Assistance with plant inspections can be obtained from occupational health specialists, such as occupational physicians or industrial hygienists.

Industrial Hygiene Sampling and Monitoring

Equipment is available to measure airborne concentrations of toxic xenobiotics, noise levels, radiation levels, temperature, and humidity. Employees can be fitted with pumps and other devices to measure individual exposure levels at the breathing zone, where, depending on what controls are used, concentrations may vary from those in the general work area. These results then can be compared with Occupational Safety and Health Act (OSHA) and other available standards to help determine the extent of the hazard and to formulate a control plan. OSHA requires that

employers monitor the levels of only a few specific hazards, including asbestos, formaldehyde, lead, vinyl chloride, noise, and ethylene oxide. Ongoing sampling of the remaining estimated 60,000 chemicals used in the workplace is not required. Where industrial hygiene sampling is performed, OSHA's medical access standard gives any exposed worker or his or her representative the right to review and copy all sampling data.

Control of Workplace Hazards

Workplace hazard control traditionally has relied on a hierarchy of methods to protect workers from exposure. The preferred solution is complete elimination of the hazard by *substitution*. Where substitution is not possible, the next preferred method consists of controls that shield workers or reduce their exposure. The least favored method us personal protective equipment, which requires a positive action from the worker.

Engineering Controls

Health and safety professionals prefer, and OSHA regulations require where feasible, the use of engineering controls to reduce worker exposure to hazardous xenobiotics because such controls intercept hazards at their source or in the workplace atmosphere before they reach the worker. Engineering controls include redesign or modification of process or equipment to reduce hazardous emissions, isolation of a process through enclosure, automation of an operation, and installation of exhaust systems that remove hazardous dusts, fumes, and vapors. Local exhaust systems, such as hoods, are preferable to general dilution ventilation because the former removes contaminants closer to their source and at relatively high rates.

Engineering controls have several advantages over control measures focused on the worker. Properly installed and maintained

engineering controls are reliable and consistent, and their effectiveness does not depend on human supervision or interaction. They can limit exposure through several routes, such as inhalation and skin absorption, simultaneously. In addition, engineering controls do not place a burden on the worker or interfere with worker comfort or safety.

Work Practices

Work practices are procedures that the worker can follow to limit exposure to hazardous agents. Examples are the use of high-powered vacuum cleaners instead of compressed air cleaning and pouring techniques that direct hazardous material away from the worker. Although not as effective as engineering controls, work practice can be a useful component of an overall hazard control program.

Administrative Controls

Administrative controls reduce the duration of exposure for any individual worker or reduce the total number of workers exposed to a hazard. Examples are rotating workers into and out of hazardous areas so that no single worker is exposed full time and scheduling procedures likely to generate high levels of exposure, such as cleaning or maintenance activities, during nights or weekends. Administrative controls sometimes have the side effect of exposing more workers to a hazard, albeit at lower doses that are hoped do not cause health effects.

Personal Protective Equipment

Personal protective equipment, such as respirators, earplugs, gloves, and hard hats, is the least effective but most commonly used control method. Employers may often favor personal protective equipment over the institution of more costly

engineering and administrative controls.

Respirators and other forms of personal protective equipment often are hot, uncomfortable, and awkward to wear and may make it difficult for workers to breathe, speak, or hear, depending on the equipment involved. Consequently, workers often remove or refuse to wear the protection. Respirators place extra stress on the heart and the lungs. Both respirators and earplugs limit conversation and therefore present a safety hazard in themselves.

Because personal protective equipment does not stop a hazard from entering the environment, the worker is entirely vulnerable to exposure if the equipment fails. In addition, generally only one route of exposure is protected. For example, the commonly used half-mask respirator still leaves the skin and eyes exposed.

Choosing the right piece of personal protective equipment can be difficult and may depend on the nature and extent of the hazard. For example, each type of respirator is rated for the amount of protection it provides; as expected, the cost of a respirator increases with its protection factor. Use of the wrong type of respirator can leave the worker insufficiently protected.

Half-mask respirator cartridges are available in various colors, coded to the contaminant filtered out of the breathing environment. If the wrong cartridge is used, the worker is essentially unprotected from the hazardous contaminant. To be effective, a respirator must be meticulously fit to the individual worker. Failure to achieve a proper seal negates the respirator's usefulness. High cheekbones, dentures, scars, perspiration, talking, head movements, and facial hair can prevent a proper seal. These factors often are ignored or overlooked by an employer who adopts a â€œone-size-fits-allâ€• policy.

Even if each employee is provided the proper respirator, the respiratory protection program may not be effective. OSHA

requires that employers institute a program of proper fit testing, cleaning, maintenance, and storage of respirators, which can be at least as costly as the institution of engineering controls.

In some instances, use of personal protective equipment may be unavoidable. An employer may need to control a hazardous exposure through a combination of measures, such as engineering controls and personal protective equipment. Ideally, the employer is using personal protective equipment as a control of last resort and in strict compliance with OSHA standards.

Worker Education and Training

Regardless of the control measures used, workers and supervisors must be educated in the recognition and control of workplace hazards and the prevention of work-related illness and injury. The OSHA Hazard Communication Standard requires that employers train workers in ways to detect the presence or release of hazardous chemicals, their physical and health hazards, methods of protection against the hazards, and proper emergency procedures, as well as how to read the labeling system and how to read and use an MSDS.

With the passage of federal, state, and local right-to-know laws, many consulting companies now offer hazard communication training. These programs are of uneven quality. Those that tend to focus on acute hazards, ignore chronic effects, and emphasize personal protective equipment over other control measures may not be effective in training workers to recognize and control chemical hazards.

Medical Monitoring

Together with worker education and industrial hygiene, a medical program can form the foundation of an effective occupational disease prevention regimen. However, medical monitoring is

fraught with technical and ethical pitfalls. Medical monitoring encompasses both medical screening and medical surveillance.

Medical screening refers to the cross-sectional testing of a population of workers for evidence of excessive exposure or early stages of disease that may or may not be related to work and that may or may not influence the ability to tolerate or perform work.

Preemployment and preplacement physical examinations are another type of medical screening, often favored by employers. The new Americans with Disabilities Act (ADA) regulates the timing, scope, content, and use of these examinations and the information gathered. Comprehensive resources for information on the ADA are available at http://www.adata.org. The ADA prohibits â€œpreemploymentâ€• medical examinations and inquiries. After a job offer has been made, â€œpreplacementâ€• examinations and inquiries can be conducted to determine whether an applicant can perform a job safely and effectively. The physician evaluates past medical history, current symptoms, and physical laboratory findings to determine whether an individual currently has the physical or mental abilities necessary to perform the essential functions of the job and whether the individual can do so without posing a â€œdirect threatâ€• to the health or safety of self or others. This threat must be more than theoretical and cannot be based on some future time; the threat must be concrete and relatively immediate.

Few tests and few conditions are good predictors of either ability to perform a task or increased susceptibility to a particular exposure. Many workers and their advocates view preplacement examinations as a way for employers to choose the â€œfittestâ€• worker and to avoid their legally mandated obligation to provide a safe and healthy workplace for all workers. This is not true for most employers. Physicians asked by an employer to perform preplacement examinations should be sure that each component of the examination relates to the actual job the individual is being

hired to perform and the actual risks he or she will encounter on the job. Both the law and sound occupational medical practice dictate that the employer's attention and efforts be directed toward redesign of the job and its hazards so that it is safe and healthy for all workers to perform.

Medical surveillance refers to the ongoing evaluation, by means of periodic examinations, of high-risk individuals or potentially exposed workers to detect early pathophysiologic changes indicative of significant exposure. OSHA requires little in the way of medical surveillance, although several OSHA standards require employers to institute medical surveillance programs, for example, for workers exposed to asbestos, arsenic, vinyl chloride, lead, and ethylene oxide. Depending on the potential exposure, medical surveillance can include a history and physical examination, chest radiograph, pulmonary function tests, blood and urine tests, and other laboratory evaluations.

A medical surveillance program also can include biologic monitoring, the purpose of which is not to identify the occurrence of disease but to measure the uptake or presence of a particular substance or its metabolites in body fluids or organs. Ideally, this occurs before any pathophysiologic damage occurs. Consequently, biologic monitoring is potentially a primary preventive measure. For example, several volatile organic compounds, such as benzene and toluene, if inhaled or absorbed through the skin, produce metabolites that can be measured in urine.

Biologic monitoring can have some advantages over air monitoring because biologic monitoring measures the *actual* absorption of a substance by the body as opposed to ambient levels in the workplace. The amount of a chemical absorbed may not be closely correlated to ambient levels for several reasons, including differences in individual work habits, use and effectiveness of personal protective equipment, dermal absorption of chemicals unrelated to their concentration in the air, and nonoccupational

exposures.

Biologic monitoring, however, has several significant limitations. For most xenobiotics, there are no standards of â€œnormalâ€• or â€œsafeâ€• levels against which results can be compared. Obtaining specimens may be difficult, expensive, and invasive (eg, fat biopsies to detect dioxin). The timing of specimen collection is critical because different xenobiotics have different biologic half-lives. The

storage and handling of specimens and interpretation of results are vulnerable to error. Nevertheless, if carefully designed and implemented, biologic monitoring can be a useful complement to a comprehensive industrial hygiene program.

With the exception of biologic monitoring, medical monitoring programs identify disease processes already underway and therefore are, at best, a form of secondary prevention. Employers use results to remove workers rather than remediating the hazard abuse medical and biologic monitoring programs. To be an effective preventive measure, these programs must be coordinated with environmental monitoring programs that identify the nature, source, and extent of workplace hazards; implementation of engineering controls and other measures that control hazards as close as possible to the source; and worker education programs that, at a minimum, inform workers of exposures, their effects, and proper control measures.

Both medical monitoring programs and preplacement examinations raise issues of doctorâ€“patient confidentiality. Employee medical records should be available only to the corporate medical or first-aid department and not to the personnel office and general management. Unless required by statute, employers should never be told the results of history, physical, or diagnostic examinations unless the patient gives his or her written consent. The examining physician need only inform the employer that an individual is or is

not capable of performing a particular job with or without specified restrictions. The physician should not disclose diagnostic information about medical conditions.

Information Resources

Healthcare professionals require information on industrial toxins in a number of situations, ranging from caring for an acutely ill patient in an emergency department, when information must be obtained quickly, to caring for a patient with chronic symptoms that may reflect an occupational disease. The American College of Occupational and Environmental Medicine publishes a suggested reading list (http://www.acoem.org) that provides reference sources for information on toxicology, acute and chronic health effects, diagnosis, and treatment; assists in screening and surveillance; and provides information on groups at risk, product uses, and sources of further information. However, use of these resources depends on the proper identification of the substance in question. If the substance, its generic name, and ingredients are not known, the research process becomes more difficult.

The practitioner should take a logical approach to seeking information about industrial xenobiotics. First, the xenobiotics must be identified by its generic name. This can be done by reviewing the MSDS or by contacting poison control centers (PCCs), the employer, manufacturer, unions, or government agencies. MSDSs also are available by searching online. MSDS Online (http://www.msdsonline.com) is a good starting point, but typing â€œMSDSâ€• into any online search engine yields a number of sites offering data sheets.

Poison Control Centers

Regional PCCs can provide assistance even when the exact chemical name is unknown because information on xenobiotics and

their management may be cross-referenced by trade name and manufacturer. Moreover, PCC personnel usually can suggest additional resources. Most PCCs have computerized listings of poisons that are updated regularly. The best-known system is POISINDEX (Micromedex, Englewood, CO). Subscribers to this system receive quarterly updates of an alphabetically organized listing of approximately 500,000 industrial and nonindustrial xenobiotics. The system includes trade names, the components, and the concentrations, when available, of each compound listed. These elements are then cross-referenced to management protocols. The name of the manufacturer is also listed.

Employers and Manufacturers

Many state and federal laws require manufacturers to generate, retain, and disclose information that may help physicians care for persons with work-related health problems. Scientific information, exposure data, information on health effects, and collected medical data are included in the types of information that must be retained.

The Chemical Transportation Emergency Center (CHEMTREC; 1-800-262-8200; http://www.chemtrec.org), sponsored by the Chemical Manufacturers Association, has as its primary responsibility providing information to healthcare practitioners responding to hazardous spills. However, it also will provide information on commercial products found in a patient's workplace. Employers are required to furnish this information to employees in the form of MSDSs.

Worker's Compensation Insurance Carriers

Smaller companies often lack internal health and safety staffs. Worker's compensation or company risk insurance carriers may

have valuable information about exposures and controls in the workplace. As a service to their clients, carriers often will do walk-throughs and hazards evaluations for clients that lack these resources and suggest appropriate engineering controls. Healthcare professionals can contact the carrier directly to see what additional information is available.

Regulatory Agencies

OSHA requires chemical manufacturers to create a MSDS for each chemical they produce, and employers who use chemicals must retain the MSDSs in the workplace. Required information includes chemical and common names; physical, safety, and health hazard data; exposure limits; precautions for safe handling and use; generally applicable control measures; and emergency and first-aid procedures. The OSHA Hazardous Communication Standard requires individual employers to provide employees with information on the xenobiotics used in their workplaces. With the patient's permission, a call to the plant manager, foreperson, or safety officer may be all that is necessary to determine the name of the substance in question. Employers may be able to provide information on exposure levels in the patient's work environment. In addition, company medical departments (where they exist) may have results of medical testing done on the patient.

There is an important point to reiterate about MSDSs: healthcare providers should not rely on these sheets as the sole source of information. The MSDSs are created by the chemical manufacturers as they generate scientific and health data during the course of seeking approval from the Environmental Protection Agency (EPA) to manufacture xenobiotics and will not be a complete product evaluation. In addition, Section 8(c) of the Toxic Substances Control Act (TSCA) requires chemical manufacturers to report records of significant adverse reactions to human health or the

environment. When contacting chemical manufacturers, physicians should ask to speak with a toxicologist, chemist, or someone in the products information department.

Unions

Labor unions, where they exist, can be excellent sources of information on xenobiotic exposures. At the local level, union officers, health and safety committee members, and shop stewards may be able to provide MSDSs, exposure data, medical and epidemiologic information, and reports of incidents or cases of interest in a particular plant. The health and safety department of the American Federation of Labor and Congress of Industrial Organizations (AFL-CIO), (http://www.aflcio.org) in Washington, DC, can provide information on occupational health and safety activities and advice on which member unions may be of specific help. At the international level, unions often have well-trained health and safety professionals who may provide or suggest sources of helpful information. In addition, some cities have a coalition of occupational safety and health groups that may provide information about other known exposed or affected workers.

Government Agencies

A myriad of agencies have some regulatory authority over manufacturing and services industries. These agencies and their important regulatory authority are listed in Table 118-4.

OSHA of the US Department of Labor (http://www.osha.gov) is responsible for setting and enforcing workplace health and safety standards. It is empowered to investigate occupational health and safety complaints and can inspect work sites and levy fines for violations of its standards. In approximately half of the 50 states,

the OSHA program is implemented by a state agency. Individual workers, their representatives (unions), or their physicians can file a complaint with the state or federal OSHA program and request an inspection. OSHA regulations protect workers from discrimination and punishment by their employer, who may be angered by their filing a complaint.

Some state OSHA agencies have separate enforcement and consultation arms. Thus, companies can request assistance from the occupational health specialists in the consultation branch without fear of reprisal from the enforcement branch. Healthcare workers should be familiar with the functions of their state agency and workers' rights under the law.

The National Institute for Occupational Safety and Health (NIOSH) of the US Department of Health and Human Services is part of the Centers for Disease Control (http://www.cdc.gov/niosh). It is not a regulatory agency. NIOSH is responsible for researching the causes of occupational disease and injury and methods for their prevention and control; evaluating workplace conditions; recommending exposure limits to OSHA for standard setting; and training occupational health and safety professionals. It is empowered to conduct on-site evaluations of health hazards in response to requests from employee representatives or employers. After conducting these evaluations, NIOSH investigators immediately contact OSHA, the employees, and the employer if they find that the workers are in imminent danger.

As part of the process of recommending exposure standards to OSHA, NIOSH develops comprehensive documents that critically evaluate all available scientific data on particular chemicals. These â€œcriteria documentsâ€• review the chemical's properties, production methods, uses, and workers at risk as well as studies of exposure effects in humans and animals. Methods of screening, surveillance, and control are presented. The agency periodically issues technical reports and special occupational hazard reviews of

specific occupations. In conjunction with OSHA, NIOSH develops and disseminates health hazard alerts to inform employers, employees, and healthcare professionals of serious health effects of particular chemicals.

The EPA (http://www.epa.gov) is charged with protecting the nation's land, air, and water. The agency administers a number of laws designed to preserve the public health and environment, one of which is the TSCA. This act authorizes the EPA to collect information on chemical risks from manufacturers and processors and to review information on new chemicals and new uses of chemicals before they are manufactured. Unless designated a trade secret, this information is subject to disclosure and therefore is available. The TSCA assistance office may be most useful when resource materials and government documents contain no information about the chemicals or processes in question.

The National Toxicology Program (NTP; http://www.ntp-server.niehs.nih.gov) is a federal program established in 1978 to develop scientific information on exposure to xenobiotics.

The Agency for Toxic Substances and Disease Registry (ATSDR; http://www.atsdr.cdc.gov) is part of the Public Health Service created by Congress to implement the health-related sections of laws that protect the public from hazardous wastes and environmental spills of hazardous substances. In 1986, the Superfund Amendments and Reauthorization Act (SARA) made amendments to the initial enabling legislation of 1980 and broadened ATSDR's responsibilities in the areas of health assessment, toxicologic databases, information dissemination, and medical education. One of its offices, the Office of Health Assessment, provides emergency response for toxic and environmental disasters, consults in public health emergencies, assesses hazardous waste sites, provides technical assistance to agencies and organizations, and estimates health risks to humans from exposure to hazardous substances. The program areas in

which ATSDR operates include health assessments, toxicologic profiles, emergency response, and exposure and disease registries.

Online Databases

Printed material often is adequate for determining the adverse health effects of chemical exposures, but some resources may be unavailable to physicians, and textbook publications usually lag 2 years or more behind new information. As a result, up-to-date findings and reports may be missed if the practitioner relies solely on printed material. The National Library of Medicine (http://www.nlm.nih.gov) now sponsors Internet searching of both Medline and a number of databases in the Toxicology Data Network (TOXNET) that are very useful for finding information about industrial chemicals. Additional databases are available for searching on the OSHA, NIOSH, EPA, and ATSDR web sites.

Obligations of the Healthcare Provider to the Individual Patient, Coworkers, Employer, Government, and Community

Occupational diseases and injuries are, in principle, preventable. Physicians who diagnose a work-related disease or injury have an

opportunity, and an ethical obligation, to participate in the identification and control of workplace hazards and the prevention of further occupational illness and injury. Physicians can choose from a range of possible followup measures, the goals of which are to prevent recurrence or worsening of the disease or injury in the patient and to prevent the development of disease or injury in other potentially exposed workers. Some of these activities may necessitate contact with occupational medicine physicians,

toxicologists, industrial hygienists, lawyers, journalists, government officials, management personnel, and union officials.

TABLE 118-4. Government Agencies and Their Important Regulatory Authority of the Workplaceâ€”A Timeline

Regulation	Agency	Authority
Occupational Safety and Health Act (OSHA, 1970)	Department of Labor	Congress passed the Occupational and Safety Health Act and created the Occupational Safety and Health Administration to ensure worker and workplace safety. Their goal was to make sure employers provide their workers a place of employment free from recognized hazards to safety and health, such as exposure to toxic chemicals, excessive noise levels, mechanical dangers, heat or cold stress, or unsanitary conditions. In order to establish standards for workplace health and

			safety, the Act also created the National Institute for Occupational Safety and Health (NIOSH) as the research institution for the Occupational Safety and Health Administration. Part 1910.1200 of the Act established the Hazardous Communication Standard (HazCom). The purpose of this section is to ensure that the hazards of all chemicals produced or imported are evaluated and that information concerning their hazards is transmitted to employers and employees. This transmittal of information is to be accomplished by means of comprehensive hazard communication programs, which are to include container	

		labeling and other forms of warning, material safety data sheets, and employee training.
Resource Conservation and Recovery Act (RCRA, 1976)	Environmental Protection Agency (EPA)	RCRA (pronounced â€œrick-rahâ€•) gave the EPA the authority to control hazardous waste from â€œcradle to grave.â€• This includes the generation, transportation, treatment, storage, and disposal of hazardous waste. RCRA also set forth a framework for the management of nonhazardous wastes. The 1986 amendments to RCRA enabled the EPA to address environmental problems that could result from underground tanks storing petroleum and other hazardous substances. RCRA focuses only on active and future facilities

		and does not address abandoned or historic sites (see CERCLA). HSWA (pronounced â€œhiss-waâ€•), the Federal Hazardous and Solid Waste Amendments, are the 1984 amendments to RCRA that required phasing out land disposal of hazardous waste. Some of the other mandates of this strict law include increased enforcement authority for the EPA, more stringent hazardous waste management standards, and a comprehensive underground storage tank program.
Toxic Substances Control Act (TSCA, 1976)	EPA	TSCA was enacted by Congress to give the EPA the ability to track the 75,000 industrial chemicals currently produced or imported into the United States. The EPA repeatedly

		screens these chemicals and can require reporting or testing of those that may pose an environmental or human-health hazard. EPA can ban the manufacture and import of those chemicals that pose an unreasonable risk. Reporting requirements include (1) premanufacturing notification for new chemicals, (2) allegation of significant adverse reactions, (3) reporting of health and safety studies, and (4) notification of suspicion of substantial risk to health.
Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA, 1980)	EPA	The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), commonly known as the Superfund, was

			enacted by Congress on December 11, 1980. This law created a tax on the chemical and petroleum industries and provided broad federal authority to respond directly to releases or threatened releases of hazardous substances that may endanger public health or the environment. Over 5 years, $1.6 billion was collected, and the tax went to a trust fund for cleaning up abandoned or uncontrolled hazardous waste sites. CERCLA: (1) established prohibitions and requirements concerning closed and abandoned hazardous waste sites, (2) provided for liability of persons responsible for releases of hazardous waste at these sites, and (3) established a trust	

			fund to provide for cleanup when no responsible party could be identified. The law authorizes two kinds of response actions: (1) short-term removals, where actions may be taken to address releases or threatened releases requiring prompt response, and (2) long-term remedial response actions that permanently and significantly reduce the dangers associated with releases or threats of releases of hazardous substances that are serious but not immediately life threatening. These actions can be conducted only at sites listed on the EPA's National Priorities List (NPL).
	Superfund Amendments and	EPA	SARA reflected the EPA's experience in administering the

	Reauthorization Act (SARA, 1986)		complex Superfund program during its first 6 years and made several important changes and additions to the program. SARA: (1) stressed the importance of permanent remedies and innovative treatment technologies in cleaning up hazardous waste sites, (2) required Superfund actions to consider the standards and requirements found in other state and federal environmental laws and regulations, (3) provided new enforcement authorities and settlement tools, (4) increased state involvement in every phase of Superfund, (5) increased the focus on human health problems posed by hazardous waste sites, (6) encouraged greater citizen	

participation in making decisions on how sites should be cleaned up, and (7) increased the size of the trust fund to $8.5 billion. SARA also required the EPA to revise the Hazard Ranking System (HRS) to ensure that it accurately assessed the relative degree of risk to human health and the environment posed by uncontrolled hazardous waste sites that may be placed on the National Priorities List (NPL). Emergency Planning and Community Right-to-Know Act (EPCRA), also known as Title III of *SARA*, was enacted by Congress as the national legislation on community safety. This law was designated to help local communities protect public health, safety, and the environment from

		chemical hazards. The law requires manufacturers to report the amount of toxic substances released each year (Toxic Release Inventory, TRI). To implement EPCRA, Congress required each state to appoint a State Emergency Response Commission (SERC). The SERCs were required to divide their states into Emergency Planning Districts and to name a Local Emergency Planning Committee (LEPC) for each district.
Americans with Disabilities Act (ADA, 1990)	Department of Labor	ADA was enacted by Congress to establish clear and comprehensive prohibition of discrimination on the basis of disability. The act specifically covers discrimination in the areas of (1) employment, (2)

		public services, (3) public accommodations and services operated by private entities, and (4) telecommunications.

Obligations to the Patient

Inform the Patient That the Illness May Be Work Related

When the workplace is determined to be a factor in the etiology or aggravation of the patient's illness, this fact and its implications should be discussed with the patient. It should never be assumed that the patient is fully aware of the health risks associated with any workplace exposure. He or she should be provided information regarding the nature of workplace hazards, their health risks, and preventive measures, and recommendations regarding continued exposure.

Suggest How the Patient Can Reduce the Exposure

In some cases the patient can take steps to reduce exposure. Adjustments in work habits that may be helpful include using a respirator or other personal protective equipment provided by the employer, using workplace shower and dressing rooms to avoid carrying toxic chemicals from the workplace to the home, and avoiding ingestion of workplace toxins by careful hand washing before eating or smoking and by taking lunch, coffee, and smoking breaks away from the work station. Obviously, these

recommendations assume that the employer provides the appropriate equipment and facilities, which is not always the case. The most effective hazard control measures require significant commitment by, and cooperation from, the employer.

Suggest that the Patient Remove Himself or Herself from the Exposure

The employer may be willing to transfer the patient to a location away from the offending hazard. This may result in a reduction in pay, seniority, or other benefits, which may be compensable under Workers' Compensation. The employment provisions of the ADA require employers to make â€œreasonable accommodationsâ€• for both work- and nonâ€“work-related disabilities. Nevertheless, the employer may not be able to accommodate the patient. The patient should be counseled carefully, and other options should be explored.

Advise the Patient to Notify the Employer

Patients who are suffering from a work-related illness may be entitled to Workers' Compensation benefits, Social Security disability, or other government-sponsored benefit programs. In addition, they may have a valid claim against the manufacturer of a chemical, a defective product, or another third party. The degree of disability necessary to bring a successful claim varies.

Once a patient is informed that he or she has a work-related illness, strict time limits are set in motion, and failure to meet them can preclude the patient from successfully filing a claim or receiving needed benefits. The patient should be advised to provide written notice immediately to his or her employer of a work-related illness (supported by a physician's letter) and to seek advice about statutes of limitations and other requirements. This information is generally available from the State Workers'

Compensation Board and usually is required to be provided to the employee by the employer. If a union is available at the workplace, it may be able to advise and assist the patient.

Obligations to Coworkers

A patient with a work-related illness should be advised to inform coworkers about his or her condition. If the patient belongs to a union, he or she should inform the union representative. If there is no union, the patient may contact OSHA or discuss the situation with the employer.

If the patient is a union member and agrees, the physician can contact the union, which may assist in hazard investigation, identify and warn other workers potentially affected by the hazard, and pressure the employer to take corrective action if it is unwilling to do so. The union can help the patient to obtain any available benefits. The patient may be able to identify appropriate contacts, such as shop stewards, members of the union's health and safety or workers' compensation committees, an occupational health specialist employed by the union at the local or national level, or an official of the union local.

Committees on Occupational Safety and Health (COSH), coalitions of labor, health, and legal professionals and community and environmental activists working to prevent job-related illness and injury, may be able to help with diagnosis and followup of occupational diseases. These groups provide education and technical assistance nationwide on a range of topics, including the health effects of specific hazards, control measures, how to use government agencies, and the legal rights of disabled workers.

Obligation to Notify the Employer

When treating an occupational injury or illness, healthcare providers often are required to report to government agencies,

health departments, or insurance carriers. As part of that reporting process, the employer should also be notified. When there is imminent danger to coworkers or the public health, the employer should be contacted to correct the exposure situation.

Obligations to Notify the Government

States may have laws that require direct physician reporting of occupational disease. If management is uncooperative despite notification of a hazardous situation, OSHA should be contacted, with the patient's consent. In addition to the federal agencies specifically empowered to protect worker health and safety, physicians may contact the state or local health department, which may initiate action or refer the problem to one of the federal agencies. Many states also require physicians to report any occupational injury or illness to the Workers' Compensation carrier.

Obligation to Inform Colleagues and the Public

On occasion, an individual primary care physician or specialist is the first to suspect a link between a workplace exposure and a serious health problem. This is likely to recur in the future, especially if the physician practices in a small town or industrial area or provides healthcare to worker groups through a company or union. Armed with an increased index of suspicion and the occupational history, the physician may be able to alert workers and companies and prevent the occurrence of a major health problem. Even if the

physician chooses not to be involved in subsequent investigation or research, it is important that information about suspected problems and hazards be made available to workers and employers

in similar industrial settings, government agencies, healthcare professionals, and, perhaps, the public at large. Case reports discussed in the medical literature, at medical meetings, or through the media can be helpful in this regard.

Summary

Industrial, workplace, and environmental exposures represent a different kind of challenge to primary care and emergency physicians. Patients often present as a diagnostic dilemma or with common symptoms that do not respond to the usual medical treatment. The challenge for the nonoccupational health professional is to correctly establish and treat the condition. This chapter offers a basic approach to all patients that will aid in the diagnosis and treatment of occupational and environmental diseases. This approach uses additional questions applied to the medical history and access to printed and electronic information resources. Exposures to these materials have public health implications. Physicians who make the diagnosis of an occupationally or environmentally related disease have an obligation to prevent further injury. They should work with employee groups, employers, and government agencies to identify the toxic agent and prevent the development of disease in other potentially exposed individuals.

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Chapter 119

Simple Asphyxiants and Pulmonary Irritants

Lewis S. Nelson

On a daily basis our bodies are exposed to a variety of potentially damag influences. Although most organs remain relatively protected from influer skin and respiratory tract, by their nature, maintain constant contact with external environment. At rest, the respiratory tract encounters nearly 300 during a typical 8-hour workday, and even mild exertion can triple the vo inhaled. Several critical mechanisms exist within the respiratory system t or minimize toxicity from without and allow humans to breathe safely in v potentially is a toxic environment. Although these efficient mechanisms p substantial protection under normal circumstances, occasionally they can overburdened. Additionally, the lungs are a common portal of entry for s toxic xenobiotics that have no pulmonary effects; the best examples are l 91), carbon monoxide (Chap. 120), and cyanide (Chap. 121).

The respiratory tract performs several important physiologic functions (Cl Its most important role involves the transfer of oxygen to hemoglobin acr pulmonary endothelium. This transfer facilitates oxygen distribution throu

body to permit effective cellular respiration. Diverse xenobiotics may act points in this distribution pathway to limit or impair tissue oxygenation. F example, opioids or paralytic agents may induce hypoventilation, whereas monoxide or methemoglobin inducers may prevent binding of oxygen to Certain xenobiotics prevent adequate oxygenation of hemoglobin at the le pulmonary gas exchange. Two mechanistically distinct groups of xenobiot capable of interfering with gas exchange: simple asphyxiants and pulmor irritants. Impairment of transpulmonary oxygen diffusion, regardless of t reduces the oxygen content of the blood and can result in tissue hypoxia.

Simple Asphyxiants

Case 1 A 50-year-old medical researcher was discovered dead in a small refrigerated room that contained 10-cubic-inch blocks of dry ice. Fifteen arrived blocks of dry ice were placed in the refrigerated room (39.2Â°F [4 approximately 9 AM on the day of the scientist's death. The researcher w at approximately noon, suggesting that at least 3 hours had elapsed betw initial dry ice storage and his first exposure. Scene analysis suggested tha time of his death, the decedent was crouching several inches from the gr store samples in a container. There were no signs of struggle, and the de no history of psychiatric disorders, recent personal crises, or medical illn

Postmortem examination and toxicologic evaluation of the decedent were unrevealing. Blood PCO_2 was not performed because of its well-described postmortem rise. In order to confirm the cause of death, the conditions a of the event were reproduced using the same cold room. Air was sampled several heights; the O_2 concentration fell and the CO_2 concentration rose minutes and peaked by 3 hours. Three hours after dry ice storage, FiO_2 v and CO_2 concentration was 27.6%, both at a height of 9 inches. Concent 20â€“30% (200,000â€“300,000 ppm) CO_2 are associated with rapid deve unconsciousness and death. In addition, the room temperature had fallen (â€“15Â°C). Thus, it appears that even at the cold temperatures of the c sublimation of dry ice progresses rapidly.

Pathophysiology

Simple asphyxiants displace oxygen from ambient air, thereby reducing t of oxygen in air, or FiO_2 , to <21%, resulting in a fall of the partial press oxygen. The partial pressure is a measure of the oxygen contribution to t inspired air and is based on both FiO_2 and barometric pressure. For exam because the ambient pressure at sea level (less water vapor, 47 mm Hg) Hg and the percentage of oxygen is 21%, the partial pressure of oxygen is 150 mm Hg. Under these typical conditions, FiO_2 is a suitable surrogate partial pressure of oxygen. However, this relationship is not applicable at barometric pressures. For example, at the summit of a mountain, the red barometric pressure results in a fall in the partial pressure of oxygen des normal FiO_2 . This reduced partial pressure may be insufficient to allow a oxygen saturation, and supplemental oxygen becomes necessary. As bar pressure falls, exposure to simple asphyxiant gases may further reduce t partial pressure to life-threatening levels. Conversely, underwater divers their FiO_2 to <21% by adding simple asphyxiant gases, such as helium, t breathing mixture in order to avoid oxygen toxicity, yet they still maintai oxygenation. This

is because the elevated barometric pressure raises the partial pressure of normal levels despite the addition of an asphyxiant gas. However, syster poisonous gases that enter the breathing mixture would have a magnified given their increased partial pressure at depth.

In general, simple asphyxiants have no pharmacologic activity. For this r exceedingly high ambient concentrations of these gases are necessary to asphyxia. Asphyxiation occurs in confined spaces or with extremely conc forms of the simple asphyxiants. Recommendations for use of simple asp a relatively undetectable method for committing suicide can be found on Internet.[57 , 65] The widespread use of liquefied gas, which expands seve fold on depressurization or warming, accounts for a substantial number o injuries.[106 , 159]

Clinical Manifestations

A patient exposed to any simple asphyxiant gas will develop characteristi

of hypoxia (Table 119-1), which are directly related to the partial pressu gas in the air or, more correctly, to the reduction in ambient oxygen part pressure.[106] Cardiovascular and central nervous system complications of asphyxiants predominate, because these organ systems have the greates requirements. As hypoxemia becomes severe, multisystem organ failure a may occur.[42]

During simple asphyxiation, carbon dioxide exchange is not impaired, and hypercapnia does not occur. Because dyspnea develops more rapidly from hypercapnia than hypoxemia, the breathlessness associated with physical chemical asphyxiation does not develop until severe hypoxemia intervene these circumstances, victims may succumb to hypoxemia without develop expected warning symptoms. In the case of carbon dioxide inhalation, hy may occur very rapidly, which itself can produce acute cognitive impairm

Specific Agents

Noble Gases: Helium, Neon, Argon, Xenon

Noble gases, which are stored almost exclusively in the compressed form numerous industrial and medical roles. Argon is predominantly used as a gas during welding operations. Neon is used in lighting manufacture. Xenc radioactive gaseous form, has diagnostic medical applications in ventilationâ€“perfusion scans. Helium has the lowest molecular weight and smallest member of the noble gas family of elements. Because of its lowe solubility, helium is used by divers to replace nitrogen to prevent nitroge at depth (see Nitrogen). Even at diving gas mixtures of 50% helium, div no adverse effects as long as a normal partial pressure of oxygen is mair the mixture. The fact that helium has a lower density than nitrogen result lower viscosity, or a marked decrease in flow resistance. This property of the basis for its use in patients with increased airway resistance, such as It also facilitates breathing by divers at depth, where the quantity (molar not volume) of air inspired per breath is several-fold greater than that at Similarly, helium's low viscosity has led to its use as an inflation gas for balloons, for which rapid inflation and deflation are critical. All noble gase

compressed, form cryogenic liquids, which expand rapidly to their gas pha decompression. Liberation of these gases in closed spaces may result in or freezing injuries. Xenon has unique anesthetic properties because of its solubility. The other noble gases have no direct toxicity.

21
None
16â€“12
Tachypnea, hyperpnea, (resultant hypocapnia), tachycardia, reduced atte alertness, euphoria, headache, mild incoordination
14â€“10
Altered judgment, incoordination, muscular fatigue, cyanosis
10â€“6
Nausea, vomiting, lethargy, air hunger, severe incoordination, coma
< 6
Gasping respiration, seizure, coma, death
[a] At sea-level barometric pressure appropriate adjustments must be made altitude and depth exposures.

FiO_2 [a] Symptoms/signs

TABLE 119-1. Clinical Findings Associated with Reduction of I Oxygen

Short-Chain Aliphatic Hydrocarbon Gases: Me Ethane, Propane, Butane

Methane (CH_4) has no direct toxicity. Animals can breathe a mixture of 8 methane and 20% oxygen without manifesting hypoxic symptoms because , and thus their oxyhemoglobin saturation, essentially is normal. Methane known as natural gas and â€œswamp gas,â€• may be present in high an concentrations in bogs of decaying organic matter. In addition, compress gas now is used as an alternative fuel for automotive use. Methane expos occupational hazard for miners, who historically carried canaries into the

as an â€œearly warningâ€• sign for the presence of toxic gases or oxyge deficiency. Theoretically, the higher metabolic and respiratory rates of sr (and children) make them more rapidly susceptible to gas exposures.

Methane is odorless and undetectable without sophisticated equipment.[28] reason, natural gas is intentionally adulterated with a small concentration mercaptan, a stenching agent, which is responsible for the well-recognize odor of natural gas. Cooking with natural gas may lead to increased resp symptoms and pulmonary dysfunction.[79] However, methane itself is unlike the etiology because its combustion is generally complete, and ambient le negligible. It is likely that exposure to nitrogen dioxide (NO_2), one of th of combustion of methane in air (70% nitrogen), is the explanation for th symptoms.

Ethane ($C_2 H_6$) is an odorless gas with characteristics similar to methane occasionally is implicated as a simple asphyxiant. It is also a component gas and is used as a refrigerant. Propane ($C_3 H_8$) is widely used in comp liquefied form both as an industrial and domestic fuel and as an industria Butane ($C_4 H_{10}$) is a prevalent fuel and solvent. Deliberate butane inhala cigarette lighters or air fresheners for recreational purposes predominantl adolescents is associated with cardiovascular dysfunction and cerebral da (Chap. 79).[50 , 155]

Carbon Dioxide (CO_2)

Introduction

Although not a simple asphyxiant gas by definition because it produces p effects, carbon dioxide closely resembles simple asphyxiants from a toxi viewpoint. Carbon dioxide gas has many practical industrial uses, such as of carbonation in soft drinks and use as a shielding gas during welding. C dioxide is widely used to extinguish fires because of its ability to safely d oxygen from the local environment.[64] Dry ice, the frozen form of carbon an

extremely cold substance (â€“141.3Â°F [â€“78.5Â°C]) that undergoes co

from solid to gas without liquefaction, a process known as *sublimation.* F poisoning may occur when dry ice is allowed to sublimate in a closed spa as the cabin of a car or, as in the case above, in a cold storage room at (4Â°C).[64] The large-scale emission of carbon dioxide from Lake Nyos, a volcanic crater lake in Cameroon, West Africa, resulted in nearly 2000 hu many more livestock deaths (Chap. 2).[9] In this disaster, simple asphyxia likely because medical evaluation of both survivors and fatalities demons neither signs of cutaneous or pulmonary irritation nor toxicologic abnorn Furthermore, inadvertent connection of respirable gas hoses to carbon di other nonrespirable sources has occurred in both industrial[76 , 160] and m settings, with resultant worker and patient fatalities. This occurrence is because of the mandated use of engineering controls to prevent the inco connection of hose and source terminals.

Pharmacology/Pathophysiology

Carbon dioxide, an end product of normal human metabolism, dissolves ir plasma and is in equilibrium with carbonic acid (H_2CO_3). Dissolved carb measured as PCO_2 , is primarily responsible for our respiratory drive, and tightly controlled by the central nervous system through regulation of br this reason, exogenous carbon dioxide, combined with oxygen, was at one medically as a respiratory stimulant in neonates. Under normal conditions air contains approximately 0.03% CO_2 . When ambient concentrations ris level, uptake of carbon dioxide occurs, which stimulates respiration furth increasing the uptake of ambient carbon dioxide. Accordingly, closed ane systems use scrubbers containing sodium hydroxide to chemically elimina carbon dioxide. Failure of the scrubber system results in increasing depth anesthesia from hypercapnia-induced hyperventilation.

Clinical Manifestations

Carbon dioxide produces both acute and subacute poisoning syndromes. T occurs during hypoventilation, when a patient fails to eliminate endogeno dioxide, develops hypercapnia, and typically presents with gradual somno occurrence may be linked to respiratory failure, as in the case of emphys

opioid poisoning, or it may be iatrogenic, as occurs during permissive hypercapnia.[116] Alternatively, intense carbon dioxide exposure may produ and lethal poisoning. However, unlike other simple asphyxiants, experime of acute carbon dioxide poisoning in which FiO_2 is maintained at normal l demonstrate that central nervous and respiratory systems manifestations within seconds.[78] This finding suggests that CO_2 is not solely a simple as but also possesses a potential for systemic effects.

Nitrogen (N_2) Gas

Introduction

Although nitrogen, like carbon dioxide, may produce clinical effects indep hypoxemia, most poisonings are characterized by the manifestations of s asphyxiants. Nitrogen gas is used as a carrier gas for chromatography, as fertilizer, as a cryogenic gas for surgery, and extensively in manufacturir Poisoning by nitrogen gas is uncommon but may occur following rapid ev the liquid.[83]

Clinical Manifestations

Inadvertent connection of air-line respirator hoses to nitrogen and other sources results in acute asphyxiation, with unconsciousness occurring in approximately 12 seconds[76, 106, 159] and death shortly thereafter. More inhalational poisoning by nitrogen is characterized by impairment of inte function and judgment, giddiness, and euphoria, which is qualitatively sim ethanol intoxication.[109] More severely poisoned patients may manifest le coma.[56] Systemic absorption is not rapid, however, and prolonged, high- exposure is required for poisoning. Nitrogen poisoning, also known as *nit narcosis*, occurs in underwater divers while they are breathing air, which 70% nitrogen. It has been called *rapture of the deep* (*l'ivresse des grand profondeurs*) and has led to many deaths in the subaquatic environment. underlying mechanism of nitrogen narcosis is unknown,[41] but the simple and relatively high lipophilicity of nitrogen suggest a mechanism similar to the anesthetic gases.[56] To avoid nitrogen narcosis, less lipid-soluble inert

as hydrogen or helium are generally substituted for nitrogen. Substitution oxygen, although intuitively logical, is inappropriate because of the risk o toxicity (see Oxygen).

Dermal exposure to liquid nitrogen produces frostbite because of liquid r extremely cold temperature.[137] Ingestion of liquid nitrogen similarly prod freezing injury of the gastrointestinal tract.[87] Rarely, bubbles introduced skin embolize through the vascular system and impair organ blood flow.[49

Treatment

Treatment of all individuals poisoned by simple asphyxiants begins with removal of the persons from exposure and ventilatory assistance. Provisio supplemental oxygen is preferable, but room air usually suffices. Hyperba therapy is unnecessary. Restoration of oxygenation through spontaneous mechanical ventilation occurs after only several breaths. Support of vital the mainstay of therapy but generally is unnecessary following a brief ex

Pulmonary Irritants

Case 2 In an attempt to clean a grimy bathtub in a newly purchased hous year-old woman mixed several over-the-counter cleaning products includi and toilet bowl cleaner. Seconds after the mixture was created, an acrid o green-tinted gas filled the room. The woman was able to escape the fum but quickly began feeling pain in her eyes and throat. She remained at ho minutes but her symptoms progressed. She arrived in the emergency de with significant dyspnea, cough, and diffuse chest discomfort.

Her vital signs were: blood pressure, 120/85 mm Hg; pulse, 120 beats/m respiratory rate, 32 breaths/min; oral temperature 99Â°F (37.2Â°C). Puls revealed 83% saturation on room air, and 2 L nasal oxygen was administ Pertinent findings on physical examination included teary, red eyes with vision. Her oropharyngeal mucosa was unremarkable, although she was She had no stridor, hoarseness, or dysphagia. Lung examination demons bilateral crackles, and her heart sounds were normal. Arterial blood gas measurement yielded: pH, 7.50; PCO_2 , 25 mm Hg; PO_2 , 50 mm Hg, on

oxygen by nasal cannula. She was attached to a nonrebreather oxygen fa and her oxygen saturation climbed to 94%. Electrocardiogram showed sir tachycardia.

Portable chest radiograph showed significant bilateral alveolar filling with sized heart.

She received one dose of nebulized dilute sodium bicarbonate and several albuterol and was admitted to the intensive care unit (ICU) for observatic next 24 hours, her symptoms and abnormal pulmonary findings resolved, was discharged. At 2-week followup she was asymptomatic with a normal examination.

Introduction

The irritant gases are a heterogeneous group of chemicals that produce t via a final common pathway: destruction of the integrity of the mucosal b the respiratory tract (Table 119-2).

Pathophysiology

Pathologically, irritant chemicals damage both the more prevalent type I pneumocytes and the surfactant-producing type II pneumocytes.[89] Neutro recruited in response to macrophage-derived inflammatory cytokines such necrosis factor-Î±, releases toxic mediators that disrupt the integrity of endothelial cells.[99 , 134] This host defense response results in accumulatio cellular debris and plasma exudate in the alveolar sacs, producing the c clinical findings of acute lung injury (ALI). The specific mechanisms by wh irritant gases damage the pulmonary endothelial and epithelial cells vary. irritant gases require dissolution in lung water to liberate the ultimate to which often is an acid, as occurs when hydrogen chloride gas produces h acid. The exact mechanism by which acids damage cells and induces an response remains uncertain. Oxidation of intracellular proteins may result cytoskeletal shortening, creating spaces between endothelial cells and all movement into the alveolar spaces.[165] Other gases, such as oxygen, indu

pulmonary damage solely through free radicalâ€“mediated oxidative stress cellular membranes. NO_2 and chlorine are characteristic of a group of gas produce both acid and free radical oxidants. Furthermore, other respirabl xenobiotics, such as metals, injure the respiratory tract through oxidant other mechanisms. Because the precise toxicologic and pathophysiologic widely depending on the physicochemical properties of the chemical, thes mechanisms are covered more completely in the discussions of the specif

Ammonia
Fertilizer, refrigeration, synthetic fiber synthesis
90
5
50
300
35
Cadmium oxide fumes
Welding
I

0.005 mg/m^3
9 mg/m^3 (as Cd)

Carbon dioxide
Exhaust, dry ice sublimation
0.2

5,000
40,000
30,000
Chloramine
Bleach plus ammonia

Chlorine
Water disinfection, pulp and paper industry
0.7
0.3
0.5
10
1
Copper oxide fumes
Welding
I

0.1 mg/m^3
100 mg/m^3 (as Cu)

Ethylene oxide
Sterilant
M

1
800
5
Formaldehyde
Chemical disinfection
M
0.8
0.016
20
2
Hydrogen chloride
Chemical
67
1â€“5
5

50
5
Hydrogen fluoride
Glass etching, semiconductor industry
M

3 (as F)
30 (as F)
6
Hydrogen sulfide
Petroleum industry, sewer, manure pits
0.4
0.025

100
50
Mercury vapor
Electrical equipment; thermometers; catalyst; dental fillings; metal extra
heating or vacuuming elemental mercury
I

0.1 mg/m^3
10 mg/m^3
0.05
Methane
Natural heating gas, swamp gas

200

Methyl bromide
Fumigant
2

20
250

Nickel carbonyl
Nickel purification, nickel coating, catalyst
0.05

0.001
2 (as N)

Nitrogen
Nitrogen dioxide
Chemical synthesis; combustion emission

0.12
5
20
5
Nitrous oxide
Anesthetic gas, whipping cream dispensers (abuse), racing fuel additive

50

Ozone
Disinfectant; produced by high-voltage electrical equipment
0.001
0.05
0.1
5
0.1
Phosgene

Chemical synthesis; combustion of chlorinated compounds
sl
0.5
0.1
2
0.1
Phosphine
Fumigant; semiconductor industry
sl
2
0.3
50
1
Propane
Liquified propane gas

Odorless
1000
2100

Sulfur dioxide
Environmental exhaust
23
1
2
100
5
Zinc chloride fumes
Artificial smoke (no longer in use)

1 mg/m^3
50 mg/m^3
2 mg/m^3

Zinc oxide	Welding	Odorless	5 mg/m^3	500 mg/m^3	10 mg/m^3

[a] gm% = grams of gas per 100 mL water; if applicable; I = insoluble; M
[b] Standards are generally TLV-TWA, set by the ACGIH; some are PEL, set
[c] Immediately dangerous to life and health: NIOSH, Revised 1995 (docu
for each IDLH is available at http://www.cdc.gov/niosh/idlh/idlhintr.html
STEL: NIOSH and OSHA 15 minute or ceiling.

Gas	Source/Exposure	Solubility (gm%)[a]	Detection Threshold (ppm)	Regulatory Standard (ppm)[b]	IDLH (ppm

TABLE 119-2. Characteristics of Common Respiratory Irritants

By virtue of its use as a war agent, phosgene has received more investig
the other irritant gases. In fact, much of our

current understanding of irritant gas poisoning derives from the study of
toxicity. Although the specific mechanisms of toxicity of the other irritant
poorly defined, they likely cause injury through a similar process. The ac
upon dissolution in the mucosal water react with functional groups on ep
endothelial cell membranes and, via cellular messengers, result in a com
systemic inflammatory response. Phosgene stimulates the synthesis of li
derived leukotrienes. Leukotrienes are important chemotactic factors for
which accumulate, liberate oxidants, and produce ALI.[77] ALI can be preve
rabbits by tomelukast, a leukotriene receptor antagonist,[70] and by
methylprednisolone, which blocks leukotriene synthesis, although both x
offer postexposure benefit.[70] Ibuprofen, an inhibitor of the arachidonic a
and xenobiotics capable of reducing neutrophil influx, such as colchicine

cyclophosphamide, reduce lung injury and mortality in mice when they ar administered shortly following phosgene exposure.[63, 145] Intratracheal cyclic adenosine monophosphate (DBcAMP), a cAMP analog, and other cAl amplifiers, such as terbutaline or aminophylline, inhibit the release of le and reduce toxicity.[82, 146] Intratracheal *N*-acetylcysteine (NAC), adminis minutes postexposure to phosgene-poisoned rabbits, decreases the forma leukotrienes by an undefined means and limits the development of ALI.[14] Presumably administration via nebulization would prove similarly effectiv Intravenous administration of NAC to patients with mild-to-moderate ALI, whom had phosgene-induced pulmonary damage, improved systemic oxy and reduced the need for ventilatory support.[161] However, progression to failure was not altered. Because damage to the lung had already occurred observed benefit of NAC may be related to improved hemodynamic functi than an antioxidant effect (Antidotes in Depth: *N*-Acetylcysteine).[73]

Free radicals are highly reactive molecular derivatives, typically from oxy nitrogen, that bind to and destroy tissue near their site of generation. Th initiation of a lipid peroxidative cascade, free radicals destroy lipid memb inhibit energy production through the electron transport chain (Chap. 12 of lipid peroxidation and cellular damage initiate neutrophilic influx, presu an immunologic attempt to combat a pathogen. Ironically, free radicals g the invading inflammatory cells contribute to pulmonary damage. Fortuna lung has antioxidant systems, both enzymatic (eg, superoxide dismutase, glutathione peroxidase, catalase) and nonenzymatic (eg, glutathione, as which detoxify virtually all free radicals present in the lung.[131] However, burden imposed by oxidant gases can preempt these detoxifying systems produce cellular damage. For example, nebulization of manganese superc dismutase into the airway 1 hour after smoke inhalation, a form of oxidar injury, did not improve lung edema or pulmonary gas exchange.[97]

Clinical Manifestations

Regardless of the mechanism by which the mucosa is damaged, the clinic presentations of patients exposed to irritant gases are similar. Those exp gases that result in irritation within seconds generally develop mucosal i

to the upper respiratory tract. The rapid onset of symptoms usually is a signal to the patient to escape the exposure. Patients may present with c and pharyngeal pain in addition to drooling, mucosal edema, cough, or s Conjunctival irritation or chemosis, as well as dermatologic irritation, is c because concomitant ocular and cutaneous exposure to the gases usually unavoidable. Gases that are less rapidly irritating may not provide an ad signal of their presence and may not prompt expeditious escape. In this prolonged breathing allows entry of the toxic gas further into the bronch system, where delayed toxic effects may subsequently be noted. Trache bronchiolitis, bronchospasm, and ALI are typical inflammatory responses anatomic region and represent the spectrum of acute lower respiratory tr

Experimental models assessing the water solubility of a gas to predict the its associated lesions have largely agreed with the clinical data.[84] Howev exceptions to this relationship of a gas and its expected toxicity are comr example, in situations where escape from ongoing exposure is prevented may develop lower respiratory tract injury after prolonged exposure to a irritating gases. Alternatively, rapid onset of upper respiratory irritation m noted in patients following exposure to concentrated gases that are gene associated with delayed symptomatology. Exposure to exceedingly high concentrations of any gas may produce hypoxemia analogous to that resu exposure to a simple asphyxiant gas.

The most characteristic and worrisome clinical manifestation of irritant ga is ALI, a syndrome formerly described as noncardiogenic pulmonary eden consists of the clinical, radiographic, and physiologic abnormalities caused pulmonary inflammation and alveolar filling that must be both acute in on attributable solely to pulmonary capillary hypertension as occurs in patier congestive heart failure.[12] The most severe manifestation of ALI is the ac respiratory distress syndrome (ARDS). The criteria for diagnosis of ARDS the ratio of the partial pressure of dissolved oxygen (PaO_2) to the inspir fraction (FiO_2),[12] that is, patients with an appropriate history and clinica presentation for ALI with $PaO_2/FiO_2 < 200$ meet the definition of ARDS. positive end-expiratory pressure (PEEP) is not part of the oxygenation cr (Chap. 22). Both ALI and ARDS are nonspecific syndromes resulting from physiologic insults such as sepsis or trauma. Patients with ALI may prese

dyspnea, chest tightness, chest pain, cough, frothy sputum, wheezing or arterial hypoxemia. Typical radiographic abnormalities include bilateral p infiltrates with an alveolar filling pattern and a normal cardiac silhouette differentiate this syndrome from congestive heart failure.

Specific Agents

Acid- or Base-Forming Gases

Highly Water-Soluble Agents

Ammonia (NH_3)

Ammonia is a common industrial and household chemical used in the syn plastics and explosives, and as a fertilizer, a refrigerant, and a cleaning a odor is characteristic and may be an effective warning signal of exposure stimulus to avoid further exposure. Dissolution of NH_3 in water to form th ammonium hydroxide (NH_4 OH) rapidly produces severe upper airway irr Patients with exposures to highly concentrated NH_3 or exposures for prol periods may develop tracheobronchial or pulmonary inflammation. Exper inhalation of nebulized high-dose ammonia causes ALI that is manifested b oxygen saturation and a rise in airway pressure within 2 minutes of the s exposure.[151] Corroborating the

development of ALI, ultrastructural study of the lungs from two individua acutely of ammonia inhalation revealed marked swelling and edema of typ pneumocytes.[27] Chronic inhalation of low concentrations of NH_3 or repeti exposure to high concentrations of ammonia may cause pulmonary fibros

A. $3\ NaOCl + 2\ NH_3 \rightarrow NH_2Cl + NHCl_2 + 3\ NaOH$

B. $NH_2Cl + H_2O \rightarrow HOCl + NH_3\uparrow$

$HOCl \rightarrow HCl + [O]$

Figure 119-1. Chloramine chemistry. A. Sodium hypochlorite (bleach) p

ammonia form monochloramine and dichloramine. B. Chloramine dissolves to liberate hypochlorous acid, hydrochloric acid, ammonia, and nascent o an oxidant.

Chloramines

This series of chlorinated nitrogenous compounds (Figure 119-1) include monochloramine (NH_2 Cl), dichloramine ($NHCl_2$), and trichloramine (NCl_3 chloramines are most commonly generated by the admixture of ammonia sodium hypochlorite (NaOCl) bleach, often in an effort to potentiate their cleaning powers.[58 , 122] Interestingly, the addition of bleach to septic sys result in liberation of the chloramines following the reaction of bleach wit nitrogenous compounds.[107] On dissolution of the chloramines in the epit fluid, hypochlorous acid, ammonia, and oxygen radicals are generated, all act as irritants. Although less water soluble than ammonia, the chloramir promptly result in symptoms. Because these initial symptoms are often n however, they may not prompt immediate escape, resulting in prolonged recurrent exposure.[135] Exposure to trichloramine occurs at indoor swimm and is responsible for inducing permeability changes in the pulmonary e the consequences of which are not yet understood.[30]

Hydrogen Chloride (HCl)

The largest and most important use of hydrogen chloride gas is in the pr hydrochloric acid. Dissolution of hydrogen chloride gas in lung water afte similarly produces hydrochloric acid.[26 , 129] Pyrolysis of polyvinyl chloride commonly used in pipe fabrication, generates HCl and is an occupational firefighters.[119] By adsorbing to respirable carbonaceous particles generate fire, HCl may be deposited at the alveolar level and produce pulmonary

Hydrogen Fluoride (HF)

Hydrogen fluoride and its aqueous form, hydrofluoric acid, are used in th glassware, building renovation, and semiconductor industries. Hydrogen f dissolves in epithelial lining fluid to form the weak acid hydrofluoric acid.

HF molecule is the predominant form in solution, and few free hydronium liberated. Low-dose inhalational exposures may result in irritant sympton large exposures may cause bronchial and pulmonary parenchymal destru Death following inhalation may result from ALI but usually is related to s fluoride poisoning independent of the route of exposure because of the r calcium binding and subsequent hypocalcemia and hyperkalemia.[18 , 47]

Patients with inhalational exposure to hydrogen fluoride should undergo electrocardiographic evaluations and correction of serum electrolytes. A of nebulized 2.5% calcium gluconate should be considered in order to lim fluoride absorption (made as 1.5 mL 10% calcium gluconate plus 4.5 mL sodium chloride solution or sterile water).[86 , 91] By binding fluoride ion l nebulized calcium may prevent fluoride-induced cellular and systemic tox Systemic calcium salts should be administered as needed to correct hypo (Chap. 101 and Antidotes in Depth: Calcium).

Sulfur Dioxide/Sulfuric Acid (SO_2 /H_2 SO_4)

Sulfur dioxide has multiple industrial applications and is a byproduct found smelting and oil refinery industries. It may also be generated by the inad mixing of chemicals, such as an acid with sodium bisulfite ($NaHSO_3$). Su is highly water soluble and has a characteristic pungent odor that provide of its presence at concentrations well below those that are irritating. In t of catalytic metals (Fe, Mn), environmental sulfur dioxide is readily conve sulfurous acid (H_2 SO_3) within water droplets. Sulfurous acid is a major environmental concern and the cause of â€œacid rain.â€• Atmospheric s dioxide and H_2 SO_4 have severe health consequences. During the London incident in 1952, 4000 deaths occurred primarily from respiratory causes to atmospheric sulfur dioxide results in a roughly dose-related bronchosp is most pronounced and difficult to treat in asthmatic patients. Inhalation sulfurous acid or dissolution of sulfur dioxide in epithelial lining fluid pro typical pathologic and clinical findings associated with ALI.[136] In addition effect of acid generation upon dissolution, sulfur dioxide can cause oxida to the lungs.[105] Large acute exposure to either xenobiotic produces the acute irritant response of both the upper and lower respiratory tracts,[33] a

pulmonary dysfunction (see Asthma and Reactive Airways Dysfunction Sy may persist for several years.[126]

Intermediate Water-Soluble Agents

Chlorine (Cl_2)

Chlorine gas is a valuable oxidizing agent with various industrial uses, an occupational exposure is common. Chlorine gas was used as a chemical w agent by both the French and the Germans in World War I (Chap. 126). chlorine gas is not generally available for use in the home, domestic expo chlorine gas is common. The admixture of an acid to bleach liberates chlo (Figure 119-2).[66, 113] Because the anionic component of the acid is not the reaction, combining hypochlorite with virtually any acid, such as pho hydrochloric, or sulfuric acid, may result in the release of chlorine gas. As inappropriate mixing of cleaning agents is the cause of most nonoccupati exposures.[113] Rarely patients have intentionally generated chlorine gas in manner for purportedly â€œpleasurableâ€• purposes.[132] Concentrated ch may be generated when aging swimming pool chlorination tablets, such a

calcium hypochlorite [$Ca(OCl)_2$] or trichloro-*s*-triazinetrione (TST), dec [180] Inadvertent mixture of $Ca(OCl)_2$ and TST results in excessive chlorine generation and may be explosive.[96] Acute chlorine toxicity may occur wh compressed chlorine gas is used for direct chlorination of public swimmin or drinking water systems. Occasional mass poisoning may occur during industrial, or transportation incidents.[32, 168]

A. $HCl + HOCl \rightarrow Cl_2\,[\uparrow] + H_2O$

B. $Cl_2 + H_2O \rightarrow 2\,HCl + [O]$

$Cl_2 + H_2O \rightarrow HCl + HOCl$

Figure 119-2. Chlorine chemistry. A. Formation of chlorine gas from the acidification of hypochlorous acid. B. Dissolution of chlorine in mucosal w

generate both hydrochloric and hypochlorous acids (HCl and HOCl) and o

The odor threshold for chlorine is low, but distinguishing toxic from perm levels may be difficult until toxicity is manifest. The intermediate solubili characteristics of Cl_2 result in only mild initial symptoms following moder exposure and permit a substantial time delay, typically several hours, be symptoms develop. Chlorine dissolution in lung water generates HCl and hypochlorous (HClO) acids. Hypochlorous acid rapidly decomposes into HC nascent oxygen (O^-). The unpaired nascent oxygen atom produces addit pulmonary damage by initiating a free radical oxidative cascade. Although majority of life-threatening chlorine poisonings follow acute, large expos patients with chronic, low-concentration exposure or recurrent, moderate concentration poisonings may manifest increased bronchial responsivenes

Hydrogen Sulfide (H_2 S)

Hydrogen sulfide exposures occur most frequently in the waste managem petroleum, and natural gas industries,[74] although poisoning occurs in asp synthetic rubber, and nylon industry workers and rarely in hospital worke acid to clean drains clogged with plaster of Paris sludge.[124] Hydrogen sulf present in natural sources such as volcanic emission, in caves, and in su It is a decay product of organic material found in sewers or manure pits. sulfide, hydrogen fluoride, and phosphine are differentiated from the oth gases by their ability to produce significant systemic toxicity. Hydrogen s inhibits mitochondrial respiration in a fashion similar to that of cyanide (C).[51 , 133]

H_2 S has the distinctive odor of â€œrotten eggs,â€• which, although help diagnosis, is not specific for the agent. Despite a sensitive odor threshold parts per billion,[133] rapid olfactory fatigue ensues, providing a mispercep the exposure and its attendant risk have diminished. At low and moderate to 500 ppm), upper respiratory tract mucosal irritation occurs and is the toxicity.[163] The rapidity of death in patients exposed to high H_2 S levels likely that either simple asphyxiation or cytochrome oxidase inhibition is most cases.

Poorly Water-Soluble Agents

Phosgene (Carbonyl Chloride [$COCl_2$])

During World War I, phosgene was an important weapon of mass destruc produced countless deaths (Chap. 126). Currently, phosgene is used in t synthesis of various organic compounds, such as isocyanates, and it occ produces poisoning. It is a byproduct of heating or combustion of various organic compounds.[153]

Exposure to phosgene initially may produce limited manifestations but car acute mucosal irritation following intense exposure. In fact, the pleasant fresh hay, rather than prompting escape, ironically may promote deep ar breathing of the toxic gas. The most consequential clinical effect related exposure is delayed-onset ALI.[19] Because of the accumulation of a signif alveolar burden of phosgene, symptoms generally are severe once they o delay in onset may be nearly one day, so prolonged observation of patien to be phosgene poisoned is warranted. The mechanism of phosgene toxici dependent on the dissolution of the gas into the fluid of the epithelial lini resultant liberation of hydrochloric acid and reactive oxygen species.[143]

Oxidant Gases

Rather than acidic or alkaline metabolites, free radicals mediate the puln toxicity of certain irritant gases. Many of the chemicals discussed particip acidâ€“base and oxidant types of injury. However, the clinical distinction acid- or alkali-forming agents and oxidant gases is difficult but ultimately therapeutically relevant.

Oxygen (O_2)

Oxygen toxicity is uncommon in the workplace but, ironically, is common hospitalized patients. Although O_2 may produce central nervous system a toxicity, pulmonary damage is more common.[152] Several clinical studies that humans can tolerate 100% O_2 at sea level for up to 48 hours witho

acute pulmonary damage.[29 , 44] Under hyperbaric conditions (2.0 atmosp absolute), such as during compressed-air diving or while inside a pressur hyperbaric chamber, oxygen toxicity may develop within 3â€“6 hours.[36] A in approximately 5% of patients administered hyperbaric oxygen for ther purposes.[152] Delayed pulmonary fibrosis, presumably from healing of su injury, may develop in patients breathing lower concentrations of O_2 at s shorter periods.

Although it appears paradoxical that O_2 , an essential molecule, may be at elevated concentrations, it is not. In mitochondria, O_2 plays a critical r ultimate acceptor for electrons completing the electron transport chain. It same potent oxidizing activity that allows O_2 to remove electrons from ot compounds generating the reactive oxygen intermediates.[139]

Generation of reactive oxygen species, including superoxide (O_2^-), hydr (OHÂ·), hydrogen peroxide (HOOH), and singlet oxygen (OÂ·), and nitric produces cellular necrosis, increases pulmonary capillary permeability, an apoptosis.[120 , 139] NO, produced by inducible NO synthase in the setting stress, is directly cytotoxic or can combine with superoxide anions to form reactive oxidant peroxynitrite.[75] Experimental prevention of these effects administration of either parenteral NAC,[140 , 175] a chemical antioxidant, c superoxide dismutase, an enzymatic antioxidant,[29 , 169] suggests that th mechanism of toxicity relates to the oxidant, or electrophilic, effects of t reactive oxygen species (Chap. 12). Although several other agents have promise in preventing oxygen-mediated toxicity, none has yet proved to therapeutic for patients who already manifest pulmonary toxicity. Curren for preventing pulmonary oxygen toxicity emphasize reduction of the ins oxygen concentration by use of PEEP ventilation, although this approach prove beneficial in at least one clinical trial. The potential role of liquid v the lung with perfluorocarbons to prevent or treat pulmonary oxygen toxi under investigation.[7]

Oxides of Nitrogen (NO_x)

Oxides of nitrogen are a series of variably oxidized nitrogenous compoun most important substances included in this series are the stable free radi

and NO, as well as nitrogen tetroxide (dinitrogen tetroxide [N_2O_4]), nitr trioxide (N_2O_3), and nitrous oxide (N_2O). The oxides of nitrogen are of value in industrial operations, although they may be generated during we brazing. NO_2, in addition to

hydrogen cyanide, is produced in the pyrolysis of nitrocellulose, which is substantial component of radiographic film. For example, a fire in the rad department of the Cleveland Clinic in 1929 resulted in 125 casualties, wi all deaths resulting from cyanide or NO_2 gas poisoning.[67] NO_2 toxicity car when propane-driven ice-cleaning machines are used in indoor ice skating poor ventilation, thereby allowing accumulation of the generated NO_2.[92] exposure to high NO_2 levels may occur during closed-space fires, as in s NO_2 also causes silo-filler's disease, in which the toxic gas generated dur decomposition of silage accumulates within the silo shortly after grain st eliminating rodents that feast on the grains.[48, 182] In the absence of ve high concentrations of NO_2 may accumulate in the silo such that an indiv entering the silo is rapidly asphyxiated from the depletion of oxygen.[68] A substantial quantities of NO_2 remaining after incomplete ventilation may delayed-onset pulmonary toxicity characteristic of silo filler's disease. Ch exposure to NO_2, generated during cooking,[79] or outdoor exposure to p smog, of which the oxides of nitrogen are a component, may predispose t development or exacerbation of chronic lung diseases.

The various oxides of nitrogen may directly oxidize respiratory tract cellu membranes but more typically generate reactive nitrogen intermediates, such as peroxynitrite ($ONOO^-$), which subsequently damage the pulmona cells.[123] In addition to generating oxidant cascades, dissolution in respira water generates nitric acid (HNO_3) and NO, which produce injury consist other inhaled acids. In fact, inhalation of HNO_3 produces the same clinica pathologic syndrome.[71] Antioxidants afford significant protection to huma endothelial cells exposed to NO_2, indicating an important role of free rad toxicology of these agents.[170]

NO, an endogenous compound important as a neurotransmitter and vaso used clinically as exogenous inhalational therapy for pulmonary hypertens ALI.[166] In patients with ALI not resulting from sepsis (although not speci

inhalational injury), low-level inhaled NO (5 ppm) did not improve clinica outcome.[166] However, one patient with NO_2 pulmonary toxicity improved following NO therapy, so further consideration is warranted.[90] Furthermore in premature infants with respiratory distress syndrome is well accepted.[less soluble in the fluid lining the epithelial surfaces than are the other o nitrogen and produces irritant effects following large exposures.[72 , 178] It pulmonary oxidative toxicity, the manifestations of which are typical of th gases, is substantially enhanced by conversion to reactive nitrogen inter such as $ONOO^-$.[11] This radical selectively interacts with tyrosine to prod nitrotyrosine, which may subsequently serve as a marker for oxidant dan may be absorbed from the lung and is rapidly bound by hemoglobin to fo nitrosylhemoglobin and methemoglobin.

Ozone (O_3)

Ozone is abundant in the stratospheric region found between 5 and 31 m the planet. Ozone is formed by the action of ultraviolet light on oxygen m thus reducing the amount of solar ultraviolet irradiation reaching Earth. T concentration in passenger aircrafts may at times be above regulatory lir although a specific relationship with the development of clinical effects in crew members is elusive.[114] Ozone is another important component of photochemical smog and, as such, contributes to chronic lung disease.[24] produced in significant quantities by welding and high-voltage electrical and in more moderate doses by photocopying machines and laser printers of its high electronegativity (only fluorine is higher), ozone is one of the oxidizing agents available. For this reason it is used as a bleaching agent particularly as an alternative to chlorine in water purification and sewage

The pulmonary toxicity associated with ozone primarily results from its h reactivity toward unsaturated fatty acids and amino acids with sulfhydryl groups.[13 , 81] Ozonation and free radical damage to the lipid component o membrane initiates an inflammatory cascade, with resultant influx of infl cells.[14 , 134] Reactive nitrogen species also are implicated, as NO synthas mice are relatively protected from ozone-induced inflammation and tissue Increased permeability of the pulmonary epithelium results in alveolar fill

the transudation of proteins and fluids characteristic of ALI. Antioxidant a vitamin E) that react preferentially with free radicals before membrane d occurs prevent or limit the pulmonary toxicity of ozone.

Miscellaneous Irritant Gases

Methylisocyanate

Methylisocyanate (MIC, Figure 119-3) is one of a series of compounds sh similar isocyanate (N=C=O) moiety. Toluene diisocyanate (TDI) and diphenylmethane diisocyanate (MDI) are important chemicals in the polyr industry. In 1984, an inadvertent release of MIC in Bhopal, India, resulte immediate and persistent respiratory symptoms in approximately 200,000 inhabitants, with approximately 2500 deaths.[10 , 45] ALI was evident both and radiographically.[108] MIC is a significantly more potent respiratory irr the other regularly used isocyanate derivatives such as TDI).[4] Cyanide p does not occur, and empiric antidotal therapy is not indicated.

Riot Control Agents: Capsaicin (OC), Chlorobenzylidenemalononitrile (CS), and Chloroacetophenone (CN)

Historically, riot control agents (Figure 126-5), or Mace, consisted prima chloroacetophenone (CN) or chlorobenzylidenemalononitrile (CS).[16] Both solids that are dispersed as aerosols. The dispersion is generally accomp through mixture with a pyrotechnic agent such as a grenade or with a vo organic solvent in a personal protection canister. Because the delivery sy these agents are of limited sophistication and are subject to prevailing environmental conditions, dosing is unpredictable, and unintended self-po common.[16] After low-level exposure, ocular discomfort and lacrimation al expected, accounting for the common appellation *tear gas.* The effects a and complete recovery within 30 minutes is typical, although long-lasting

pulmonary effects may occur (see Asthma and Reactive Airways Dysfunct

Syndrome).[138] Closed-space or close-range exposure, as well as physica during exposure, may produce significant ocular toxicity, dermal burns, laryngospasm, ALI,[167] or death.[16] Because of their high potential for sev CN and CS were replaced for civilian use by oleoresin capsicum (OC), alsc *pepper spray* or *pepper mace.* Although capsaicin, its active component, considerably less toxic, it is occasionally responsible for pneumonitis[15] ar

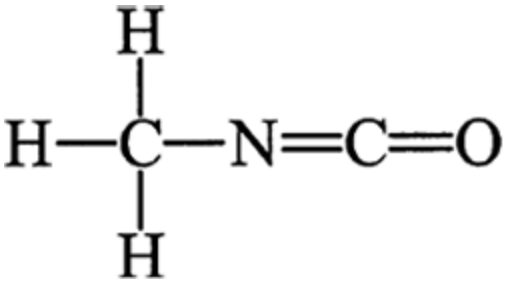

Figure 119-3. Methylisocyanate.

Capsaicin interacts with the vanilloid receptor-1 (VR1), which was recentl the transient receptor potential vanilloid-1 (TRPV1).[162] Stimulation of thi invokes the release of substance P, a neuropeptide involved with transmi pain impulses. Substance P also induces neurogenic inflammation, which, results in ALI and bronchoconstriction (see Asthma and Reactive Airways Syndrome).[162] The severe pulmonary toxicity of CS and CN likely is relat ability to alkylate tissues in a manner similar to mustard agents.[37]

Current therapy for inhalation of capsaicin, or of any tear gas, is primaril supportive. Extracorporeal membrane oxygenation has been used in child maintain oxygenation in the presence of severe pulmonary toxicity resulti capsaicin exposure.[15] Although no antidotes currently are available, the developing insight into the receptor mechanism of capsaicin suggests that active agent may hold future promise.

Metal Pneumonitis

Acute inhalational exposures to certain metal compounds produce clinical identical to the chemical irritants.[125] For example, zinc chloride ($ZnCl_2$) formerly used as artificial smoke because of the dense white character of

and an aqueous solution is still used as a soldering flux. Cadmium oxide
generated during the burning of cadmium metal in an oxygen-containing
environment, as occurs during smelting or welding. The refining of nickel
carbon monoxide (Mond process) produces nickel carbonyl [$Ni(CO)_4$], a
pulmonary oxidant.[148] Inhalation of volatilized elemental mercury,[112] whi
during the vacuuming of mercury spills or home extracting of precious m
be toxic. Although at sufficient concentration many of these metal exposu
produce warning symptoms, severe toxicity may occur even in the absenc
warning symptoms. The mechanism of toxicity may relate to overwhelmir
stress or inactivation of natural antioxidant systems.[181] Patients with m
pneumonitis present with chest tightness, cough, fever, and signs consist
ALI. Metal pneumonitis is distinguishable from other causes of ALI only by
retrospectively, by elevated serum or urine metal concentrations.[5] In pa
metal pneumonitis should be differentiated from the more common and
less consequential metal fume fever. In addition to standard supportive
patients with acute metal-induced pneumonitis should be hospitalized and
corticosteroids. Chelation therapy has no documented benefit for treatmer
but should be used based on conventional indications.

Management

Standard and Supportive Measures

Management of patients with acute respiratory tract injury begins with n
support of airway patency, by limiting bronchial and pulmonary secretions
maintaining oxygenation. Although various theoretical and experimental
modalities have been proposed, supportive care remains the mainstay of
Supplemental oxygen, bronchodilators, and airway suctioning should be u
clinically indicated. Nitrovasodilators, diuretics, and morphine have little r
management of ARDS, although low-dose morphine may prove beneficial
anxiolytic agent.[127] Corticosteroid therapy, designed to reduce the inflar
host defense response, frequently improves surrogate markers of pulmor
damage,[101, 102] such as oxygenation status, but generally offers little o
enhancement in patients with ARDS.[2] Importantly, most studies of ARDS

predominantly septic or traumatized patients, with few patients suffering inhalational poisoning. Because the inflammatory response initiated by b endotoxin differs from that caused by irritant gases, the applicability of t to the treatment of poisoned individuals is limited. There is an interesting simultaneous, presumably equivalent chlorine exposure in two sisters, wi outcome in the sister who received steroid treatment.[34] Most available r evaluates parenterally administered corticosteroids, although animal mod demonstrate a beneficial effect of nebulized beclomethasone[69] and nebul budesonide[176] following acute chlorine poisoning. However, a human pre model of inhaled budesonide fails to document a substantive alteration of of ozone inhalation.[115] Ketoconazole, an antifungal with antiinflammatory and nonsteroidal antiinflammatory agents, such as ibuprofen,[144] variably experimental lung function or mortality in patients with ALI of various n etiologies and have little current role in the therapeutic armamentarium. Furthermore, most of the aforementioned studies assess acute outcome a long-term effects in survivors. Because corticosteroids experimentally red late fibroproliferative phase during lung recovery, they ultimately may pr beneficial. Overall, there is little reason to suspect any specific benefit of corticosteroids and other antiinflammatory drugs in most poisoned patien However, because most studies demonstrate some benefit and little iden corticosteroid use appropriately remains routine and based largely on loc

The clinical similarities among patients with irritant gas exposure and oth etiologies of ALI suggest that similar management principles should be a Prone ventilation,[60] PEEP,[54] and inverse-ratio ventilation are successful i the oxygenation of patients with ALI of various etiologies but not necessa successful in improving outcome. Lower-tidal-volume mechanical ventilatio mL/kg and plateau pressures 30 cm H_2O attenuated the inflammatory re and resulted in lower mortality and less need for mechanical ventilation t traditional volume ventilation with 12 mL/kg.[1,110] Although not specifica evaluated in any of these studies, there are sound theoretical reasons to all of these modalities should improve oxygenation in poisoned patients a Although it is always important to reduce the inspired concentration of ox <50% as rapidly as possible, patients poisoned by irritant gases may be susceptible to oxygen toxicity as a result of depletion of endogenous ant

barriers.[150]

Neutralization Therapy

A therapy unique to several of the acid- or base-forming irritant gases is neutralization. Although contraindicated in acid or alkali injury of the ga tract, the large surface area of the lung and the relatively small amount xenobiotic present allow dissipation of the heat and gas generated

during neutralization. Case studies suggest that nebulized 2% sodium bi may be beneficial in patients poisoned by acid-forming irritant gases.[173] majority of these cases involve chlorine gas exposure, and most patients other symptomatic therapies as well.[20] Although there appears to be no benefit for patients exposed to chloramine, nebulized bicarbonate therapy be safe.[122] An adequately controlled, prospective evaluation of the safety of bicarbonate therapy in poisoned patients has not yet been attempted. bicarbonate solution used should be sufficiently diluted to prevent irritati Typically, 1 mL of 7.5% or 8.4% sodium bicarbonate solution is added to sterile water (resulting in an approximately 2% solution for nebulization)

Whether nebulized sodium bicarbonate therapy alters the natural course induced pulmonary damage remains uncertain. The fact that many irritan concomitant oxidant injury suggests that it may not. Nebulized 4% sodiu bicarbonate administered to chlorine-poisoned sheep improved oxygenatic failed to decrease mortality rates.[35] Therefore, patients receiving nebuliz bicarbonate therapy require observation beyond the time of symptom re Because administration of neutralizing acids for alkaline irritants, such as has not been attempted, their use cannot be recommended at this time.

Antioxidants

Antioxidant agents include reducing agents such as ascorbic acid, NAC,[85] scavengers such as vitamin E, and enzymes such as superoxide dismutas in humans have noted both increased[141] and decreased[21] endogenous a levels in bronchoalveolar lavage fluid in patients with ALI. Although the c treating pulmonary oxidant stress with antioxidants or free radical scaver

intriguing, most currently available evidence suggests that these xenobio negligible benefit.[111, 118] The rapid onset of the self-perpetuating destr effects initiated by redox reactions may hinder any postexposure therapy. interpretation is supported by pretreatment models in which antioxidants effective at preventing or at least limiting the pathologic effects. Use of t other newer therapies targeted against inflammatory mediators or the ox cascade are in the earliest investigative stages.

Advanced Pharmacologic Therapy

Perfluorocarbon Partial Liquid Ventilation

Partial liquid ventilation involves the intrapulmonary administration of perfluorocarbons, which are inert liquids with low surface tension and ex oxygen-carrying capacity. Studies in patients with nonchemically-induced suggest that exfoliated tissue, and presumably persistent xenobiotic, may effectively lavaged from the bronchopulmonary tree by this method.[40] Perfluorocarbons improve oxygenation and may have an antiinflammatory demonstrated by reduced oxidant lung injury following liquid ventilation i animals.[39] Although this may prove to be a highly useful therapy in the f limited availability, high cost, and lack of demonstrated efficacy make it only for an academic or research setting.[40]

Exogenous Surfactant

Several other recent developments may prove useful in the general mana patients with ARDS. Surfactant replacement therapy initially received atte treatment for patients with ARDS because of its beneficial effects in infan respiratory distress syndrome. Although several experimental and clinical suggested the safety and efficacy of surfactant therapy in patients with A randomized, controlled clinical trials fail to show a benefit on survival.[156] who received surfactant had a greater improvement in gas exchange durin hour treatment period than patients who received standard therapy alone suggesting the potential benefit of a longer treatment course.[156] Because studies involved patients with sepsis-related ARDS, the inability to show

effect may not adequately reflect the potential of surfactant in irritant g ARDS.[128] Many oxidant gases inactivate endogenous surfactant, although specific effects on exogenous surfactant are not well understood.[128]

Other Inhalational Pulmonary Xenobiotics

A particulate, or dust, is a solid dispersed in a gas. Dust is a substantial occupational particulate exposure and is an important cause of acute pul toxic syndromes. A respirable particulate must have an appropriately sma (generally <10 Âµm) and aerodynamic properties to enter the terminal r tree. Nonrespirable particulates, also called *nuisance dusts* , are trapped upper airways and are not generally thought to cause pulmonary damage. distinction from the irritant gases, there is no unifying toxic mechanism a respirable particulates. Many of the particulate diseases, such as asbesto and its sequelae, are chronic in nature; only the acute or subacute syndr discussed here.

Inorganic Dust Exposure

Silicosis is a range of pulmonary diseases associated with inhalation of c silica (SiO_2), or quartz. It typically occurs in workers involved in occupa rock or granite is pulverized, including mining, quarry work, or sandblast Although typically a chronic disease, intense subacute exposure may proc silicosis in a few weeks and death within 2 years. The mechanism of toxi probably relates to the relentless inflammatory response generated by th pulmonary macrophages.[117] These cells engulf the indigestible particles a destroyed, releasing their lytic enzymes and oxidative products locally wi pulmonary parenchyma. Patients present with dyspnea, cor pulmonale, r lung findings, and classic radiographic findings. Treatment is limited and steroids and supportive care.

Silica combined with other minerals are referred to as *silicates* , the mos of which include asbestos and talc. Talc, or magnesium silicate [(Mg_3 Si_4], is widely used in industry, but its use in the home has been curtailed o two decades because of cases of severe pulmonary injury.[95] Much of the

talc is related to free silica or asbestos contamination. Improvement follc massive exposure may be accompanied by progressive pulmonary fibrosis

Organic Dusts

Inhalation of dusts from cotton or similar natural fibers, usually during th refinement of cotton fibers (byssinosis), produces chest tightness, dyspne fever that typically begin within 3â€“4 hours of exposure. Symptoms ofte during the work week but

return after a weekend hiatus. Byssinosis probably is caused by an endot present on the cotton and is not immunologic in nature.[177] A similar synd â€œgrain fever,â€• which is caused by a respirable compound associated dust, as occurs during harvesting, milling, or transporting.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis, also known as *extrinsic allergic alveolitis* , common pathway for many different organic dust exposures.[158] The nam to the individual syndrome typically identifies the associated occupation c substrate. For example, *bagassosis* is the term associated with sugar can (bagasse), and *farmer's lung* is the term associated with moldy hay, alth conditions are caused by thermophilic *Actinomycetes.* When associated w mushroom spores *(Lycoperdon* spp), the syndrome is called *lycoperdonos* 113); when caused by bird droppings, it is called *bird fancier's lung.* The allergen is capable of depositing in the pulmonary parenchyma and elicitir mediated (type IV) immunologic response. Clinical findings include fever, dyspnea beginning 4â€“8 hours after exposure. The chest radiograph usu normal but may reveal diffuse or discrete infiltrates. Progressive disease associated with a honeycombing pattern on the radiograph and a restricti disease pattern on formal pulmonary function testing. Treatment includes corticosteroids and avoidance of the antigen.

Metal Fume Fever/Polymer Fume Fever

Metal fume fever is a recurrent influenzalike syndrome that develops sev after exposure to metal oxide fumes generated during welding, galvanizin smelting. Although most symptoms of metal fume fever are similar to tho with irritant gas exposures (dyspnea, cough, chest pain), the presence of typically 100.4Â°Fâ€“102.2Â°F (38Â°Câ€“39Â°C), distinguishes the synd addition, patients may experience headache, metallic taste, myalgias, and Direct pulmonary toxicity probably does not occur, and patients with meta fever generally have normal chest radiographs. Interestingly, acute toler develops, so repeat daily exposures produce progressively milder sympto However, the tolerance disappears rapidly, and after a short work hiatus s weekend, the original intensity resumes, thus accounting for the designa *morning fever.* Many metal oxides are capable of eliciting this syndrome, noted most frequently in patients who have welded galvanized steel, whi zinc. Metal fume fever also occurs commonly after the high-temperature copper-containing compounds, thus accounting for the historical appellat *foundry workers ague.* There is a strong association between welding-rela fume fever and welding-related respiratory symptoms suggestive of occu asthma.[52] Serum and urine metal concentrations typically are not elevate acute event, although they may be chronically elevated from daily occup exposure. The etiology of metal fume fever is debated, but the syndrome features suggestive of both an immunologic and a toxic etiology.[17] Antige with immunologic response appears to be responsible for the induction of On subsequent exposure, proinflammatory cytokines, such as tumor necr Î±, and various interleukins can be detected in bronchoalveolar lavage fl However, because symptoms can occur with the patient's first exposure to direct toxic effect on the respiratory mucosa presumably exists.[100] Exposu certain metal fumes, such as cadmium oxide or other zinc compounds, m direct toxic effects on the pulmonary parenchyma.[100]

The management of patients with metal fume fever is supportive and incl analgesics and antipyretics. There is no specific antidote, and chelation t should not be instituted unless otherwise indicated. Patients with ALI pro suffering from metal toxicity (eg, cadmium pneumonitis). The natural cou metal fume fever involves spontaneous resolution within 48 hours. Persis symptoms are rare and should prompt investigation for metal toxicity.

A remarkably similar syndrome occurs subsequent to inhaling pyrolysis p fluorinated polymers (eg, Teflon), which is aptly termed *polymer fume fe* Patients develop self-limited viral illness-type symptoms several hours af exposure to the fumes. As with metal fumes, very large exposures to pol may result in direct pulmonary toxicity. Supportive care is the therapy of

Asthma and Reactive Airways Dysfunction Syndrome

Asthma, or *reversible airways disease* , is a clinical syndrome that include intermittent episodes of dyspnea, cough, chest pain or tightness, wheezes auscultation, and measurable variations in expiratory airflow. Episodes ty triggered by a xenobiotic or physical stimulus and resolve over several h appropriate therapy. The underlying process is immunologic in most cases allergen-triggered release of inflammatory mediators causing bronchiolar muscle contraction and subsequent inflammation. Because asthma affects of the world's population and the triggers often are nonspecific, it is not that work-aggravated asthma is extremely common. The patients are pr sensitized, and the initial irritant exposure causes bronchospasm or simil symptoms. Thus, work-aggravated asthma is discovered early in the wor employment, and a more appropriate workplace or occupation can be pu

Occupational asthma, or asthma occasioned by a workplace exposure to xenobiotic, accounts for perhaps 10% of all newly diagnosed asthma in a Casual exposure to one of the 250 or more known sensitizers (Table 119- is associated

with a latency period of weeks or months of exposure before symptom or symptoms begin, however, they recur consistently following reexposure to inciting trigger agent. Occupational asthma with latency may be IgE depe which case it is identical to allergic asthma, or is IgE independent.[172] The dependent form is most commonly associated with high-molecular-weight (>5000 daltons) or with certain haptenic low-molecular-weight agents (eg anhydride). The low-molecular-weight agents (eg, nickel, isocyanates) m cause IgE-independent disease, which manifests as the delayed reaction

cell-mediated, or type IV, hypersensitivity. Because contact with a trigger difficult to avoid in either case, reassignment or an outright occupational may be required. Treatment for exacerbations is comparable to standard therapy and includes bronchodilators and corticosteroids.

High
Proteins
Crab shell protein
Seafood processors
Low
Acrylate
â€”
Adhesives, plastics
Glutaraldehyde
â€”
Healthcare workers
Isocyanates
Toluene diisocyanate
Polyurethane foam, automobile painters
Metals
Nickel sulfate
Nickel plating
Trimellitic anhydride
â€”
Chemical workers
Wood dust
Western red cedar (*Thuja plicata*)
Foresters, carpenters

Xenobiotics by Molecular Weight	Example of Sensitizer	Primary Occupat

TABLE 119-3. Common Xenobiotic Sensitizers Producing Occup
Asthma

Acute exposure to irritant gas may result in the development of a persist asthmalike syndrome also termed *reactive airways dysfunction syndrome irritant-induced asthma* , or *occupational asthma without latency.* Virtuall irritative xenobiotic is reported to cause this syndrome, and those not ye probably are simply unrecognized. Although asthma typically is associated massive inhalational exposure, as following the World Trade Center collap occasional patients are susceptible to low-level exposure.[25] RADS often is to occupational asthma because both disorders are chemically induced an frequently occur following chemical exposure in the workplace.[38] However comparison with those who develop occupational asthma, patients who de have a lower incidence of atopy and are exposed to agents not typically to be immunologically sensitizing.[25] In addition, the airflow improvement adrenergic agonist therapy is significantly better in patients with occupat asthma.[61] Bronchial biopsy performed in patients with RADS generally rev chronic inflammatory response.[61] RADS may have a neurogenic etiology[1(opposed to an immunologic origin, as in patients with occupational asthm may differentiate these clinically similar diseases on a mechanistic basis. inflammation results from increased vascular permeability, presumably se release of substance P from unmyelinated sensory neurons (C fibers).[46] N inflammation is inhibited by substance P depletors such as capsaicin and by substances that inhibit neutral endopeptidase, the enzyme responsible degradation of substance P.[103] The role of corticosteroids is undefined, b models suggest an antiinflammatory benefit.[43] Recovery may take months delay related to either ongoing low-level exposures to endopeptidase inhi persistent irritation of impaired tissue by environmental irritants such as

Summary

The overall quality of the air we breathe continues to deteriorate, and flu environmental pollutants periodically cause epidemic disease. Although th of xenobiotics capable of causing pulmonary toxicity is large, the patholo are rather limited. Gases that have little or no irritant potential or syster cause simple asphyxiation, in which the ambient atmosphere has a dimin oxygen concentration. Parenchymal irritation and ALI occur after exposure forming or free radicalâ€“generating gases and can progress to severe to

manifesting as ARDS. RADS is described in patients following exposure to all of the irritant gases. Treatment of all such exposures centers on symp supportive care.

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Chapter 120
Carbon Monoxide

Christian Tomaszewski

Carbon Monoxide (CO)

MW
=
28.01 daltons
Gas density
=
0.968 (air = 1.0)
Blood carboxyhemoglobin levels

Nonsmokers
=
1â€“2%
Smokers
=
5â€“10%
Action level
=

>10%
TLVâ€“TWA
=
50 ppm
A 38-year-old woman presented to the hospital complaining of vomiting, watery diarrhea, light-headedness, and headache one morning in August. husband had similar symptoms. The couple arrived 2 days earlier at a res town after a 3-hour flight on which they ate turkey sandwiches of questi quality. The woman denied taking any medications and stated that she ha contacts or recent travel outside the United States.

On physical examination, both patients appeared ill and dehydrated. The woman's vital signs were: blood pressure, 125/63 mm Hg; pulse, 100 be respiratory rate, 16 breaths/min; temperature, 100.5Â°F (38.1Â°C). Her examination was essentially normal, except for dry mucous membranes a epigastric tenderness. The only remarkable standard laboratory test was blood cell count of 12,300/mm^3 . Bicarbonate was normal at 22.4 mEq/L. receiving 1 L of 0.9% sodium chloride solution, ketorolac, and droperidol, patient was discharged several hours later feeling much better with norm signs. Her husband was treated similarly.

The next morning, the couple did not show up for the medical conference were attending. A friend convinced security to break into the room when was no answer at the door. The couple was found unconscious. The husba no pulse and could not be resuscitated. The wife, who was responsive to pain only, was transported with 100% face mask oxygen. Naloxone and were given IV en route, without any change in her symptoms. On arrival emergency department (ED), the patient's vital signs were: blood pressu 108/65 mm Hg; pulse, 112 beats/min; respiratory rate, 14 breaths/min; temperature, 101.9Â°F (38.8Â°C). Laboratory tests were unremarkable e for a glucose concentration of 306 mg/dL and a creatinine concentration mg/dL. Arterial blood gas showed: pH, 7.5; PCO_2 , 22.8 mm Hg; PO_2 , 17 Hg. Because of the strong odor of gas, a carboxyhemoglobin (COHb) leve sent for analysis and returned a value of 29.9%. The patient was immed transferred by helicopter to a tertiary medical center, where she was trea with hyperbaric oxygen (HBO). However, her course was complicated by

aspiration pneumonia, and she subsequently had persistent problems witl concentration, memory, and â€œnot being able to find my words.â€• Th source of the carbon monoxide poisoning subsequently was determined to faulty hot-water heater.

History and Epidemiology

Carbon monoxide (CO) is the leading cause of poisoning morbidity and m in the United States. Based on US national death certificate data, 2379 n fireâ€“related CO deaths occurred in 1998.[158] Of note, only 491 of the d were unintentional; more than half were related to motor vehicle sources figure remained essentially unchanged in 2002 despite increased CO dete use.[38] From 2001â€“2003, 15,200 patients were treated annually in eme departments for nonfatal, unintentional, non-fireâ€“related CO exposure. than half of the cases (64%) occurred in homes with faulty furnaces, usu the fall or winter months. CO poisoning is also a contributor to the appro 5613 smoke inhalation deaths each year.[47]

The more significant problem with CO poisoning may be the morbidity ra than mortality. The most serious complication is persistent or delayed co sequelae, which occur in up to 50% of patients with symptomatic acute poisonings.[88 , 193 , 259]

Because no method for predicting bad outcomes is completely reliable, C poisoning should be treated aggressively with HBO therapy.

Anesthetic lime absorbents[122]
Automobiles
Banked blood
Boats[36]
Camp stoves and lanterns
Charcoal grills[77]
Coffee roasting[173]
Gasoline powered equipment (eg, generators, power washers)[34]
Ice resurfacing machines[184]

Methylene chloride
Natural gas furnaces
Natural gas water heaters
Natural gas ranges and ovens
Propane powered forklifts[70]
Underground mine explosions[147]
Wood pellet storage

TABLE 120-1. Sources of Carbon Monoxide Implicated in Poisonin

Potential sources of CO abound in our society and often result in uninten poisoning (Table 120-1). Although CO is found naturally in the body as a byproduct of hemoglobin degradation,[48] it is readily available for inhalati the incomplete combustion of any carbonaceous fuel. Alternatively, absorptionâ€"dermal, ingestion, or inhalationâ€"of methylene chloride car in CO toxicity from hepatic metabolism (Chap. 102).[169] Despite use of c converters and other emission controls, more than half of unintentional C deaths are caused by motor vehicle exhaust.[47 , 158] Occupants of motor are not the only victims of exhaust gases. CO poisoning also is reported i children riding in the back of pickup trucks.[98] Workers can become symp from indoor use of propane-powered equipment, such as ice skating rink resurfacers[118] and forklifts.[67 , 72] For optimal performance, propane-pow forklifts typically are adjusted to produce no less than 10,000 ppm CO in and in fact average more than 30,000 ppm.[70] In an enclosed warehouse poor ventilation, CO levels could exceed toxic levels within one hour at th of production. Even occupants of boats are not immune to this insidious , 36 , 212

In the past 10 years, nonvehicular sources of CO have increasingly accou most unintentional poisonings, with fewer than 400 deaths each year in t United States.[38 , 47 , 158] Predominantly, these deaths have involved the of charcoal, wood, or natural gas for heating and cooking.[54 , 73 , 76 , 96] Propane-burning furnaces used for heating are often the culprits, especia when the flue is blocked.[18 , 38 , 90 , 101 , 102] Gas kitchen stoves are ano important source of CO in indigent populations with marginal heating

systems.[102 , 218] In fact, use of gas stoves for supplemental heat is pred CO poisoning in patients who present to the ED with headache and dizzin During ice storms, hurricanes and earthquakes, use of gasoline-powered generators and charcoal-burning grills, the latter particularly in immigran populations, has resulted in epidemic CO poisoning outbreaks.[37 , 109 , 26

Fires are another important source of CO exposure. CO is estimated to be cause or a major contributor to more than 1500 fire deaths annually.[47] C considered the most common hazard to smoke inhalation victims.[18 , 210]

Chemistry

CO has a molecular mass of 28.01 daltons and a density of 0.968 relative CO is found naturally in the body as a byproduct of heme degradation.[48] oxygenase, found in the liver and spleen, is the major endogenous source A second form of the enzyme in the brain that also produces CO behaves nitric oxide (NO), binding to guanylate cyclase and thereby increasing cy guanosine monophosphate (cGMP) concentrations.[148] Although low endo levels are physiologic, excessive concentrations of CO from exogenous s may be problematic because CO persists much longer than NO.[87] CO appe be a neuronal messenger by virtue of the fact that as a gas it can diffuse signal adjacent cells.[11]

CO is readily absorbed after inhalation. The Coburn-Forster-Kane (CFK) r allows the prediction of COHb levels based on exposure history.[50] This m been simplified to allow estimation of the equilibrium based on the ambie concentration of CO in ppm: COHb (%) = 100/[1 + (643/ppm CO)].[245] Th model assumes that the individual weighs 70 kg and is not anemic. With exponential uptake, more than 4 hours may be necessary to attain equili Therefore, within minutes of high CO exposures, the arterial COHb level r actually overshoot predicted estimates prior to equilibration.[16 , 27] Endog production of CO results in a COHb of 2%.

Once absorbed, CO is carried in the blood, primarily bound to hemoglobin Haldane ratio states that CO has an approximately 200â€“250 times grea affinity for hemoglobin than does oxygen.[33] Therefore, CO is primarily co

to the blood compartment, but eventually up to 15% of total CO body sto taken up by tissue, primarily bound to myoglobin.[49] The dissolved CO concentration in the serum may better reflect the ultimate potential for poisoning because dissolved CO is available for diffusion into all tissue compartments, including the brain.[139]

Elimination of CO from the blood, like absorption, can be modeled mathematically using the CFK model. The equation predicts a half-life of minutes.[50] In actual volunteer studies, means of 249 and 320 minutes ar reported.[181 , 189] With 100% oxygen, these half-lives can be reduced significantly to means of 47, 78, and 80 minutes in studies of volunteers attain COHb levels of 10â€“12%.[181 , 189 , 224] Two series of patients pois with CO showed actual mean half-lives of 74 and 131 minutes when patie were treated with 100% oxygen.[24 , 261]

Methylene chloride, a paint-stripper is another source of CO. It is readily absorbed through the skin, by ingestion, or by inhalation. It is metabolize the liver to CO.[221] After a delay of 8 hours or longer, peak levels of COHl range from 10â€“50%.[69 , 133 , 138 , 197] Because of ongoing CO productio apparent COHb half-life is prolonged to 13 hours in these patients.[195] CO levels after methylene chloride exposure appear to be proportional to the concentration and duration of exposure.[210]

Pathophysiology

The most obvious effect of CO is its binding to hemoglobin, which renders hemoglobin incapable of delivering oxygen to the cells.[64] Therefore, desp adequate partial pressures of oxygen in blood (PO_2), arterial oxygen cor decreases. Further insult occurs because CO causes a leftward shift of the oxyhemoglobin dissociation curve, thus decreasing the offloading of oxyge hemoglobin

to tissue.[200] This may result in part from a decrease in erythrocyte 2,3-diphosphoglycerate concentration.[9 , 243] The net effect of all these proce the decreased ability of oxygen to be carried by the bloodstream and rele cells.

CO toxicity cannot be attributed solely to COHb-mediated hypoxia.[196] Nei clinical effects nor the phenomenon of delayed neurologic deficits can be completely predicted by the extent of binding between hemoglobin and C [174 , 216 , 237] Furthermore, such a model fails to explain why even negli levels of COHb (4â€“5%) can result in cognitive impairment.[248] An early showed that dogs breathing 13% CO died within one hour and had COHb of 54â€“90%. However, exchange transfusion of the same blood into hea dogs caused no untoward effects.[86] Comparable levels of anemia also lac adverse effects. The appropriate conclusion was that inherent to CO toxic the delivery of CO to target organs such as the brain and heart, and that although easily measured, rarely makes a significant contribution to clini toxicity.[85 , 86]

The delivery of CO intracellularly and its subsequent binding to heme pro other than hemoglobin also may account for CO toxicity. Ten to fifteen p of the total body store of CO is extravascular, primarily binding to myogl [49] Some of this CO may interfere with cellular respiration by binding to mitochondrial cytochrome oxidase, as occurs in vitro.[10 , 40] Initial studies that this binding is especially exaggerated under conditions of hypoxia an hypotension.[25]

Inactivation of cytochrome oxidase may be only an initial part of the casc events resulting in ischemicâ€“reperfusion injury to the brain after CO p During recovery from the initial poisoning, white blood cells are attracted adhere to the damaged brain microvasculature.[240] This attraction may be attributable to endothelial changes from initial cytochrome oxidase dysfu mediated primarily through the free radical NO.[113 , 230 , 236] CO displaces from platelets that in turn form peroxynitrites, which are even stronger inactivators of cytochrome oxidase.[240] Multiple animal studies demonstrat NO ultimately is responsible for much of the endothelial damage from CO that NO synthase inhibitors can prevent toxicity.[232 , 239 , 242] In rats, CO poisoning causes an immune cascade in the brain whereby activated lym are attracted to CO-modified myelin basic protein.[233] After leukocytes att the damaged endothelium, they release proteases that convert xanthine dehydrogenase to xanthine oxidase, an enzyme that promotes formation

oxygen free radicals.[228] The end result of this process is delayed lipid peroxidation of the brain, which can be correlated with decrements in lea rodents.[227]

All this perivascular oxidative stress in the brain leads to activation of ex amino acids that ultimately may be responsible for subsequent neuronal loss.[236] In fact, glutamate increases in rat brains after CO poisoning.[270] Glutamate is an excitatory amino acid that can bind at *N* -methyl-D-aspa (NMDA) receptors and cause intracellular calcium release, resulting in de neuronal cell death (see Chap. 14).[20] Blockade of NMDA receptors can p the neuronal death and learning deficits that accompany serious CO poisc mice.[114] Newer data suggest that ultimately CO neuronal cell death may b form of apoptosis.[249] Increases in glutamate concentration in rat brain in first hour after severe CO poisoning are followed by a later rise in hydrox radicals.[190] Ultimately, at 1â€“ 3 weeks the animals show histologic evide both neuronal necrosis and apoptosis in the frontal cortex, globus pallidus cerebellum that are accompanied by deficits in learning and memory.

The role of apoptosis as the final cause of toxic damage in CO poisoning been confirmed in various models. In bovine pulmonary artery cells, CO exposure is accompanied by activation of caspase-1, a protease implicate delayed cell death.[235] The same study provided confirmatory evidence tha caspase-1 and NO synthase inhibitors blocked apoptosis. The end result o these cellular processes is brain injury, particularly in the basal ganglia a hippocampus, resulting in impaired learning.[231] Thus, animal models cor well with the final occurrence in victims of serious CO poisoning, namely, persistent or delayed deficits in learning and memory associated with str changes in the brain.

Myoglobin is another heme protein that binds CO. It has an affinity approximately 60 times greater than that of oxygen.[51] A dog model demonstrates that this binding is enhanced under hypoxic conditions.[51] T binding may partially explain the myocardial impairment that occurs both animal studies[56] and with low-level exposures in patients with ischemic h disease.[7] Isolated rat heart studies demonstrate that the effect on the he occurs regardless of COHb formation.[41] The combination of COHb formati

which decreases oxygen-carrying capacity, and the production of reduced myoglobin in the heart, which decreases oxygen extraction, may explain preterminal dysrhythmias that occur in animals.[82] Volunteers, especially with preexisting heart disease, develop an increase in life-threatening dysrhythmias and ischemic changes during stress testing even with low-l exposures (resulting in COHb levels up to 6%).[3 , 208]

Several studies suggest that CO effects on the cardiovascular system are necessary for ischemicâ€“reperfusion injury of the brain. Hypotension is a essential component and results from a combination of myocardial depre and vasodilation. CO activates guanylate cyclase, which in turn relaxes v smooth muscle.[252 , 255] CO can act on platelets to displace NO, which is a potent vasodilator.[128 , 234] These factors contribute to the hypotension tl occurs in animal experiments involving high doses of CO toxicity.[84 , 92] S episode of hypotension may be represented clinically by the syncope or lo consciousness that accompanies serious CO poisoning and portends a wo clinical outcome.[45 , 75 , 154] In the rhesus monkey, cerebral white matter correlate better with decreases in blood pressure than with COHb level.[84] Lipid peroxidation of the brain in rats develops one hour after CO exposu produced syncope and hypotension.[227] This delay is comparable to the ti necessary to produce mitochondrial destruction from oxidative stress in r exposed to CO.[269] In a feline model, central nervous system damage from can be reproduced only when hypoxia is accompanied by an interval of is confirming the ischemicâ€“reperfusion model.[176]

Clinical Manifestations

Effects of Acute Exposure

The earliest symptoms associated with CO poisoning often are nonspecific readily confused with other illnesses, typically a viral syndrome (Table 12 Headache is the initial symptom reported by volunteers within 4 hours of exposure to 200 ppm COHb levels (15â€“20%). Shorter exposures at 500 also produce nausea.[222 , 223] The incidence of CO poisoning in symptoma patients presenting to EDs in the winter with influenzalike symptoms rang

from 3â€“24% in some series.[42,63,100,102] Because the typical prese complaints include headache, dizziness, and nausea and the most freque exposures occur during winter, it is

not surprising that influenza is the most common misdiagnosis.[63,90] Hea the most common symptom, usually is described as dull, frontal, and continuous.[95] CO poisoning also is frequently misdiagnosed as food poisc gastroenteritis,[76,107] and even colic in infants.[191] Like adults, children t develop nonspecific symptoms (eg, nausea, headache, and vomiting), ma the diagnosis equally difficult.[57]

Headache
Vomiting
Nausea
Ataxia
Dizziness
Confusion
Weakness
Syncope
Chest pain
Cardiac dysrhythmias
Dyspnea
Myocardial ischemia
Visual blurred
Tachypnea

TABLE 120-2. Clinical Manifestations of Carbon Monoxide Poisoni

Continued exposure to CO can lead to symptoms attributable to oxygen deficiency in the heart. Low-level exposures (COHb 2â€“4%) in volunteers stable angina result in decreased exercise tolerance and signs and sympt myocardial ischemia.[2,6,8] At higher levels (COHb 6%), a greater frequ premature ventricular contractions is observed during exercise.[208] Myoca infarction, life-threatening dysrhythmias, and cardiac arrest are commonl

described in victims of CO poisoning.[5 , 145 , 204] In fact, acute mortality f usually results from ventricular dysrhythmias, probably predominantly cau the accompanying hypoxia.[3 , 5 , 56 , 204]

The central nervous system is the organ most sensitive to CO poisoning. otherwise healthy patients may manifest headache, dizziness, and ataxia COHb levels as low as 15â€“20%. With longer exposures, syncope, seizur coma can result.[31 , 104] Patients may present with symptoms of an acute stroke.[13 , 121] The EEG can show diffuse frontal slow-wave activity.[75 , 17 Within one day of exposures that result in coma, the computerized tomo (CT) scan can show decreased density in the central white matter and glo pallidus (Figure 120-1).[211 , 246] Autopsies show involvement of other ar including the cerebral cortex, hippocampus, cerebellum, and substantia r

Metabolic changes may reflect the toxic effects of CO better than any pa COHb level. Mild CO cases may be accompanied by respiratory alkalosis t compensate for the reduction in oxygen-carrying capacity and delivery.[14] Longer exposures with decreased levels of consciousness result in metab acidosis from the lactate production that accompanies tissue hypoxia.[216] a series of 48 CO-poisoned cases showed retrospectively that hydrogen io concentration, rather than COHb level, was a better predictor of poor rec during initial hospitalization.[251]

Although the brain and heart are the most sensitive, other organs can m the effects of CO poisoning. One fifth to one third of severe CO cases (ie, that required endotracheal intubation) develop cardiogenic pulmonary ed [217] This finding does not appear to be a direct effect of CO on lung tissue Studies of sheep with prolonged exposure to CO resulting in COHb levels showed no anatomic or physiologic change in lung function.[209] Although myonecrosis and even compartment syndromes occur, patients rarely de renal failure.[17 , 207] Retinal hemorrhages can develop with exposures >1 hours.[60 , 121] Cherry-red skin coloration occurs only after excessive expo (2â€“3% of cases referred to one hyperbaric center) and may represent a combination of CO-induced vasodilation with concomitant tissue ischemia [198] Another classic but uncommon phenomenon is the development of cu bullae following severe exposures.[166] These bullae are thought to be caus

combination of pressure necrosis and possibly direct CO effects in the epidermis.[110 , 136]

Delayed Cognitive Effects

The persistent or delayed effects of CO poisoning are varied and include dementia, amnestic syndromes, psychosis, parkinsonism, paralysis, chore cortical blindness, apraxia and agnosias, peripheral neuropathy, and incontinence.[81 , 137] Neurologic deterioration can be preceded by a lucid of 2â€“40 days after the initial CO poisoning.[45] In patients admitted to a intensive care unit for severe CO toxicity and treated with 100% oxygen, survivors had permanent neurologic impairment.[128] In a Korean series of CO-poisoned patients, only 3% continued to show memory failure or parkinsonian features one year after exposure.[45] In contrast, another ser 63 seriously poisoned patients showed memory impairment in 43% and deterioration of personality in 33% at 3-year follow-up.[216] Children also behavioral and educational difficulties after severe poisoning.[132] However, patients (age >30 years) appear to be much more susceptible to develop delayed sequelae.[45] Most cases of delayed neurologic sequelae are assoc with loss of consciousness in the acute phase of toxicity.[45 , 75 , 215]

Delayed or persistent neurologic sequelae probably involve lesions of the cerebral white matter and basal ganglia.[81] Weeks after exposure, autopsi necrosis of the white matter, globus pallidus, cerebellum, and hippocamp CT and magnetic resonance imaging (MRI) scans confirm the damage to t white matter and hippocampus.[74 , 108 , 177 , 211 , 246] Animal studies sho marked COHb alone cannot cause similar white-matter lesions; an episode hypotension also must have occurred.[84 , 176] The fact that the areas

permanently damaged in serious CO poisoning cases are the areas with t poorest vascular supply in the brain is consistent with these animal findi

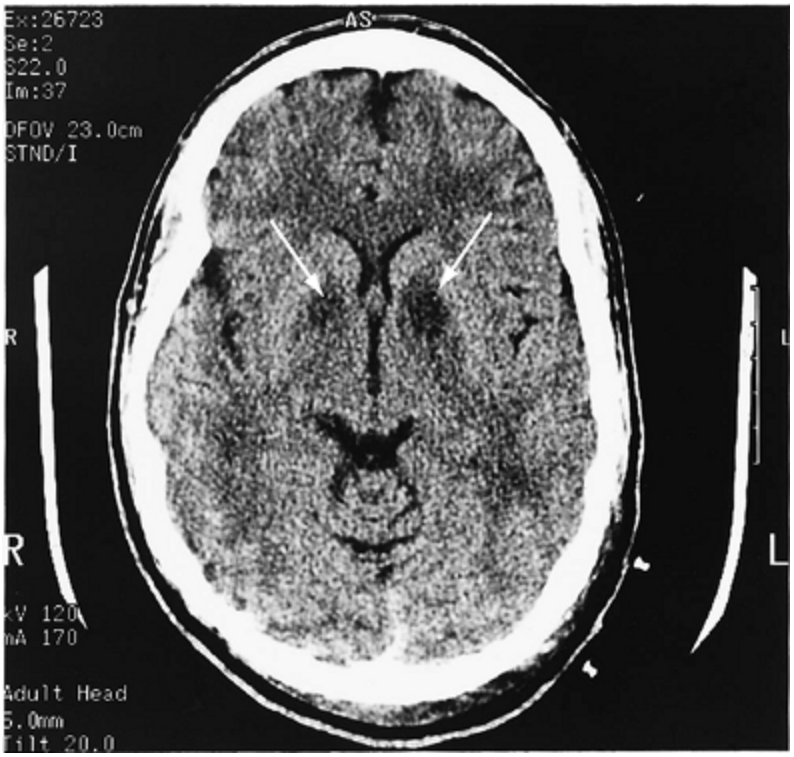

Figure 120-1. Computerized tomography of the brain showing bilateral of the globus pallidus (lucent areas) in a patient with poor recovery from carbon monoxide poisoning. (Courtesy of New York City Poison Center Fe in Medical Toxicology.)

Effects of Chronic Exposure

Patients often complain of persistent headaches and cognitive problems a long-term exposure to low levels of CO. Unfortunately, no controlled stuc have demonstrated that in the absence of a severe acute poisoning episo type of exposure results in any long-term sequelae. However, with docur continued exposure to low levels of CO, highway toll workers have troubl performing parallel processing tasks.[117] Warehouse workers chronically to CO from propane combustion have intermittent problems with headach nausea, and light-headedness.[67] Fortunately, symptoms resolve in most unless there has been an episode of severe poisoning with acute deterior One series of chronic CO poisoning demonstrates a high incidence of hea and memory complaints, along with motor slowing and memory problems

neuropsychological tests.[163] Although many of the objective deficits impr with elimination of the exposure and HBO treatment, many patients conti have posttraumatic neurosis and conversion disorders. One case report n permanent verbal memory, visual recall, and learning problems after a 3 exposure to 180 ppm CO from a faulty furnace.[202] Although it is unclear chronic exposure to low levels of CO can cause permanent damage, heal providers still should be vigilant for symptomatic individuals in order to p continued or catastrophic outcomes.

Diagnostic Testing

The most useful diagnostic test for suspected CO poisoning is the COHb l Normal COHb levels range from 0â€“5%. Levels at the high end of this ra occur in neonates and patients with hemolytic anemia,[265] as CO is a natu byproduct of the breakdown of protoporphyrin to bilirubin.[48] COHb levels average 6% in 1-pack-per-day smokers but can be as high as 10%.[220] Al high COHb levels confirm exposure to CO, particular levels are not neces predictive of symptoms or outcome. In fact, COHb can return to normal o zero if the patient was treated with oxygen prior to the blood test.[162 , 17

The usual method for measuring COHb is with a co-oximeter, which spectrophotometrically reads the percentage of total hemoglobin saturate CO.[14 , 52] Traditionally, arterial blood is used for this determination; hov venous blood concentrations are just as accurate.[248] Of note, refrigerate heparinized samples yield accurate COHb levels for months, making retrospective evaluations possible.[62 , 130] Bedside tests with ammonia or hydroxide cannot reliably differentiate various levels of COHb versus con Breath-sampling methods may be used for screening patients; however, a common cointoxicant, can falsely elevate breath levels unless an activa charcoal filter is used.[131 , 189 , 250] Because of the similarities in extincti coefficients, COHb is misinterpreted as oxyhemoglobin on pulse oximetry 22).[12] Thus the pulse oximeter reading overestimates oxyhemoglobin by approximate amount of COHb present.[23 , 29 , 94]

Some clinicians have started to measure CO, rather than COHb, directly i samples.[139] This technique involves assaying CO directly with infrared

spectrophotometry after it is extracted from the blood sample with a manometer.[159] Based on calculations rather than true experimental data, assumption is made that for a patient with a normal hemoglobin, a CO concentration of 1 mmol/L corresponds to 11% COHb.[180] A simpler metho measuring plasma CO content is to add a known solution of hemoglobin t by sodium dithionite to form COHb.[43] The resulting COHb is measured spectrophotometrically, with the assumption that 1 mole of hemoglobin bi moles of CO. Interestingly, in one study, plasma CO ranged from 0.14â€“ mg/L but was the same in smokers and nonsmokers (average COHb 4.6% 1%, respectively).[43] Further research is required to determine the clinica importance of plasma CO content.

Additional laboratory tests may be useful in severe poisoning cases. Arter venous blood gas analysis will confirm the presence of metabolic acidosis presumably is a reflection of high lactate and may serve as a more reliab of severity than COHB.[216] Unfortunately, arterial pH does not correlate w either initial neurologic examination or the COHb level, making it a poor for deciding the need for HBO treatment.[162]

Cardiac monitoring and a 12-lead ECG are essential for documenting ischo dysrhythmias in symptomatic patients with preexisting coronary artery d or severe exposure. Mild elevations of creatine phosphokinase are commo (range 20â€“1315 IU/L in a series of 65 cases) and usually result from rhabdomyolysis rather than cardiac sources.[207] However, CO can cause myocardial infarction, even in the presence of normal coronary arteries.[1 Therefore, it is not surprising to observe nonspecific rises in troponin concentrations, which may reflect diffuse cardiac myonecrosis rather than coronary artery disease.[39]

The problem with using COHb levels as the basis for treatment is the wid variation in clinical manifestations with identical COHb levels.[161 , 168] Furthermore, particular COHb levels are not predictive of symptoms or fi outcome.[149 , 162 , 174 , 216] In a large prospective study of CO poisoning, levels did not correlate with loss of consciousness and were not predictive delayed neurologic sequelae.[193] Part of the problem is that admission CO levels are inaccurate predictors of peak levels.[162] Use of nomograms to

extrapolate to earlier levels has not been validated. The credibility of nomograms is suspect because of the great variability in COHb half-lives differences in treatment with oxygen.

Because of the inherent unreliability of COHb levels in predicting outcome researchers are investigating other surrogate markers. Rats have early i in glutathione release from erythrocytes, a potential marker for CO oxida stress that ultimately could lead to brain injury.[238] Another promising ma serum S100B, a structural protein in astroglia that is released from the b after hypoxic stress.[22] A series of 38 consecutive patients poisoned with showed that those who presented with normal neurologic findings and no consciousness had normal S100B levels. Patients who presented with loss consciousness and neurologic deficits all had elevated levels.[28] However, studies have failed to find a difference between CO-poisoned patients and controls with respect to such markers (ie, S100B protein and neuron-spe enolase).[194]

Neuropsychological Testing

The extent of neurologic insult from CO can be assessed with a variety of The most basic is documentation of a normal neurologic examination with miniâ€“mental status examination. A more sensitive indicator of the acut effects of CO on cortical function is a detailed neuropsychological test ba developed

specifically for CO patients.[165] The advantages of such testing, which usu takes approximately 30 minutes, are that the test (1) can reliably disting 79% of the time between CO-poisoned patients and controls, and (2) sho improvement with appropriate HBO treatment.[152] Unfortunately, such tes has a sensitivity of only 77% and specificity of 80% for CO poisoning.[199] addition, practice effects may be observed if repeated testing is performe Another study suggested that the degree of impairment displayed by CO on a test of short-term rote and context aided verbal memory correlated with the number of HBO treatments needed.[150] The biggest problem with neuropsychiatric testing is the uncertainty as to whether deficits in the te

during the acute CO poisoning phase are at all predictive of the developm neurologic sequelae and therefore the need for HBO treatment.

Neuroimaging

Acute changes on CT scan of the brain occur within 12 hours of CO expos resulted in loss of consciousness.[119 , 155 , 170] Symmetric low-density are the region of the globus pallidus, putamen, and caudate nuclei are frequ noted.[111 , 123 , 170] Although a normal initial CT scan usually predicts a favorable outcome, changes in the globus pallidus and subcortical white early on the first day after poisoning are associated with poor outcomes (120-1).[155 , 192] The corollary to this finding is that, in a series of 18 pa negative CT within 1 week of admission was associated with favorable outcome.[246] The use of contrast may enhance early isodense changes no on initial CT scan.[268] MRI appears to be superior for detecting basal gan lesions after CO poisoning.[108 , 120] One study found a much higher incide periventricular white matter changes on MRIs performed on the first day exposure. However, such changes had no correlation with COHb level or cognitive sequelae.[182] Diffusion-weighted MRI may have more promise in detecting changes in subcortical white matter within hours of serious CO poisoning.[225] Regardless, neuroimaging usually does not influence patien management and its use reserved for patients who show poor response o an equivocal diagnosis.

The most promising area of neuroimaging after CO poisoning is in assess regional cerebral perfusion. Single-photon emission computed tomograph (SPECT) gauges regional blood flow noninvasively using an iodine or tech tracer.[61] In a series of 13 patients with delayed neurologic sequelae, all showed patchy hypoperfusion throughout the cerebral cortex within 11 da poisoning.[46] These changes in perfusion can occur as early as one day af poisoning and primarily involve watershed regions such as the temporoparietooccipital area.[61] Xenon-enhanced CT, which may be more available, appears to parallel perfusion changes noted on SPECT scanning Perfusion defects on SPECT scanning appear to be associated with neuropsychological impairment months after serious CO poisoning.[44 , 74

Unfortunately, because of the scant availability of the procedure and the comprehensive studies, SPECT scanning is not the definitive tool for dete prognosis or need for HBO at this time.

Positron emission tomography (PET) also can be used for assessing regio blood flow and oxygen metabolism in the brain after CO exposure. In a s severely CO-poisoned patients, PET examination after HBO treatment sho increased oxygen extraction and decreased blood flow in the frontal and temporal cortices.[58] Of note, patients with permanent deficits persisted i showing these abnormalities on PET scanning. One delayed PET study demonstrated that increases in dopamine D_2 receptor binding in the caud putamen after CO poisoning were improved with bromocriptine, at which neuropsychiatric symptoms resolved.[267] Although PET scanning cannot be to predict outcome, abnormalities that persist on the scan may be indicat patients with permanent neurologic sequelae.

To complement perfusion studies, EEG mapping has been performed on C poisoned patients. Although initial studies demonstrate that many patient regional EEG abnormalities after poisoning, whether these abnormalities predictive of persistent or delayed neurologic problems is unknown.[61 , 65] mapping may be discrepant relative to SPECT scanning, as EEG preferen demonstrates subcortical lesions.[61]

Management

The mainstay of treatment is initial attention to the airway. One hundred oxygen should be provided as soon as possible by either non-rebreather mask or endotracheal tube. It is important to remember that a non-rebre mask delivers only 70â€“90% oxygen; a positive pressure mask or an endotracheal tube is necessary to achieve higher oxygen concentrations.[3] immediate effect of oxygen is enhancement of the dissociation of COHb.[2] volunteers, the COHb half-life is reduced from a mean of 5 hours (range hours) when breathing room air (21% oxygen) to approximately one hou 36â€“137 minutes) when breathing 100% oxygen at normal atmospheric pressure.[181 , 189] Actual poisonings show a range in half-lives of 36â€“13 minutes (mean 85 minutes) when breathing 100% oxygen; the longer

elimination half-lives appear to be most often associated with long, low-l exposures.[116 , 164 , 260] With oxygenation and intensive care treatment, mortality rates for serious exposures range from 1.0â€“30%.[13 , 75] The of treatment is unclear, with a valid endpoint being resolution of symptor usually accompanied by COHb <5%.[112]

Cardiac monitoring and intravenous access are necessary in any patient v systemic toxicity from CO poisoning. Hypotension initially can be treated intravenous fluids. Inotropic agents may also be necessary to treat myoc depression.[143] Evaluation for cardiac ischemia, including ECG and cardiac enzyme concentrations, should be considered in symptomatic patients at Standard advanced cardiac life support protocols for treatment of life- threatening dysrhythmias can be followed. A rapid bedside blood glucose should be performed in patients with depressed mental status. Animal stu CO poisoning suggest that hypoglycemia can be deleterious.[185 , 186 , 188] Correction of any acidemia with bicarbonate is controversial and could res further cellular injury secondary to a left shift of the oxyhemoglobin diss curve.

Hyperbaric Oxygen

HBO therapy appears to be the treatment of choice for patients with sign CO exposures.[71 , 174] At 2.5 atmospheres absolute (ATA), the half-life of is reduced to 20 minutes.[181 , 189 , 203] Actual CO-poisoned victims treated HBO have half-lives ranging from 4â€“86 minutes.[164] HBO also increases amount of dissolved oxygen by approximately 10 times, which alone is s to supply metabolic needs.[20] However, this situation is rarely an importa clinical issue because most patients have already been stabilized, have appreciably decreased COHb with

ambient oxygen alone, and have the time required for transport to an HB facility.

N
343

65
26
191
152
Double blind
No
No
No
Yes
Yes
Syncope (%)
0
0
0
53
53
Suicide (%)
0
Unknown
Unknown
69
31
Treatments
1
1
2
3â€“6
3
Time to treatment (h)
<12
2 = 0.2
<2
7.1
5.8 Â± 2.9

Lost to followup (%)
10
11
~35
54
2
Time to followup (mo)
1
1
0.75
1
1.5
HBO benefit
No
Yes
Yes
No
Yes

Study Raphael[193] Thom[241] Ducasse[65] Scheinkestel[205] Wea

TABLE 120-3. Summary of Randomized Clinical Trials of Hyperb
Oxygen in Carbon Monoxide

HBO is more than just a modality for clearing COHb more quickly than ar
oxygen. More importantly, in rats following loss of consciousness from CO
exposure, hyperbaric, but not normobaric, oxygen therapy prevents brain
peroxidation.[226] HBO appears to prevent ischemicâ€“reperfusion injury by
variety of mechanisms. First, in animal models, HBO accelerates regenera
inactivated cytochrome oxidase, which may be the initiating site for CO r
damage.[26] Second, HBO prevents subsequent leukocyte adherence to bra
microvascular endothelium, a process essential for amplification of centra
nervous system damage from CO.[41 , 229] This may explain why HBO, but
100% oxygen at atmospheric pressure, prevented delayed deficits in a le

and memory maze model.[247]

Clinical studies of the effectiveness of HBO in preventing neurologic dama from CO are not as convincing as basic science studies would suggest. In uncontrolled human clinical series, the incidence of persistent neuropsyc symptoms, including memory impairment, ranged from 12â€“43% in pati treated with 100% oxygen and was as low as 0â€“4% in patients treated HBO.[89 , 149 , 167 , 174 , 214]

Several controlled clinical trials have evaluated the efficacy of HBO in CO poisoning (Table 120-3). The first randomized study of CO poisoning had than 300 patients and failed to show a benefit from HBO in patients who initial loss of consciousness.[193] Unfortunately, seriously ill patients were randomized to surface pressure oxygen; they received either one or three treatments. Flaws in that study included significant delays to treatment a of suboptimal pressure of 2.0 ATA. A smaller (n = 60), more recent cont study avoided some of these flaws and showed that HBO was able to dec delayed neurologic sequelae from 23% to 0% in CO-poisoned patients wi loss of consciousness.[241] However, all patients with syncope, a marker of serious poisoning, were excluded. A very small study (n = 26) of patients presenting with GCS >12 after CO poisoning included almost half with los consciousness.[65] Randomization to HBO versus 100% normobaric oxygen resulted in decreased EEG abnormalities and less reduction in blood flow reactivity to acetazolamide at 3 weeks. Unfortunately, all of these studies to definitively study all CO-poisoned patients, including those with syncop coma.

The first randomized trial to really address the issue of HBO efficacy in s CO-poisoned patients was completed with 191 patients.[205] All CO-poisone patients referred for HBO treatment were randomized to a minimum of 3 treatments of HBO (2.8 ATA for 60 minutes) or 100% oxygen at 1.0 ATA. Although the HBO group had a higher incidence of persistent neurologic at 1 month, there was no significant difference between the 2 groups; mo two thirds of each group had persistent problems. This study is the larges controlled, randomized study to date but has several flaws.[157] Fewer than the patients had follow-up at 1 month. Disproportionate numbers of suici

cases (approximately two thirds) and drug toxicity (44%), with accompa neuropsychological defects, could have confounded any beneficial effect HBO. Finally, HBO treatment was delayed for more than 6 hours, making treatment much less likely to be effective.[89 , 193]

The most recent randomized, doubleâ€“blind, controlled study showed a beneficial effect of HBO in CO-poisoned patients.[259] Most of these patient ill, with a mean initial COHb level of 25% and a 50% incidence for loss of consciousness. Patients were all treated within a 24-hour window after e but the success of the study might stem from the <2-hour mean time to treatment. Patients were treated 3 times at intervals of 6â€“12 hours, ea 2.0 ATA, except for the first hour of the first treatment, which was at 3.0 Control patients received sham treatments in the HBO chamber with 100 oxygen at 1.0 ATA. At 6 weeks, the HBO group had a 24% incidence of c sequelae versus 46% in the control group. Based on these data, the numb patients needed to treat in order to prevent one case of cognitive impairm only five. Critics of this study point out that the neuropsychiatric tests we significantly different between the groups except for digit spam and trail in addition, there was no difference in activities of daily living. However, authors' defense, patients had increased self-reported memory problems a weeks (28% vs. 51%), and the beneficial effect on cognitive sequelae las into 12 months.

Based on these studies, it is not surprising that the Underwater and Hyp Medical Society recommends HBO treatment for any CO patient with signs serious intoxication.[71] Given the low risk associated with this procedure,[2] almost 1500 patients in the United States are treated with HBO for CO p each year.[97] Therefore, HBO has become the standard of care for serious poisoning despite the lack of evidence-based guidelines for patient select

Indications for Hyperbaric Oxygen Therapy

Specific indications for HBO after acute CO poisoning are listed in Table 1 but these indications have not been prospectively evaluated. The patients likely to benefit are those most at risk for persistent or delayed neurolog sequelae, such as those presenting

in coma.[125, 214, 266, 271] Another potential marker for delayed neurolog sequelae is a history of syncope.[45, 75, 154, 215] This may represent the episode of hypotension that is necessary for causing neuronal damage fro induced ischemicâ€“reperfusion injury in animal models.[84, 177] However, syncope is neither an extremely sensitive nor specific marker for cognitiv sequelae.[259] Patients with long exposures, or â€œsoakingâ€• periods, al at greater risk for neurologic sequelae.[21, 258] The presence of significant metabolic acidosis may be a surrogate marker.[135, 216, 251] Some autho advocate ongoing myocardial ischemia as an indication for HBO; however, experience, these patients usually already meet neurologic criteria for tr (eg, loss of consciousness, ongoing mental status changes). More import isolated cardiac ischemia deserves immediate proven myocardial salvagin therapy rather than delayed treatment with an unproven therapy such as

Syncope
Coma
Seizure
Altered mental status or confusion
Carboxyhemoglobin >25%
Abnormal cerebellar examination
Fetal distress in pregnancy

TABLE 120-4. Suggested Indications for Hyperbaric Oxygen

Some authors advocate HBO treatment for all patients with COHb levels â‰¥40%.[112, 160] Many HBO centers arbitrarily use a more conservative of 25% as an indication for HBO treatment. More important than actual le patient history and examination. Further analysis of data from the most controlled trial[259] demonstrates that in patients not treated with HBO, no factorsâ€”COHb level, loss of consciousness, or base excessâ€”reliably p who progressed to cognitive sequelae (L. Weaver, Personal Communicatio March 2005). Therefore, at this time it would be prudent to refer for HBO treatment those patients with the most serious neurologic symptoms, re

of COHb level. Symptoms include coma, seizures, focal neurologic deficits altered mental status, and, although controversial, loss of consciousness. group of patients who probably could be excluded from HBO therapy are who experienced a cardiac arrest from CO; these cases have been univer fatal.[99]

Whether mild neurologic symptoms (eg, confusion, headache, dizziness, blurring) or abnormal mental status testing on initial presentation after C poisoning is prognostic for cognitive sequelae is unclear. These symptoms represent CO poisoning, which, at COHb levels approaching 10% in volur can cause temporary impairment of learning and memory.[4] In a prospect clinical trial of CO poisoning, the incidence of cerebellar dysfunction porte higher incidence of cognitive sequelae (odds ratio 5.7 [95% confidence i 1.7â€“19.3]).[259] Therefore, difficulty with finger-to-nose, heel-to-shin, r alternating hand movements, or even ataxia, should all be considered in for HBO. Patients with other mild neurologic findings (eg, headache) warr least several hours of oxygen by non-rebreather face mask until sympton resolve. If symptoms do not resolve, HBO can be considered; however, a delay in HBO may decrease its efficacy.[89]

Some authors recommend selective use of HBO because of cost and diffic transport if the primary facility lacks a chamber.[178] However, complication can make such transfers and treatment unsafe are rare.[213] Although HBO be recommended for every patient with CO poisoning, it is a relatively sa treatment that should be considered in all serious exposures. Fortunately without HBO, anywhere from one third to three fourths of cases with per cognitive sequelae resolve over the subsequent year.[45 , 259]

Delayed Administration of Hyperbaric Oxyg

The optimal timing and number of HBO treatments for CO poisoning are Patients treated more than 6 hours after exposure tend to have worse ou in terms of delayed sequelae (30% vs. 19%) and mortality (30% vs. 14% This may explain the failure of one of the first randomized trials on HBO i which had a mean time to treatment of more than 6 hours after poisoning Meanwhile, HBO treatments delivered within 6 hours after poisoning in p

with loss of consciousness after CO seem to almost completely prevent neurologic sequelae.[168, 271] However, patients may benefit if treated ev later. In the most recent randomized clinical trial showing beneficial effec HBO, although all patients were treated within 24 hours of exposure, only of patients were treated after more than 6 hours. Therefore, it is not unreasonable to consider HBO, contingent on transport limitations, within hours of presentation for symptomatic acute poisoning.

One case series suggests beneficial effects for HBO used up to 21 days postexposure, once patients have developed neuropsychological sequelae The problem with studies showing HBO benefits days after an acute poisc after chronic poisoning, is that these cases are all anecdotal and lack cor In fact, almost all cases of delayed neurologic sequelae resolve within 2 in mild poisoning,[241] and one third resolve within 1 year of serious CO p that survives to HBO treatment.[259] The benefits in delayed or chronic cas simply represent the salutary effects of HBO. A preliminary study shows HBO improves memory scores temporarily by >50% in normal (nonpoisor volunteers.[115]

Repeat Treatment with Hyperbaric Oxygen

A randomized clinical trial demonstrated that three HBO treatments within first 24 hours improves cognitive outcome.[259] Unfortunately, no group wa treated with only one or two HBO sessions. Regardless, some authors ad multiple treatments for patients who have persistent symptoms, particula coma, and do not clear after their first HBO session.[59] In a nonrandomize retrospective study, CO-poisoned patients who received a second HBO tr had a reduction in delayed neurologic sequelae from 55% to 18% compar controls who had only one treatment.[88] Prospective studies comparing si versus multiple courses of HBO therapy failed to confirm any benefit from repeated HBO treatment; therefore, multiple treatments cannot be recon at this time.[193] The most recent clinical guidelines from the Underwater a Hyperbaric Society state that the optimal number of HBO treatments for poisoning is unknown at this time, and that multiple treatments should be reserved for patients who do not fully recover after one treatment.[71]

Treatment of Pregnant Patients

The management of CO exposure in pregnant patients is difficult because potential adverse effects of both the xenobiotic and its treatment. A liter review of all CO exposures during pregnancy revealed a high incidence of central nervous system damage and stillbirth after severe maternal poisonings.[254] A series of three severely symptomatic patients who did n receive HBO

had adverse fetal outcomes: two stillbirths and one case of cerebral palsy Cases of limb malformations, cranial deformities, and a variety of mental disabilities in children poisoned in utero are reported.[32 , 140] Although neurologic sequelae have been noted after severe acute exposures, a retrospective case control study showed no association between CO expos the last trimester and low birth weight.[1]

Traditionally, it was thought that fetal hemoglobin had a high affinity for Studies of pregnant ewe show a delayed but substantive rise in COHb lev the fetus exceeding the level and duration of that in the mother.[142] Thus, appears that the fetus is a sink for CO and could be poisoned at levels lo than the mother. However, such data may not apply to humans because i work shows that, as opposed to sheep, human fetal hemoglobin actually l affinity for CO than maternal hemoglobin, at a ratio of 0.8.[68] The more important issue with maternal CO exposure is the precipitous drop in feta arterial oxygen content that occurs within minutes at levels of 3000 ppm. Therefore, the ensuing hypoxia of the fetus, rather than the increase in f COHb, is of concern.

Maternal COHb levels do not accurately reflect fetal hemoglobin or tissue levels.[53] In primate studies, a single CO exposure insufficient to cause cl disease in the mother led to intrauterine hypoxia, fetal brain injury, and increased rate of fetal death.[83 , 84] A few cases of fetal demise, with ext low maternal COHb levels (ie, less <10%), are reported in humans.[32] Par problem is that some mothers in the series were treated with oxygen prio determination of their COHb level. In one case of fetal loss, the fetus had

higher levels than the peak COHb of 24% measured in the mother.[55] Ano issue with some of these data is that the mothers often had been chronic â€œsoakedâ€• with CO, making levels difficult to interpret. Rodent studi that chronic low-level CO exposure in pregnant mothers can result in per cognitive deficits in the subsequent progeny.[144]

Because maternal COHb does not necessarily predict fetal demise, clinicia must direct their attention to maternal symptoms of CO toxicity. Multiple series demonstrate that pregnant women who present with normal menta and no loss of consciousness have excellent outcomes in terms of normal deliveries.[32 , 127 , 175] Their infants have no subsequent delay in attainin developmental milestones.[127] Therefore, it appears that mothers who ap well after acute CO poisoning will have good pregnancy outcomes.

The bigger dilemma facing the clinician is the approach to treatment of s symptomatic CO-poisoned pregnant patients. All mothers should receive oxygen by face mask, at least until symptoms resolve. Some authors rec longer oxygen therapy. The problem is that CO absorption and eliminatior slower in the fetal circulation than in the maternal circulation.[83 , 141] A mathematical model predicts that elimination of CO from the fetus takes times longer than maternal CO elimination.[105] However, based on the fac some of these data are based on sheep fetal hemoglobin kinetics, the op time for treatment of the mother cannot be recommended at this time.

For more ill pregnant patients with loss of consciousness or high COHb le HBO might be considered. Unfortunately, pregnant patients were excluded all prospective trials documenting HBO efficacy. In addition, treatment of pregnant patients with HBO is not without theoretical risk. Animal studies conflicting results on the effects of HBO on fetal development.[254] Some s showed that HBO causes developmental abnormalities in the central nerv cardiovascular, and pulmonary systems of the rodent fetus.[153] This is in contrast to the extensive Russian experience, in which hundreds of pregr women treated with HBO apparently had no significant perinatal complica and showed improvement in fetal/maternal status of their underlying cor (eg, toxemia, anemia, diabetes).[156] Cases of HBO use for mild CO poison the United States have resulted in normal infants at birth.[66 , 106 , 127 , 2

However, less than optimal outcomes have occurred in sicker cases where mother had loss of consciousness or presented in coma.[66] Thus, it appear HBO should be safe and have the same efficacy for pregnant patients as i nonpregnant patients. However, its effect in preventing adverse fetal out is unclear.

There currently is no scientific validation for an absolute level at which to provide HBO therapy for CO exposure in pregnant patients. Arbitrarily, CO levels >20% have been touted as an indication in pregnant patients rega of symptoms.[254] Pregnant patients should not be treated any differently i meet the criteria for HBO therapy (Table 120-4). Additional criteria inclu signs of fetal distress, such as abnormal fetal heart rate.

Treatment of Children

Children have been suggested to be more sensitive to the effects of CO b of their increased metabolic rate.[57] Epidemiologic studies suggest that ch can become symptomatic at COHb levels <10%, which is lower than com expected in adults.[126] The other problem is that children may have unusu presentations. Most children manifest nausea, headache, or lethargy.[57] H an isolated seizure or vomiting may be the only manifestation of CO toxic an infant or child.[104]

When drawing COHb levels in infants, clinicians must be aware of two confounding factors. First, many cooximeters can give falsely elevated CO levels, in proportion to the amount of fetal hemoglobin present.[256] Second produced during breakdown of protoporphyrin to bilirubin. Therefore, infa normally have higher levels of COHb that are even higher in the presence kernicterus.[219 , 257] Thus, before an elevated COHb level is assumed to b poisoning in an infant, the contribution of jaundice and fetal hemoglobin considered in the final analysis.

Although children may be more susceptible to acute toxicity with CO, the term outcomes appear to be more favorable than the outcome in adults. I series of 2360 serious CO cases, all incidences of delayed neurologic seq were in adults older than 30 years.[45] Two series of CO poisoning in childr

demonstrated an approximately 10% incidence of delayed neurologic seq after severe CO poisoning.[124, 151] This low incidence in patients treated with 100% oxygen at 1.0 ATA has been used as an argument against HBO therapy.[151] However, there still is a real risk of sequelae, which are succ prevented by HBO use.[201] If surface-pressure oxygen is used to treat a c is comforting to know that the COHb half-life is approximately 44 minutes is comparable to that in adults.[126]

Novel Neuroprotective Treatments

A variety of neuroprotective agents have been tested in animal models. T targeted primarily at preventing the delayed neurologic sequelae associat serious CO poisoning. One of the simplest treatments tested is insulin. Hyperglycemia has been shown to exacerbate neuronal injury from stroke during arrest situations. In CO poisoning of rodents, hyperglycemia is as with worse neurologic outcome.[188] However, insulin, independent

of its glucose-lowering effect, may be the protective agent after ischemia rodent studies, insulin treatment improved neurologic outcome after CO poisoning, as measured by locomotor activity.[263] In light of these findings reasonable to aggressively treat documented hyperglycemia with insulin i of serious CO poisoning.

Many neuroprotective xenobiotics involve blockage of excitatory amino ac are implicated in neuronal cell death after CO poisoning. Pretreatment of with dizocilpine (MK-801), which blocks the action of glutamate at NMDA receptors, ameliorates learning, memory, and hippocampal deficits result from CO poisoning.[114] Ketamine, another glutamate antagonist, decrease mortality of rats poisoned with CO after carotid ligation.[187] Posttreatment mice with various glutamate antagonists prevents learning and memory in a model of CO poisoning.[78, 244] Blockage earlier in the immunologic c using a neuronal NO synthetase inhibitor also prevented NMDA receptor activation, thus protecting mice from learning deficits after CO poisoning.[236] One exciting approach is the use of antioxidants, such as dimethyl su and disulfiram, which prevent learning and memory deficits when given a

poisoning in mice.[79, 80] Use of such related xenobiotics appears promisin awaits further animal testing because of potential adverse effects.

Other modalities for preventing neuronal damage from CO have been tes without much success. Hypothermia, rather than being beneficial, actuall increases mortality in animals.[183] Allopurinol given to prevent formation radicals through xanthine oxidase has been tested. This drug, when given pretreatment, prevents lipid peroxidation mediated by xanthine oxidase in poisoning.[228] This strategy has not been promising because of the need f pretreatment.

Prevention

Early diagnosis prevents much of the morbidity and mortality associated poisoning, especially in unintentional exposures. The increased quality of CO-detecting devices will allow personal intervention to prevent CO expo If a patient complains that his or her CO alarm sounded, realize that the threshold limit of the alarm is set to approximate a COHb level of 10% at Therefore, manufacturers must set their alarms to activate within 189 mi 70 ppm CO, 50 minutes at 150 ppm, and 15 min at 400 ppm (Underwrite Laboratories, UL2034). Alarms are not to activate for prolonged exposure ppm in order to prevent epidemic alarms during winter inversions in large cities.[19] Government ordinances for obligatory CO alarms potentially coul prevent many poisonings, particularly during winter storms.[37]

Routine laboratory screening of ED patients during the winter is not effic in diagnosing unsuspected CO poisoning. The yield is <1% when patients whom the diagnosis of CO exposure was already excluded by history are tested.[103, 250] Instead, selecting patients with CO-related complaints, su headache, dizziness, or nausea, increases the yield to 5â€“11%.[91, 250] D winter, risk factors such as gas heating or symptomatic cohabitants in pa with influenzalike symptoms (eg, headache, dizziness, nausea) will be the useful method for deciding when to obtain COHb levels in potential cases [101 and 102]

The issue of symptomatic cohabitants is especially important from a prev

standpoint. Alerting other cohabitants to this danger and effecting evacu may prevent needless deaths.[262] Most communities have multiple resourc on-site evaluation. Usually the local fire department or utility company ca either check home appliances or measure ambient CO levels with portable monitoring equipment. Current workplace standard for ambient CO expos 35 ppm averaged over 8 hours, with a ceiling limit of 200 ppm (measured 15-minute period).[172] Just a 4-hour exposure to 100 ppm CO can result i >10% with symptoms.[189] Until rescue personnel arrive, appliances fueled natural gas should be turned off and the area evacuated, leaving all wind doors open.

Summary

Unintentional exposures to CO can easily be misdiagnosed. Patients with suspected influenza should be screened for potential home sources of CO symptomatic cohabitants alerted. CO should be suspected in any patient coma, acidosis, or signs of cardiac ischemia, especially if attempted suicid suspected. Fire victims, in addition to suffering airway problems and pote cyanide toxicity, may die of CO toxicity.[15] In all these cases, the mainsta treatment is good supportive care with early oxygenation to increase CO elimination. Because of the overwhelming clinical successes with HBO and limited risks, early use of this treatment modality in severe exposures is encouraged. Discussion with a regional poison control center or hyperbar facility will help identify those patients most likely to benefit from such treatment.

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Antidotes in Depth

Hyperbaric Oxygen

Stephen R. Thom

Hyperbaric oxygen (HBO) therapy is a treatment modality in which a person breathes 100% O_2 while exposed to increased atmospheric pressure. Treatments are performed in either a monoplace (single person) or a multiplace (typically 2â€“14 patients) chamber. Pressures applied while patients are in the chamber usually are 2 to 3 atmospheres absolute (ATA), defined as the sum of the atmospheric pressure (1 atmosphere = 14.7 PSI) plus additional hydrostatic pressure equivalent to 1 or 2 atmospheres. Treatments typically last for 2â€“8 hours, depending on the indication, and may be performed 1â€“3 times daily. Monoplace chambers usually are compressed with pure oxygen. Multiplace chambers are pressurized with air, and patients breathe pure oxygen through a tight-fitting face mask, a head tent, or endotracheal tube. During treatment, the arterial oxygen tension typically exceeds 2000 mm Hg, and levels of 200â€“400 mm Hg occur in tissues.[130]

HBO should be viewed as a treatment modality and the hyperbaric

chamber as a dosing device. Elevating tissue O_2 tension is a primary effect. Although this may alleviate physiologic stress to hypoxic tissues, lasting benefits of HBO appear to relate to abatement of underlying pathophysiologic processes.

In the context of an antidote, HBO is most commonly used for treatment of carbon monoxide (CO) poisoning. Experience using HBO for life-threatening poisonings from cyanide (CN), hydrogen sulfide (H_2S), or carbon tetrachloride (CCl_4) and in patients with high methemoglobin levels is limited. HBO has been suggested for management of diverse poisonings, but discussion of these applications is beyond the scope of this Antidotes in Depth because of the absence of supporting clinical or experimental evidence.[138]

Therapeutic mechanisms of action for HBO are based on elevation of both hydrostatic pressure and the partial pressure of oxygen. Elevation of the hydrostatic pressure causes a reduction in the volume of gas according to Boyle's law. This action has direct relevance to pathologic conditions in which gas bubbles are present in the body, such as arterial gas embolism and decompression sickness. All perfused tissues are subjected to elevated partial pressures of oxygen in association with HBO exposure. Under normal environmental conditions, hemoglobin is virtually saturated with oxygen on passage through the pulmonary microvasculature, so the primary effect of HBO is to increase dissolved oxygen content of plasma. Application of each additional atmosphere of oxygen increases the dissolved oxygen concentration in the plasma by 2.2 mL O_2/dL (vol%) (Chap. 22).

Mechanisms of HBO relevant to its use as an antidote are its ability to diminish hypoxic stress by increasing tissue oxygen tension and its ability to accelerate production of free radicals. Elevated concentrations of free radicals have been demonstrated in persons exposed to hyperoxia, and specifically those undergoing HBO therapy. Humans exposed to 100% O_2 versus air have ~38%

more nitric oxide (â€¢NO) in their exhaled breath.[104] Hyperbaric hyperoxia appears to increase â€¢NO-containing substances in both the pulmonary and systemic vascular beds. *S*-nitrosohemoglobin concentration is approximately doubled in arterial and venous blood of rats exposed to 3 ATA versus 1 ATA O_2.[120] Ascorbate free radicals are found in erythrocytes taken from persons exposed to 2.7 ATA O_2 for 60 minutes. The concentration of radicals diminishes to baseline within 10 minutes following exposure.[85] Oxidative stress from HBO causes DNA single strand breaks by the comet assay, and they have been shown to occur in circulating leukocytes following exposure to 2.5 ATA O_2 for 60 minutes. This insult does not occur with subsequent treatments, however, because the first hyperoxic exposure leads to adaptive changes in cells, including induction of heat shock protein-32 (heme oxygenase-1).[35,36,99]

Free radicals are generally perceived as toxic agents, and to suggest that they be purposefully generated as part of an alleged therapy may seem an anathema. Yet intracellular production of â€¢NO appears to be the basis for the inhibitory effect of HBO on neutrophil adhesion.[128] Exposure to 2.8â€“3.0 ATA O_2 for 45 minutes temporarily inhibits neutrophil adherence mediated by the activation-dependent Î²$_2$-integrins on the neutrophil membrane. This effect initially was demonstrated in rodents and subsequently in human studies.[24,129,134] Similar findings with humans have since been corroborated by two other groups.[60,65] Neutrophils remain viable, the effect is reversible, and functions such as degranulation and oxidative burst to chemoattractants appear to be unaltered.[129,134] The ability of HBO to inhibit function of neutrophil Î²$_2$-integrins ameliorates reperfusion injuries of brain, skeletal muscle, and intestine, as well as smoke-induced lung injury, decompression sickness, and encephalopathy resulting from CO poisoning in animals.[5,75,125,126,129,137,142,145,153,154 and 155] Alterations of neutrophil adherence by HBO may be the basis for benefits shown in several human clinical trials. HBO reduces

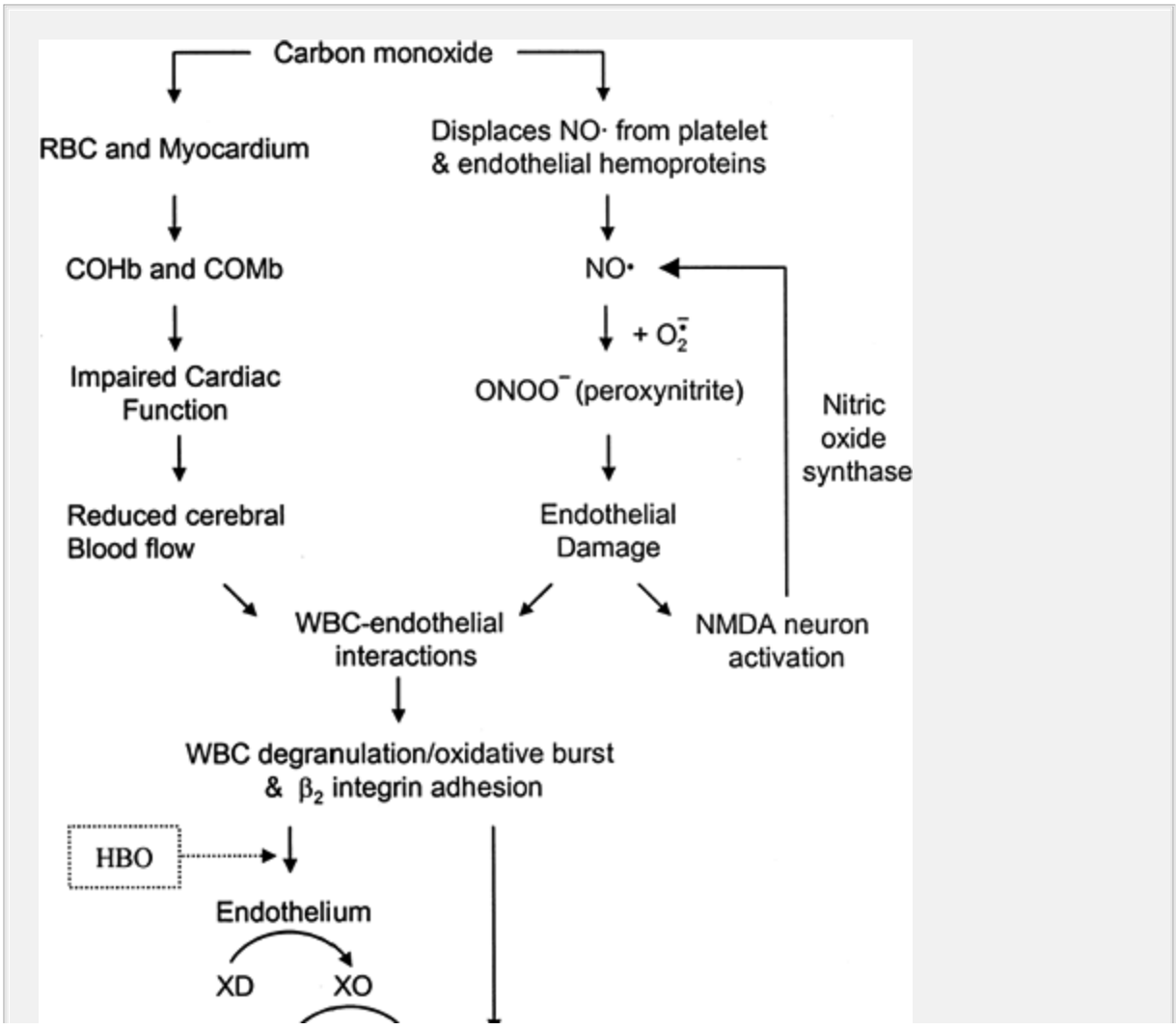
coronary artery restenosis after balloon angioplasty/stenting,[108,109] decreases muscle loss after thrombolytic treatment for myocardial infarction,[107,121] and reduces the incidence of CO-mediated encephalopathy.[150]

Administration of supplemental oxygen is the cornerstone for treatment of CO poisoning.[56] Its use is based on the affinity of CO for heme proteins and formation of carboxyhemoglobin (COHb). Elevated COHb can precipitate tissue hypoxia, and this stress appears to be responsible for fatalities, cardiac injuries, and the acute neurologic abnormalities that develop in approximately 14% of survivors of serious CO poisoning.[2,29,32,41] Oxygen inhalation hastens dissociation of CO from hemoglobin and provides enhanced tissue oxygenation. HBO causes COHb dissociation to occur at a rate greater than that achievable by breathing pure O_2 at sea-level pressure.[88] Additionally, HBO accelerates restoration of mitochondrial oxidative processes.[16]

Delayed neurologic sequelae are the most frequent form of CO-mediated morbidity. Studies indicate that between 23 and 46% of patients with CO poisoning develop impairments of concentration and learning, dementia, cog wheel rigidity, amnesia and/or depression, between 6 days and 7 weeks after poisoning.[25,43,54,78,79,84,95,135,150] Additional pathophysiologic mechanisms beyond COHb-mediated hypoxia are thought to exist for delayed neurological sequelae. COHb levels correlate poorly with clinical outcomes, and delayed neurological sequelae still occur even when CO poisoning appears to be relatively mild.[47,97,98,102,105,135] A number of clinical

studies using several different neuroimaging techniques on CO victims have found acute vascular abnormalities and atypical coupling between cerebral blood flow and neuronal O_2 demand.[37,73,112,115] This finding suggests that CO poisoning causes vascular injury.

Vascular abnormalities occur in animal models of CO poisoning. These changes precipitate neutrophil adherence, and activated neutrophils initiate a cascade of events that ultimately causes delayed neurologic dysfunction (Figure A34-1).[57,132,133] HBO inhibits CO-mediated neutrophil adherence and subsequent pathologic events.[129,131] Animals poisoned with CO and treated with HBO have more rapid improvement in cardiovascular status,[38] lower mortality,[90] and lower incidence of neurologic sequelae.[131] Benefits likely are based on both improved oxygenation and secondary effects pertaining to inhibition of neutrophil adhesion. These observations provide additional motivation for clinical use of HBO.



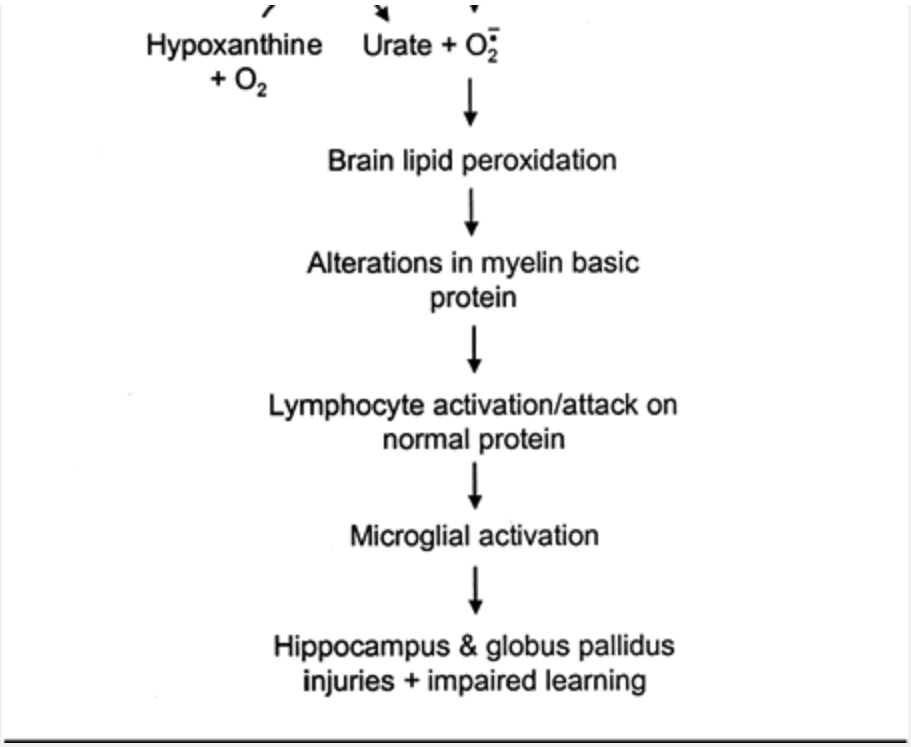


Figure A34-1. Cascade of events as identified in rat model of carbon monoxide poisoning.[57,132,133] COHb = carboxyhemoglobin; COMb = carboxymyoglobin; HBO = hyperbaric oxygen; NMDA = *N*-methyl-D-aspartate; NOÂ· = free radical nitric oxide; RBC = red blood cell; WBC = white blood cell; XD = xanthine dehydrogenase; XO = xanthine oxidase.

Since 1960, HBO has been used with increasing frequency for severe CO poisoning, as clinical recovery appeared improve beyond that expected with ambient-pressure oxygen therapy. Support for HBO use comes from this experience.[43,44,55,66,77,84,86,100] To date, six prospective studies have assessed the efficacy of HBO for acute CO poisoning.

The first prospective clinical trial involving HBO therapy failed to find HBO superior to ambient-pressure treatment.[95] This study has

been criticized because the authors used a low oxygen partial pressure (2 ATA) versus the more usual protocols with 2.5â€“3 ATA and because nearly half of the patients received hyperbaric treatments more than 6 hours after they were discovered.[15] In 1969, a retrospective study indicated that HBO reduced mortality and morbidity only if HBO was administered within 6 hours of CO poisoning.[44] HBO was effective in several prospective investigations. In a trial involving mildly to moderately poisoned patients, 23% of patients (7/30) treated with ambient-pressure oxygen developed neurologic sequelae, whereas no patients (0/30; $p < 0.05$) treated with HBO (2.8 ATA) developed sequelae.[135] In another prospective, randomized trial, 26 patients were hospitalized within 2 hours of discovery and were equally divided between 2 treatment groups: ambient-pressure oxygen or 2.5 ATA O_2.[37] Three weeks later, patients treated with HBO had significantly fewer abnormalities on electroencephalogram, and single-photon emission computed tomography (SPECT) scans showed that cerebral vessels had nearly normal reactivity to carbon dioxide, in contrast to diminished reactivity in patients treated with ambient-pressure oxygen.

A fourth trial randomized 191 CO-poisoned patients of different severity to daily HBO (3.0 ATA for 60 minutes) with intervening high-flow oxygen for 3 or 6 days versus high-flow normobaric oxygen for 3 or 6 days.[103] The outcome measure was neuropsychological testing after treatment one month later, and no benefit from HBO was documented. Multiple flaws in the design and execution of this study are discussed in the literature, so it is impossible to draw meaningful conclusions from the data.[48,82] For example, the CO poisonings were suicide attempts in 69% of the cases, and half of the patients had also ingested alcohol or other drugs. The presence of depression and psychoactive substances in many of the patients may have confounded the results of neuropsychological testing. Neither the HBO nor the normobaric oxygen protocol followed standard treatment recommendations,

and both regimens were potentially toxic. Finally, less than half (46%) of the patients completed the followup examination at one month.

One randomized trial has been reported only in abstract form at this time. This trial is the only multicenter study of treatment of CO poisoning.[78] At an interim analysis, 575 patients had been randomized to HBO treatment (90 minutes of O_2 at 2.5 ATA) versus 12 hours of normobaric oxygen administration. All patients were followed serially for one year. At three months, neurologic sequelae were significantly less in the HBO_2 treatment group (8.7%) than in the normobaric oxygen (NBO) group (15.2%, p = 0.016). The difference lessened by 6 months (6.4 vs. 9.5%; p = 0.09) and disappeared by 12 months.

Finally, a double-blind randomized trial demonstrated that HBO therapy reduces the incidence of neurologic sequelae after acute CO poisoning.[150] In this study, patients were stratified by age >40 years or <40 years, time to end of CO exposure, starting

treatment >6 hours or <6 hours, and history of unconsciousness. All patients were treated 3 times at 6- to 12-hour intervals in a monoplace chamber. CO poisoning questionnaires, functional outcome evaluations, and the neuropsychological test battery were given 2 weeks, 6 weeks, 6 months, and 12 months after CO poisoning. Cognitive sequelae were considered present if any 6-week neuropsychological subtest score was >2 standard deviations below the mean or if at least 2 subtest scores were each >1 standard deviation below the mean of demographically corrected standardized scores.

The pretreatment characteristics of the 152 patients enrolled in the trial were similar except that cerebellar dysfunction was more frequent in the NBO treatment group. The mean COHb was 25%, and 49% of the patients had sustained an interval of unconsciousness. The group treated with HBO had a lower

incidence of cognitive sequelae than the group treated with NBO after adjustment for prechamber cerebellar dysfunction and stratification (odds ratio 0.45, 95% confidence interval 0.22â€“0.92, p = 0.03). Post hoc subgroup analysis incorporating risk factors for which HBO therapy is generally recommended showed that HBO reduced cognitive sequelae in patients with any of the following: unconsciousness, COHb â‰¥25%, age â‰¥50 years, or base excess â‰¤2 mEq/L. HBO did not improve outcome in patients with none of these criteria.

HBO treatment of acute CO poisoning rests on a solid scientific rationale, basic science research, and randomized controlled clinical trials. However, important caveats remain for future investigations. As yet no objective method is available for staging the severity of CO poisoning, although preliminary reports suggest plasma markers may be used in the future.[17] Psychometric screening tests have not proved reliable because abnormalities during the initial screening do not correlate with development of delayed sequelae.[135] Along similar lines, the etiology and risk factors for delayed neurologic syndrome are unknown. Animal evidence suggests that the oxidative stress triggered by neutrophil adherence/activation in the cerebral vasculature causes brain lipid peroxidation, which has been linked to delayed neuropathology because it precipitates an adaptive immunologic response to normal and abnormal brain protein.[132,133] CO can also cause late programmed cell death in the brain.[91]

The optimal dose of HBO (ie, number of treatments and treatment pressure) and the time after which it is no longer effective therapy are not clearly defined. Randomized trials have treated patients as soon as possible after CO poisoning based on work suggesting the existence of a 6-hour window of greatest opportunity.[44] However, it is possible that the time of potential benefit goes beyond what has been investigated for some patients. The requisite number of treatment also remains unclear. Finally, the mechanisms of action remain unclear. Action for HBO therapy in CO poisoning may

include hastened dissociation of CO from hemoglobin and from cytochrome oxidase and temporary inhibition of leukocyte adhesion molecules to blunt the cascade of vascular injury.[16,88,129] Clinical indications for HBO in CO poisoning are reviewed in greater detail in Chap. 120 and specifically in Table 120-3.

Methylene Chloride

Methylene chloride (CH_2Cl_2) is an organic solvent used commercially in aerosol sprays, as a solvent in plastics manufacturing, photographic film production, and food processing, as a degreaser, and as a paint stripper. It is readily absorbed through the skin or by inhalation. It is metabolized by the cytochrome P450 oxidase system to yield CO.[123] This process is slow, and peak COHb levels of 10â€“50% may not be reached for 8 hours or more.[22,23,39,61,67,73,74,114,123] Methylene chloride toxicity can have many of the same acute manifestations as CO poisoning.[119] Acute signs and symptoms are attributable to the direct effects of this solvent on the central nervous system and to concomitant hypoxia. Effects that are present after 1 hour or more, especially if the COHb level is elevated, may be partially caused by CO toxicity. Treatment with HBO in this setting is reported.[53,101]

Combined Carbon Monoxide and Cyanide

CO and CN poisonings can occur concomitantly in victims of smoke inhalation.[3,4,7,8 and 9,11,26,31,64,70,72,80,113,116,147,151] Experimental evidence suggests that these xenobiotics can produce synergistic toxicity.[6,83,87,88,92] Toxicity from CN stems from binding to cytochrome a-a_3 thereby inhibiting oxidative phosphorylation. Animal studies demonstrate that ambient-

pressure 100% O_2 can enhance protection from CN toxicity[110] and also can enhance CN metabolism to thiocyanate when thiosulfate is used concomitantly.[13] HBO may have direct effects on reducing CN toxicity[30,58,59,117,127] or augmenting antidote treatments.[21,110,149] However, not all animal studies have found HBO improved outcome,[148] and clinical experience regarding CN treatment with HBO is sparse.[2] In a series of smoke-inhalation victims with both toxic CO and CN levels who received both HBO and treatment for CN involving sodium nitrite and sodium thiosulfate, 4 of 5 patients survived without apparent neurologic damage.[51] Clinical case reports where HBO was used along with standard antidote treatment (sodium nitrite plus sodium thiosulfate) for isolated CN poisonings are equivocal.[42,69,106,139] One case showed dramatic improvement,[139] but another showed no response.[69] Further research in this area is necessary. Because CN is among the most lethal poisons and toxicity is rapid, standard antidotal therapy for isolated CN poisoning is of primary importance. Hyperbaric oxygen may be an adjunct for consideration in refractory cases (Chap. 121).

Hydrogen Sulfide

Hydrogen sulfide (H_2S) binds to cytochrome a-a_3 and impairs oxidative phosphorylation. Hence, one of its mechanisms of toxicity is similar to that of CN, although it is more readily dissociated from cytochrome oxidase by O_2.[124] Clinical manifestations of toxicity are similar to those with CO and CN.[124] Management of patients with serious H_2S poisoning principally involves oxygenation and cardiovascular support, as well as consideration of sodium nitrite.[46] HBO may be more effective than sodium nitrite in preventing mortality in animals.[12] In several instances, HBO appeared to be beneficial.[20,45,119,152] Relatively late treatment with HBO (ie, â‰¥10 hours after poisoning) is reported to be beneficial in some[144] but not all cases.[1] No definitive data regarding use of HBO for H_2S poisoning are

available, but HBO should be considered in refractory cases.

Carbon Tetrachloride

Carbon tetrachloride (CCl_4) hepatotoxicity may be diminished by HBO. Mortality was decreased in a number of animal studies,[10,19,81,96]

and there are several case reports of patients surviving potentially lethal ingestions with HBO therapy.[68,122,140,156] HBO appears to inhibit the mixed-function oxidase system responsible for conversion of CCl_4 to hepatotoxic free radicals.[18,76] Because there are no proven antidotes for CCl_4 poisoning, HBO should be considered for potentially severe CCl_4 exposures. However, there may be a delicate balance between oxidative processes that are therapeutic and those that mediate hepatotoxicity.[14] Therefore, when HBO is being considered, it should be instituted before the onset of liver function abnormalities.

Patient Management

A fundamental aspect to emergency patient management and treatment is the knowledge and training of the healthcare team. Hyperbaric treatment centers typically have the ability to manage patients who require critical care support. Plans for treatment begin while the patient is still in the emergency department, before transport to the hyperbaric chamber is initiated. Issues to be addressed include informed consent, determination that all intravenous/arterial lines and nasogastric tubes/Foley catheters are secured, capping all unnecessary intravenous catheters, placing chest tubes to 1-way Heimlich valves, replacing air in endotracheal tube cuffs with water to prevent excessive air leakage at pressure, and adequately sedating or paralyzing the patient as clinically indicated. Substantial clinical experience demonstrates that patients can be transported without adverse

events.[118]

HBO therapy should never be considered unless proper supportive medical care can be delivered. Most chamber facilities today have equipment and treatment protocols analogous to an intensive care unit. Intensive care support for pediatric cases also can be achieved.[62,146] The inherent toxicity of O_2 and potential for injury resulting from elevations of ambient pressure must be addressed whenever HBO is used therapeutically. Preexisting conditions that require evaluation for possible management before initiation of HBO include claustrophobia, sinus congestion, and patients with scarred or noncompliant structures in the middle ear, such as otosclerosis.[63]

Middle ear barotrauma is the most common adverse effect of HBO treatment.[22] As the ambient pressure within the hyperbaric chamber increases, a patient must be able to equalize the pressure within the middle ear by autoinsufflation. When autoinsufflation fails, tympanostomy tubes must be placed. The incidence of tube placement is reported to be approximately 4% in one series.[28] Others report an overall incidence of aural barotrauma of between 1.2 and 7%.[93,141] Pulmonary barotrauma during HBO treatment is rare but should be suspected if any chest or hemodynamic alterations occur during, or shortly after, decompression. If pneumothorax is suspected, placement of a chest tube is appropriate. Preexisting pneumothorax should be treated with chest tube drainage prior to initiating therapy.

Biochemical toxicity resulting from O_2 can be manifested by injuries to the CNS, lungs, and eyes. CNS O_2 toxicity is manifested as a grand mal seizure and occurs at an incidence of approximately 1â€“4/10,000 patient treatments.[34,50,93] The risk is higher in hypercapnic patients and possibly in those who are acidotic or have compromise resulting from sepsis, as an incidence of 7% (23/322 patients) was reported in case series of HBO_2 treatment of gas gangrene.[33,49] Pulmonary insults can impair

mechanics (elasticity), vital capacity, and gas exchange (reviewed in reference 56). These conditions typically do not arise when standard treatment protocols are followed.[27,40,52,94] There is one report of reversible small airways changes in 4/21 patients treated daily for 90 minutes at 2.4 ATA for 21 days.[136] Progressive myopia may occur in patients undergoing prolonged daily therapy but typically reverses within 6 weeks after treatments are terminated.[71] Excessive treatments, exceeding a total of 150â€“200 hours, are associated with development of nuclear cataracts.[89] Although there is a theoretical risk for retrolental fibroplasia in neonates, experimental and clinical evidence does not indicate that typical HBO therapy protocols have detrimental effects on neonates or the unborn fetus.[143] As with any environment having an elevated concentration of O_2 there is a fire hazard, so scrupulous attention must be devoted to avoiding an ignition source. Over the past 20 years, no fires resulting in injury were reported in the United States, but 52 deaths were reported worldwide.[111] Virtually all these deaths were preventable. In 10 incidents, fire resulted when banned substances such as cigarettes and lighters were taken into the chamber.

In conclusion, the mechanisms of action and efficacy of HBO in toxicology continue to be investigated. Some research findings are provocative because they highlight the fact that traditional assessments of mechanisms for toxicity of some agents are incomplete. Questions persist on many issues. Further investigation is required to discern those cases where clear benefit arises with HBO treatment and to define the constraints that may limit its efficacious use.

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Chapter 121
Cyanide and Hydrogen Sulfide

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Cyanide

MW:	=	26.02 daltons
Whole blood:	=	<1 Âµg/mL
	=	38.5 Âµmol/L

Airborn

Immediately fatal	=	270 ppm
Life threatening	=	110 ppm >30 min

Hydrogen Sulfide

MW: = 34.08 daltons

Airborne concentrations:

Odor threshold = 0.02â€“0.13 ppm

Olfactory fatigue = 100â€“150 ppm

Immediately fatal = 700 ppm

Cyanide Poisoning

Case 1

A previously healthy 45-year-old chemistry professor was found unresponsive on the laboratory floor by his coworkers. They initiated cardiopulmonary resuscitation (CPR), with mouth-to-mouth breathing, until first responders arrived. Paramedics intubated the patient because of apnea. Prehospital vital signs were: blood pressure, 80 mm Hg by palpation; pulse, 110 beats/min. The patient did not respond to intravenous naloxone (0.8 mg) or dextrose (25 g). Systolic blood pressure increased to 100 mm Hg after bolus administration of 1000 mL 0.9% sodium chloride solution during transport. A telephone call to the emergency department (ED) prior to patient arrival reported that a partially empty 5-g vial of sodium cyanide was found on the patient's laboratory workbench, along with a suicide note.

Upon arrival to the ED, the patient was transferred to the decontamination room, where he was thoroughly irrigated with water while resuscitation was continued. The initial survey revealed a comatose man with vital signs of blood pressure, 90 mm Hg by palpation; pulse, 74 beats/min; rectal temperature 98.8Â°F (37.1Â°C); pulse oximetry 99% on 100% oxygen. The bedside rapid reagent glucose concentration was 276 mg/dL (after dextrose

bolus). A detailed physical examination was remarkable for dilated and sluggish pupils, roving ocular movements, occasional nonpurposeful movement, and bilateral decorticate posturing. The remainder of the examination was normal. Initial arterial blood gas (ABG) analysis showed pH, 7.01; PCO_2, 21 mm Hg; PO_2, 575 mm Hg on 100% oxygen. Whole blood lactate concentration was 10 mmol/L. The patient received 100 mEq sodium bicarbonate intravenously and the cyanide antidote kit, which included 300 mg sodium nitrite IV and 12.5 g sodium thiosulfate IV.

Serum electrolytes sent for analysis prior to antidote administration were normal except for serum bicarbonate 8.9 mEq/L. ECG revealed nonspecific ST changes. Computed tomography of the head was normal. Repeat ABG analysis and cooximetry 30 minutes after administration of the cyanide antidote kit demonstrated improvement in pH to 7.17 with a methemoglobin level of 6.5%. A second bolus of sodium thiosulfate and sodium nitrite was given at half the initial dose. The metabolic acidosis resolved over the next 12 hours. Serum acetaminophen, salicylate, toxic alcohol, and urine drug-abuse screens were negative.

The coworker who performed mouth-to-mouth assisted breathing on the patient also was evaluated in the ED. The coworker complained of dyspnea, palpitations, chest pain, near syncope, and tingling of his fingers and toes. On examination, he was anxious and tremulous, with vital signs of blood pressure, 156/95 mm Hg; pulse, 148 beats/min; respiratory rate; 48 breaths/min. Concern regarding the potential for oral mucosa absorption of residual cyanide during mouth-to-mouth resuscitation prompted the initial healthcare workers to consider administration of the cyanide antidote kit to the second patient.

However, the attending physician performed ABG analysis, which showed pH, 7.61; PCO_2, 14 mm Hg; PO_2, 575 mm Hg; bicarbonate, 25 mEq/L on a non-rebreather oxygen mask. The patient's symptoms resolved, and he was diagnosed with acute stress

reaction.

The remainder of the acute course of the patient who ingested the sodium cyanide was uneventful. At 5-month followup, however, he complained of difficulty with memory and limb stiffness. Physical examination revealed generalized bradykinetic movements consistent with secondary parkinsonism.

History and Epidemiology

In 1782, the Swedish chemist Carl Wilhelm Scheele first isolated hydrogen cyanide. He reportedly died from the adverse health effects of cyanide poisoning in 1786. Napoleon III was the first to use hydrogen cyanide as a chemical warfare agent. Hydrogen cyanide was used on the battlefield in World War I and later as a genocidal agent (Zyklon B) by the Germans during World War II.

The majority of reported cyanide exposures are unintentional (Chap. 130). These events frequently involve chemists or technicians working in laboratories where cyanide salts are common reagents.[22,31,53,54,77,156] The potential for cyanide poisoning also exists following smoke inhalation.[10,42,91,121,138] The combustion of materials such as wool, silk, synthetic rubber, and polyurethane releases cyanide.

Approximately 10% of documented cyanide exposures are suicidal in etiology (Chap. 130). Potassium cyanide (KCN) was used in the 1978 Jonestown mass suicide, in which more than 900 people died. Seven deaths resulting from consumption of cyanide-tainted acetaminophen occurred in 1982,[28] and a death from a cyanide-laced decongestant occurred in 1991.[40] Cyanide has also been used for illicit euthanasia.[25]

Ingestion of cyanogenic chemicals (eg, acetonitrile, acrylonitrile, and proprionitrile) is another source of cyanide poisoning.[21,34,38,151] Acetonitrile (C_2H_3N) and acrylonitrile (C_3H_3N) are themselves nontoxic, but biotransformation via cytochrome

P450 liberates cyanide (Figure 121-1).[161] Numerous reports of unintentional poisoning of children ingesting acetonitrile-based, artificial nail remover are published.[38,59,87,90]

Many plants, such as the *Manihot* spp, *Linum* spp, *Lotus* spp, *Prunus* spp, *Sorghum* spp, and *Phaseolus* spp contain cyanogenic glycosides.[146] The *Prunus* species (eg, apricots, bitter almond, cherry, and peaches) have pitted fruits containing the glucoside amygdalin (D-mandelonitrile-Î²-*d*-glucoside). When ingested, amygdalin is biotransformed by intestinal Î²-*d*-glucosidase to glucose, aldehyde, and cyanide (Figure 121-1). Laetrile, which contained amygdalin, was a purported antineoplastic available in the 1970s. It was administered as intravenous infusion, bypassing the necessary enzymes in the gastrointestinal tract to liberate cyanide, although when ingested it was associated with cyanide poisoning.[66] Despite data demonstrating its lack of utility in the treatment of cancer,[102] it still is available via the Internet.

Cassava (*Manihot esculenta*) root is a major source of food for millions of people in the tropics. It is a hardy plant that can remain in the ground for up to 2 years and needs relatively little water to survive. Because the shelf life of a cassava root is very short once it is removed from the stem, cassava root must be processed and sent to market as soon as it is harvested. However, proper processing must occur to assure the food's safety. Processed cassava is called *Gari.* Linamarin (2-hydroxyixo-buty-nitrite-Î²-D-glycoside) is the major cyanogenic glycoside in cassava roots. It is hydrolyzed to hydrogen cyanide and acetone in two steps during the processing of cassava roots.[159] Soaking peeled cassava in water for a single day releases approximately 45% of the cyanogens, whereas soaking for 5 days causes 90% loss.[3] If processing is inefficient, linamarin and cyanohydrin, the immediate product of hydrolysis of linamarin, remain in the food.[113,114] Consumed linamarin is hydrolyzed to cyanohydrins by Î²-glucosidases of the microorganisms in the intestines. Cyanohydrins present in the food and formed from linamarin then dissociate spontaneously to cyanide in the alkaline

pH of the small intestines.[3,6,30,112]

Iatrogenic cyanide poisoning may occur during use of nitroprusside as a vasodilator given to reduce blood pressure and afterload. Each nitroprusside molecule contains five cyanide molecules, which are slowly released in vivo. If endogenous sulfate stores are depleted, as in the malnourished or postoperative patient, cyanide may accumulate even with therapeutic nitroprusside infusion rates (2â€“10 Âµg/kg/min).

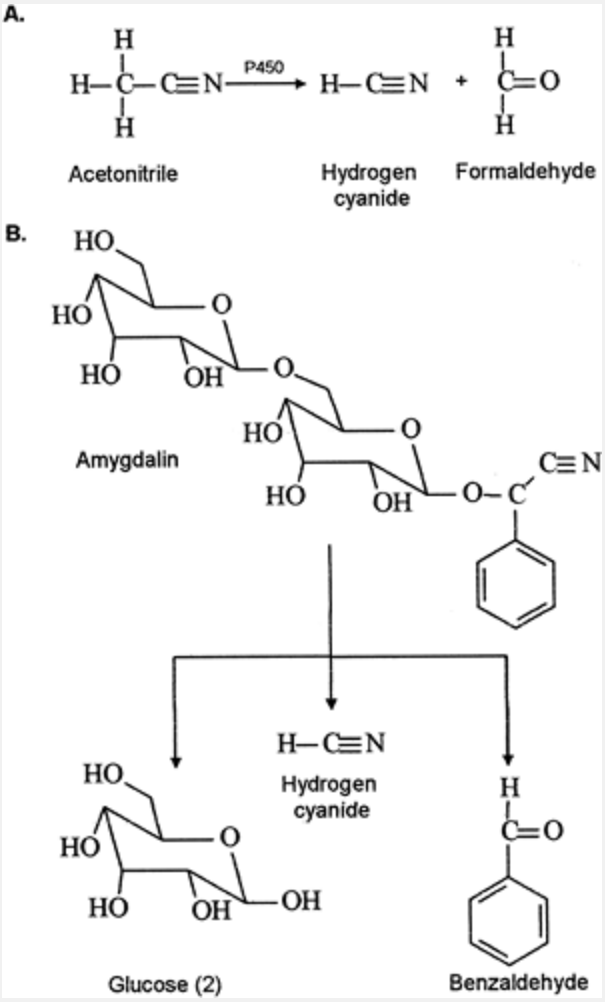

Figure 121-1. Biotransformation of cyanogens (A) acetonitrile and (B) amygdalin to cyanide.

Pharmacology

The dose of cyanide required to produce toxicity is dependent on the form of cyanide (gas or salt), the duration, and the route of

exposure. However, cyanide is an extremely potent toxin; even small exposures lead to symptoms. An adult oral lethal dose of KCN is approximately 200 mg. An airborne concentration of 270 ppm (Âµg/mL) hydrogen cyanide (HCN) may be immediately fatal, and exposures >110 ppm for more than 30 minutes are generally considered life threatening. The threshold limit value for hydrogen cyanide is 10 ppm during an 8-hour day.

Acute toxicity occurs through a variety of routes, including inhalation, ingestion, dermal, and parenteral.[24,139] Hydrogen cyanide, a gas under standard temperature and pressure, readily crosses membranes because it has a low molecular weight (27 daltons) and is nonionized. After absorption and dissolution in blood, cyanide exists in equilibrium as the cyanide anion (CN^-) and undissociated HCN. Hydrogen cyanide is a weak acid with a pK_a of 9.21. Therefore, at physiologic pH 7.4, it exists primarily as HCN. Rapid diffusion across alveolar membranes followed by direct distribution to target organs accounts for the rapid lethality associated with HCN inhalation.

Pharmacokinetics and Toxicokinetics

Cyanide is eliminated from the body by multiple pathways. A number of minor pathways of metabolism (<15% of total) account for cyanide elimination including conversion to 2-aminothiazoline-4-

carboxylic acid, incorporation into the 1-carbon metabolic pool, or in combination with hydroxycobalamin to form cyanocobalamin.

The major route for detoxification of cyanide is the enzymatic conversion to thiocyanate. Two sulfur transferase enzymes, rhodanese (thiosulfate-cyanide sulfurtransferase) and Î²-mercaptopyruvate-cyanide sulfurtransferase, catalyze this reaction. The primary pathway for metabolism is thought to be rhodanese, which is widely distributed throughout the body and has the highest concentration in the liver. This enzyme catalyzes the transfer of a sulfane sulfur from a sulfur donor (eg, thiosulfate) to cyanide to form thiocyanate. In acute poisoning, the limiting factor in cyanide detoxification by rhodanese is the availability of adequate quantities of sulfur donors. The endogenous stores of sulfur are rapidly depleted, and cyanide metabolism slows. Hence, sodium thiosulfate's efficacy as an antidote stems from its normalization of the metabolic inactivation of cyanide. The sulfation of cyanide is essentially irreversible, and the sulfation product thiocyanate has relatively little inherent toxicity. Thiocyanate is eliminated in urine.

Limited human data regarding the cyanide elimination half-life are available. Elimination appears to follow first-order kinetics,[86] although it varies widely in reports (range 1.2â€“ 66 hours).[10,62,65,86] Disparity in values may result from the number of samples used to perform calculations and the effects of antidotal treatment. The volume of distribution of cyanide varies according to species and investigator, with 0.075 L/kg reported in humans.[48]

Pathophysiology

Cyanide is an inhibitor of multiple enzymes, including succinic acid dehydrogenase, superoxide dismutase, carbonic anhydrase, and cytochrome oxidase.[164] Cytochrome oxidase is an iron-containing metalloenzyme essential for oxidative phosphorylation and, hence, aerobic energy production. It functions in the electron transport chain within mitochondria, converting catabolic products of glucose

into adenosine triphosphate (ATP). Cyanide induces cellular hypoxia by inhibiting cytochrome oxidase at the cytochrome a_3 portion of the electron transport chain (Figure 121-2).[120,164] Hydrogen ions that normally would have combined with oxygen at the terminal end of the chain are no longer incorporated. Thus, despite sufficient oxygen supply, oxygen cannot be utilized, and ATP molecules are no longer formed.[93] Unincorporated hydrogen ions accumulate, contributing to acidemia.

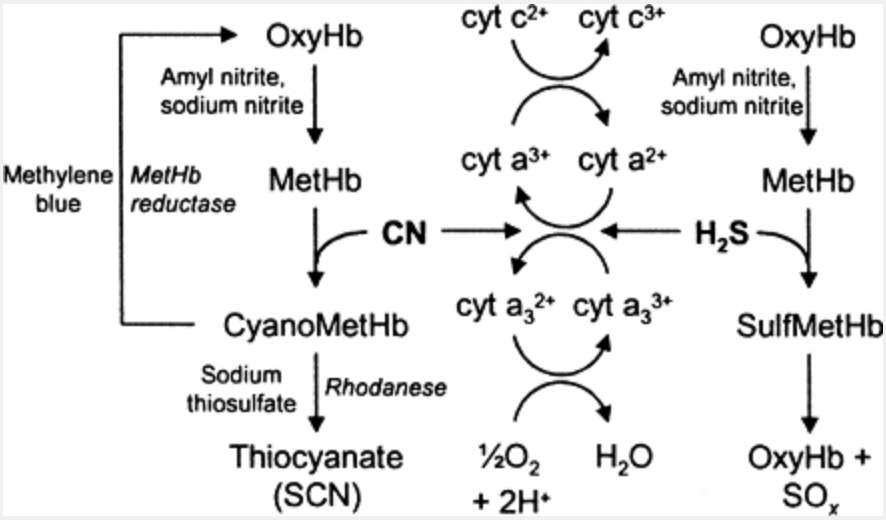

Figure 121-2. Pathway of cyanide and hydrogen sulfide toxicity and detoxification.

Hyperlactemia occurs following cyanide poisoning because of failure of aerobic energy metabolism. During aerobic conditions, when the electron transport chain is functional, lactate is converted to pyruvate by mitochondrial lactate dehydrogenase. In this process, lactate donates hydrogen moieties that reduce nicotinamide adenine dinucleotide (NAD^+) to NADH. Pyruvate then enters the tricarboxylic acid cycle, with resulting ATP formation. When cytochrome a_3 within the electron transport chain is inhibited by cyanide, there is a

relative paucity of NAD^+ and predominance of NADH, favoring the reverse reaction, in which pyruvate is converted to lactate as a result of stimulation of anaerobic glycosis.[10,20,40,59,62,87,137,139]

Cyanide is a potent neurotoxin. It exhibits a particular affinity for regions of the brain with high metabolic activity and regions with a high affinity to cyanide.[124,170] Central nervous system (CNS) injury occurs via several mechanisms, including impaired oxygen utilization, oxidant stress, and enhanced release of excitatory neurotransmitters. Cranial imaging of survivors of cyanide poisoning reveals that injury occurs in the most oxygen-sensitive areas of the brains, such as the basal ganglia, cerebellum, and sensorimotor cortex.[17,26,53,132,133]

Cyanide enhances *N*-methyl-D-aspartate (NMDA) receptor activity and directly activates the NMDA receptor,[5,117,118] which increases release of glutamate[116] and inhibits voltage-dependent magnesium blockade of the NMDA receptor.[171] This NMDA receptor stimulation results in Ca^{2+} entry into the cytosol of neurons. Cyanide also activates voltage-sensitive calcium channels[75] and mobilizes Ca^{2+} from intracellular stores.[95,125] As a result, cytosolic Ca^{2+} rises and activates a series of biochemical reactions that lead to the generation of reactive oxygen species and nitrous oxide.[82,101,123,134,135] These reactive oxygen species initiate peroxidation of cellular lipids, which together with cyanide-induced inhibition of the respiratory chain adversely affect mitochondrial function, initiating cytochrome c release and execution of apoptosis, necrosis, and subsequent neurodegeneration.[8,75,122,123,136] Experimental studies demonstrate that NMDA inhibitors (eg, dextrorphan and dizocilpine), antioxidants, and cyclooxygenase inhibitors protect neurons against cyanide-induced damage.[71,89,160]

Sulfurtransferase metabolism via rhodanese is crucial for detoxification. However, the aforementioned cyanide-induced metabolic derangement may decrease enzyme detoxification.

Decreased ATP and reactive oxygen species and increased cytosolic calcium stimulate protein kinase C activity, which in turn inactivates rhodanese.[92]

Clinical Manifestations

Acute Exposure to Cyanide

The amount of cyanide, duration of exposure, route of exposure, and premorbid condition of the individual influence the time to onset and severity of illness. A critical combination of these factors overwhelms endogenous detoxification pathways, allowing cyanide to diffusely affect cellular function within the body. No reliable pathognomonic symptom or toxic syndrome is associated with acute cyanide poisoning.[60,61] Clinical manifestations reflect dysfunction of oxygen-sensitive organs, with central nervous and cardiovascular findings predominating. The time to onset of symptoms typically is seconds with inhalation of gaseous HCN or intravenous injection of a water soluble cyanide salt and several minutes following ingestion of an inorganic cyanide salt. The clinical effects of cyanogenic chemicals often are delayed, and the time course varies among individuals (range 3â€“24 hours), depending on their rate of biotransformation.[151] Clinically apparent cyanide toxicity may occur within hours to days of initiating nitroprusside infusion, although concurrent administration of thiosulfate or hydroxocobalamin may prevent toxicity (Chap. 60).[130]

CNS signs and symptoms are typical of progressive hypoxia and include headache, anxiety, agitation, confusion, lethargy, seizures, and coma. A centrally mediated tachypnea occurs initially, followed by bradypnea.

Cardiovascular responses to cyanide are complex. Studies of isolated heart preparations and intact animal models show that the principal cardiac insult is slowing of rate and loss of contractile force. Several reflex mechanisms, including catecholamine release

and central vasomotor activity, may modulate myocardial performance and vascular response in patients with cyanide poisoning. In laboratory investigations, a brief period of increased inotropy caused by reflex compensatory mechanisms occurs before myocardial depression. Clinically, an initial period of bradycardia and hypertension may occur, followed by hypotension with reflex tachycardia, but the terminal event is consistently bradycardia and hypotension. Ventricular dysrhythmias do not appear to be an important factor.

Both cardiogenic pulmonary edema and acute lung injury (ALI) are found at necropsy.[38,53,61,137] In cyanide poisoning ALI may be neurogenic in origin or result from membrane leak from direct pneumocyte toxicity. Inhalation of HCN may be associated with mild corrosive injury to the respiratory tract mucosa.

Gastrointestinal toxicity may occur following ingestion of inorganic cyanide and cyanogens and include abdominal pain, nausea, and vomiting.[3,38,59,62,78,87,90,137] These symptoms are caused by hemorrhagic gastritis identified on necropsy and are thought to be secondary to the corrosive nature of cyanide salts.[54] However, if death occurs rapidly, this gastritis may not be seen at autopsy because development of inflammation occurs over time.[60,61]

Cutaneous manifestations may vary. Traditionally, a cherry-red skin color is described as a result of increased venous hemoglobin oxygen saturation, which results from decreased utilization of oxygen at the tissue level.[31,139] This phenomenon may be more evident on funduscopic examination, where veins and arteries may appear similar in color. Despite the inference in the name, cyanide does not directly cause cyanosis. The occurrence of cyanosis in some cases likely is secondary to shock.[156,167]

Delayed Clinical Manifestations of Acute Exposure

Survivors of serious, acute poisoning may develop delayed neurologic sequelae.[17,26,39,53,63,98,132,133,170] Parkinsonian symptoms, including dystonia, dysarthria, rigidity, and bradykinesia, are most common. Symptoms typically develop over weeks to months, but subtle findings can be present within a few days. Cranial computerized tomography and magnetic resonance imaging consistently reveal basal ganglia (globus pallidus, putamen, and hippocampus) damage, with radiologic changes appearing several weeks after onset of symptoms. Extrapyramidal manifestations may progress or resolve. Response to pharmacotherapy with antiparkinsonian agents is generally disappointing. Whether delayed manifestations result from direct cellular injury or secondary hypoxia is unclear.

Chronic Exposure to Cyanide

Chronic exposure to cyanide may result in insidious syndromes, including tobacco amblyopia, tropical ataxic neuropathy, and Leber hereditary neuropathy. Tobacco amblyopia is a progressive loss of visual function that occurs almost exclusively in men who smoke cigarettes. Affected smokers have lower plasma cyanocobalamin and thiocyanate concentrations than unaffected smoking counterparts, suggesting a reduced ability to detoxify cyanide. Cessation of smoking and administration of hydroxocobalamin often reverses symptoms. Tropical ataxic neuropathy is a demyelinating disease associated with improperly processed cassava consumption [112,147] Neurologic manifestations include Parkinson disease, spastic paraparesis, sensory ataxia, optic atrophy, and sensorineural hearing loss.[157] Concomitant dermatitis and glossitis suggest an association of high dietary cassava with low vitamin B_{12} intake. Elevated thiocyanate concentrations in affected individuals further implicate cyanide as the etiology. Removal of dietary cassava and institution of vitamin B_{12} therapy alleviates symptoms.[52] Leber hereditary optic atrophy, a condition of subacute visual failure affecting men, is thought to be caused by rhodanese

deficiency.[55,169]

Chronic exposure to cyanide is associated with thyroid disorders.[2,81] Thiocyanate is a competitive inhibitor of iodide entry into the thyroid, thereby causing the formation of goiters and the development of hypothyroidism.[81,146] Chronic exposure to cyanide in animals is associated with hydropic degeneration in hepatocytes and epithelial cells of the renal proximal tubules; however, these morphologic lesions are not linked to functional alternations.[146]

Diagnostic Testing

Because of nonspecific symptoms and delay in laboratory cyanide confirmation, the clinician must rely on historical circumstances and some initial findings to raise suspicion of cyanide poisoning and institute therapy (Table 121-1).

Laboratory findings suggestive of cyanide poisoning reflect the known metabolic abnormalities, which include metabolic acidosis, elevated lactate concentration, and increased anion gap. Elevated venous oxygen saturation results from reduced tissue extraction.[66,77,94]

A venous oxygen saturation >90% from superior vena cava or pulmonary artery blood indicates decreased oxygen utilization. This finding is not specific for cyanide and could represent cellular poisoning from other agents (eg, carbon monoxide, clenbuterol, hydrogen sulfide, and sodium azide) or medical conditions such as sepsis or high-output cardiac syndromes.

TABLE 121-1. Cyanide Poisoning: Emergency Management Guidelines

When to suspect cyanide

Sudden collapse of laboratory or industrial worker

Fire victim with coma or acidosis

Suicide with unexplained coma or acidosis

Ingestion of artificial nail remover

Ingestion of seeds or pits from *Prunus* species

ICU patient with altered mental status, acidosis, and tachyphylaxis to nitroprusside

Supportive care

Control airway, ventilate, and give 100% oxygen

Crystalloids and vasopressors for hypotension

Administer $NaHCO_3$; titrate according to ABG and serum HCO_3

Antidote

Amyl nitrite pearls are included in the kit for prehospital use. For hospital management, sodium nitrite is the preferred methemoglobin inducer and is given in lieu of the pearls.

Give sodium nitrite ($NaNO_2$) as a 3% solution over 2â€“4 minutes IV:

Adult dose: 10 mL (300 mg)

Pediatric dose: See TABLE 121-2

Caution: Monitor blood pressure frequently and treat hypotension by slowing infusion rate and giving crystalloids and vasopressors. Obtain methemoglobin level 30 minutes after dose and consider possible excessive methemoglobin formation if patient deteriorates during therapy.

Give sodium thiosulfate (NaS_2O_3) as a 25% solution IV:

Adult dose: 50 mL (12.5 g)

Pediatric dose: 1.65 mL/kg

Decontamination

Protect healthcare provider from contamination

Cutaneous: carefully remove all clothing and flush the skin

Ingestion: lavage with a large-bore orogastric tube and instill 1 g/kg activated charcoal

Laboratory
Arterial blood gas
Electrolytes and glucose
Blood lactate
Whole-blood cyanide concentration (for later confirmation only)
Consider a central venous blood gas

Lactic acidosis is found in numerous critical illnesses and typically is a nonspecific finding. However, a significant association exists between blood cyanide and plasma lactate concentrations.[11] In a small group of patients in whom the diagnosis of cyanide poisoning was strongly suspected clinically, a plasma lactate concentration >72 mg/dL (8 mmol/L) was associated with sensitivity 94%, specificity 70%, positive predictive value 64%, and negative predictive value 98% for a blood cyanide concentration >1.0 Âµg/mL. ABG analysis may provide additional information. Arterial pH correlates inversely with cyanide concentration.[11] The finding of a narrow arterialâ€“venous oxygen difference also may suggest cyanide toxicity.

Cyanide results in nonspecific electrocardiographic findings. Bradycardia, tachycardia, myocardial injury pattern, or atrioventricular conduction block may occur.

Blood cyanide determination can confirm toxicity, but this determination is not available in a sufficiently rapid manner to affect initial treatment. Whole blood or serum usually is analyzed. In mammals, including primates, whole-blood concentrations are twice serum concentrations[9] as a result of cyanide sequestration in red blood cells. Background whole-blood concentrations in nonsmokers range between 0.02 and 0.5 Âµg/mL.[62,67,91] Higher blood concentrations suggest toxicity. Coma and respiratory depression are associated with concentrations >2.5 Âµg/mL and death with concentrations >3 Âµg/mL. Detecting urinary cyanide is

difficult, and urinary thiocyanate is a more readily detectable and useful marker of cyanide exposure. Serum thiocyanate concentrations are of little value in assessing patients with acute poisoning because of little correlation with symptoms but are useful in confirming exposure.

A semiquantitative assay that uses calorimetric paper test strips may immediately detect cyanide. Cyantesmo test strips currently are used by water treatment facilities to detect cyanide. An investigation of the utility of these strips in clinical practice found that the test strips incrementally increased to a deep blue color over a progressively longer portion of the test strip with increasing concentrations of cyanide.[128] These strips accurately and rapidly detected, in a semiquantifiable manner, CN concentrations >1 Âµg/mL.

Management

Because cyanide poisoning is rare, it is easy to overlook the diagnosis unless there is an obvious history of exposure. Thus, the most critical step in treatment is considering the diagnosis in high-risk situations (Table 121-1) and initiating empiric therapy with 100% oxygen and the cyanide antidote kit which contains both nitrites. The initial care (Table 121-1) of the cyanide-poisoned patient begins by directing attention to airway patency, ventilatory support, and oxygenation. Oxygen and sodium bicarbonate also are critical for cyanide treatment, enhancing the antidotal effect of nitrite and thiosulfate.[36] Acidemia should be treated with adequate ventilation and sodium bicarbonate administration.

Intravenous access should be rapidly obtained and blood samples sent for renal function, glucose, and electrolyte determinations. A whole-blood cyanide concentration can be obtained for later confirmation of exposure. ABG analysis and serum lactate concentration will help assess acidâ€“base status. Initiation of crystalloid and infusion of vasopressor for hypotension are

warranted.

First responders should exercise extreme caution when entering potentially hazardous areas such as chemical plants and laboratories where a previously healthy person is â€œfound down.â€• Exposure to cyanide may occur by multiple routes, including ingestion, inhalation, dermal, and parenteral. For patients with inhalation exposure, removal from the area of exposure is critical. Further decontamination is generally unnecessary. Decontamination of the cyanide-poisoned patient occurs concurrently with initial resuscitation. The healthcare provider should always be protected from potential dermal contamination by using personal protective devices such as water-impervious gowns, gloves, and eyewear. For patients with cutaneous exposure, remove their clothing, brush any powder off from the skin, and flush the skin with water. Particular attention should be given to open wounds because CN^- or HCN is readily absorbed through abraded skin.

Instillation of activated charcoal often is considered ineffective because of low binding of cyanide (1 g activated charcoal adsorbs 35 mg cyanide).[4] However, a potentially lethal oral dose of cyanide (ie, a few hundred milligrams) is within the adsorptive capacity of a 1 g/kg dose of activated charcoal. Prophylactic activated charcoal administration improved survival in animals given LD_{100} doses of KCN.[88] Based on the potential benefits and minimal risks, activated charcoal may be considered in the patient with an intact airway.

The cyanide antidote kit should be administered as soon as cyanide poisoning is suspected (Tables 121-1 and 121-2). The kit contains amyl nitrite, sodium nitrite, and sodium thiosulfate. Both thiosulfate and nitrite individually have antidotal efficacy when given alone in animal models of cyanide poisoning, but they have even greater benefit when they are given in combination.[43] Thiosulfate donates the sulfur atoms necessary for rhodanese-mediated cyanide biotransformation to thiocyanate. The mechanism of nitrite is less

clear. Traditional rationale relies on the ability of nitrite to generate methemoglobin. Because cyanide has a higher affinity for methemoglobin than for cytochrome a_3, cytochrome oxidase function is restored. However, improved hepatic blood flow and nitric oxide formation are alternate explanations (Antidotes in Depth: Sodium and Amyl Nitrites, Sodium Thiosulfate and Hydroxocobalamin).

Amyl nitrite is contained within glass pearls that are crushed and intermittently inhaled or intermittently introduced into the ventilator system to initiate methemoglobin formation. The amyl nitrite pearls are reserved for cases where intravenous access is delayed or not possible. Intravenous sodium nitrite is preferred and is supplied as a 10-mL volume of 3% solution (300 mg). The outdated goal of intravenous nitrite therapy is to achieve a methemoglobin level of 20â€“30%. This level is not based on cyanide treatment data but represents the maximum tolerated concentration without adverse symptoms from methemoglobinemia in a healthy individual. Clinical response is reported at lower methemoglobin levels of 3.6â€“9.2%. These reports are not conclusive because levels typically are not drawn serially, and peak levels may be misrepresented. Also, methemoglobin levels do not include cyanomethemoglobin. Therefore, lower than expected methemoglobin levels may represent indirect evidence of cyanide poisoning.

Adverse effects of nitrites include excessive methemoglobin formation and, because of potent vasodilation, hypotension and tachycardia. Avoiding rapid infusion, monitoring blood pressure, and adhering to dosing guidelines will limit adverse effects. Because of excessive methemoglobinemia during nitrite treatment, pediatric dosing guidelines are available.[15] Based on the premise that nitrite oxidizes hemoglobin on a mole-for-mole basis, doses were calculated for various hemoglobin concentrations (Table 121-2). These values are useful if the patient is known to be anemic. However, when giving nitrite empirically, treatment is based on a presumed 12-g hemoglobin concentration. Do not delay treatment

while awaiting a hemoglobin measurement. Amyl nitrite pearls are aromatic and should be used with caution in closed spaces because persons administrating them can become hypotensive and dizzy.

TABLE 121-2. Cyanide Management: Pediatric Nitrite Guidelines[a]

Hemoglobin (g)	$NaNO_2$ (mg/kg)	3% $NaNO_2$ solution (mL/kg)
7.0	5.8	0.19
8.0	6.6	0.22
9.0	7.5	0.25
10.0	8.3	0.27
11.0	9.1	0.30
12.0	10.0	0.33
13.0	10.8	0.36
14.0	11.6	0.39

[a]Pediatric thiosulfate dose: 1.65 mL/kg of 25% solution.
Adapted, with permission, from Berlin CM: The treatment of cyanide poisoning in children. Pediatrics 1976;46:793â€“796.

Sodium thiosulfate is the second component of the cyanide antidote kit. It is supplied as 50 mL of 25% solution (12.5 g). It is a substrate for the reaction catalyzed by rhodanese that is essentially irreversible, converting a highly toxic entity to a relatively harmless compound. However, thiocyanate does, have its own toxicity in the presence of renal failure, including abdominal pain, vomiting, rash, and CNS dysfunction (Chap. 60).[45] Thiosulfate itself is not associated with significant adverse reactions. The pediatric dose of thiosulfate is adjusted for weight.

Patients who do not survive cyanide poisoning are suitable organ donors. Heart, liver, kidney, pancreas, cornea, skin, and bone were successfully transplanted following cyanide poisoning.[33,69,149] (See Special Considerations, SC-1.)

Other Therapies

Although the cyanide kit is the mainstay of antidotal therapy in the United States, other treatments are used abroad. In Europe, 4-dimethylaminophenol (4-DMAP), rather than sodium nitrite, is the methemoglobin-inducing agent of choice. It generates methemoglobin more rapidly than sodium nitrite, with peak methemoglobin concentrations at 5 minutes after 4-DMAP rather than 30 minutes after sodium nitrite. The dose of 4-DMAP is 3 mg/kg and is coadministered with thiosulfate. As with sodium nitrite, its major adverse effect is excessive methemoglobin formation and potential for hypotension.

Hydroxocobalamin, a vitamin B_{12} precursor, is used for acute and chronic cyanide poisoning in Europe.[22] Hydroxocobalamin is a metalloprotein with a central cobalt atom that complexes cyanide, forming cyanocobalamin (vitamin B_{12}). Cyanocobalamin is eliminated in the urine or releases the cyanide moiety at a rate sufficient to allow detoxification by rhodanese. For this reason, thiosulfate is coadministered with hydroxocobalamin. One molecule

of hydroxocobalamin binds one molecule of cyanide, yielding a molecular weight binding ratio of 50:1. The standard initial dose of hydroxocobalamin is 4 g which is expected to bind 200 mg cyanide. The dose can be repeated in cases of massive poisoning. Hydroxocobalamin has few adverse effects, which include allergic reaction and a transient reddish discoloration of the skin, mucous membranes, and urine.[32,68] No hemodynamic adverse effects other than a potential mild transient rise of blood pressure are observed.[14,131] (See Antidotes in Depth: Hydroxocobalamin.)

Cobalt in the form of dicobalt edetate has been used as a cyanide chelator, but its usefulness is limited by serious adverse effects such as hypotension, cardiac dysrhythmias, decreased cerebral blood flow, and angioedema.[30,105]

Stroma-free methemoglobin, oxidized hemoglobin from which the cell membrane has been removed, is an investigational agent. It attenuates lethality and prevents hemodynamic changes in animal models.[29,150] The advantage to this treatment lies in providing exogenous methemoglobin to bind cyanide without compromising the oxygen-carrying capacity of native hemoglobin and removal of the cell membrane eliminates antigenicity.

Dihydroxyacetone (DHA) is an investigational antidote that restores mitochondrial respiration inhibited by cyanide in isolated rat hepatocytes.[108] It also diminishes cyanide lethality in animal models and has synergistic effects with thiosulfate.[107,109] DHA binds readily to cyanide to form a cyanohydrin, but this binding is reversible and cyanide's clinical effects reappear between 1 and 24 hours without readministration.[107]

Î±-Ketoglutarate is another investigational antidote. It rapidly complexes cyanide to form a cyanohydrin.[103] Pretreatment with Î±-ketoglutarate reduced lethality and increased sodium thiosulfate efficacy in animal studies.[19,50,74,110] The advantage of Î± ketoglutarate is direct binding of cyanide without generation of

methemoglobin. Preliminary evidence demonstrates that Î±-ketoglutarate at a dose offering maximum antidotal efficacy is nontoxic and potentially safe for treatment of cyanide poisoning.[18]

In animal models, antioxidant vitamins (eg, vitamins A, C, and E) diminish the extent of tissue damage caused by subacute cyanide intoxication.[111] This is especially important in the tropics, where the majority of dietary staples are cyanophoric crops such as cassava.

Hyperbaric oxygen (HBO) has been used for cyanide treatment, often with dramatic clinical improvement.[47,54,62,133,137,153] However, the patients received multiple therapies during resuscitation, so improvement cannot be attributed to HBO alone. Experimental data regarding HBO are contradictory. In a murine model, survival increased with 100% oxygen at 2 ATA compared to normobaric oxygen. However, combined HBO and nitrite/thiosulfate did not confer additional protection compared to normobaric oxygen and nitrite/thiosulfate. Currently, the Undersea and Hyperbaric Medical Society supports hyperbaric therapy for cases of cyanide poisoning complicated by coincident carbon monoxide toxicity.[166] Until further studies clearly demonstrate the efficacy of hyperbaric therapy for isolated cyanide poisoning, it should not supplant the combination of normobaric oxygen, nitrite, and thiosulfate.

Hydrogen Sulfide Poisoning

Case 2

A 23-year-old man entered an empty petroleum storage tank to perform repairs. He rapidly collapsed and fell unconscious. Two coworkers attempted a rescue, but both collapsed immediately after they entered the tank. Firefighters wearing self-contained breathing apparatus (SCBA) entered the tank and removed all 3 victims. Both of the would-be rescuers regained consciousness after they were removed from the tank. The first worker to collapse was removed

and noted to be cyanotic, with minimal respiratory effort. When paramedics arrived on the scene, the worker was immediately intubated.

When the worker arrived in the emergency department, he was intubated and receiving 100% oxygen by assisted ventilation. He had shallow spontaneous respirations and responded only to deep painful stimuli. Vital signs were: blood pressure, 110/72 mm Hg; pulse, 140 beats/min; respiratory rate, 34 breaths/min; rectal temperature 102Â°F (38.4Â°C). Pertinent findings on physical examination included dilated pupils, marked conjunctival injection, and diffuse crackles in both lung fields.

Laboratory data with arterial blood gas (ABG) analysis revealed: pH, 7.21; PCO_2, 30 mm Hg; PO_2, 48 mm Hg; bicarbonate, 11 mEq/L. The carboxyhemoglobin level was 1.5%, and the lactate concentration from ABG was 10.5 mEq/L. The electrocardiogram showed sinus tachycardia with normal intervals and axis. Chest radiograph showed diffuse alveolar infiltrates and a normal-sized heart.

The patient was attached to a ventilator with 100% oxygen and positive end-expiratory pressure of 10 cm H_2O. Over the next hour, his oxygenation improved, and his PO_2 was 335 mm Hg. He rapidly required less ventilatory support. The metabolic acidosis resolved over the next 8 hours. His neurologic status slowly improved over the next 20 hours, at which point he appeared alert and would follow commands. Following extubation, a repeat neurologic examination was normal. Followup 1 week later did not show any adverse effects. Air samples from the tank, taken the day after the exposure, revealed hydrogen sulfide, 880 ppm; methane, 420 ppm; carbon, dioxide 400 ppm; carbon monoxide, 50 ppm; oxygen, 18%.

History and Epidemiology

Hydrogen sulfide (H_2S) toxicity is not common. The American

Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System (TESS) reported only 1336 exposures in 2003 (Chap. 130). Only 325 of these exposures required evaluation at a healthcare facility, fewer than 150 reported moderate or major effects, and only 4 deaths occurred. From 1983â€“1992, 5563 exposures and 29 deaths attributed to hydrogen sulfide were reported.[145] US Occupational Safety and Health Administration (OSHA) records show 80 occupationally related fatalities between 1984 and 1994.[56] Between 1990 and 1999, hydrogen sulfide poisoning was associated with the deaths of 18% of US construction workers killed by toxic inhalation.[49] Many died while working in confined spaces.

Hydrogen sulfide's rapid and deadly onset of clinical effects have been termed the *slaughterhouse sledgehammer effect.* Poisoned workers are â€œknocked down,â€• most frequently in an agricultural or industrial event. Numerous case reports describe multiple victims in these events. Would-be rescuers often themselves become victims when they attempt a rescue in an environment having high concentrations of hydrogen sulfide.[41,46,85,115,145] In the OSHA data, 25% of fatalities involved rescuers.[56]

Hydrogen sulfide is implicated in environmental disasters. In 1950, 22 people died and 320 were hospitalized in Poza Rica, Mexico, when a local natural gas facility inadvertently released hydrogen sulfide into the air.[96] Hydrogen sulfide claimed nine lives when a sour gas well failed, releasing a cloud of the poisonous gas into the Denver City, Texas community in 1975.[104] In 2003, a gas drilling incident in southwest China released natural gas and a cloud of hydrogen sulfide into a populated mountainous area. More than 200 people died, 9000 were treated for injuries, and more than 40,000 were evacuated.[165]

Hydrogen sulfide is produced naturally by bacterial decomposition of proteins and is used or produced in many industrial activities.

Industrial sources of hydrogen sulfide include pulp paper mills, heavy-water production, the leather industry, roofing asphalt tanks, vulcanizing of rubber, viscose rayon production, and coke manufacturing from coal.[35,72,115,143,158] It is a major industrial hazard in oil and gas production, particularly in sour gas fields (natural gas containing sulfur). Decay of sulfur-containing products (eg, fish, sewage, and manure) also produces hydrogen sulfide. Several farm workers and rescuers have died from exposure to hydrogen sulfide generated in liquid manure pits.[101,115] An adolescent laboratory worker lost consciousness while cleaning a reoxygenation tank in a fish hatchery, and a sailor died from exposure to sewage and hydrogen sulfide fumes while repairing an on-board sewage collection system.[97,106] Natural

sources are volcanoes, caves, sulfur springs, and underground deposits of natural gas.[46,72,127]

Pharmacology

Hydrogen sulfide is a colorless gas, more dense than air, with an irritating odor of â€œrotten eggs.â€• It is highly lipid soluble, a property that allows easy penetration of biologic membranes. Systemic absorption usually occurs through inhalation, and it is rapidly distributed to tissues.[127] The tissues most sensitive to hydrogen sulfide are those with high oxygen demand. Hydrogen sulfide's systemic toxicity results from its potent inhibition of cytochrome oxidase, thereby interrupting oxidative phosphorylation.[144] Hydrogen sulfide binds to the ferric (Fe^{3+}) moiety of cytochrome a_3 oxidase complex with a higher affinity than does cyanide (Figure 121-2). The resulting inhibition of oxidative phosphorylation produces cellular hypoxia and anaerobic metabolism.[141] In addition to cytochrome oxidase inhibition, hepatocyte studies suggest H_2S toxicity involves opening the mitochondrial permeability transition pore, generating reactive oxygen species and compromising glycolysis.[51,152] Besides

producing cellular hypoxia, hydrogen sulfide causes potassium channelâ€“mediated hyperpolarization of neurons and potentiates other neuronal inhibitory mechanisms. It also alters brain neurotransmitter content and release.[1,127] A proposed mechanism of death is poisoning of the brainstem respiratory center through selective uptake by lipophilic white matter in this region.[162]

In addition to systemic effects, hydrogen sulfide produces intense dermal irritation. It reacts with the moisture on the surface of mucous membranes to form sodium sulfide, which produces the irritant chemical effect. Despite skin irritation, it has little dermal absorption.

Toxicokinetics

The major pathways of hydrogen sulfide detoxification are enzymatic and nonenzymatic oxidation of sulfides and sulfur to thiosulfate and polysulfides.[23] Other pathways, such as methylation to dimethyl sulfide and conversion to sulfite or sulfate by oxidized glutathione, also may play a role in detoxification and elimination.[12] Hydrogen sulfide binds to metalloproteins such as heme proteins. It is a detoxification pathway when it binds to endogenously produced methemoglobin to form sulfmethemoglobin. However, binding to heme proteins such as cytochrome oxidase is its major mechanism of toxicity. Only small amounts of sulfide are excreted in urine or exhaled into the air. Sulfhemoglobin is not found in significant concentrations in the blood of animals or fatally poisoned humans.[143]

Clinical Manifestations

Acute Manifestations

Hydrogen sulfide poisoning should be suspected whenever a person is found unconscious in an enclosed space, especially if the odor of

rotten eggs is noted. The primary target organs of hydrogen sulfide poisoning are those of the CNS and respiratory system. The clinical findings reported in two large series are listed in Table 121-3.[7,35] The intensity of exposure likely accounts for the diverse clinical findings in the reports. A distinct dose response to hydrogen sulfide is identified. The odor threshold is between 0.02 and 0.13 ppm, and a strong intense odor is noted at 20â€“30 ppm. Mild mucous membrane irritation occurs at 50â€“100 ppm, and olfactory fatigue occurs at 100â€“150 ppm. Thus, the ability to perceive the odor is rapidly extinguished because of olfactory nerve paralysis at higher levels. Prolonged exposure can occur when the extinction of odor recognition is misinterpreted as dissipation of the gas. Strong irritation of the upper respiratory tract and eyes and ALI occur at 200â€“300 ppm. At >500 ppm, H_2S produces systemic effects. Rapid unconsciousness and cardiopulmonary arrest occur at concentrations >700 ppm.[12,127]

Mucous membrane irritation of the eye produces keratoconjunctivitis. If exposure persists, damage to the epithelial cells produces reversible corneal ulcerations (â€œgas eyeâ€•) and, rarely, irreversible corneal scarring.[99] The irritant effects on the respiratory tract include rhinitis, bronchitis, and ALI.[7,35]

Neurologic manifestations are common and may be severe. In a series, 75% of 221 patients with acute hydrogen sulfide exposure lost consciousness at the time of exposure.[35] In acute, massive exposures, rapid loss of consciousness (â€œknockdownâ€•) results from loss of central respiratory drive.[100,144] If the patient is rapidly removed from the exposure, recovery may be prompt and complete. Secondary neurologic effects can result from hypoxia secondary to respiratory compromise.[12,127] Neurologic outcome can be quite variable, ranging from no neurologic impairment to permanent sequelae. Delayed neuropsychiatric sequelae may occur after acute exposures.[35,37,72,84,145,148,154,155,163] Most evidence suggests that the early rapid CNS effects are direct neurotoxic effects of hydrogen sulfide, whereas the permanent neurologic sequelae result from

hypoxia secondary to respiratory insufficiency.[12,99,100,127] Reported neuropsychiatric changes include memory failure (amnestic syndrome), lack of insight, disorientation, delirium, and dementia.[163] Neurosensory abnormalities include transient hearing impairment, vision loss, and anosmia. Motor symptoms likely are caused by injury to the basal ganglia and result in ataxia, position/intention tremor, and muscle rigidity.[154] Common neuropathologic findings observed on CT scan and at autopsy are subcortical white matter demyelination and globus pallidus degeneration.[57,155]

Acute exposures affect other organ systems. Myocardial hypoxia or direct toxic effects of hydrogen sulfide on cardiac tissue may cause cardiac dysrhythmias, myocardial ischemia, or myocardial infarction.[64] Because unresponsiveness is rapid, trauma from falls should not be overlooked.[7] In a report, 7% of patients experiencing a â€œknockdownâ€• had associated traumatic injuries.[7]

Chronic Manifestations

Most data about chronic, low-level exposures to hydrogen sulfide come from oil and gas industry workers.

Mucous membrane irritation seems to be the most prominent problem in patients with low-level exposures. Workers report nasal, pharyngeal, and eye irritation, fatigue, headache, dizziness, and poor memory with low-level, chronic exposures. One third of viscous rayon workers left their jobs because of persistent eye irritation (spinner's eye). The chronic irritating effects of hydrogen sulfide were thought to be the cause of reduced lung volumes observed in sewer workers.[129] Volunteer studies have not demonstrated significant cardiovascular effects at low-level exposures (<10 ppm).[16] The liver, kidneys, and endocrine system are unaffected. No studies demonstrate increased incidences of cancer with low-level exposures.[44]

TABLE 121-3. Hydrogen Sulfide Poisoning

When to suspect hydrogen sulfide poisoning
Person rapidly loses consciousness (â€œknocked downâ€•)
Rotten eggs odor
Rescue from enclosed space, such as sewer or manure pit
Multiple victims with sudden death syndrome
Collapse of a previously healthy worker at work site
Clinical Manifestations

System	Signs and Symptoms
Cardiovascular	Chest pain, bradycardia
Central nervous	Headache, weakness, dysequilibrium, convulsions, coma
Gastrointestinal	Pharyngitis, nausea, vomiting
Ophthalmic	Conjunctivitis
Pulmonary	Dyspnea, cyanosis, hemoptysis, crackles

Rapid loss of consciousness after a high-level exposure was a well known and, amazingly, accepted part of the workplace in the gas and oil industry for many years.[70] Some workers experienced repeated â€œknockdowns,â€• and these workers reported an increased incidence of respiratory diseases and cognitive deficits. Clearly, single or repeated high-level exposures resulting in

unconsciousness can cause serious cognitive dysfunction. Case series suggest that protracted low-level exposures cause subtle changes that can be measured by only the most sensitive neuropsychiatric tests.[37,83]

Epidemiologic data regarding the effects of low-level environmental exposures to hydrogen sulfide are clouded in populations exposed to complex mixtures of pollutants. Other malodorous sulfur compounds (eg, methyl mercaptan and methyl sulfide) are generated as byproducts of pulp mills. Study populations exposed to this complex mixture of pollutants demonstrate a dose-related increase in nasal symptoms, cough, nausea, and vomiting.[44]

Hydrogen sulfide's strong odor at low concentrations can magnify irritant effects by triggering a strong psychological response.[101] Hydrogen sulfide has been the alleged source of mass psychogenic illness cases.[57,101] Clinical, epidemiologic, and toxicologic analyses suggested that 943 cases of illness in Jerusalem were caused by the odor of low concentrations of hydrogen sulfide gas. The most frequent associated symptoms are headaches, faintness, dizziness, nausea, chest tightness, difficulty breathing (hyperventilation), irritation of eyes, nose, and throat, weakness, and extremity numbness.[27] Mild-to-moderate hydrogen sulfide toxicity produces nonspecific signs and symptoms that could closely mimic psychogenic illness. Attempting to identify true toxicity from a powerful emotional reaction can be extremely difficult.[58] Therefore, symptomatic patients must be assessed for toxicity even when mass psychogenic illness is suspected (Chap. 124).

Diagnostic Testing

Because no available rapid method of detection is of clinical diagnostic use, management decisions must be made based on history, clinical presentation, and diagnostic tests that infer hydrogen sulfide's presence. Circumstances surrounding the patient's illness often will provide the best evidence for hydrogen

sulfide poisoning (Table 121-3). At the bedside, the smell of rotten eggs on clothing or emanating from the blood, exhaled air, or gastric secretions suggests hydrogen sulfide exposure.[73] In addition, darkening of jewelry is a clue to exposure. Paper impregnated with lead acetate changes color when exposed to hydrogen sulfide and is used to detect its presence in the patient's exhaled air but is not rapidly available.[44]

Specific tests for confirming hydrogen sulfide exposure are not readily available in clinical laboratories. Therefore, the presence of hydrogen sulfide is best confirmed by directly measuring the gas in the environment. It can be detected in atmospheric air samples by monitoring devices such as colorimetric tubes or toxin-specific air sampling devices. Many emergency response teams investigate the toxic environment of a hazardous materials incident with detection devices that measure hydrogen sulfide by electrochemical sensors.

In acute poisoning, readily available diagnostic tests that are biomarkers of hydrogen sulfide poisoning may be useful but are nonspecific. ABG analysis demonstrating metabolic acidosis with an associated elevated serum lactate concentration is expected, and oxygen saturation should be normal unless ALI is present. Hydrogen sulfide, like cyanide, decreases oxygen consumption and is reflected as an elevated mixed venous oxygen measurement. Because sulfhemoglobin typically is not generated in patients with hydrogen sulfide poisoning, an oxygen saturation gap is not expected.[143]

After serious injury from hydrogen sulfide, diagnostic testing for neurologic structure and function may show abnormalities for weeks or months. Brain MRI and head CT studies demonstrate structural changes such as globus pallidus degeneration and subcortical white matter demyelination. Neuropsychological testing after serious hydrogen sulfide poisoning demonstrates specific abnormalities in cortical functions, such as concentration, attention, verbal abstraction, and short-term retention. Single-photon emission computed tomography (SPECT)/PET brain scans define neurotoxin-

induced lesions that correlate well with clinical neuropsychological testing.[37]

Clinical laboratory tests may be useful for confirming exposure but are not readily available for clinical decision making in an acute exposure. Whole-blood sulfide concentrations >0.05 mg/L are considered abnormal. Reliable measurements are ensured only if the concentration is obtained within 2 hours after the exposure and analyzed immediately.[127] In acute exposures, blood and urine thiosulfate concentrations may be reflective of exposure, and urinary thiosulfate excretion is used to monitor chronic low-level exposure in the workplace.[80]

Sulfide concentrations obtained in postmortem investigations may be useful, but their use requires rapid sample collection because sulfide concentrations rise with tissue decomposition.[127] In addition to blood sulfide concentrations, sulfide and thiosulfate concentrations are at their highest in lung and brain.[76,99] At autopsy, a greenish discoloration of the gray matter, viscera, and bronchial secretions may be noted.[79,80]

Management

The initial treatment (Table 121-4) is immediate removal of the victim from the contaminated area into a fresh-air environment. Administer high-flow oxygen as soon as possible. Optimal supportive care has the greatest influence on the patient's outcome. Because death from inhalation of hydrogen sulfide is rapid, limited human cases reaching the hospital for treatment are reported in the literature. Most patients experience significant delays before receiving treatment. Therefore, specific treatments and antidotal therapies do not show definitive improvement in patient outcome.

Most animal studies and human case reports suggest that oxygen therapy is beneficial for hydrogen sulfide poisoning.[13,23,126,143] In rats, HBO was more effective than normobaric oxygen, nitrite, or

sham treatment in preventing mortality from sulfide poisoning.[23] Studies showing benefit of HBO for cyanide toxicity have led to the use of HBO in hydrogen sulfide poisoning. Case reports suggest that HBO is beneficial, although use of HBO may be impractical in most cases.[140,168] No studies evaluating the role of HBO for preventing delayed neurologic sequelae are available.

Proposed mechanisms for oxygen's beneficial effects are competitive reactivation of oxidative phosphorylation by inhibiting hydrogen sulfideâ€“cytochrome binding, enhanced detoxification by catalyzing oxidation of sulfides and sulfur, and improved oxygenation in the presence of ALI.[13,140] All patients suspected of hydrogen sulfide poisoning should receive supplemental oxygen. Patients with persistent neurologic or cardiovascular effect may benefit from HBO therapy. Consider using HBO if it is immediately available, but because data on the efficacy of HBO are limited, it is not necessary to transfer the patient solely for HBO therapy.

TABLE 121-4. Hydrogen Sulfide Poisoning: Emergency Management

Supportive care
Prehospital
Attempt rescue only if using SCBA
Move victim to fresh air
Administer 100% oxygen
During extrication, consider traumatic injuries from falls
Apply ACLS protocols as indicated
Emergency department
Maximize ventilation and oxygenation
Consider PEEP for ALI
Treat acidosis based on arterial pH and serum bicarbonate analysis

Administer crystalloid and vasopressors for hypotension

Antidote

Give sodium nitrite (3% $NaNO_2$) IV over 2â€“4 minutes

Adult dose: 10 mL (300 mg)

Pediatric dose: see Table 121-2

Caution:

Monitor blood pressure frequently

Obtain methemoglobin level 30 minutes after dose

Consider HBO if immediately available

The similarities in the toxic mechanism between hydrogen sulfide and cyanide created an interest in the use of nitrite-induced methemoglobin as an antidote. Methemoglobin protects animals from toxicity of hydrogen sulfide poisoning in both pretreatment and postexposure models.[141,142,144] Nitrite-generated methemoglobin acts as a scavenger of sulfide. Hydrogen sulfide's affinity for methemoglobin is greater than that for cytochrome oxidase.[141] When hydrogen sulfide binds to methemoglobin, it forms sulfmethemoglobin.[13] Because hydrogen sulfide poisoning is rare, no studies have evaluated the clinical outcomes of patients treated with sodium nitrite. Animal studies suggest that nitrite must be given within minutes of exposure to ensure effectiveness.[13] However, several human case reports showed rapid return of normal sensorium when nitrites were administered soon after exposure.[72,119,148] Patients with suspected hydrogen sulfide poisoning who have altered mental status, coma, hypotension, or dysrhythmias probably should receive sodium nitrite by slow infusion at the same dose given for cyanide poisoning. Sodium thiosulfate is of no benefit in the treatment of hydrogen sulfide.

Treatment of patients with hydrogen sulfide poisoning requires optimal supportive care. Treatments and antidotes beyond supportive care are not of proven clinical benefit. Because hydrogen sulfide toxicity is severe and case reports suggest the occurrence of

delayed sequelae, the potential benefits of nitrite therapy and HBO should be considered for seriously ill patients exposed to hydrogen sulfide. These therapies should be initiated after optimum supportive care has been ensured.

Summary

Both cyanide and hydrogen sulfide are high-risk industrial agents. Industrial precautions are essential to limit worker risk. Cyanide is of great concern with regard to homicide and suicide. There are particular metabolic risks and concerns with regard to exposure to both agents because they bind specifically to the ferric moiety of the cytochrome a_3 oxidase complex. Odor recognition is unreliable and is not a definitive approach to diagnosis. The laboratory evaluation usually is not timely for diagnostic purposes. Decontamination, removal from the site of exposure, and oxygen are essential. The controversies over the ideal therapeutic modalities for these agents are substantial, and extensive research continues.

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Antidotes in Depth

Sodium and Amyl Nitrites

Mary Ann Howland

Amyl and sodium nitrite are effective cyanide antidotes when they are administered in timely fashion. Amyl nitrite is volatile and available in ampules that can be broken and administered by inhalation until sodium nitrite can be administered intravenously. Although the exact mechanism of action of the nitrites is unclear, the production of methemoglobin is both therapeutic and potentially life threatening if nitrites are administered to a patient with impaired oxygen-carrying capacity, such as lung injury from smoke inhalation, or elevated carboxyhemoglobin or methemoglobin from any cause. In the latter cases, sodium thiosulfate can be administered intravenously with impunity. Hydroxocobalamin, currently available elsewhere in the world and soon to be available in the United States, also has this advantage.

History

Expanding on earlier work that demonstrated the limited role of

methylene blue and the efficacy of sodium nitrite in cyanide-poisoned animals, inhaled amyl nitrite was used successfully in dogs.[2] Amyl nitrite administered by inhalation protected dogs from up to 4 minimum lethal doses of sodium cyanide (24 mg/kg subcutaneously). In the regimen used, therapy started within 5 to 7 minutes of exposure and continued for several hours. The frequency of inhalations was based on clinical response. Inhalation of amyl nitrite prevented and protected against cyanide-induced seizures and muscular rigidity.[2] The results of these experiments were so convincing that use of inhaled amyl nitrite was justified in patients poisoned by cyanide. Later that year, the same authors discovered that intravenous (IV) use of sodium thiosulfate alone protected against 3 minimum lethal doses of cyanide in dogs and that the combination of sodium thiosulfate with either inhaled amyl nitrite or IV sodium nitrite protected against 10 and 13â€“18 minimum lethal doses, respectively.[3,4] This finding confirmed the synergistic effects of a nitrite and sodium thiosulfate administered together.[3] Chen[4] credits Pedigo in 1888 with first noting the antidotal effect of amyl nitrite on cyanide poisoning, Lang in 1895 with demonstrating the beneficial effects of sodium thiosulfate, and Mota in 1933 with first using sodium nitrite in a patient. The first case series of combined antidotal therapy with nitrites and thiosulfate was reported in 1949.

Chemistry

The chemical formula for sodium nitrite is $NaNO_2$ and for amyl nitrite is $C_5H_{11}NO_2$. Sodium nitrite has a molecular weight of 69 daltons and amyl nitrite 117 daltons. Amyl nitrite is volatile even at low temperatures, and it is highly flammable.

Mechanism of Action

Cyanide quickly and reversibly binds to the ferric iron in cytochrome oxidase, inhibiting effective energy production

throughout the body. The ferric iron in methemoglobin preferentially combines with cyanide, producing cyanomethemoglobin. This drives the reaction toward cyanomethemoglobin and liberates cyanide from cytochrome oxidase. Stroma-free methemoglobin is effective against 4 minimum lethal doses of cyanide in rats.[16] Nitrites oxidize the iron in hemoglobin to produce methemoglobin. Because nitrites are accepted antidotes for cyanide poisoning, for many years methemoglobin formation was assumed to be their sole antidotal mechanism of action of nitrites.[12,20] Other, faster methemoglobin inducers, such as 4-dimethyaminophenol and hydroxylamine, also are effective as cyanide antidotes.[12,18] The benefits of sodium nitrite are maximal in experiments when sodium nitrite is given prophylactically, but the benefits still are evident when sodium nitrite is administered following cyanide poisoning. The production of methemoglobin by nitrite is slow, but when methylene blue is administered to prevent methemoglobin formation, nitrite still is an effective antidote.[12,20] Reasoning that nitrite-induced vasodilation might be part of the mechanism of action, the antidotal actions of other vasodilators were investigated. Only the Î±-adrenergic antagonists and ganglionic blockers demonstrate antidotal activity, and only when they are administered with sodium thiosulfate.[20] It is possible that the benefits of nitrites given shortly after cyanide result from reversal of cyanide-induced circulatory effects rather than reversal of the effects of cyanide on cytochrome oxidase.[17] Evidence in experimental heart and organ damage induced by hypoxia or hypotension suggest that the benefits of nitrite may be related to its ability to be converted to nitric oxide, a potent vasodilator. The conversion to nitric oxide appears to occur only in tissues or blood with the lowest oxygen concentrations.[5,13] Regardless of the exact mechanism of action, sodium nitrite clearly is effective soon after administration, even when methemoglobin levels are low. Thus a target methemoglobin level should not be used to determine the correct dose of sodium

nitrite, although care must be taken to avoid excessive methemoglobinemia.[10]

Administration of sodium nitrite should always be followed by sodium thiosulfate. Sodium thiosulfate donates a sulfur, which with the help of rhodanese (cyanide sulfur transferase) and mercaptopyruvate sulfurtransferase, carries sulfane sulfur to bind to cyanide, producing thiocyanate. Thiocyanate is a much less toxic substance than cyanide and is renally eliminated.[2]

Pharmacokinetics and Pharmacodynamics

The pharmacokinetics of sodium nitrite are not established. Most studies have been directed at measuring methemoglobin levels rather than nitrite levels.[18]

Sodium nitrite administered intramuscularly to dogs is not effective as a cyanide antidote unless atropine is given as pretreatment.[19] Most likely the rapid reversal of cyanide-induced bradycardia by

atropine allows sufficiently rapid absorption of sodium nitrite, which then can be effective.[19]

Clinical Use

As early as 1952, 16 patients were reported who had either ingested a cyanide salt or been exposed to hydrocyanic acid as a fumigant and survived with administration of nitrites and sodium thiosulfate.[4] Even patients who were unconscious or apneic have survived when given timely cardiopulmonary resuscitation and antidotal therapy.[4] Case reports attest to the ability of amyl nitrite, sodium nitrite, and sodium thiosulfate to reverse the effects of cyanide if they are administered in a timely fashion.[8,21] A 34-year-old man who ingested 1 g potassium cyanide became

comatose within 45 minutes. One hour after ingestion, he arrived in the emergency department, became apneic, and was intubated. His blood pressure was 134/84 mm Hg and pulse 84 beats/min; his pupils were dilated. At 1 hour 15 minutes, he was given 300 mg sodium nitrite intravenously over 20 minutes, followed by 12.5 g sodium thiosulfate. Seizure activity that began just prior to sodium nitrite infusion resolved rapidly, and by the time the sodium thiosulfate had finished infusing, his pupils were reactive and spontaneous respirations had returned.[8]

In another case, a 4-year-old child ingested twelve 50-mg tablets of laetrile (amygdalin), became unresponsive, and developed seizures within 90 minutes.[7] Upon arrival at a second hospital, the patient required intubation, he had no blood pressure, and his pupils were dilated and minimally responsive. Arterial blood gas analysis revealed: pH, 6.85; PCO_2 15 mm Hg; PO_2 169 mm Hg on 100% oxygen. The anion gap was 26. The patient's vital signs improved with intermittent inhalation of amyl nitrite pearls. Six hours after ingestion (and 1 hour 45 minutes after amyl nitrite administration), sodium nitrite and sodium thiosulfate obtained from another hospital were administered. Within 30 minutes of completion of 5 mL (0.33 mL/kg) 3% sodium nitrite solution by IV infusion, spontaneous respirations returned, and his blood pressure and pulse normalized. Over the next 3 hours, the patient's mental status and acidâ€“base balance improved. By 15 hours after ingestion, he was alert, oriented, and extubated. Elevated whole blood cyanide concentrations verified the ingestion.

Adverse Effects

Sodium nitrite works by inducing methemoglobinemia, but too much methemoglobinemia is potentially lethal. Therefore, nitrite dosages must be carefully calculated and nitrites administered to avoid excessive methemoglobinemia, especially in cases where other coexisting conditions, such as carboxyhemoglobin,

sulfhemoglobin, and anemia, might compromise hemoglobin oxygen saturation.[9,14] Children are particularly at risk for medication errors because of dosage miscalculations. The first reported death from methemoglobinemia was caused by the administration of an adult dose of sodium nitrite to a 17-month-old child suspected of ingesting a toxic amount of cyanide.[1]

In healthy adults, 300 mg IV sodium nitrite can produce peak methemoglobin concentrations of 10â€“18%.[4] Inhalation of crushed amyl nitrite ampules in human volunteers produces insignificant amounts of methemoglobin but does cause headache, fatigue, dizziness, and hypotension.[11]

Nitrites are potent vasodilators, so transient hypotension may occur. Other adverse effects include headache, nausea and vomiting.[4]

Administration and Dosing

Cyanide

Adults

Sodium nitrite 300 mg (10 mL of 3% solution) should be injected intravenously at a rate of 2.5â€“5 mL/min. The dose can be repeated at half the initial dose if manifestations of cyanide toxicity reappear or at 2 hours as prophylaxis.[15]

Amyl nitrite can be used prior to IV administration of sodium nitrite, but only as a temporizing measure until IV sodium nitrite can be administered. Break one amyl nitrite ampule and hold it in front of the patient's mouth for 15 seconds on and 15 seconds off.[6,15] Inhalation of amyl nitrite should be discontinued prior to sodium nitrite administration. The healthcare provider should not inhale the amyl nitrite.

Immediately following sodium nitrite infusion, 12.5 g (50 mL of 25% solution) sodium thiosulfate should be infused intravenously. The same needle and vein can be used. The dose can be repeated at half the initial dose if manifestations of cyanide toxicity reappear or at 2 hours as prophylaxis.[6,15]

In situations where additional formation of methemoglobin would be harmful, as in patients with smoke inhalation from a fire, the nitrite can be withheld and only the sodium thiosulfate administered, or, if hydroxocobalamin is available, sodium thiosulfate can be administered following the hydroxocobalamin.

Children

Intravenously inject 6â€“8 mL/m^2 (~0.2 mL/kg) of 3% sodium nitrite solution, not to exceed 10 mL or 300 mg.[15] A 0.2 mL/kg dose of 3% sodium nitrite solution is 6 mg/kg sodium nitrite. Based on an in vitro calculation, this dose would be safe for a child with a hemoglobin of 7 g/100 mL in the absence of other factors that could compromise hemoglobin oxygen saturation, such as carboxyhemoglobin or sulfhemoglobin.[1] The dose can be repeated at half the initial dose if manifestations of cyanide toxicity reappear or at 2 hours after the first dose as prophylaxis (see Table 121-2).[15]

As for adults, amyl nitrite can be used prior to IV administration of sodium nitrite, but only as a temporizing measure until IV sodium nitrite can be administered. Break 1 amyl nitrite ampule and hold it in front of the patient's mouth for 15 seconds on and 15 seconds off.[6,15] Inhalation of amyl nitrite should be discontinued prior to sodium nitrite administration. Immediately following sodium nitrite infusion, 7 g/m^2 or 0.5 g/kg (2 mL/kg) of 25% solution of sodium thiosulfate, not to exceed the adult dose of 12.5 g (50 mL of 25% solution) sodium thiosulfate, should be infused intravenously. The same needle and vein can be used. The dose can be repeated at half the initial dose if manifestations of cyanide toxicity reappear

or at 2 hours as prophylaxis.[6,15]

In situations where additional formation of methemoglobin would be harmful, as in patients with smoke inhalation from a fire in which other toxic gases may coexist, the nitrite can be withheld and only the sodium thiosulfate administered, or, if hydroxocobalamin is available, sodium thiosulfate can be administered following the hydroxocobalamin.

Availability

Sodium nitrite is available in ampules containing 300 mg in 10 mL (3% concentration) water for injection (USP). It contains no additives

or preservatives. It also is available in a kit containing 2 ampules of sodium nitrite (300 mg in 10 mL) with 12 ampules of amyl nitrite inhalants (0.3 mL) and 2 vials of sodium thiosulfate 12.5 g in 50 mL water for injection (USP), with boric acid or sodium hydroxide added to adjust the pH.[6]

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Antidotes in Depth

Sodium Thiosulfate

Mary Ann Howland

Sodium thiosulfate is an effective, relatively nontoxic antidote that detoxifies cyanide by donating a sulfur moiety to form thiocyanate. Thiocyanate is a much less toxic substance than cyanide and is renally eliminated. Sodium thiosulfate works synergistically with nitrites and hydroxocobalamin in the detoxification of cyanide. Because sodium thiosulfate does not compromise hemoglobin oxygen saturation, it can be used without nitrites in circumstances where the formation of methemoglobin would be detrimental, as in patients with smoke inhalation from fires who have elevated carboxyhemoglobin or preexistent methemoglobinemia.

History

In 1933 Chen et al.[2] noted that intravenous (IV) sodium thiosulfate was able to protect against 3 minimum lethal doses of sodium cyanide in dogs. Even more remarkable was the synergistic effects of combining sodium thiosulfate with either inhaled amyl nitrite or IV sodium nitrite, which protected the dogs against

10â€“18 minimum lethal doses of cyanide.[2,3]

Chemistry

The chemical formula of sodium thiosulfate is $Na_2S_2O_3$. The molecular weight of sodium thiosulfate is 248 daltons. It is a pentahydrate that is highly water soluble. Sodium hyposulfite is a synonym.

Mechanism of Action

The sulfur provided by sodium thiosulfate binds to cyanide with the help of rhodanese (cyanide sulfur transferase) and mercaptopyruvate sulfur transferase.[2,19,20] This sulfur, a sulfane sulfur (a divalent sulfur bound to one other sulfur), is the only type of sulfur that reacts with cyanide. Thiocyanate, a minimally toxic substance, is renally eliminated. In many different animal models, sodium thiosulfate protects against several minimum lethal doses of cyanide.[9,12] The addition of rhodanese increases the efficacy of sodium thiosulfate, but its use is impractical in the clinical setting.[12,21] The cationic site on rhodanese is crucial to cleaving the sulfurâ€“sulfur bond of thiosulfate and forming a sulfurâ€–rhodanese complex that readily reacts with cyanide.[20]

Rhodanese likely is not solely responsible for sulfurâ€–sulfur bond cleavage, as rhodanese is largely a mitochondrial enzyme found in the liver and skeletal muscle, and sodium thiosulfate is a divalent ion that poorly crosses membranes.[6,12,16,19,20] An additional theory proposes that both mercaptopyruvate sulfurtransferase and rhodanese are involved in the formation of sulfane sulfur in the liver from sodium thiosulfate and that serum albumin then carries the sulfane sulfur from the liver to other organs. When cyanide is present, albumin delivers this sulfur to cyanide, forming thiocyanate.[10,19,20,21]

Pharmacokinetics and Pharmacodynamics

Animal Studies

Sodium thiosulfate is a large divalent anion. Canine studies suggest that sodium thiosulfate rapidly distributes into the extracellular space and then slowly into the cell, perhaps with a carrier facilitating entry into the mitochondria.[16] When administered prior to cyanide, thiosulfate was able to convert >50% of the cyanide to thiocyanate within 3 minutes and increased the endogenous conversion rate more than 30 times.[18] Thiosulfate is filtered in the kidney and then secreted. At low plasma concentrations, thiosulfate is largely reabsorbed. At high plasma concentrations, filtration and secretion predominate.[7,16]

Human Volunteers

A volunteer study examined the pharmacokinetics of sodium thiosulfate and the fate of thiosulfate.[9,16] After injection of 150 mg/kg, Vd was 0.15 L/kg, distribution half-life was 23 minutes, and elimination half-life was 3 hours. The peak plasma thiosulfate concentration rose 100-fold. Approximately 50% of the drug was eliminated in 18 hours, mostly within 3 hours. Baseline thiosulfate concentrations were higher in starved patients and children, presumably because of their higher protein utilization and metabolism to thiosulfate.[9] Normally the kidney actively reabsorbs thiosulfate, but this study found that with exogenous administration, thiosulfate clearance equaled creatinine clearance.[9]

Another report researching the effects of thiosulfate as a cisplatin neutralizer found that thiosulfate had a half-life of 80 minutes, and that renal clearance accounted for only 30% of the total clearance.[17] Oral sodium thiosulfate is poorly absorbed and acts as

a laxative.[16]

Clinical Use

Cyanide

As early as 1952, 16 patients were reported who had either ingested a cyanide salt or been exposed to hydrocyanic acid as a fumigant and survived with administration of nitrites and sodium thiosulfate.[3] Even patients who were unconscious or apneic survived when given timely cardiopulmonary resuscitation and antidotal therapy.[3]

Case reports attest to the ability of sodium nitrite and sodium thiosulfate to reverse the effects of cyanide if they are administered in timely fashion.[4,15,16]

In the few reported cases where cyanide was ingested and sodium thiosulfate alone was used, all patients had favorable outcomes.[16] We advocate the use of amyl or sodium nitrite, or hydroxocobalamin if available, prior to sodium thiosulfate unless the

methemoglobin produced by administration of sodium nitrite is already at a potentially dangerous level, as occurs in patients with smoke inhalation from a fire who have elevated carboxyhemoglobin or methemoglobin levels.

Nitroprusside

Canine experiments reveal that when the nitroprusside infusion rate is >0.5 mg/kg/h, cyanide concentrations in the blood begin to rise. Coadministration of sodium thiosulfate with sodium nitroprusside in a 5:1 molar ratio (because nitroprusside contains 5 cyanide ions) prevents the rise in cyanide concentration.[16]

Adverse Effects

The toxicity of sodium thiosulfate is low. The LD_{50} for animals is approximately 3â€“4 g/kg, with death attributed to metabolic acidosis, elevated sodium concentration, and decreased blood pressure and PO_2.[12] Sodium thiosulfate delivers a significant sodium load and is hyperosmolar. Administering the infusion over 10â€“30 minutes attenuates some of these adverse effects.[16]

Adverse effects associated with therapeutic dosing include hypotension, nausea, and vomiting. The osmotic and diuretic effects presumably result from both the formation of thiocyanate and the intrinsic osmotic properties of the drug.[16]

Administration and Dosing

Cyanide

Adults

In a patient with presumed cyanide poisoning, the adult dose of sodium thiosulfate is 12.5 g (50 mL of 25% solution) administered intravenously either as a bolus injection or infused over 10â€“30 minutes, depending on the severity of the situation.[5] The dose of sodium thiosulfate can be repeated at half the initial dose if manifestations of cyanide toxicity reappear or at 2 hours as prophylaxis.[5]

In situations where the formation of methemoglobin by a nitrite would not be harmful, intravenously inject 300 mg sodium nitrite (10 mL of 3% solution) at a rate of 2.5â€“5 mL/min prior to administration of sodium thiosulfate. The dose of sodium nitrite can be repeated at half the initial dose if manifestations of cyanide toxicity reappear or at 2 hours as prophylaxis.[5]

Amyl nitrite can be used prior to IV administration of sodium

nitrite, but only as a temporizing measure until IV sodium nitrite can be administered. Break one amyl nitrite ampule and hold it in front of the patient's mouth for 15 seconds on and 15 seconds off.[5] Inhalation of amyl nitrite should be discontinued prior to administration of sodium nitrite.

Immediately following sodium nitrite infusion, 12.5 g (50 mL of 25% solution) of sodium thiosulfate should be infused intravenously. The same needle and vein can be used. The dose can be repeated at half the initial dose if manifestations of cyanide toxicity reappear or at 2 hours as prophylaxis.[5]

In situations where the additional formation of methemoglobin would be harmful, as in patients with smoke inhalation from a fire in which carboxyhemoglobin or methemoglobin may be present, the nitrite can be withheld and only the sodium thiosulfate administered.

When hydroxocobalamin becomes available in the United States, combined therapy of hydroxocobalamin with sodium thiosulfate, which is synergistic, would be ideal. When the formation of methemoglobin would not be detrimental, a combination of hydroxocobalamin, sodium nitrite, and sodium thiosulfate should be studied to determine if it is advantageous.[11]

Children

The dose of sodium thiosulfate in children is 7 g/m^2, up to the adult dose[5] or 0.5 g/kg (2 mL/kg of 25% solution) up to the adult dose of 12.5 g (50 mL of 25% solution).[16] The dose can be repeated at half the initial dose if manifestations of cyanide toxicity reappear or at 2 hours as prophylaxis.[5]

In situations where the formation of methemoglobin by a nitrite would not be harmful, intravenously inject 3% sodium nitrite solution at 6â€“8 mL/m^2 (~0.2 mL/kg), not to exceed 10 mL or 300 mg, prior to administration of sodium thiosulfate.[5] A 0.2

mL/kg dose of 3% sodium nitrite solution is approximately 6 mg/kg sodium nitrite. Based on an in vitro calculation, this dose would be safe for a child with a hemoglobin of 7 g/100 mL in the absence of other factors that could compromise hemoglobin oxygen saturation, such as carboxyhemoglobin, methemoglobin, or sulfhemoglobinemia.[1] The dose of sodium nitrite can be repeated at half the initial dose if manifestations of cyanide toxicity reappear or at 2 hours after the first dose as prophylaxis.[5]

Amyl nitrite can be used prior to IV administration of sodium nitrite, but only as a temporizing measure until IV sodium nitrite can be administered. Break one amyl nitrite ampule and hold it in front of the patient's mouth for 15 seconds on and 15 seconds off. Amyl nitrite inhalation should be discontinued prior to administration of sodium nitrite. The healthcare provider should not inhale the amyl nitrite.

Immediately following sodium nitrite infusion, sodium thiosulfate should be administered intravenously at a dose of 7 g/m^2 of 25% solution or 0.5 g/kg (2 mL/kg of 25% solution), up to the adult dose of 12.5 g (50 mL of 25% solution).[16] The same needle and vein can be used. The dose can be repeated at half the initial dose if manifestations of cyanide toxicity reappear or at 2 hours as prophylaxis.[5]

In situations where additional formation of methemoglobin would be harmful, as in patients with smoke inhalation from a fire, the nitrite can be withheld and only the sodium thiosulfate administered.

Nitroprusside

The usual dosage of sodium nitroprusside is 3 Âµg/kg/min (range 0.25â€“10 Âµg/kg/min).[13] Each mole of nitroprusside contains 5 cyanide ions. Prolonged infusion or doses in excess of the body's detoxifying capability may lead to thiocyanate or cyanide toxicity.

Some authors recommend adding 0.5 g sodium thiosulfate to each 50 mg of nitroprusside.[14] This dose of sodium thiosulfate usually is sufficient to prevent cyanide toxicity from nitroprusside; however, thiocyanate may accumulate, especially in patients with renal insufficiency. Thiocyanate is relatively nontoxic compared to cyanide but may produce dose-dependent tinnitus, miosis, hyperreflexia, and hypothyroidism, especially at serum concentrations >60 Âµg/mL,[13] and thiocyanate is hemodialyzable. Nitroprusside-induced cyanide toxicity should be treated like cyanide toxicity from any other cause: stop the nitroprusside dosage and administer sodium thiosulfate, sodium nitrite, or hydroxocobalamin (if available) according to the doses and precautions listed.

Availability

Sodium thiosulfate is available in 50-mL vials containing 12.5 g in water for injection (USP), with boric acid or sodium hydroxide

added to adjust the pH. It also is available in a kit containing 2 ampules of sodium nitrite (300 mg in 10 mL water for injection) with 12 ampules of amyl nitrite inhalants (0.3 mL) and 2 vials of sodium thiosulfate 12.5 g in 50 mL water for injection, with boric acid or sodium hydroxide added to adjust the pH.[5]

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Antidotes in Depth

Hydroxocobalamin

Mary Ann Howland

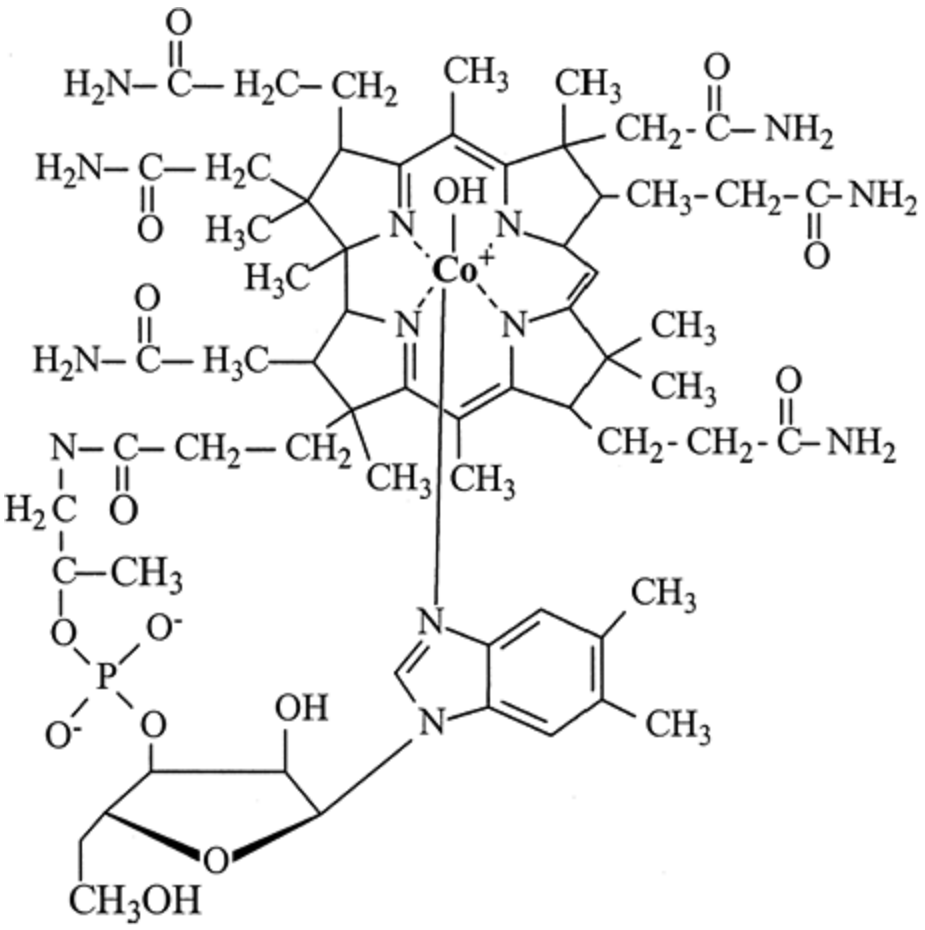

Figure. No Caption Available.

Hydroxocobalamin has been used as a cyanide antidote in France for many agent and then in combination with sodium thiosulfate.[14] This combination FDA as an orphan drug in 1985, and two US manufacturers are in the pro commercially available.

History

The antidotal actions of cobalt as a chelator of cyanide were recognized a Muschett is attributed with first using the cobalt-containing compound hy antidote to cyanide in mice.[21] Hydroxocobalamin subsequently was shown protecting against several minimum lethal doses of cyanide as long as an hydroxocobalamin to cyanide was used.[21 , 22 , 27]

Chemistry

The chemical formula for hydroxocobalamin is $C_{62}H_{89}CoN_{13}O_{15}P$. Its r 1346.47 daltons. It is a vitamin B_{12} precursor often referred to as vitamir difference between cyanocobalamin (vitamin B_{12}) and hydroxocobalamin CN group with an OH group. In vitro studies demonstrate that cyanide dis hydroxocobalamin to form cyanocobalamin.[20, 24] Hydroxocobalamin is a solubility of 1 part in 50 parts of water.[24]

Mechanism of Action

The cobalt in hydroxocobalamin combines with cyanide to form the relati cyanocobalamin.[21, 22] An ex vivo study using human skin fibroblasts de hydroxocobalamin penetrates intracellularly to form cyanocobalamin.[3] Oth as dicobalt ethylenediaminetetraacetic acid (EDTA), have been used both clinically in other countries, but their therapeutic index is narrow, especia cyanide. Additionally, idiosyncratic adverse effects make these compound [28] One mole of hydroxocobalamin binds 1 mole of CN. Given the molecula requires 52 g of hydroxocobalamin to bind 1 g of cyanide.[14] Use of hydr thiosulfate is synergistic and comparable to the sequential use of sodium thiosulfate.[14, 27]

Pharmacokinetics and Pharmacodynamics

Under an FDA Investigational New Drug Permit, the first pharmacokinetic hydroxocobalamin was performed in the United States and published in 1 who were heavy smokers were intravenously administered 5 g hydroxoco been obtained from a French manufacturer. The first four patients receive over 20 minutes. They then received 12.5 g (50 mL of 25% solution) of intravenously infused over 20 minutes. The next eleven patients received hydroxocobalamin but diluted with 100 mL water for injection (USP) and The serum and urine sampling of hydroxocobalamin differed in the two p somewhat different half-lives (4 hours vs. 1.27 hours). The alpha distribu hours in the group 1 patients. Peak hydroxocobalamin concentration aver Âµmol/L), and Vd averaged 0.38 L/kg. A mean dose of 62% was recovered

hours. Whole-blood cyanide concentrations significantly decreased in all hydroxocobalamin. A problem with this study was the short collection time plasma hydroxocobalamin concentrations making the pharmacokinetic an

A second pharmacokinetic study performed in adult victims of smoke inha dramatically different results.[18] This finding is not unexpected given the populations.[1, 19] These patients were administered hydroxocobalamin 5 g over 30 minutes, starting within 30 minutes of their removal from the fir half-life of hydroxocobalamin was 1.86 hours, elimination half-life was 26. sampling up to 6 days, and Vd was 0.45 L/kg. The peak plasma cyanoco 212 Âµmol/L. In the one patient who subsequently was determined not to cyanide, the hydroxocobalamin elimination half-life was 13.6 hours and Vd clearance of hydroxocobalamin was 37% in the cyanide-exposed patients unexposed patient.

A study of 12 fire victims in France who were suspected of having cyanid conducted.[16] These patients received intravenous hydroxocobalamin 5 g in (USP) over 30 minutes, and pretreatment and posttreatment cyanide cor cyanocobalamin concentrations were analyzed. In patients with cyanide Âµmol/L, a linear relationship existed between the blood cyanide concent of cyanocobalamin. In the 3 patients with blood cyanide levels >40 Âµmo cyanocobalamin reached a plateau, implying that all of the hydroxocobala the one patient with a blood cyanide level >40 Âµmol/L who received a s hydroxocobalamin, the cyanocobalamin concentration subsequently rose.[2

The protein binding and tissue distribution of cyanide, hydroxocobalamin, likely are different.[17] In addition, hydroxocobalamin probably causes redi the intracellular to the intravascular space.[17]

Clinical Use

Many case reports in France document the efficacy of hydroxocobalamin thiosulfate for treatment of cyanide toxicity.[7, 15] In one study, 69 patie were administered a mean dose of 8 g hydroxocobalamin by IV infusion Two thirds of the patients with documented cyanide levels >39 Âµmol/L,

considered a fatal concentration, survived.

Hydroxocobalamin was also able to prevent the rise in cyanide concentra nitroprusside infusion in patients who received hydroxocobalamin compare not.[8]

Most animal studies demonstrate a synergistic effect of hydroxocobalamir

Adverse Effects

Hydroxocobalamin has a large therapeutic index and appears to be well doses have been administered to animals, with no adverse effects.[22, 25] g/kg.

Red discoloration of mucous membranes, plasma, and urine may occur and days after therapy.[6] Rarely, allergic reactions are reported.[24] Prior chroni hydroxocobalamin or cyanocobalamin for treatment of vitamin B_{12} deficie with development of anaphylaxis.[14]

The hydroxocobalamin solution should not be administered through the sa same time as the thiosulfate solution[10] because sodium thiosulfate binds renders it inactive.[23]

An in vitro study found statistically significant alterations in serum conce aminotransferase (AST), total bilirubin, creatinine, magnesium, and iron administration.[9] Colorimetric assays are most likely to be adversely affec hydroxocobalamin and cyanocobalamin have an intensely red color.

Administration and Dosing

Cyanide

A dose of 70 mg/kg (not to exceed 5 g initially) administered intravenous recommended. This dose can be administered as an IV push in cases of arrest.[6, 7] The dose can be repeated (not to exceed a total dose of 15 g The second and subsequent doses are to be infused intravenously over a hours), except in refractory cardiac arrest or collapse.[6]

The World Health Organization has recommended 10 mL (4g) of 40% sol intravenously over 20 minutes.[29]

The adult dose of sodium thiosulfate is 12.5 g (50 mL of 25% solution) a intravenously as either a bolus injection or infused over 10 to 30 minutes severity of the situation. The dose of sodium thiosulfate can be repeated manifestations of cyanide toxicity reappear or at 2 hours as prophylaxis. methemoglobin would not be detrimental, a combination of hydroxocobala sodium thiosulfate may be considered.[14 , 27]

Nitroprusside

When nitroprusside is administered, use of concomitant hydroxocobalamir accumulation and toxicity in both animal models and in humans.[7 , 8 , 30]

Availability

The FDA designated hydroxocobalamin as an orphan product on Septembe is Orphan Medical in Minnesota, and the trade name will be CYANOKIT.[12]

Hydroxocobalamin is available in France under the trade name Cyanokit 2 a 2.5-g vial of lyophilized powder by LIPHA SA-Le Pressoir Vert. The solu reconstituted by diluting one 2.5-g vial of lyophilizate in 100 mL sterile, chloride solution for injection.[10]

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Chapter 122
Methemoglobin Inducers

Dennis Price

A 27-year-old man was brought to the emergency department (ED) by a with a complaint of shortness of breath. The patient had a history of acq immunodeficiency syndrome (AIDS), complicated by *Candida* esophagitis episodes of *Pneumocystis carinii* pneumonia. His medical regimen include zidovudine and dapsone. He recently had become depressed over the deat close friend and had taken â€œall of his medicationsâ€• in a suicide atte hours before arrival at the ED. He had vomited once at home and began short of breath approximately 2â€“3 hours later.

On physical examination, the patient appeared cachectic, cyanotic, and sh breath. He appeared less short of breath than his level of cyanosis sugge vital signs were: blood pressure, 90/40 mm Hg; pulse, 140 beats/min; r rate, 40 breaths/min; rectal temperature, 100.2Â°F (37.9Â°C). A pulse o revealed 88% oxygen saturation on room air. The skin was diaphoretic wi track marks. Examination was remarkable for perioral cyanosis. His neck supple and without jugular venous distension. The chest was clear to aus with good airflow. Cardiac examination revealed a tachycardia with norma S_2 heart sounds and a grade 1/6 systolic ejection murmur heard best at t

lower sternal border. The abdomen was nontender with good bowel sound hepatomegaly. Examination of the extremities revealed no clubbing or ed the nail beds were markedly cyanotic. His neurologic examination was no 100% non-rebreather oxygen mask was applied, and the patient was atta cardiac monitor. An intravenous (IV) line was inserted, and blood sample obtained for a complete blood count, electrolytes, blood urea nitrogen (B glucose, and acetaminophen concentration. After a few minutes of oxyge the patient's heart rate decreased to 128 beats/min, but he was still cya tachypneic. The pulse oximeter continued to read 86â€“88% oxygen sat Arterial blood gas analysis was obtained while the patient was receiving supplemental oxygen, but the house officer thought that the specimen m venous because it was darkly colored. The results were: pH, 7.34: PCO_2 Hg; PO_2 , 400 mm Hg; calculated oxygen saturation, 99%. The patient w 60 g activated charcoal in a slurry of water.

The electrocardiogram (ECG) showed a sinus tachycardia with normal axi intervals, ST segments, and T waves. The chest radiograph was normal. acetaminophen concentration was zero. All other laboratory test results unremarkable. Cooximetry of an arterial specimen revealed total hemoglo g/dL; oxyhemoglobin, 64%; methemoglobin, 33%; deoxyhemoglobin, 1% carboxyhemoglobin, 2%.

The patient received 60 mg methylene blue (0.1 mL/kg of 1% solution) intravenously over 20 minutes. Pulse oximetry dropped to 73â€“75% for minutes with no change in his clinical symptoms. Approximately 40 minu methylene blue infusion, the patient was less cyanotic, and a repeat methemoglobin level was 6%. Three hours later, he was again short of b cyanotic, and his methemoglobin level had risen to 24%. Another 60 mg methylene blue was infused and led to improvement in his color and tac within 20 minutes. His repeat methemoglobin level was 4%.

Over the first 24 hours, the patient required a total of 3 doses of methyl therapy. His hemoglobin subsequently fell to 6.2 g/dL, resulting in a tran 2 units of packed red blood cells. While in the hospital, he was evaluated psychiatrist and enrolled in an AIDS support group. The patient was disc days after admission with a hemoglobin of 9.7 g/dL and normal cooximet

Introduction

Biologic systems constantly use endogenous mechanisms to protect them from oxidants to survive. Cellular components such as enzyme systems a structural elements are spontaneously oxidized and have increased rates oxidation when exposed to exogenous oxidants. Methemoglobin occurs wh iron atom in hemoglobin loses 1 electron to an oxidant, and the ferrous (state of iron is transformed into the ferric (Fe^{3+}) state. Although methe is always present at low levels in the body, methemoglobinemia is define as an abnormal elevation of methemoglobin level.

Reduced hemoglobin functions reliably as an oxygen transporter because protected heme pocket it shares an outer valence electron with the oxyge transports. Normally it releases this oxygen without giving up an electron occasionally this electron is lost to the departing oxygen in the process o autooxidation. Oxidation is increased in the presence of some hereditary conditions such as hemoglobin M disease. However, oxidizing xenobiotics produce methemoglobin by direct interaction with the Fe^{2+} moiety. These exogenous products are the major source of oxidant stress to the individu the most frequent cause of methemoglobinemia. Although typically not lif threatening, methemoglobinemia may produce symptoms of cellular hypo should be considered in the differential diagnosis of the

cyanotic patient who has no apparent cardiovascular cause. In the cases methemoglobinemia and sulfhemoglobinemia, cyanosis is not caused by deoxyhemoglobin but rather by the color imparted to the skin as a result oxidized hemoglobin. Methylene blue, an exogenous electron carrier, red oxidized hemoglobin in patients with methemoglobinemia.

History and Epidemiology

Methemoglobin was first described by Felix Hoppe-Seyler in 1864.[32] In 18 case of transient drug-induced methemoglobinemia was described.[68] In t 1930s, methemoglobinemia was recognized as a predictable adverse effec sulfanilamide use, and methylene blue was recommended for treatment o

ensuing cyanosis.[44] Some authors recommended concurrent use of methy when sulfanilamides were used.[106] In 1948, an enzyme defect was report twin brothers. The defect caused cyanosis in the absence of cardiopulmor disease that responded to ascorbic acid therapy.[34]

Methemoglobinemia can be hereditary or acquired. The hereditary types a with only several hundred cases reported in the literature.[8, 23, 46, 62, The frequency with which xenobiotic-induced methemoglobinemia occurs unknown. The American Association of Poison Control Centers (AAPCC) a Toxic Exposure Surveillance System (TESS) data show approximately 100 methylene blue as an antidote. However, these data certainly underestim incidence of this poisoning because Poison Control Centers are not notifie cases.

Cooximetry data were collected at two teaching hospitals and a significan of elevated methemoglobin levels were found. A total of 5248 cooximetry were performed over 28 months on 1267 patients. Six hundred sixty test revealed methemoglobin levels >1.5% in 414 patients (some patients had than one test). Thus, 12.5% of all tests and 19.1% of all patients who u cooximetry had an abnormal methemoglobin level. One hundred thirty-ei patients with peak methemoglobin levels >2% were identified. The mean methemoglobin level was 8.4% (range 2.1â€“60.1%), and patients ranged from 4 days to 86 years.

Benzocaine spray accounted for the most seriously poisoned patients (n = a mean peak methemoglobin of 43.8% (range 19.1â€“60.1%). Dapsone for the largest number of cases (n = 58), with a mean peak of 7.6% (ran 2.1â€“34.1%). Thirty three of 35 patients who had methemoglobin levels were considered to have signs and symptoms consistent with acquired methemoglobinemia and 12 received methylene blue. There was 1 fatality near fatalities that were directly attributed to methemoglobinemia. These likely represent an underestimation of the true number of cases of methemoglobinemia at these institutions because cooximetry was perform upon physician orders (the physician suspected a dyshemoglobinemia), ar fourth of cases with levels >2% were found incidentally when cooximetry performed in the catheterization laboratory to provide data on oxyhemog

deoxyhemoglobin. In addition, not all patients taking dapsone were teste Extrapolating these data throughout the country suggests underreporting substantial underrecognition of this entity with its potential danger.

The incidence of methemoglobinemia induced in the workplace is poorly documented. Two reports, one in 1964 and another in 1986, document s hundred cases of chemically induced cyanosis resulting from methemoglc Several more workplace exposures are documented as case reports. Underreporting and underrecognition associated with minimal symptoms by low levels may account for this phenomenon.[14 , 95]

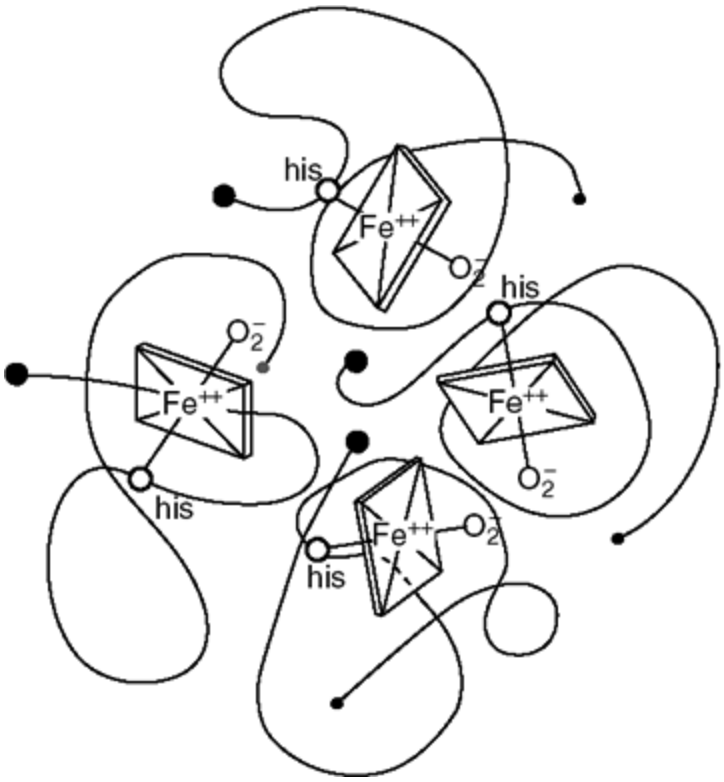

Figure 122-1. Hemoglobin molecule symbolically represented with its he center surrounded by the globin portion of the molecule.

his = histidine

Hemoglobin Physiology

Hemoglobin consists of 4 polypeptide chains noncovalently attracted to o another. Each of these subunits carries 1 heme molecule deep within the structure. The polypeptide chain protects the iron moiety of the heme m from inappropriate oxidation (Figure 122-1).

The iron is held in position by 6 coordination bonds. Four of these bonds between iron and the nitrogen atoms of the protoporphyrin ring; the fifth bond sites lie above and below the protoporphyrin plane. The fifth site is by histidine of the polypeptide chain. Changes in the amino acid sequence polypeptide chain, as occur in hemoglobin M, influence this protective â€œpocket,â€• allowing easier iron oxidation (Figure 122-2).

This process is referred to as *hemoglobin autooxidation.* The sixth coord site is where most of the activity within hemoglobin occurs. Oxygen trans occurs here, and this site is involved with formation of methemoglobin or monoxide poisoning (Figure 122-3). It is at this site that an electron is l oxidant xenobiotics, transforming iron from its ferrous to its ferric form, producing oxidized hemoglobin or methemoglobin.

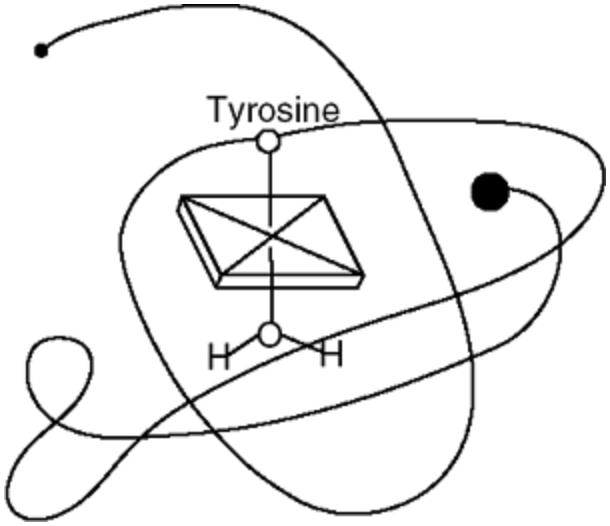

Figure 122-2. Hemoglobin M occurs when histidine is replaced by tyrosin amino acid sequence of the polypeptide chain. Hemoglobin M is more eas autooxidized (as shown) to methemoglobin.

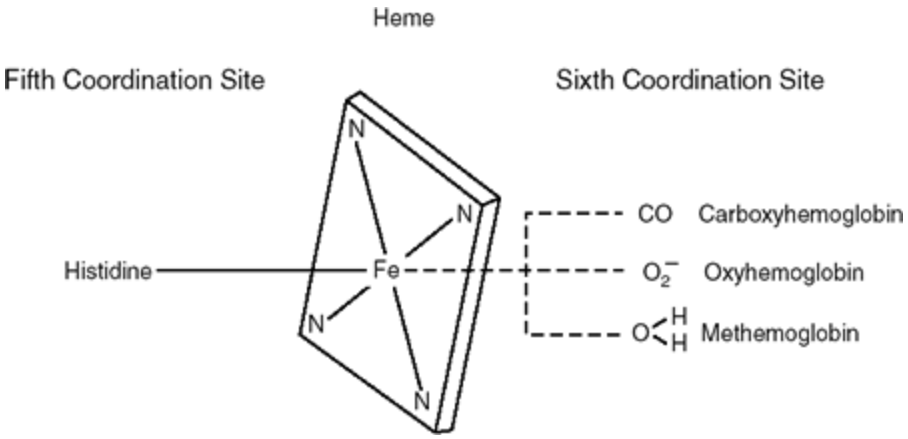

Figure 122-3. Heme molecule depicted with its bonding sites. Oxyhemo carboxyhemoglobin, and methemoglobin all involve the sixth coordination site of iron.

Hemoglobin transports an oxygen molecule only when its iron atom is in reduced ferrous state (Fe^{2+}). During oxygen transport, the iron atom ac transfers an electron to oxygen, thus transporting oxygen as a superoxid particle $Fe^{3+}\ O_2^{-}$. When oxygen is released, the ferrous state is restore hemoglobin is ready to accept another oxygen molecule. Interestingly, a percentage of oxygen is released from hemoglobin with its shared electro (forming superoxide $\hat{A}\cdot O_2$), leaving iron oxidized. This sixth coordination becomes occupied by a water molecule. This abnormal unloading of oxyg contributes to the steady-state level of approximately 1% methemoglobin normal individuals. In summary, the differences between hemoglobin and methemoglobin are subtle and involve only a small part of the hemoglobi molecule but make hemoglobin incapable of oxygen transport.

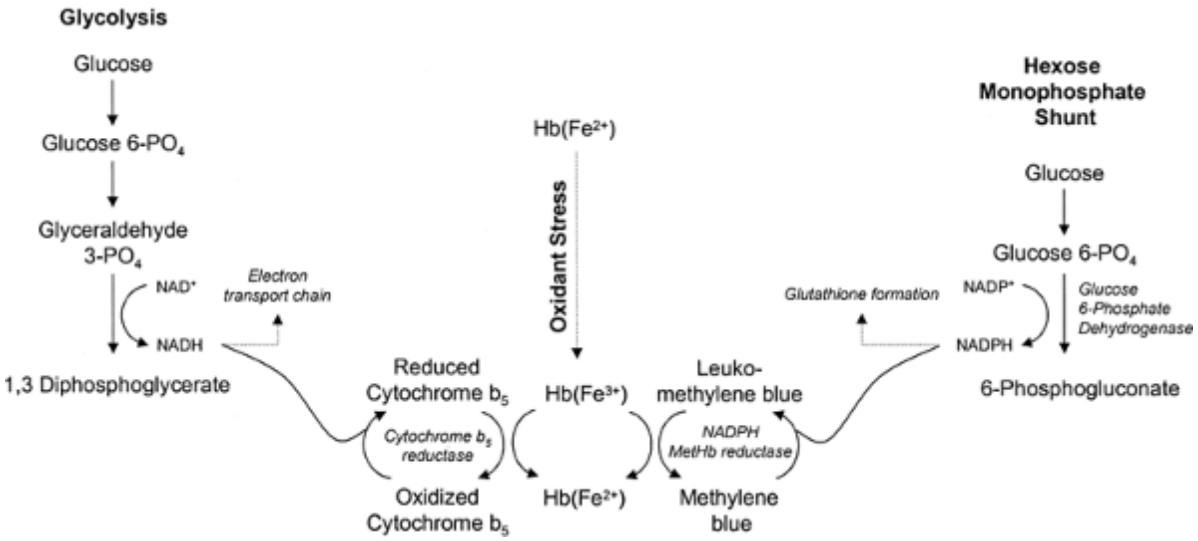

Figure 122-4. Role of glycolysis in the Embden-Meyerhof pathway and th methylene blue in the reduction of methemoglobin.

Methemoglobin Physiology and Kinetics

Because of the spontaneous and xenobiotic-induced oxidation of hemoglo erythrocyte has developed multiple mechanisms to maintain the normal le methemoglobin at <1%.[11] All of these systems donate an electron to the iron atom. The half-life of methemoglobin acutely formed as a result of e to oxidants is between 1 and 3 hours.[50 , 67] With continuous exposure to oxidant, the half-life of methemoglobin appears prolonged.

Quantitatively the most important reductive system requires nicotinamide dinucleotide (NADH), which is generated in the Embden-Meyerhof glycoly pathway (Figure 122-4). NADH serves as an electron donor, and along w enzyme NADH methemoglobin reductase, reduces the oxidized ferric (Fe^{3} to the more functionally favorable ferrous (Fe^{2+}) iron state. There are r cases of hereditary deficiencies of the enzyme NADH methemoglobin red [63] Individuals who are homozygotes for this enzyme deficiency usually ha methemoglobin levels of 10â€“50% under normal conditions without any xenobiotic stressors. Individuals who are heterozygotes do not ordinarily demonstrate methemoglobinemia except when they are subject to oxidan stresses. Additionally, because this enzyme system lacks full activity unti

approximately 4 months of age, infants are more susceptible than adults oxidizing stresses.[73, 109]

Oxidized iron can be reduced nonenzymatically using ascorbic acid and r glutathione as electron donors, but this method is much slower and quar less important under normal circumstances.

Within the red cell is another enzyme system for reducing oxidized iron th dependent on the nicotinamide adenine dinucleotide phosphate (NADPH) in the hexose monophosphate shunt pathway (Figure 122-4). NADPH red a small percentage of methemoglobin under normal circumstances. Becaus relatively minor role in methemoglobin reduction, patients with a deficien NADPH methemoglobin reductase do not exhibit methemoglobinemia unde circumstances.[94]

When the NADPH methemoglobin reductase system is provided with an e electron carrier such as methylene blue, this system is accelerated and ca in the reduction of oxidized hemoglobin.[30] (Methylene blue is reduced to leukomethylene blue by NADPH-dependent methemoglobin reductase, usi NADPH as the electron donor; leukomethylene blue directly reduces the h [Antidotes in Depth: Methylene Blue]).

Etiologies

Nitrates and nitrites are powerful oxidizing agents that are 2 of the most methemoglobin-forming compounds. Sources of nitrates and nitrites inclu water, food, industrial compounds, and pharmaceuticals. The contaminatio drinking water occurs mainly with nitrates because nitrites are easily oxid the highly soluble nitrates in the environment. When water containing ni based fertilizers and nitrogenous waste from animal and human sources i to run off fields, it easily contaminates shallow rural wells. Foods such as cauliflower, carrots, spinach, and broccoli have high nitrate content, and enter the food chain as preservatives in meat products such as hot dogs sausage.[4, 5, 18]

The oxidation reaction of nitrates that occurs both in vivo and in vitro is

and poorly understood. Ingested nitrates are reduced to nitrites by bacter gastrointestinal tract (especially in infants) and then can be absorbed, u leading to methemoglobin production. This conversion is not essential, h because nitrates themselves can oxidize hemoglobin.[30 , 42 , 98] Some qu whether well water consumption alone can cause serious methemoglobine the absence of comorbid disease.[26]

In the past, nitrates were a too common cause for well water contaminati infant fatalities were associated with methemoglobinemia.[20 , 59 , 66] A nu reports from the midwest United States demonstrated the problems of pc constructed shallow wells that permit contamination by surface waters c chemicals, pesticides, fertilizers, and microorganisms.[69] In several South studies, 20â€“50% of wells contained both coliform bacteria and water th exceeded the Environmental Protection Agency (EPA) standards for perm quantities of nitrogen as nitrates (10 ppm or 10 mg/L).[51] In New York St wells from rural farms demonstrated elevated concentrations of nitrogen compounds, and 15.7% were found to have nitrate concentrations >10 m

Nitroglycerin (glyceryl trinitrate) and organic nitrates are more effectivel absorbed through mucous membranes and intact skin than from the gastrointestinal (GI) tract. Their onset of action is more rapid, and the to is much greater, when mucous membrane or cutaneous absorption occurs [82] Aromatic amino and nitro compounds may indirectly produce methemo These agents do not form methemoglobin in vitro; therefore, they are ass do so by in vivo metabolic chemical conversion to some active intermedia [55 , 99]

Elevated methemoglobin and carboxyhemoglobin concentrations are found victims of fires and automobile exhaust fume poisoning.[10 , 49 , 52 , 60] He induced hemoglobin denaturation in burn patients and the inhalation oxid nitrogen from combustion are suggested to be causative factors for methemoglobin formation.

Topical anesthetics are widely used to facilitate multiple procedures and l implicated in the most serious of toxic methemoglobin cases.[1 , 40 , 56 , 75] Cetacaine spray (14% benzocaine, 2% tetracaine, 2% butylaminobenzoat Hurricaine spray (20% benzocaine) are the agents most commonly associ

production of methemoglobin. The dosing recommendations are difficult t comprehend (eg, 0.5-second spray repeat once) and often are ignored. O showed that the dose is dependent on the residual volume in the canister physical orientation of the canister as the spray is being applied.[57]

A review of 52 months of data from the FDA's Adverse Event Reporting S demonstrated 132 cases of benzocaine-induced methemoglobinemia. Ben spray was implicated in 107 severe adverse events and 2 deaths. In 123 the product was a spray. In 69 cases where the dose was specified, 37 p received a single spray.[70]

This FDA effort is exclusively based on self-reporting and probably greatl underestimates the extent of the problem.[38] The FDA itself has estimated approximately 10% of serious events are reported and that some studies â‰¤1% serious event reporting.[70]

Nitric oxide delivered by inhalation is used to treat persistent pulmonary hypertension of the newborn and other cardiopulmonary diseases associa pulmonary hypertension because it is a potent vasodilator.[90] Although nit is a potent oxidant, limited methemoglobin production with minimal clinic significance occurs when nitric oxide doses <40 ppm are used. Most patie maintain methemoglobin levels <4%.[47 , 105] Some cases of serious toxici occurred because of excessive dosing or unintentional overdose. Patients nitric oxide therapy, particularly at higher doses, who develop unexplaine cyanosis or a fall in oxygen saturation by pulse oximetry should be evalu methemoglobinemia.

Dapsone is increasingly implicated as a cause of methemoglobinemia beca its frequent use by patients with AIDS. Cases of prolonged methemoglob from dapsone ingestion are related to the long half-life of dapsone and th conversion to its methemoglobin-forming metabolites.[25] Patients receivin dapsone should be carefully monitored for methemoglobinemia.[108]

The bladder anesthetic phenazopyridine is among the most commonly re causes of methemoglobinemia.[19 , 28 , 35 , 37 , 72 , 96] For this reason its u limited today. Other causes of methemoglobinemia are listed in Table 12

Clinical Manifestations

The clinical manifestations of methemoglobinemia are related to impaired carrying capacity and delivery to the tissue. The clinical manifestations o methemoglobinemia usually are more severe than those produced by a corresponding degree of anemia. This discordance occurs because methe not only decreases the available oxygen-carrying capacity but also increa affinity of the unaltered hemoglobin for oxygen. This shifts the oxygen h dissociation curve to the left, which further impairs oxygen delivery (Chap This effect is attributed to the formation of heme compounds intermediat between normal reduced hemoglobin (all 4 iron atoms are ferrous) and methemoglobin, in which one or more of the iron moieties are in the ferr , [22] The degree to which this high oxygen affinity hemoglobin reduces ox delivery to the tissue from arterial blood is unclear, but is clinically signi

Because the symptomatology associated with methemoglobinemia is relate impaired oxygen delivery to the tissue, concurrent diseases such as anen congestive heart failure, chronic obstructive pulmonary disease, and pne may greatly increase the

clinical effects of methemoglobinemia (Figure 122-5). Predictions of sym and recommendations for therapy are based on methemoglobin concentra previously healthy individuals with normal total hemoglobin concentration

Hereditary

- Hemoglobin M
- Cytochrome b_5 reductase deficiency (homozygote and heterozygote)

Acquired

A. Medications

- Amyl nitrite
- Benzocaine
- Dapsone
- Lidocaine
- Nitric oxide
- Nitroglycerin

Nitroprusside
Phenacetin
Phenazopyridine
Prilocaine (local anesthetic)
Quinones (chloroquine, primaquine)
Sulfonamides (sulfanilamide, sulfathiazide, sulfapyridine, sulfamet

B. Other xenobiotics

Aniline dye derivatives (shoe dyes, marking inks)
Butyl nitrite
Chlorobenzene
Fires (heat-induced denaturation)
Food adulterated with nitrites
Food high in nitrates
Isobutyl nitrite
Naphthalene
Nitrates
Nitrites
Nitrophenol
Nitrous gases (seen in arc welders)
Silver nitrate
Trinitrotoluene
Well water (nitrates)

Pediatric

Reduced NADH methemoglobin reductase activity in infants (<4 months

Associated with low birth weight, prematurity, dehydration, acidosis, c and hyperchloremia.

TABLE 122-1. Common Etiologies of Methemoglobinemia

Cyanosis is a consistent physical finding in patients with substantial methemoglobinemia due to the deeply pigmented color of methemoglobin Cyanosis typically occurs when just 1.5 g/dL of methemoglobin is present represents only 10% conversion of hemoglobin to methemoglobin if the hemoglobin is 15 g/dL. In contrast, 5 g/dL deoxyhemoglobin (representing

hemoglobin) in the deoxygenated form is needed to produce the same de cyanosis.

In previously healthy individuals, methemoglobin concentrations of 10â€' usually result in cyanosis without apparent adverse clinical manifestations 20â€“50% methemoglobin levels, dizziness, fatigue, headache, and exer dyspnea may develop. At approximately 50% methemoglobin, lethargy ar usually appear. The lethal concentration probably is >70% (Table 122-2).

The cyanosis associated with methemoglobinemia is generalized, being b peripheral and central. Patients often appear in less distress or less ill th patients with cyanosis secondary to cardiopulmonary causes. A wide rang pigment levels produce the same degree of cyanosis.

Some patients may have a mixed etiology for their cyanosis, such as cardiopulmonary-induced hypoxia in addition to methemoglobinemia. The oxygen-carrying capacity in such situations may be drastically reduced (F 122-5 ; O_2 content of blood is discussed in Chap. 22).

Symptomatology of methemoglobinemia is determined not only by the ab concentration of methemoglobin but also by its rates of formation and e Levels of methemoglobin that may be clinically benign when caused by h defects or maintained chronically, likely will produce more severe signs w acutely acquired. Healthy subjects lack the compensatory mechanisms th develop over a lifetime in individuals with hereditary compromise, such a erythrocytosis and increased 2,3-diphosphoglyceric acid.

Certain xenobiotics characteristically produce prolonged methemoglobinem instance, dapsone has a very long half-life.[24 , 25] In the presence of rena drugs such as phenazopyridine are eliminated slowly and cause prolonged methemoglobinemia.

Some compounds producing oxidant stress may have associated toxicities unrelated to the development of methemoglobinemia, such as seizures ca benzocaine and lidocaine or hypotension caused by nitrates.[77]

Diagnostic Testing

For individuals in whom methemoglobinemia is suspected, a source for th stress should be sought. Arterial blood gas sampling may reveal blood wit characteristic chocolate brown color. (See ILMETHB in the Image Library http://www.goldfrankstoxicology.com) (In patients with known methemoglobinemia, a venous blood gas will

be accurate in demonstrating the degree of methemoglobinemia.) Arterial should be normal, reflecting the adequacy of pulmonary function to deliv dissolved oxygen to the blood. However, arterial PO_2 does not measure t important physiologic parameter, the hemoglobin oxygen saturation (SaO oxygen content of the blood. When the partial pressure of oxygen is know oxyhemoglobin and deoxyhemoglobin are the only species of hemoglobin, saturation can be calculated accurately from the arterial blood gas. Howe other hemoglobins are present (eg, methemoglobin, sulfhemoglobin, or carboxyhemoglobin), then the fractional saturation of the hemoglobin mus determined by the cooximeter.

1â€“<3 (Normal)
None
3â€“15
Possibly none
Slate gray cutaneous coloration
Pulse oximeter will read low SaO_2
15â€“20
Cyanosis
Chocolate brown blood
20â€“50
Dyspnea
Exercise intolerance
Headache
Fatigue
Dizziness, syncope
Weakness
50â€“70
Tachypnea

Methemoglobin Concentration (%)	Signs and Symptoms
Metabolic acidosis	
Dysrhythmias	
Seizures	
CNS depression	
Coma	
>70	
Grave hypoxic symptoms	
Death	

TABLE 122-2. Signs and Symptoms Typically Associated wit Methemoglobin Concentrations in Healthy Patients with Nor Hemoglobin Concentrations

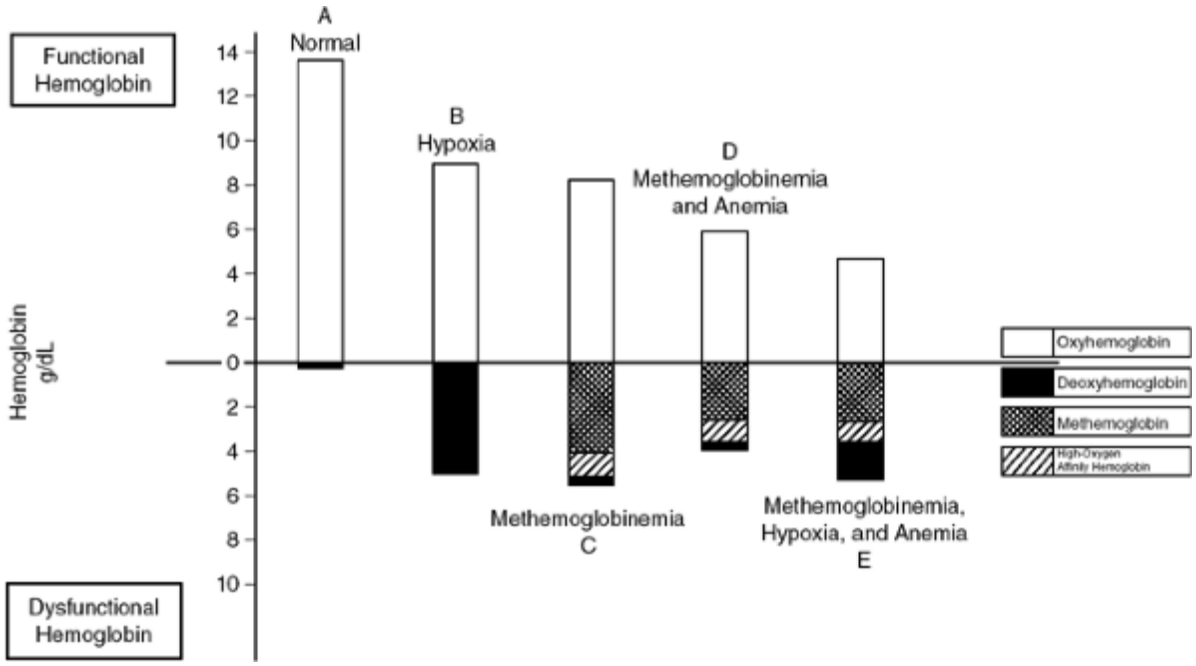

Figure 122-5. Clinical manifestations of methemoglobinemia depend on of methemoglobin and on host factors such as preexisting disease, anemi hypoxemia. Five examples of arterial blood gas and cooximeter analyses presented. A. Blood gas from a normal individual with 14 g/dL of hemogl Almost all hemoglobin is saturated with oxygen. B. Blood gas from a pati

cardiopulmonary disease producing cyanosis in which only 9 g/dL of hemo capable of oxygen transport. C. Methemoglobin level of 28% in an otherv normal individual will reduce hemoglobin available for oxygen transport to (approximately 4 g/dL of methemoglobin and 1.3 g/dL of high-oxygen-af hemoglobin because of the left shift of the oxyhemoglobin dissociation cu Same degree of methemoglobin as in C but in a patient with a hemoglobir g/dL. Only 6 g/dL of hemoglobin would be capable of oxygen transport. E Methemoglobinemia and anemia to the same degree as D but in a hypoxi

The cooximeter is a spectrophotometer that identifies the absorptive characteristics of several hemoglobin species at different wavelengths. B oxyhemoglobin, deoxyhemoglobin, methemoglobin, and carboxyhemoglobi have different absorptions at the different measuring points of the cooxi their proportions and concentrations can be determined. Some newer ins have an expanded spectrum of detection and are able to identify fetal he and sulfhemoglobin.[29 , 111]

The pulse oximeter applied to a patient's finger at the bedside was develo estimate oxygen saturation trends in critically ill patients. The device tak advantage of the unique absorptive characteristics of oxyhemoglobin and deoxyhemoglobin and the different concentrations of these 2 hemoglobin during different phases of the pulse. Each manufacturer has calibrated its using volunteers breathing progressively increasingly hypoxic gas mixtures absence of a dyshemoglobin.[86 , 97 , 104] In other words, the oxygen satu values displayed on the pulse oximeter are derived independently by eacl manufacturer, who develops a formula using their own hardware and sens manufacturer then compares this value to a set of validation data derived experimental population.

Methemoglobin interferes with pulse oximetry in a complicated fashion. N manufacturer provides any validation data for situations where any dysh is present. All manufacturers disclaim accuracy under such circumstances. similar fashion to the cooximeter, the pulse oximeter reads absorbance of wavelengths of 660 and 940 nm, which are selected to efficiently separat oxyhemoglobin and deoxyhemoglobin. However, methemoglobin absorptio

these wavelengths is greater than that of either oxyhemoglobin or deoxyhemoglobin.[6, 76] Therefore, when methemoglobin is present, the r become inaccurate. The degree of inaccuracy is unique for each brand of instrument and may be influenced by signal quality, skin temperature, re error induced by blood cells and other factors, such as finger thickness ar perfusion.[88]

In the dog model, the pulse oximeter oxygen saturation (SpO_2) values d increasing methemoglobin levels. This fall in SpO_2 is not exactly proportio the fraction of methemoglobin, however, as the pulse oximeter overestim level of actual oxygen saturation. For example, in a case where the methemoglobin

level measured in the blood using a cooximeter was 20%, the pulse oxim indicated an SpO_2 of 90%. However, as the methemoglobin concentration approached 30%, the pulse oximeter saturation values decreased to abou and then leveled off, regardless of how much higher the methemoglobin became.[6, 103]

Blood gas analyzer
Blood
Partial pressure of dissolved oxygen in whole blood
PO_2
Also gives information about pH and PCO_2
Calculates SaO_2 from the partial pressure of oxygen in plasma; inaccurate of Hb other than OxyHb and DeoxyHb are present
An abnormal Hb form may exist if gap exists between ABG and pulse oxi
Cooximeter
Blood
Directly measures absorptive characteristics of oxyhemoglobin, deoxyhe methemoglobin, carboxyhemoglobin at different wavelength bands in who
SaO_2 % MethHb, %CoHb, %OxyHb, %DeoxyHb
Measures hemoglobin species directly
Provides data on hemoglobin only; most instruments will not measure sulfhemoglobin, HbM, and some other forms of Hb

Measuring Device	Source	What is Measured?	How Are Data Expressed?	Benefits	Pitfalls
Most accurate method to determine oxygen content of blood					
Pulse oximeter					
Monitor Sensor on patient					
Absorptive characteristics of oxyhemoglobin in pulsatile blood assuming t presence of only OxyHb and DeoxyHb in vivo					
SpO_2					
Moment-to-moment bedside data					
Inaccurate data, if interfering substances are present: methemoglobin, sulfhemoglobin, carboxyhemoglobin, methylene blue					
Maximum depression 75â€“85%, regardless of how much methemoglobin present					

TABLE 122-3. Hemoglobin Oxygenation Analysis

From our experience and that of others, levels of oxygen saturation (SpO lower than 85% in humans can be indicated by pulse oximetry when methemoglobin levels rise above 30%.[39, 56, 87, 92, 102] These differenc from variations in the way different model pulse oximeters deal with methemoglobin interference.[87, 88] Therefore, the clinician must (1) und how the particular pulse oximeter measures oxygen saturation when methemoglobin levels are elevated and (2) recognize that cooximetry determination is needed when methemoglobinemia is suspected.

Although the pulse oximeter reading in patients with methemoglobinemia be as accurate as desired, it may, nevertheless, be helpful when it is cor with that of the arterial blood gas. If there is a difference between the *m* oxyhemoglobin saturation of the pulse oximeter (SpO_2) and the *calculate* oxyhemoglobin saturation of the arterial blood gas (PO_2), then a â€œsa gapâ€• exists. The calculated SpO_2 will be greater than the measured Sp methemoglobin is present (Table 122-3). Hyperlipidemia may also interf accurate cooximetry determinations.[71, 100]

Acquired Methemoglobinemia and Infancy

Infants are more susceptible to methemoglobinemia than adults. The NAD methemoglobin reductase of an infant is not fully active until age 4â€“6 Infants who are bottle-fed may be exposed to nitrates and nitrites in well Additionally, infants have a relatively large body surface area, making al of oxidants via the skin more of a threat to them than to adults.

Methemoglobinemia of unknown origin is often reported in infants,[53 , 78 110] who are usually ill for other reasons, such as dehydration, acidosis, a diarrhea.[41] These infants can have methemoglobin levels in the 20â€“67% with severe consequences.[48]

Methemoglobinemia and Hemolysis

The enzyme defect responsible for most instances of oxidant-induced her glucose-6-phosphate dehydrogenase (G6PD) deficiency. A review of hem addressed the confusion regarding the relationship between hemolysis an methemoglobinemia.[9 , 31]

Confusion persists today for a number of reasons. Both hemolysis and methemoglobinemia are caused by oxidant stress, and hemolysis can occ following episodes of methemoglobinemia. Certain protective mechanisms oxidants (NADPH production) are the same in both disorders. Excessive blue treatment of methemoglobin reportedly produces hemolysis.[36 , 45]

However, oxidants damage the erythrocyte at different locations in the tw disorders. Hemolysis occurs when oxidants damage the hemoglobin chain directly as electron acceptors or through the formation of hydrogen perox other oxidizing free radicals. Oxidants forming irreversible bonds with su groups of hemoglobin cause denaturation and precipitation of the protein precipitates are quantitatively sufficient to form

Heinz bodies within the erythrocyte. Cells with large numbers of Heinz bo removed by the reticuloendothelial system, producing hemolysis. Alterna some oxidants can destroy the erythrocyte membrane directly, causing

nonâ€“Heinz body hemolysis. Methemoglobinemia does not necessarily pr hemolysis if untreated.

Numerous cases describe the occurrence of hemolysis following methemoglobinemia, although most poisonings with oxidant compounds d manifest both types of toxicity. The combined occurrence is reported with dapsone,[24 , 25 , 74] phenazopyridine,[19 , 28 , 37 , 72 , 96] amyl nitrite,[15] an aniline.[43 , 51 , 65] These instances of combined occurrences may represen incidental toxicity of an oxidizing agent or the depletion of all cellular de against oxidants. Currently, it is not possible to predict with any level of when hemolysis will follow methemoglobinemia, but clearly there is an ir incremental risk.

Another source of confusion concerning hemolysis and methemoglobinemia reduced glutathione (GSH) is required to protect against both toxic man Erythrocytes can withstand hemolytic oxidant damage as long as they car maintain adequate levels of reduced glutathione, the principal cellular ar Glutathione is maintained in its reduced form by using NADPH as its redu agent. Thus, cells with reduced capacity to produce NADPH (ie, erythrocy patients with G6PD deficiency, or cells with depleted reduced glutathione are susceptible to hemolysis. In the presence of methemoglobinemia, red glutathione plays a minor role as a reducing agent, but NADPH is necessa successful antidotal therapy with methylene blue. This codependence on reducing power of NADPH links the two disorders. Competition for NADPH oxidized glutathione and exogenously administered methylene blue is po to be the cause of methylene blue-induced hemolysis, that is, competitive inhibition of glutathione reduction. Methylene blue itself is an oxidant, but assessment of the hemolytic potency of varied drugs, methylene blue in d 390â€“780 mg proved to be only a moderate hemolytic agent.[54] The clin importance of this phenomenon is uncertain. It may be easier to consider hemolysis and methemoglobin formation as subclasses of disorders of ox stress. They should be considered separate clinical entities that share lim characteristics.

Management

For most patients with mild methemoglobinemia, no therapy is necessary than withdrawal of the offending xenobiotic, as reduction of the methem will occur by intact normal reconversion mechanisms (NADH methemoglo reductase). However, even small elevations of methemoglobin levels shou considered problematic because they suggest the individual is at a point further oxidant stress may cause methemoglobin levels to rise. An indivic receiving dapsone with a small elevation of methemoglobin level may be susceptible to clinically significant methemoglobinemia if challenged with benzocaine-containing anesthetic or an increase in dapsone dose. In the setting, continued absorption, prolonged half-life, and toxic intermediate metabolites may prolong methemoglobinemia. Patients should be examin carefully for signs of physiologic stress related to decreased oxygen deliv the tissue (Figure 122-6). Obviously, changes in mental status or ischem pain necessitates immediate treatment, but subtle changes in behavior or inattentiveness may be signs of global hypoxia and should be treated. Ab vital signs (eg, tachycardia and tachypnea) or lactic acidosis thought to b by tissue hypoxia or the functional anemia of methemoglobinemia should treated aggressively. A methemoglobin level alone generally is not an ad indication of need for therapy, although many recommend empiric therapy patients with methemoglobin concentrations above 25%.

The most widely accepted treatment of methemoglobinemia is administrat methylene blue 1â€“2 mg/kg body weight infused intravenously over 5 m (0.1â€“0.2 mL/kg of 1% solution). Use of a slow 5-minute infusion helps painful local responses from rapid infusion. When a painful reaction occurs be minimized by flushing the IV rapidly with at least 15â€“30 mL of fluid the infusion. Clinical improvement should be noted within 1 hour of meth blue administration if an elevated methemoglobin level is etiologic. If cya does not disappear within 1 hour of the infusion, a second dose should be while other factors are considered. Methylene blue causes a transient dec the pulse oximetry reading because of its blue color and excellent absorp 660 mm.[58 , 61 , 107]

Use of methylene blue in patients with G6PD deficiency is controversial. G deficient patients have been excluded from most treatment protocols bec methylene blue is a mild oxidant and case reports suggest methylene blu

An estimated 200 million people worldwide have this enzyme deficiency a incidence in the United States is highest among African Americans (11%) However, because of the lack of immediate availability of the test for G6F deficiency, most patients who need treatment

receive methylene blue therapy before their G6PD status is known. Althou patients with G6PD deficiency undoubtedly have been treated unknowingl case reports of toxicity are described.

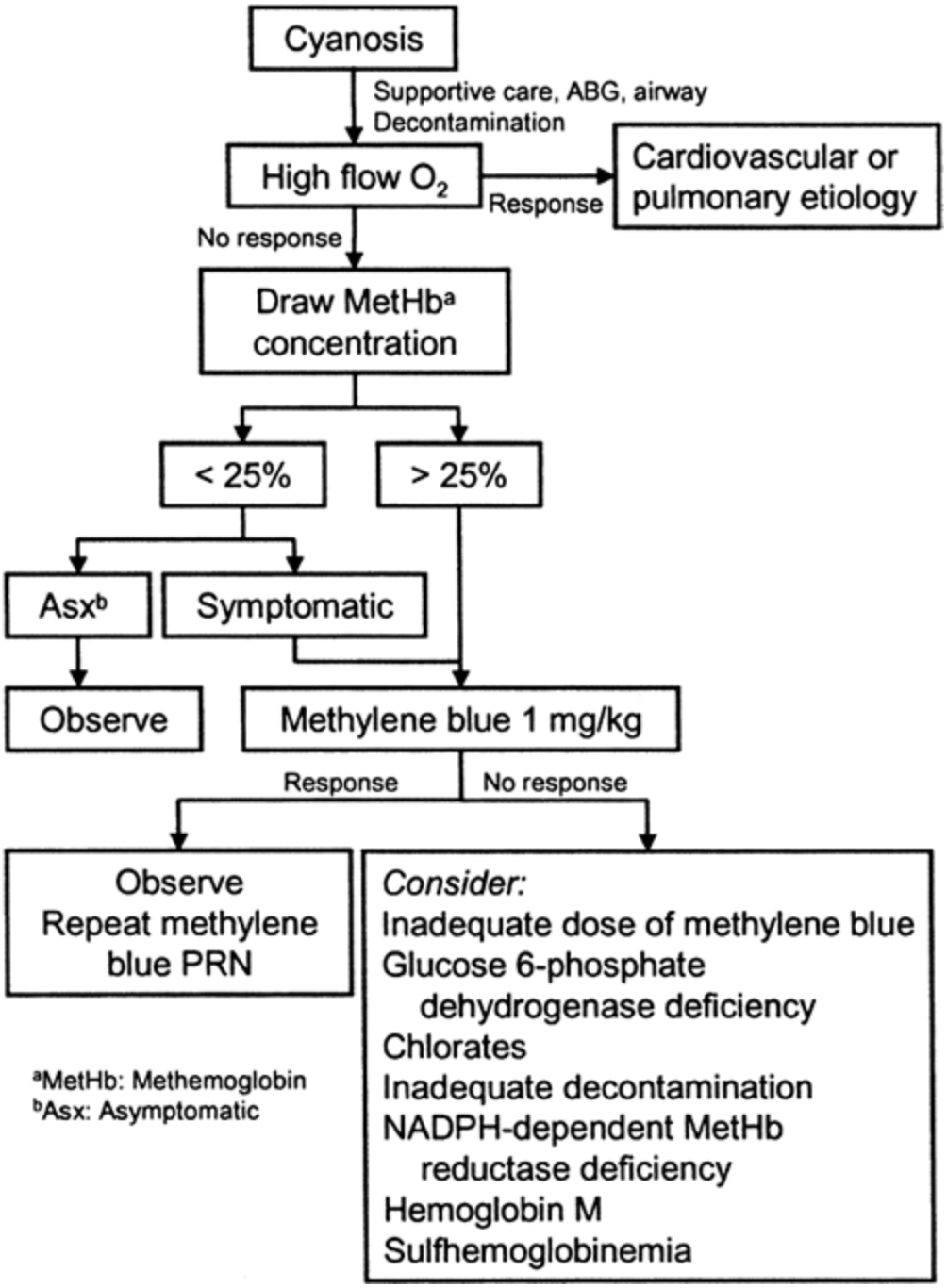

Figure 122-6. Toxicologic assessment of the cyanotic patient.

Even the authors of the review most frequently cited as a rationale for w methylene blue treatment were unsure whether the methylene blue given G6PD-deficient patient produced hemolysis.[91] The dose of methylene blue

the patient under study was small, and the patient had taken other xeno capable of producing hemolysis. The enzyme activity in patients with G6P deficiency is variable and they manifest different levels of disease in resp oxidant stress. For all of these reasons, the judicious use of methylene bl warranted in most patients with G6PD deficiency and symptomatic methemoglobinemia.

If methylene blue treatment fails to significantly relieve the methemoglob number of possibilities should be considered. The cause of the oxidant str not have been identified and adequately removed, allowing for continuing oxidation. In such situations, decontamination of the gut and skin cleansi be assured. Additional doses of methylene blue are also indicated. Patient have sulfhemoglobinemia, or are deficient in NADPH methemoglobin redu have severe G6PD deficiency, may not improve following methylene blue

Theoretically, exchange transfusion or hyperbaric oxygen may be benefici methylene blue is ineffective. Both interventions are time consuming and but hyperbaric oxygen allows the dissolved oxygen time to protect the pa while endogenous methemoglobin reduction occurs. Ascorbic acid is not in the management of acquired methemoglobinemia because the rate at w ascorbic acid reduces methemoglobin is considerably slower than the rate normal intrinsic mechanisms.[12] Methylene blue has no therapeutic effect sulfhemoglobinemia.[83]

Specific Management for Dapsone-Induced Methemoglobinemia

Treatment of dapsone deserves special consideration because of the freq with which it occurs and its tendency to produce prolonged methemoglob -hydroxylation of dapsone to its hydroxylamine metabolite by a cytochrom mediated reaction is partly responsible for methemoglobin formation in b therapeutic and overdose situations. Both the parent compound and it m are oxidants with long half-lives. Cimetidine is an inhibitor of this metabo pathway and reduces methemoglobin levels during therapeutic dosing.[89] overdose situations, cimetidine may exert some protective effects and sh

used with methylene blue. When dapsone is therapeutically indicated but levels of methemoglobin are found, cimetidine should be considered as a for reducing oxidant stress.

Sulfhemoglobin

Sulfhemoglobin is a hemoglobin variant in which a sulfur atom is incorpo the heme molecule, but is not attached to iron. The exact location of the atom in the porphyrin ring is unclear. Sulfhemoglobin is a darker pigment methemoglobin, producing cyanosis when only 0.5 g/dL of blood is affect cyanosis produced is similar to that produced by methemoglobinemia. Sulfhemoglobin also produces a drop in pulse oximetry readings.[2 , 79] In laboratory, sulfhemoglobin is characterized by its spectrophotometric ap and its lack of reaction when cyanide is added to the mixture. In contrast methemoglobin absorption peak is eliminated by the addition of cyanide. this reading is not routinely done in clinical laboratory practice, and the often is made based upon the patient's failure to improve with methylene [16 , 64 , 79 , 80] In the laboratory, isoelectric focusing techniques allow for delineation.

Sulfhemoglobin is an extremely stable compound that is eliminated only v blood cells are removed naturally from circulation. Although the oxygen-capacity of hemoglobin is reduced by sulfhemoglobinemia, unlike methemoglobinemia there is a decreased affinity for oxygen in the remai â€œunalteredâ€• hemoglobin. The oxyhemoglobin dissociation curve is s the right (see Figure 22-2), making oxygen more available to the tissues phenomenon reduces the clinical effect of sulfhemoglobin at the tissue le

Sulfhemoglobin can be produced experimentally in vitro by the action of sulfide on hemoglobin and was produced in dogs fed elemental sulfur.[62] A of drugs induce sulfhemoglobin in humans, including acetanilid, phenacet nitrates, trinitrotoluene, and sulfur compounds. Most of the drugs that pr methemoglobinemia have been reported to produce

sulfhemoglobinemia in various degrees. Sulfhemoglobinemia is recognized individuals with chronic constipation and in those who abuse laxatives.[62]

122-4 lists some differences between methemoglobin and sulfhemoglobin

Definition
Commonly accepted: hemoglobin with an oxidized heme moiety
Less well understood: hemoglobin with sulfur attached through an oxidat reaction
Clinical appearance
Cyanosis, may appear ill
Cyanosis, appears less ill at a comparable concentration
Spectrophotometric characteristics
Peak absorption at 570 and 620 mm
Peak absorption at 520 and 626 mm
Reversible by antidote
Yes
No
Level necessary to detect cyanosis
1.5 g/dL
0.5 g/dL
Etiologies
See Table 122-1
Similar to methemoglobin, an oxidant and a source of sulfur needed to p sulfhemoglobin
Diagnosis
Cooximetry
Cyanide added to blood in laboratory will completely eliminate methemog not sulfhemoglobin; some newer cooximeters measure directly
Effects on oxyhemoglobin dissociation curve
Decreased oxygen-carrying capacity, shifts curve to left with impaired O_2 to tissues
Decreased oxygen-carrying capacity, shifts curve to right, improving O_2 tissue
Response to methylene blue
Very good
Eliminated only with RBC natural turnover, no specific treatment

Methemoglobin Sulfhemoglobin

TABLE 122-4. Differences Between Methemoglobin and Sulfhemo

Sulfhemoglobinemia usually requires no therapy other than withdrawal of offending xenobiotic. It appears that patients with sulfhemoglobinemia co the attention of clinicians earlier because sulfhemoglobinemia produces r cyanosis than methemoglobinemia at a lower sulfhemoglobin level. There antidote for sulfhemoglobinemia because it results from an irreversible c bond that occurs within the hemoglobin molecule. Exchange transfusion sulfhemoglobin levels, but this approach usually is not necessary.

Summary

Oxidation of hemoglobin is a rare but treatable etiology of cyanosis. In th absence of findings of cardiopulmonary disease, cyanosis from methemo is likely. The diagnosis is confirmed by evaluation of blood by cooximetry treatment is clinically indicated, methylene blue is the treatment of choic source of oxidant stress should be sought and eliminated. Patients with lo methemoglobin levels should be considered to be under oxidant stress an for more serious methemoglobinemia if oxidant stressors persist.

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Antidotes in Depth

Methylene Blue

Mary Ann Howland

Methylene blue is an extremely effective antidote for acquired methemoglobinemia. Methylene blue also has other actions, including inhibition of nitric oxide synthase and guanylyl cyclase and inhibition of the generation of oxygen free radicals. These effects are used to explain the beneficial effects of methylene blue in the hepatopulmonary syndrome,[39] treatment of priapism, modulation of streptozocin-induced insulin deficiency, prevention and treatment of ifosfamide-induced encephalopathy, and reduction of development of postsurgical peritoneal adhesions.[14,15,19,22,32,39,45]

History

Methylene blue was initially recommended for use as an intestinal and urinary antiseptic and subsequently recognized as a weak antimalarial agent.[18] In 1933, Williams and Challis successfully used methylene blue for treatment of aniline-induced methemoglobinemia.[49]

Pharmacology

Methylene blue is tetramethylthionine chloride,[18] a basic thiazin dye. Methylene blue is an oxidizing agent, which, in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) and NADPH methemoglobin reductase, is reduced to leukomethylene blue (see Figure 122-5). Leukomethylene blue then becomes available to reduce methemoglobin to hemoglobin.[10,18,46] Reduction of methemoglobin via this NADPH pathway is limited under normal circumstances. However, in the presence of methylene blue, the role of the NADPH pathway is dramatically increased (4â€“5 times in dogs) and becomes the most efficient means of methemoglobin reduction. This property makes methylene blue the treatment of choice for methemoglobinemia.

Pharmacokinetics

The pharmacokinetics of methylene blue were studied in animals and now volunteers following IV and oral administration of 100 mg.[10,11,12,33] Methylene blue exhibits complex pharmacokinetics consistent with extensive distribution into deep compartments, followed by a slower terminal elimination with a half-life of 5.25 hours. Peak concentrations after oral administration were reached in 1â€“2 hours, but were approximately 80â€“90 nmol/L, as opposed to 8000â€“9000 nmol/L following IV administration. Based on the human data in conjunction with the data obtained in rats, extensive first-pass distribution following oral administration is responsible for the substantial differences in whole-blood concentrations achieved by the routes of administration.[33] Total urinary excretion at 24 hours accounts for 28.6% after IV administration versus 18.5% after oral administration. In both cases, one third was in the leukomethylene blue form.

Adverse Effects

Reports of the apparent paradoxical ability of methylene blue to induce methemoglobinemia suggest an equilibrium between the ability of methylene blue to oxidize hemoglobin directly to methemoglobin and the ability of methylene blue (through the NADPH and NADPH methemoglobin reductase pathway and leukomethylene blue production) to reduce methemoglobin to hemoglobin.[5,6] Methylene blue does not produce methemoglobin at doses of 1â€“2 mg/kg. The equilibrium seems to favor the reducing properties of methylene blue, unless excessively large doses of methylene blue are administered[4,17,48] or the NADPH methemoglobin reductase system is abnormal. This equilibrium constant may vary substantially, as 20 mg/kg IV in dogs and 65 mg/kg intraperitoneally in rats failed to produce methemoglobinemia.[42] In the earliest studies, 50â€“100 mL of a 1% concentration (500â€“1000 mg) of methylene blue was used intravenously in volunteers[29] and to treat patients with aniline dye-induced methemoglobinemia.[49] In these studies, methemoglobin levels, measured when symptoms were most pronounced, were approximately 1.0 g/dL (0.4â€“8.3% of total hemoglobin), and unlikely to be solely responsible for the adverse effects demonstrated. Other consequential adverse effects included shortness of breath, tachypnea, chest discomfort, burning sensation of the mouth and stomach, initial bluish-tinged skin and mucous membranes, paresthesias, restlessness, apprehension, tremors, nausea and vomiting, dysuria, and excitation. Urine and vomitus had a blue color. These studies with limited evidence led to the recommendation to avoid doses >7 mg/kg.

In high doses, methylene blue can induce an acute hemolytic anemia independent of the presence of methemoglobinemia.[17,27] In doseâ€“response studies in glucose-6-phosphate dehydrogenase (G6PD)-deficient homozygous African American men, daily doses of 390â€“780 mg (5.5â€“11 mg/kg) of methylene blue produced hemolysis,[26] which was comparable to the results following exposure to 15 mg of primaquine base.[26] Because of the

sensitivity of neonates (hemoglobin F [HbF] and diminished NADH reductase) to these risks, the smallest effective dose of methylene blue should be used.[21,25] Because oxidizing agents can independently result in chemical-induced Heinz body hemolytic anemia, the contribution of methylene blue often is difficult to elucidate.[25]

Methylene blue is a dye. It will alter pulse oximeter readings.[7] Large doses may interfere with the ability to detect a clinical decrease in cyanosis; therefore, repeat cooximeter measurements and arterial blood gas analysis should be used in conjunction with clinical findings.

Intraamniotic injection of methylene blue may result in a number of adverse effects, including infants born with skin dyed blue (with resultant inaccurate pulse oximetry readings), methemoglobin, hemolysis, phototoxic skin reactions, or intestinal obstruction.[7,9,24,27,28,30,36,44] One infant exposed in utero at 5.5 weeks was normal at birth.[24] Enteral methylene blue in an excessive dose with subsequent leakage into the peritoneum of a premature neonate most likely resulted in a hemolytic anemia appearing 3 days later.[1]

Methylene blue leads to a bluish-green discoloration of the urine and may cause dysuria.[35] Intravenous methylene blue is irritating

and exceedingly painful. It may cause local tissue damage even in the absence of extravasation.[36] Subcutaneous and intrathecal administration are contraindicated.[36]

Xenobiotic-Induced Methemoglobinemia

Methylene blue doses of 1â€“2 mg/kg intravenously or 65 to 130 mg orally every 4 hours reversed sulfanilamide-induced methemoglobinemia.[20,47] With these regimens, a very rapid fall in

methemoglobin occurred accompanied by disappearance of cyanosis. Subsequent investigations confirmed the effectiveness and safety of IV doses of 1â€“2 mg/kg methylene blue in reversing the methemoglobinemia produced by sulfanilamide,[47] aniline dye,[13] and silver nitrate, among other xenobiotics.[43]

Use in Patients with Glucose-6-Phosphate Dehydrogenase Deficiency

Methylene blue is suggested to be ineffective in reversing methemoglobinemia in patients with G6PD deficiency[38] because G6PD is essential for generation of NADPH (Chap. 24). Without NADPH, methylene blue cannot act in the reduction of methemoglobin. However, G6PD deficiency is an X-linked hereditary deficiency with more than 400 variants. The red cells containing the more common G6PD A^- variant found in 11% of African Americans retain 10% residual activity, mostly in younger erythrocytes and reticulocytes. In contrast, the enzyme is barely detectable in those of Mediterranean descent who have inherited the defect. Therefore, it is impossible to predict before the use of methylene blue who will or will not respond, and to what extent. Currently, it appears that most individuals have adequate G6PD and express deficiency states in relative terms. This variable expression of their deficiency allows an effective response to most oxidant stresses.

Theoretically, normal cells might convert methylene blue to leukomethylene blue, and the leukomethylene blue might diffuse into G6PD-deficient cells and effectively reduce methemoglobin to hemoglobin.[3] Before it is assumed that G6PD deficiency is responsible for continued methemoglobin levels despite administration of methylene blue, continued toxin absorption and/or continued methemoglobin production must always be excluded. However, when therapeutic doses of methylene blue fail to have an impact on the methemoglobin level, the possibility of

G6PD deficiency should be considered, further doses of methylene blue should not be administered and because of the risk for methylene blue-induced hemolysis. In these cases, exchange transfusion and hyperbaric oxygen are potential alternatives (Chap. 122).

Dosing

Methylene blue is indicated in patients with symptomatic methemoglobinemia. This usually occurs at methemoglobin levels >20%, but may occur at lower levels in anemic patients or those with cardiovascular, pulmonary, or central nervous system compromise.

In most cases, doses of 1â€“2 mg/kg given intravenously over 5 minutes, followed immediately by a fluid flush of 15â€“30 mL to minimize local pain, is both effective and relatively safe. In neonates, 0.3â€“1 mg/kg doses often are effective.[23] The onset of action is rapid, and effects usually occur within 30 minutes.

Repetitive dosing of methylene blue may be required in conjunction with efforts to decontaminate the GI tract when there is continued absorption or slow elimination of the xenobiotic producing the methemoglobinemia, such as with dapsone.[41] Additionally, cimetidine is indicated to prevent further formation of the methemoglobin-inducing metabolite of dapsone.[8,37]

A continuous IV infusion of methylene blue at 0.1 mg/kg/h or 3â€“7 mg/h (in a concentration of 0.05% in 0.9% sodium chloride solution) also has been used.[2,41] However, this method of administration is not adequately studied.

Intraosseous administration of 0.3 mL of 1% solution (1 mg/kg) of methylene blue over 3â€“5 minutes into the anterior tibia of a 6-week-old infant was well tolerated.[21,31] Methylene blue is ineffective in treating other entities such as sulfhemoglobinemia (Chap. 122).

Availability

Methylene blue is available in 10-mL 1% ampules containing 10 mg/mL.

Summary

Methylene blue is an effective reducing agent for patients with acquired induced methemoglobinemia. When used in the proper dose, its onset of action is rapid and adverse reactions are limited. Repeat doses often are required when methemoglobin-producing drugs with a long duration of effect such as dapsone are ingested.

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Chapter 123
Smoke Inhalation

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Firefighters discovered an unresponsive 39-year-old man in a smoke-filled room at an apartment building fire. At the scene, his initial vital signs were: palpable blood pressure, 70 mm Hg; pulse, 160 beats/min; respiratory rate, 0/min. A large amount of soot was noted in the patient's upper airway during endotracheal intubation in the field. He was placed on 100% oxygen during transport. On arrival at the emergency department (ED), he was unresponsive to painful stimuli and had a palpable systolic blood pressure of 100 mm Hg. No evidence of head trauma or skin burns was noted. Pupils were equal and reactive to light; conjunctival irritation and corneal burns were noted. He had singed nasal hairs and soot in his oropharynx, and carbonaceous material was suctioned from his endotracheal tube. Diffuse wheezing was present in all lung fields. He was attached to a ventilator with 100% oxygen, and aerosolized albuterol was administered. His blood pressure improved with intravenous (IV) fluid therapy. He did no respond to IV naloxone (2 mg), thiamine (100 mg), or dextrose (25 g).

His initial electrocardiogram (ECG) revealed sinus tachycardia at 160 beats/min without evidence of ischemic changes. Initial laboratory data revealed: white blood cell count, 14,000 cells/mm^3; hemoglobin, 11.3 g/dL; sodium, 141 mEq/L; potassium, 3.5 mEq/L; chloride, 111 mEq/L; bicarbonate, 12 mEq/L; BUN, 27 mg/dL; creatinine, 0.7 mg/dL; blood glucose, 80 mg/dL. Blood lactate concentration was 14 mEq/L. Arterial blood gas analysis on 100% oxygen revealed pH, 7.17; PCO_2, 30 mm Hg; PO_2, 150 mm Hg. Cooximeter measured a carboxyhemoglobin concentration of 38% and a methemoglobin concentration of 0.8%. Blood ethanol concentration was 179 mg/dL. A chest radiograph was unremarkable.

Because of his critical condition, the presence of metabolic acidosis, and his exposure to a fire environment, the possibility of cyanide poisoning was entertained, and 12.5 g of sodium thiosulfate was given intravenously. The patient was transferred to the intensive care unit, where mechanical ventilation and fluid resuscitation continued. He had no further significant hemodynamic instability. Within 4 hours of admission, he received hyperbaric oxygen therapy. He had progressive improvement in mental status and was awake 6 hours after admission. The patient had complete recovery with no neurologic deficits. An admission whole-blood cyanide concentration of 1.80 Âµg/mL (<1 Âµg/mL normal) was reported 12 hours later.

Introduction

Smoke inhalation is the leading cause of death from fires. Smoke contains numerous toxins that are generated during combustion. Combustion, or pyrolysis, is the rapid decomposition or oxidation of a substance (fuel) by heat. Smoke is a complex mixture of heated air, suspended solid and liquid particles, gases, fumes, aerosols, and vapors. Combustion products resulting from a fire are difficult to predict; in fact, even the composition of smoke is quite variable within the same fire environment.[10,37,112] The chemical composition of the fuel, oxygen availability, and temperature determine the

combustion products found in smoke (Table 123-1).[10,30,42,50,61,101,112,118,119,137] The extensive variety of materials used in our environment contributes to the broad spectrum of combustion products present in typical smoke.[30]

The association of smoke inhalation with burns produces a more serious systemic illness.[41,130,135,141,158] Burn victims with smoke inhalation injury have higher morbidity and mortality than those with burns only; the incidence of acute respiratory failure is 61% in burn victims with smoke inhalation injury versus 12% in those with burns only.[8,29,143,156,159] In addition, burn edema is accentuated and nonburned tissue has increased vascular permeability when associated with smoke inhalation injuries.[40]

History and Epidemiology

Disastrous fires are frequent reminders of the role of inhalation injuries in fire deaths.[37,79] In the United States, a fire department responds to a fire every 20 seconds.[73] In 2003, the National Fire Protection Agency reported 1,584,500 fire incidents in the United States, with 3925 fire deaths and 18,125 fire injuries.[73] Compared with other countries, the United States has one of the highest fire death rates in the world.[90] An estimated 50â€“80% of these fire deaths result from smoke inhalation injuries, rather than dermal burns or trauma.[16,62,101,160] More than 30% of patients hospitalized in burn units develop concomitant pulmonary complications, and 75% of these patient die.[65,136] World Health Organization data show that smoke from solid fuel is one of the four most common causes of death and disease in developing countries.[15]

Fire injuries can result from an array of inhaled toxic xenobiotics and/or thermal burns. Prior to 1942, toxic inhalation from dwelling fires was considered unusual. However, in that year, a fire at the Cocoanut Grove Night Club in Boston proved that toxic gases can be generated in typical dwelling fires.[111] From 1955â€“1972, death from smoke inhalation injury increased 3-fold and was attributed to

abundant use of newer synthetic materials for building and furnishings.[16] Despite improved firefighting resources, mass casualties from smoke inhalation continue. On November 11, 2000, 170 deaths occurred when a cable train carrying skiers caught fire in a

tunnel in Austria. Most of the victims apparently managed to escape the burning train but were killed by â€œacrid smokeâ€• as they tried to flee.[3] On February 20, 2003, a fire in a crowded Rhode Island nightclub killed 100 people and injured more than 200 people, with the majority suffering from smoke inhalation.[36] On December 31, 2004, a fire at an Argentina night club killed 175 people and injured more than 700. Most of the victims died of smoke inhalation.[4]

TABLE 123-1. Common Materials and Their Combustion Products

Products	Combustion Products
Wool	Carbon monoxide, hydrogen chloride, phosgene, chlorine, cyanide
Silk	Sulfur dioxide, hydrogen sulfide, ammonia, cyanide
Nylon	Ammonia, cyanide
Wood, cotton, paper	Carbon monoxide, acrolein, acetaldehyde, formaldehyde, acetic acid, formic acid, methane

Petroleum products	Carbon monoxide, acrolein, acetic acid, formic acid
Polystyrene	Styrene
Acrylic	Acrolein, hydrogen chloride, carbon monoxide
Plastics	Cyanide, hydrogen chloride, aldehydes, ammonia, nitrogen oxides, phosgene, chlorine
Polyvinyl chloride	Carbon monoxide, hydrogen chloride, phosgene, chlorine
Polyurethane	Cyanide, isocyanates
Melamine resins	Ammonia, cyanide
Rubber	Hydrogen sulfide, sulfur dioxide
Sulfur-containing material	Sulfur dioxide
Nitrogen-containing material	Cyanide, isocyanates, oxides of nitrogen
Fluorinated resins	Hydrogen fluoride

Fire-retardant materials	Hydrogen chloride, hydrogen bromide

Pathophysiology

Toxic combustion products are classified into three categories: simple asphyxiants, irritant toxins, and chemical asphyxiants (Table 123-2). Simple asphyxiants such as carbon dioxide exert a space-occupying effect; they simply displace oxygen.[37,42,133,158] In addition, combustion utilizes oxygen, potentially resulting in an oxygen-deprived environment (Chap. 119).[37]

TABLE 123-2. Toxic Combustion Products

Simple Asphyxiants Carbon dioxide	Irritants High water solubility (upper airway injury)
Chemical Asphyxiants Carbon monoxide Hydrogen cyanide Hydrogen sulfide Oxides of nitrogen (methemoglobinemia)	Acrolein Sulfur dioxide Ammonia Hydrogen chloride Intermediate water solubility (upper and lower respiratory tract injury) Chlorine Isocyanates Low water solubility (pulmonary parenchymal injury)

	Oxides of nitrogen Phosgene

Irritant xenobiotics are chemically reactive compounds that exert a local effect on the respiratory tract (Chap. 119). For example, high concentrations of acrolein are measured in air samples from fire environments and in the blood of fire victims.[2,86,150] Acrolein penetrates cell membranes easily because it is lipid soluble, injuring cells by denaturing intracellular proteins and nucleic acids.[51,160] Ammonia is generated when wool, silk, nylon, or synthetic resins are burned. It reacts with the mucosal moisture to produce the alkaline agent ammonium hydroxide.[31,81] Sulfur dioxide, an oxidation product of sulfur-containing material, is found in >50% of air samples from fires.[23] Sulfurous acid forms when sulfur dioxide reacts with the water of the respiratory mucosa. Hydrogen chloride, chlorine, and phosgene are formed from the oxidation of polyvinyl chloride (PVC), a plastic widely used in home and office furnishings, floor coverings, and electrical insulation.[17,20,37,42,88] In the presence of mucosal water, these combustion products generate damaging hydrogen chloride and reactive oxygen species.[38] Phosgene produces delayed alveolar injury.[21] Isocyanates, combustion products generated from upholstery, cause intense irritation of the upper and lower respiratory tracts.[115]

Combustion of organic material produces finely divided carbonaceous particulate matter (soot) suspended in hot air and gases. Inhalation of soot particles and aerosols enhances exposure to irritant xenobiotics in a fire environment. These particles are not just composed of carbon; organic acids, aldehydes, and reactive chemicals such as sulfur dioxide, hydrogen chloride, chlorine, and phosgene are adsorbed to their surfaces.[23,42,66,88,133,158] Soot adheres to the mucosa of the airways, allowing adsorbed irritant xenobiotics to react with the mucosal surface moisture. The deposition of these particles in the respiratory tract depends on their

size, with particles of 1â€“3 Âµm reaching the alveoli.[94] Experimental animals have markedly decreased lung injury when they are exposed to smoke that was filtered to remove particulates.[76] Irritant gases can â€œpiggybackâ€• on aerosol droplets and alter the site of gas deposition.[63]

Water solubility is the most important chemical characteristic in determining the timing and anatomic level of respiratory tract injury. Injury from water-soluble xenobiotics occurs in the upper airway and results in damage to mucosal cells with release of mediators of inflammation and/or reactive oxygen species.[22,82,95,118] The rapidity with which this process occurs provides a warning that the environment is unsafe and prompts escape. Following more than a trivial exposure, the intense inflammatory response increases microvascular permeability and allows movement of fluid from the intravascular space into the tissues of the upper airway. The loosely attached underlying tissue of the supraglottic larynx can become markedly edematous, causing upper airway obstruction within minutes to hours.[69] The obstruction can progress such that the upper airway is completely occluded.[124] Xenobiotics with low water solubility react with the upper respiratory mucosa very slowly and do not elicit an escape response. These xenobiotics reach the distal lung parenchyma, where they react slowly to create a delayed toxic effect. In addition to water solubility, factors such as concentration of the substance inhaled, duration of exposure, particle size, respiratory rate, absence of protective reflexes, and preexisting disease influence the region of respiratory tract injury.

Tracheobronchial injuries result from inhaled particulates and toxic gases, which cause increased airway resistance from intraluminal debris, airway mucosal edema, inspissated secretions, and brochospasm.[29,87,144] Damaged cells release chemotactic factors

that stimulate production of an exudate rich in protein and inflammatory cells.[152] This reaction eventually results in sloughing of the mucosa, which combines with the exudate to create casts of the

airways. In victims of smoke inhalation, casts block major airways, increasing airway resistance and mechanically preventing passage of oxygen to the alveoli.[29,33,99,144,152] Increased tracheobronchial vascular permeability leads to interstitial edema of the airways and increased airway resistance. Bronchoconstriction and subsequent wheezing are caused by a response to mediators of inflammation, a reflex response to toxic mucosal injury.[58,148]

Toxic xenobiotics that reach the alveoli injure the lung parenchyma.[105] Caustics, proteolytic enzymes, reactive free radicals, and mediators of inflammation all contribute to acute lung injury (ALI).[75,78,114,148,158] Pathophysiologic changes of ALI decrease lung compliance and bacterial defenses and lead to ventilationâ€“perfusion mismatch with intrapulmonary shunting, increased extravascular lung water, and microvascular permeability.[29,52,148,152,155] Decreased lung compliance from atelectasis is produced when toxic chemicals deactivate pulmonary surfactant.[29,105,113,152] In animals, patchy atelectasis occurs rapidly after smoke is inspired.[29,105,152] In addition, ventilationâ€“perfusion mismatch occurs when pulmonary blood flow is diverted by hypoxia and vasoactive mediators of inflammation.[83,84,104,148] Xenobiotics cause further injury by impairing mucociliary clearance, altering alveolar macrophage function, and impairing phagocytosis of bacteria, which all contribute to development of pulmonary infections and sepsis.[12,13,47,64,123] The combination of delayed toxic effects of some inhaled xenobiotics and slowly developing inflammatory response may explain the limited initial manifestations of parenchymal injury during the first 24 hours after smoke exposure.

Chemical asphyxiants exert their toxic effects at extrapulmonary sites. Incomplete combustion of organic materials generates carbon monoxide, which is considered the most common serious acute hazard to victims of smoke inhalation injury (Chap. 120).[1,14,37,150,160] Carbon monoxide prevents oxygen from binding to hemoglobin, creating a functional anemia. It also hinders the release of oxygen at the tissues by shifting the oxyhemoglobin

dissociation curve to the left. Other mechanisms, such as lipid peroxidation, contribute to the toxicity of carbon monoxide (Chap. 120).[139] Cyanide is produced from combustion of organic nitrogen-containing products such as plastics, melamine resins, polyurethanes, wool, silk, nylon, nitrocellulose, polyacrylonitriles, synthetic rubber, and paper.[112] High concentrations of cyanide are measured in air samples from fires and elevated blood cyanide concentrations occur in both fire survivors and fire fatalities.[5,9,10,27,37,60,72,128,129,134,154] Cyanide has at least an additive, if not synergistic, effect with carbon monoxide in smoke inhalation toxicity (Chap. 121).[9,93,108,117,119] Nitrogen-containing materials generate oxides of nitrogen, which are irritants and methemoglobin inducers (Chap. 122).

Smoke inhalation associated with burns results in an elevation of systemic nitric oxide because of the increased activity of inducible nitric oxide synthase.[44,45 and 46,131] The elevation of nitric oxide may result in myocardial contractile dysfunction with subsequent hypotension.[131] Nitric oxide can combine with superoxides to form the highly reactive peroxynitrite $ONOO^-$, which may lead to further alveolar capillary membrane damage and subsequent ALI.[44]

Depending on the fuel, other combustion products are aerosolized and act by local irritation or systemic toxicity. Metal oxides, hydrocarbons, hydrogen fluoride, and hydrogen bromide may contribute to toxicity. Antimony, bromine, cadmium, chromium, cobalt, gold, iron, lead, and zinc often are recovered from air samples taken during fires and from soot removed from the surface of the trachea and bronchi of fire victims.[14,37] Unusual fires at industrial sites, clandestine drug laboratories, transportation incidents, or natural disasters such as erupting volcanoes produce additional toxic inhalants.

Clinical Manifestations

The primary clinical problem in smoke inhalation victims is

respiratory compromise. The patients may have voice changes, and their speech may progressively worsen as the airway becomes increasingly edematous. Stridor and acute respiratory arrest may develop. Patients may have difficulty managing airway secretions, with expectoration of copious quantities of soot containing sputum. Visualization of the vocal cords by direct laryngoscopy may be difficult because of soot accumulation, secretions, or edema.

Auscultation of the chest may demonstrate rhonchi, crackles, and wheezing suggestive of ALI.[56] ALI is defined as diffuse alveolar filling of acute onset with hypoxemia but without left atrial hypertension.[11] The most severe manifestation of ALI is the acute respiratory distress syndrome (ARDS), which is defined based on the patient's ability to oxygenate (Chaps. 22 and 119). Bronchospasm may occur, particularly in patients with underlying reactive airway disease. Breath sounds, including wheezing, may be virtually inaudible in patients with severe bronchospasm.

Tachycardia and tachypnea may be pronounced and hypotension may occur, with faint or no peripheral pulses noted.[131] Smoke inhalation victims may develop an altered mental status, including agitation, confusion, or coma. Conjunctival injection, corneal ulcerations, marked lacrimation, and blepharospasm may be noted on ophthalmologic examination.

Diagnostic Testing

Because smoke inhalation injury causes pulmonary and airway damage, diagnostic studies should focus on assessing oxygenation and ventilation. Therefore, arterial blood gas (ABG) analysis, carboxyhemoglobin and methemoglobin concentrations, and chest radiography are the most important tests to obtain.

ABG analysis assesses both pulmonary function and blood pH. The presence of metabolic acidosis may be an early clue to tissue hypoxia. Serial measurements of arterial oxygenation and alveolar

ventilation are helpful in identifying hypoxemia or ventilatory failure. The accuracy of oxygen saturation measurement depends on the method used. Oxygen saturation calculated from ABG analysis may be unreliable in the setting of carbon monoxide poisoning, but measured oxygen saturation determined by cooximeter accurately reflects the percent saturation of hemoglobin. Transcutaneous measurement of oxygen saturation by pulse oximetry is unreliable in the patient with smoke inhalation because it overestimates oxygen saturation in the presence of carboxyhemoglobin.[7,43,107,151]

A carboxyhemoglobin concentration should be obtained for all smoke inhalation victims.[28,159] Either arterial or venous samples can be used to accurately measure carboxyhemoglobin concentrations.[85,147] The carboxyhemoglobin concentration alone is a poor predictor of the severity of smoke inhalation because a low or nondetectable concentration does not exclude the possibility of developing inhalation injury.[92,132] Because elevated methemoglobin concentrations are rarely reported in fire victims, methemoglobin

concentrations should also be obtained in the initial laboratory evaluation.[67,127] Blood cyanide analysis is of little clinical use because results of analysis are not available for hours, and therapy should never await laboratory confirmation of the presence of cyanide. Accurate measurement depends on acquiring the sample soon after exposure because cyanide is rapidly eliminated from the blood following smoke inhalation.[9,74]

A chest radiograph obtained early in the course of smoke inhalation is an insensitive indicator of pulmonary injury.[28,56,116,157] The most frequent abnormal findings on initial chest radiograph are diffuse alveolar and interstitial changes found in 34% of patients, followed by focal abnormalities in 12%.[56] In one series, no significant differences in the duration of either ventilation or stay in the intensive care unit were observed between smoke inhalation victims who exhibited abnormal findings on the first chest radiographic examination and those without any abnormalities.[56] Subtle findings

within 24 hours of exposure include perivascular haziness, peribronchial cuffing, bronchial wall thickening, and subglottic edema.[80,136] Serial chest radiographs following a baseline study are helpful in detecting pulmonary disease following smoke inhalation.[58] Widespread airway disease usually occurs more than 24 hours after inhalation injury and may represent ALI, aspiration, volume overload, infection, or cardiogenic pulmonary edema.[136]

Nuclear imaging and pulmonary function testing, although not readily available for initial evaluation, can detect pulmonary injury after smoke inhalation. Xenon ventilation studies can detect small airway and alveolar injuries before changes are seen radiographically.[58,96] Abnormal flow volume curves can indicate early upper airway obstruction.[57] Abnormal spirometry, especially forced expiratory volume at 1 second (FEV_1), detects early obstructive pulmonary defects of smoke inhalation, which may precede abnormalities of ABGs or radiography.[58,98]

Management

Critical airway compromise may be present upon the patient's arrival at the hospital, or it may develop subsequently.[34,57,124] A major pitfall in managing a patient with smoke inhalation is failing to appreciate the possibility of rapid deterioration. The history and physical findings help to determine significant smoke exposure and the potential for clinical deterioration. The clinical effects of smoke exposure and their appropriate treatment are described in Figure 123-1. Upper airway patency must be rapidly established. When obvious oropharyngeal burns are observed, upper airway injury almost certainly is present, even if overt injuries are not seen, and distal injury may be present and underestimated.[57] Direct evaluation of the upper airway, preferably with fiberoptic endoscopy, is essential for assessing patients at high risk for inhalation airway injury.[34,57,58,69] When evidence of upper airway injury exists, early endotracheal intubation should be performed under controlled

circumstances. Other indications for early intubation include coma, stridor, and full-thickness circumferential neck burns.[8,57,58,124] Massive fluid resuscitation of the burned patient contributes to upper airway edema.[57,58,100,124] Therefore, early intubation may be necessary in the patient with dermal burns undergoing aggressive fluid management.[57]

Although inhaled Î²$_2$-adrenergic agonists are effective and considered first-line therapy for acute reversible bronchoconstriction resulting from asthma or chronic obstructive pulmonary disease, their efficacy in patients with smoke inhalation is unknown.[18,89] However, pathophysiologic changes induced by irritant toxins in smoke are partially reversible, suggesting that Î²$_2$-adrenergic agonists improve airflow obstruction.[71,91] The benefits of corticosteroids given for treatment of smoke inhalation injury are not demonstrated in either clinical or animal studies.[103,125]

Pathophysiologic changes in the lung may cause progressive hypoxia over hours to days. Treatment of progressive respiratory failure includes mechanical ventilation, continuous positive airway pressure, positive end-expiratory pressure, and vigorous clearing of pulmonary secretions.[102] Frequent airway suctioning, chest physiotherapy, and therapeutic bronchoscopy can clear inspissated secretions, plugs, and casts.[33,99] Inhalation injury can progress to ALI or ARDS. Experimental treatment has examined high-frequency ventilation, percutaneous arteriovenous carbon dioxide removal, perfluorocarbons, inhaled nitric oxide, extracorporeal membrane oxygenation, instillation of natural surfactant into the lung, continuous IV infusion of heparin, and deferoxamineâ€“hetastarch complex for improving inhalation injury.[26,32,39,59,70,77,97,106,109,110,120,121] However, none of these modalities has been definitively proven to improve outcome.

Treatment of carbon monoxide poisoning consists of supplemental oxygen therapy, administered by a high-flow, tight-fitting mask, endotracheal tube, or hyperbaric oxygen therapy, depending on the

circumstances. Studies suggest that hyperbaric oxygen is superior to normobaric 100% oxygen in correcting toxicity and preventing delayed neurologic sequelae.[138,142,145,153] If readily available, hyperbaric oxygen should be considered in patients with smoke inhalation and a history of loss of consciousness, confusion, coma, headache, malaise, forgetfulness, fatigue, dizziness, visual disturbances, nausea, vomiting, cardiac ischemia, focal neurologic findings, or pregnancy.[140,153] Hyperbaric oxygen should be administered to patients only after life-threatening conditions such as associated trauma or hemodynamic instability are treated and the patient's condition has stabilized (Chap. 120 and Antidotes in Depth: Hyperbaric Oxygen).

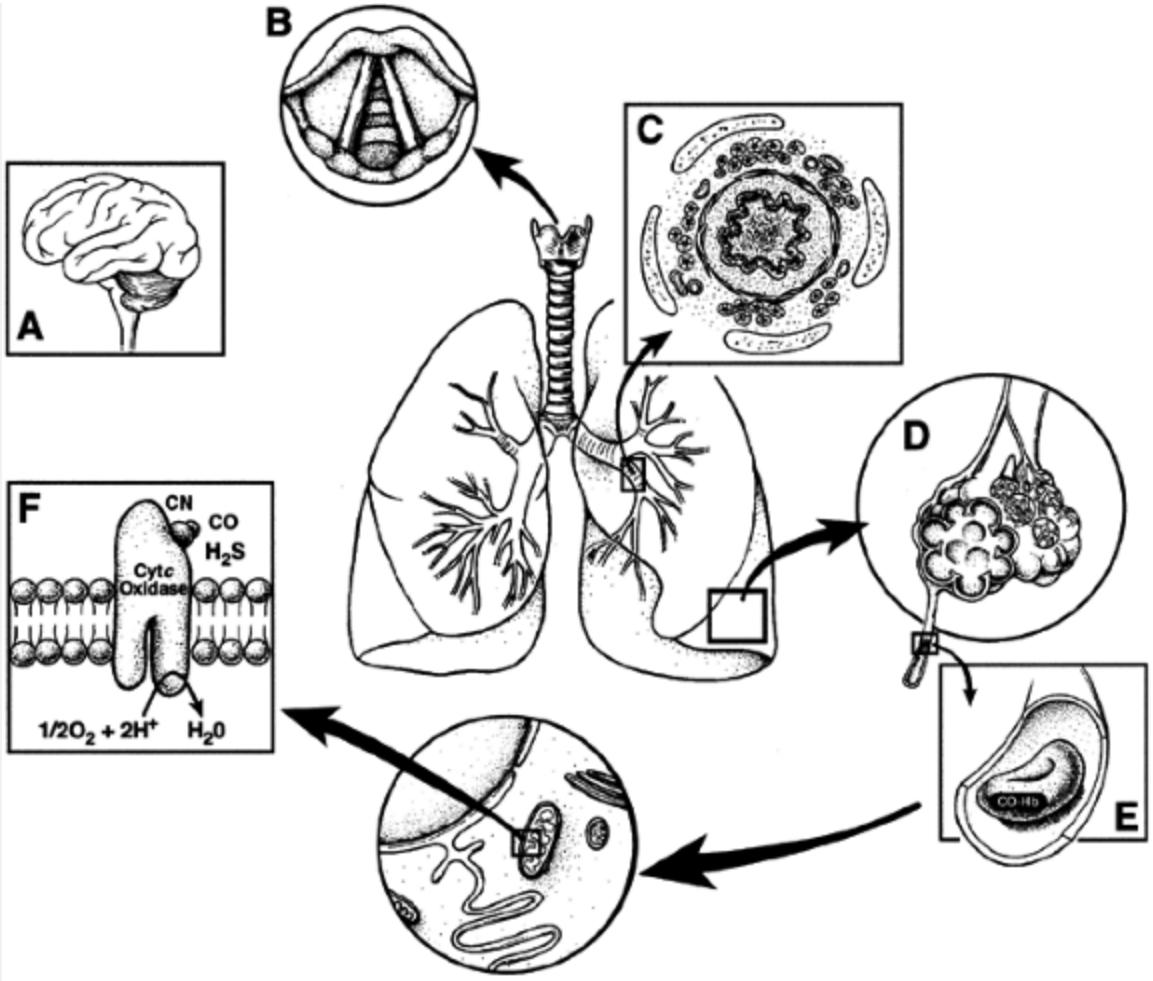
Cyanide poisoning should be suspected in seriously ill patients with smoke inhalation and metabolic acidosis.[48,122] Plasma lactate concentrations at the time of hospital admission correlate closely with blood cyanide concentrations, with plasma lactate concentrations >10 mmol/L reported to be a sensitive indicator of cyanide toxicity.[9] Treatment of cyanide toxicity should be considered while other life support measures, including 100% oxygen therapy, are instituted.[9,93,108,117,118,129] Treatment options include supportive care alone, administration of all or part of the cyanide antidote kit, and hyperbaric oxygen therapy. Patients have survived potentially lethal cyanide concentrations with simply oxygen therapy and supportive care.[19,126] Hyperbaric oxygen has been suggested to improve the outcome of cyanide toxicity, although the data supporting its use alone are not convincing.[49,60,149] Currently, hyperbaric oxygen therapy is considered only an adjunct treatment of cyanide poisoning in the presence of concomitant carbon monoxide poisoning.[146]

The cyanide antidote kit (amyl nitrite, sodium nitrite, and sodium thiosulfate) is the only antidote for cyanide poisoning available in the United States. Amyl nitrite and sodium nitrite produce methemoglobinemia. Detoxification occurs when methemoglobin binds cyanide to form cyanomethemoglobin, but alternate

mechanisms to methemoglobin formation are proposed. Sodium thiosulfate donates sulfur to the enzyme rhodanese, which converts cyanide to thiocyanate. Nitrite-induced methemoglobin and

sodium thiosulfate work synergistically to detoxify cyanide.[24,25] Unfortunately, methemoglobin is a dysfunctional hemoglobin that is unable to carry oxygen; in addition, its presence increases the affinity of the remaining hemoglobin for oxygen, which prevents its release to the tissues.[35] Impairing oxygen-carrying capacity and oxygen delivery to tissues with nitrite-induced methemoglobinemia is a valid concern in the presence of tissue hypoxia from carboxyhemoglobinemia and other factors. In a small series of fire victims treated with sodium nitrite, methemoglobin concentrations peaked at 7.8â€“13.4% between 35 and 70 minutes after slow IV infusion.[74] Corresponding carboxyhemoglobin concentrations decreased before peak methemoglobin concentrations had been reached. To the contrary, a case of hypotension and prolonged impairment of oxygen-carrying capacity was reported in a smoke inhalation victim following rapid infusion of sodium nitrite.[53] Because the safety of nitrites has not been studied in a large population of concomitant cyanide and carbon monoxide poisoning and the effect of cyanomethemoglobin on oxygen-carrying capacity is not well understood, initial treatment with thiosulfate alone is reasonable, with use of nitrite reserved for refractory cases or those patients with documented low carboxyhemoglobin concentrations. Sodium thiosulfate has few adverse side effects and can be safely administered to all patients seriously ill from smoke inhalation. When hyperbaric oxygen therapy is available, sodium nitrite can be administered just before the patient enters the hyperbaric chamber, if still clinically indicated, with less concern for impairing oxygen-carrying capacity.[54] Hydroxocobalamin chelates cyanide and is a safe and effective antidote.[9,48,55,68] Because of its apparent safety and efficacy, it can be given empirically to patients seriously ill from

smoke inhalation, thus eliminating the need for nitrites.[9,55] Hydroxocobalamin is designated but not yet approved for use in the United States (Chap. 121 and Antidotes in Depth: Amyl and Sodium Nitrites, Sodium Thiosulfate, and Hydroxocobalamin).



Pathophysiology	Signs and Symptoms	Management
A) Direct CNS toxic effects	Coma Hypoventilation	Oxygen; Secure unprotected airway
B) Upper airway edema	Hypoxemia; Respiratory distress Stridor Hoarse voice	Oxygen Direct visualization of vocal cords Endotracheal intubation
C) Bronchiolar airway obstruction Mucosal edema Intraluminal debris and casts Inspissated secretions Bronchospasm	Respiratory distress Hypoxemia Wheezes Cough Increased peak airway pressures	Oxygen Removal of debris and secretions Chest physiotherapy Frequent airway suctioning Therapeutic bronchoscopy Inhaled β-adrenergic agonists
D) Atelectasis Surfactant destruction Acute Lung Injury (ALI)	Respiratory distress Hypoxemia Crackles Chest radiographic changes	Oxygen Continuous positive airway pressure Mechanical ventilation Positive end–expiratory pressure
E) Impaired oxygen–carrying capacity (carbon monoxide or methemoglobinemia)	CNS depression or seizures Myocardial ischemia Dysrhythmias Metabolic acidosis	Oxygen Consider hyperbaric oxygen Consider methylene blue
F) Impaired oxygen use at tissues (cyanide, hydrogen sulfide, or carbon monoxide)	CNS depression or seizures Myocardial ischemia Dysrhythmias Metabolic acidosis	Oxygen Assure adequate tissue perfusion Consider treating suspected cyanide toxicity with sodium thiosulfate Consider hyperbaric oxygen

Figure 123-1. The final common pathway from all pathophysiologic changes that occur in smoke inhalation is hypoxia. All treatments should be focused on improving oxygen delivery and oxygen utilization.

Although rarely reported in fire victims, methemoglobinemia can result from inhalation of certain toxic combustion products.[67,127] Elevated methemoglobin concentrations in the presence of elevated carboxyhemoglobin concentrations increase tissue hypoxia. Oxygen therapy alone should be effective for most cases, and the need for methylene blue therapy is rarely clinically indicated following smoke inhalation (Chap. 122 and Antidotes in Depth: Methylene Blue).

Respiratory compromise and other conditions may not result from smoke inhalation, but rather from trauma or underlying medical problems. Trauma from falls or explosions must be suspected and treatment started simultaneously with treatment of burns and inhalation injury. Comatose patients should be considered to have other etiologies for their injuries and should receive naloxone, thiamine, and hypertonic dextrose as indicated. Inhaled xenobiotics, such as carbon monoxide, can directly cause altered mental status, but drug and ethanol intoxication contribute significantly to adult fire fatalities and injuries. Blood ethanol concentrations correlate with elevated concentrations of carbon monoxide and cyanide, implying that intoxication impairs escape and prolongs toxic smoke exposure.[6,14,101] Intracranial pathology should be considered and CT scans obtained as indicated.

Xenobiotics may injure the skin or mucous membranes in addition to the respiratory mucosa.[31] The duration of contact of a xenobiotic with tissue is an important factor in determining the extent of chemical injury to the skin and eyes. Rapid removal of soot from skin or eyes may prevent continued injury. The eyes should be evaluated for corneal burns caused by thermal or irritant chemical injury. The eyes of patients with signs of ocular irritation should be irrigated.

Dermal decontamination should be considered to prevent dermal burns from toxin-laden soot adherent to the skin.

Summary

Smoke inhalation continues to contribute significantly to the morbidity and mortality of fire victims. Clinicians caring for these patients must have a basic knowledge of the pathophysiology of smoke inhalation injury. A spectrum of events is possible, ranging from rapid upper airway occlusion to delayed ALI and ARDS. There are controversies regarding the care of these patients and further research is warranted. However, definitive therapies are available and should be considered.

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Chapter 124

Risk Assessment and Risk Communication

Charles McKay

Cases

- A mother called the poison center (PC) with a question about her 6-year-old child who had head lice (*pediculosis capitis*). She followed instructions listed on a topical pyrethroid shampoo yesterday, but was concerned that the infestation persisted. She wanted to know if it was safe to re-treat; today she also asked about treating the 1-year-old sibling because she had seen him â€œtugging at his ears.â€•

  Focusing on the mother's implied concern that â€œlice are everywhere,â€• the PC provided some practical advice regarding washing of bedclothes and reemphasized the importance of removing nits from the 6-year-old's hair. She was instructed to thoroughly examine the younger child's hair

and contact the pediatrician for follow-up. The residual effects following active treatment and the potential risk of repeated treatments or treatments of those without indications were also communicated. This combination of practical action steps and information on possible risks of excessive treatment was well-received and the mother thanked the PC specialist for her/his assistance.

- A worker came to the toxicology clinic concerned that she was being poisoned by her work environment. She worked in a stressful office setting with little privacy. Many of her co-workers try to grow potted plants in the area and have applied a variety of fertilizers and insecticides. She identified one of the products as containing pyrethrins and piperonyl butoxide. The patient noted intermittent headaches, burning eyes, stuffy nose, and â€œcloudy thinking.â€• She did not have any gastrointestinal symptoms, rash, breathing difficulties, or tremors. She asked if these symptoms were related to exposure to the insecticide in her office area.

  The patient was asked if others in the office area were experiencing similar symptoms. As they were not and there had been no large spill or other significant exposure, she was told that the symptoms she described were not likely to result from a toxic exposure to these compounds. She was told that the major effect that usually occurs with casual exposure to pyrethrins would be allergic symptoms in susceptible individuals. As some of her symptoms could be allergic in nature, a history of past and current atopic symptoms or seasonal allergy was sought. Examination of the upper airways and mucosal surfaces was normal. A site visit and industrial hygiene evaluation were arranged, although the patient expressed some concern about â€œstirring up trouble.â€• Most of the patient's workday was spent sitting at a computer terminal where the lighting seemed suboptimal. The insecticide was verified to be a pyrethroid/piperonyl butoxide

product. No other substances of note were identified in the workplace. The industrial hygienist found moderate changes in such â€œcomfort featuresâ€• as temperature, humidity, ambient CO_2 as a measure of air exchanges, particulates, and general assessment of cleanliness. During a follow-up visit, these results were discussed with the patient, along with a discussion of individual discomfort levels and a possible contribution of workplace stress and job routine. Some recommendations were made regarding varying her routine to decrease monotony. A follow-up was suggested for persistent symptoms, including the possibility of arranging for skin-prick allergen testing. The potential costs and possible nonspecific nature of this test were discussed. The worker was appreciative of the information, although she was still convinced that her workplace was making her ill, particularly because â€œwe are all being poisoned by this stuff all around us.â€•

- A homeowner called the PC, expressing concern about symptoms in himself and his family. He noted that they all had â€œsick headachesâ€• that day with vomiting and that they felt awful. He noted that they recently had work performed on the house, and wondered if everyone was feeling ill from the paint and wood stain vapors from the remodeling.

  Concerned that these symptoms may represent carbon monoxide poisoning, rather than low-level hydrocarbon exposure, the PC recommended that all family members leave the house

  immediately and activate 911 for evaluation and oxygen therapy. The fire department was contacted and found ambient air CO determinations of 100â€“300 ppm, along with a blocked chimney flue. Other volatile organic compounds were near background readings. Consultation by a medical toxicologist in the emergency department (ED) identified no mental status or

neurological symptoms, and all family members had normal mini-mental status examinations. All symptoms resolved with evacuation from the house and high flow oxygen therapy. Initial carboxyhemoglobin (COHb) measurements ranged from 7â€“15%; no one was pregnant or had any chronic cardiac disease. The toxicologist discussed the varying effects of carbon monoxide as a function of duration and amount of exposure and arranged follow-up visits with the primary care physicians 2 weeks later to evaluate for delayed neurological sequelae. The importance of a carbon monoxide alarm was discussed and the family was discharged to a nearby family's home until their chimney could be repaired.

The Certified Specialist in Poison Information (CSPI) and the medical toxicologist are often tasked with formidable challenges. Responding to an anxious parent with questions about his/her child's potentially toxic exposure or dealing with an urgent consultation for a critically ill patient in the ED or ICU. Under these difficult conditions the PC healthcare specialist must establish rapport and provide information, instructions, and when appropriate, reassurance over the telephone. For the PC, attribution of the patient's complaints to one or more potential exposures, and ascertaining the true reason or concern behind a call are also difficult given the limited information and time and lack of visual clues usually available in a clinical evaluation. The good reputation and ready availability of PCs within the United States provides the basis for authority and credibility, as does the advanced clinical training of the medical toxicologist. Nonetheless, the healthcare provider must be capable of a knowledgeable, compassionate, and well-reasoned response. This chapter focuses on two particular components of this response: risk assessment and risk communication. These principles are the same and can be applied to either an individual poison center call or to interactions with the public or medical professionals in educational outreaches,

occupational and environmental exposure evaluations, and supportive roles with other public health agencies, such as bioterrorism preparedness or environmental public health tracking, and research.

Risk Assessment

Risk assessment is the process of determining the likelihood of toxicity for an individual or group following a perceived exposure. It involves determining the nature and extent of the exposure (xenobiotic, dose, duration, route) and its specific clinical effects, defining an exposure pathway of, and assessing the likelihood of effects from, the exposure. Although it is generally true that a published body of knowledge can be applied to the risk characterization or assessment, this assessment is often based on incomplete (eg, exact dose) or unpredictable (eg, host factors that would modify a response) information. The emotional response to being â€œpoisonedâ€• makes this task even more difficult.

A good example of the practical difficulties involved in a risk assessment is evident from a description of mass psychogenic illness.[10] Many individuals in a school complained of odor-triggered symptoms that spread in a so-called â€œline of sightâ€• transmission. Extensive testing identified no toxic exposure, but demonstrated the possibility of potential exposures, such as dry floor drain traps. The extent of investigation of these events can vary, highlighting our technological abilities, but our ability to assess a â€œno-riskâ€• situation is limited, as can be seen in the letters to the editor criticizing the methods or conclusions in this event and â€œsubsequent and comparableâ€• outbreaks.[2,8,15] Those doing a risk assessment are affected by their own biases and assumptions in the interpretation of their results, as are the people to whom a risk assessment is communicated.

The response of individuals to uncertainty correlates with their affinity for one component of the negative data paradigm: â€œthe

absence of evidence of harmâ€• or â€œevidence of absence of harm.â€• Both of these positions have at their core the continued evaluation of evidence as it becomes available, with subsequent refinement of a resulting risk assessment. Unfortunately, these converging points on a spectrum of knowledge and research have been polarized into vilified caricatures of the Robert Kehoe and Precautionary Principles. The former is best summarized as â€œprove something is harmful before excluding a product with known benefits because of concern about potential, unproven future adverse effects.â€• This position has been misused in the past, for example to minimize known risks attributable to environmental lead pollution to delay removal of lead additives from gasoline.[17] Its detractors have opined that waiting for evidence of harm from a substance results in costly or irreparable damage. The alternative position of the â€œPrecautionary Principleâ€• is often summarized as â€œwhere there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent component of the principle, complaining that devotees stifle economic growth and prosperity with unfounded fears, rather than reasoned consideration of known data. This is often seen in such statements as: â€œHow could it be safe, when there are thousands of new chemicals brought into production every year?â€• Although these principles originated as policy approaches to public health issues, each individual responds similarly in his/her own personal risk assessment or tolerance. The response to uncertain situations is derived from one's framing of belief systems and assumptions about life, justice, and eternity.[1,5,7] These underlying world views should be explicitly recognized and addressed in a formal risk assessment. Table 124-1 lists components of a risk assessment.

TABLE 124-1. Components of a Risk Assessment

Hazard Identification
What is the name and amount of the suspected xenobiotic?
In the absence of a specific xenobiotic, what general or use category is suspected?
Exposure Pathway
What is the proposed route of exposure?
Is the route of exposure consistent with the nature of the xenobiotic?
Modifying Factors
Are there environmental factors that influence the systemic availability of the xenobiotic?
Are there underlying host susceptibility or resistance factors to consider?
Chronic medical conditions?
Possible xenobiotic-drug or other interactions?
Genetic polymorphisms in hepatic or other metabolic pathways?
Toxicity Assessment
What organ effects are expected from the identified xenobiotic?
Are existing symptoms consistent with known effects of the presumed xenobiotic?

(Adapted with permission from Wallace, K: Banner Health Care, Phoenix, AZ)

Differentiating Public Health from Individual Risk Assessment

It is often difficult to translate public health risk assessment done for populations by entities such as the Environmental Protection Agency (EPA) to the individual level. Simplistically, the iterative process of adjusting known noncancer adverse exposure outcome limits in an animal model (eg, lowest observed adverse effect level [LOAEL], or no observed adverse effect level [NOAEL]) to a safe level of exposure for all humans (including so-called â€œsensitive subpopulationsâ€•) has been arbitrarily set at multiplicative factors of 10. These â€œuncertainty factorsâ€• are actually safety factors that can lower exposure limits to amounts as small as 0.001 times the amount demonstrated to cause an adverse effect of interest. Thus when an individual exceeds these limits, they are encroaching into very robust safety factors, not exposing themselves to a defined harm. An example of this would be the dietary guidelines (also known as â€œfish health advisoriesâ€•) for fish consumption based on concern about methylmercury and polychlorinated biphenyls (PCB) exposure. The dietary recommendations are based on epidemiological studies that suggest subtle neuropsychiatric abnormalities in maternal-fetal pairs (in at least some populations) from levels of consumption 10â€“100 times that of the â€œusualâ€• American diet. Clinical mercury toxicity requires still higher levels of consumption. Although it is reasonable for pregnant women to limit their intake of certain high mercury-containing fish species, it would be inappropriate to avoid fish and the nutrients contained therein because of a misplaced fear of mercury exposure. These risk assessments do not apply to nonpregnant woman, children, or men.[22]

The public health modeling concept for cancer health effects risk assessment is even more often misunderstood. In this setting, modeling assumes a linear, no-threshold effect. Cancer risk from

small exposures is extrapolated from data in cancer-prone animal models with exposures so large that they are only possible in the experimental setting, ignoring potential metabolic and self-repair mechanisms in the human. The â€œacceptable riskâ€• in this setting is then taken as â€œone excess cancer in a population of 1,000,000 exposed individuals.â€• Although a limitation of this model is explicit in the statement that this represents â€œa plausible upper bound estimate of risk at low dose where true risk may be lower, including zero,â€•[6] this important caveat is rarely communicated, resulting in the common response by individuals that â€œan extra cancer may be acceptable for you, but not when it is my child.â€• Risk assessment is often imprecise. Risk characterization for the individual best avoids arbitrary numbers, aiming instead to communicate the likelihood of significant risk for the exposure actually experienced.

TABLE 124-2. Principles of Poison Center Risk Communication

	Principles	Applications
1	Accept and involve the public as a partner.	The caller must be involved to obtain the best information possible.
2	Plan carefully and evaluate your efforts.	There is a very short time to establish rapport with the caller; do not increase anxiety by asking irrelevant questions or arguing. Monitor your tone; ask for repetition of key information or

		recommendations.
3	Listen to the public's specific concerns.	Why did the person call? Was it for information, treatment recommendations, or reassurance? Make sure the underlying reason has been addressed.
4	Be honest, frank, and open.	If there is uncertainty or there are unknowns, indicate that, while providing a workable plan.
5	Work with other credible sources.	Involve medical toxicology back-up and other consultants, particularly for questions regarding chronic exposure/effects.
6	Meet the needs of the media.	If calls involve media notification or contact, make sure the critical information is stated frequently, provide a human context, and avoid sensationalism.
7	Speak clearly and with compassion.	Remember that the caller was concerned enough to initiate the contact; make sure the call is completed with a clear plan; provide follow-up appropriate to the situation.

Modified from Covello V, Allen F: *Seven Cardinal Rules of Risk Communication.* Washington, DC: US Environmental

Protection Agency, Office of Policy Analysis, 1988.

Risk Communication

Risk communication is an exchange of facts and opinions to allow an individual or group to make an informed decision regarding a course of action or treatment. Practically, risk communication is a way of translating incomplete knowledge into a form that will allow for informed decision-making. During a one-on-one interaction with a poisoned individual and his/her family or a caller to the PC, there is a need to gain the fullest attention or cooperation of the individual. Once this has occurred, the discussion is usually focused on risks and benefits of various treatment options (eg, gastrointestinal decontamination) or possible diagnostic modalities (eg, observation vs. neuroimaging vs. antidote administration). The group dynamics of environmental exposure risk communication at a public meeting are very different. Federal agencies that interact with communities in â€œSuperfundâ€• sites (eg, the EPA and the Agency for Toxic Substance and Disease Registry (ATSDR) have promulgated principles and practical recommendations for risk communication in this setting. Table 124-2 summaries general principles of risk communication.

Although some of these recommendations are more applicable to longer-term deliberations and interactions, much of the individual communication done by the PC and medical toxicologists succeed or fail based on these same principles (see second column in Table 124-2). Lacking the opportunity for repeated interactions over time to identify and discuss assumptions and biases, the toxicologist needs to establish credibility, listen to concerns and respond empathetically, admit areas of insufficient knowledge, and commit to follow-up, to effectively convey a risk characterization for an individual, based on available knowledge and experience. The scientific terms, rationale and any extrapolation from

modeling (such as animal data or case series) should be conveyed in an understandable manner to show that appropriate safety factors are incorporated into areas of uncertainty as a risk-diminishing step. The individual should leave the interaction with a clear understanding of the difference between a short-term risk of symptoms that will resolve or result in serious illness, and the degree of certainty about the potential for a long-term consequence.

The example of the 1976 industrial dioxin release in Seveso, Italy is one example of a failure in risk communication. Based on extrapolation from animal models and case reports, many dioxin-exposed pregnant women were counseled to have abortions following exposure to this â€œmost toxic industrial chemical.â€• An evaluation of birth defects did not identify an increased incidence of teratogenicity based on graded dioxin exposure amount or comparison with other unaffected regions in those who carried their pregnancies to term.[21] The question â€œis it safe? â€• and the meaning of â€œsafeâ€• lies at the heart of risk communication.[11,19]

Effective risk communication must therefore address several questions. Once the best information is obtained about the identification of the xenobiotic and the nature of the exposure, we must convey:

- The likely magnitude of the risk. This would include information on dose-response, such as â€œdoes the reported exposure to a toxic compound approach exposure amounts reported to cause symptoms?â€•
- The urgency of the risk must also be conveyed, along with recommendations to decrease toxicity or ongoing exposure.
- The applicability of a risk characterization might also need to be addressed: Is the animal data applicable to humans? Is the

exposure something of concern for an individual?

- Uncertainties of the risk assessment. This could include a â€œworst-case scenarioâ€• approach to unknown exposures or uncertainties in the quantity of an absorbed dose. The need for continued observation or follow-up for clinical changes would be expressed here. Individual risk tolerance may vary greatly. The same information may be interpreted differently by risk-averse contrasted with risk-tolerant people. A variety of comparisons or communication techniques may be used to provide an adequate characterization of risk.
- Options for management. In addition to follow-up and repeated evaluations by a medical toxicologist the range of choices, along with their relative benefits or risks, would be presented to the individual or group, along with a summary recommendation or opinion from the presenter. This last step is important to avoid the impression that â€œno one knows what is going on or what we should do.â€•

Application of Risk Assessment and Communication Principles to Acute Care Toxicology

Although it has long been recognized that many home-initiated poison center calls concern nontoxic or minimally toxic xenobiotics ingested by children,[16] the frequent lack of documented ingestion raises the possibility of the Pollyanna Phenomenon. If the patient actually took none of the xenobiotic, the individual will not experience adverse effects from that xenobiotic. It is generally assumed that the sheer volume of calls provides some reassurance regarding the accuracy of our risk assessment of these xenobiotics, but we should remain cautious in our interpretation of poison center data[9,18] (Chap. 130). Moreover, even calls about

nontoxic xenobiotics require communication between the caller and CSPI beyond simple substance identification. The importance of risk assessment and communication principles can be seen in the joint position statement on the prehospital management of â€œminimally toxic substancesâ€• supported by the American Association of Poison Control Centers (AAPCC), American Academy of Clinical Toxicology (AACT), and the American College of Medical Toxicology (ACMT). According to the position statement, in order for a CSPI to make a risk assessment that an exposure is benign or minimally toxic, the following characteristics must be true:

- â€œThe information specialist has confidence in the accuracy of the history obtained and the ability to communicate effectively with the caller.
- The information specialist has confidence in the identity of the product(s) or substance(s) and a reasonable estimation of the maximum amount involved in the exposure.
- The risks of adverse reactions or expected effects are acceptable to both the information specialist and the caller based on available medical literature and clinical experience.
- The exposure does not require a healthcare referral because the potential effects are benign and self-limited.â€• [14]

The position statement further notes that patient disposition decisions can be altered by many additional factors, including intent, environment, presence or absence of symptoms, and ongoing review of current recommendations in the face of more data. These points emphasize both the dependence of the CSPI on information derived from the caller, and his or her confidence in the level of comprehension of the caller. The caller should understand that their exposed child is safe; the conversation with the toxicology experts should alleviate concern as the nature of the assessment process is explained to whatever degree is

necessitated by the caller's risk tolerance.

In the case of a symptomatic patient or a hospital- or physician-initiated contact to a poison center and/or medical toxicologist, the caller expects more than the provision of information; but also the individual expects knowledge and expertise that will provide reassurance or direction for improved patient health. Relaying information regarding diagnosis, course, and predicted outcome is insufficient, however. There is usually another, underlying reason for the call. This could be anxiety, uncertainty, or misinformation built on a person's previous experiences or knowledge base. A sense of guilt may underlie a parent's call for an inadvertent exposure occurring when a child was unsupervised. A physician may have had a bad experience with a previous overdose. If these issues are not addressed, the caller may continue seeking reassurance by repeated calls to the PC or by seeking additional input from other sources, such as family, friends, primary physicians, or other healthcare providers. Variance in the information obtained will be considered inconsistencies between supposed experts, rather than differences in emphasis of the same information, leading to further uncertainty for the caller. Table 124-3 lists some barriers to effective risk assessment and communication.

TABLE 124-3. Factors Affecting Appropriate Risk Assessment and Effective Risk Communication

Nature of previous encounters with poison center or healthcare field
Lack of prior patient-healthcare worker relationship
Incomplete data to answer a question
Providing information contrary to â€œpopular understandingâ€• or media representation
Loss of credibility
Individual or cultural differences in perception of risk or applicability of data
Poor comprehension of scientific or statistical principles

Interpreting Public Health Concerns for the Individual

The CSPI and medical toxicologists frequently encounter callers or individuals at community events, or interact with the media regarding public healthâ€“related issues, such as heavy metal contaminants involving mercury, lead, or arsenic, or concerns for â€œmold toxicityâ€• and other environmental xenobiotics. Often these people are concerned that their symptoms or future health or family health may be adversely impacted by such exposures. Such supposed exposures are usually poorly documented, sometimes also driven by popular media depictions or litigation, and the risk to a caller is virtually impossible to ascertain during a short telephone or personal interaction. In these situations, the individual is best served by referral to a primary care physician with toxicology consultation or directly to a medical toxicology clinic. In such a setting, the data and perceptions can be reviewed completely, and a more appropriate risk assessment communicated. These interactions are very difficult, as they are often emotionally and politically charged.

In general, the communication of and response to information is dependant on a preexisting world view and prevailing circumstances. The same possible outcome will be perceived as more or less severe depending on several factors other than the nature of the outcome itself. Several authors have characterized the perceived tolerance to different risks, stratified by features such as familiarity and personal control[5,19] (Table 124-4). The emotional response of individuals confronted with these risks is sometimes characterized as â€œoutrage.â€• The greater the degree of familiarity with the particular exposure situation and the greater the voluntary nature of the exposure, the less fear or outrage will be expressed for a given adverse outcome. Although risk communicators can use analogies to place exposures in context, one must be careful to avoid equating voluntary and involuntary risk assumption, or equating those exposures or risks assumed by one segment of the population unequally. An example of this would be the presentation of a smoking risk analogy to a nonsmoker.

Risk communication has become very important in the setting of preparedness for terrorism. Although a great deal of attention and money has been directed to improvement of public health infrastructure, reporting and surveillance mechanisms, and response to perceived and actual terrorist acts, less attention has been directed to the process of communicating risk to the individual.[4,12] Although some countries practice public health emergency drills regularly, the United States has concentrated on preparation of organizational structures. Maintaining a readiness for catastrophic terrorist events (or natural occurrences such as pandemic influenza) should use the same risk assessment and communication techniques as are appropriate for other urgent public health matters. Unfortunately, there are many factors that affect the characterization of risk other than the facts, as exemplified by these two composite articles describing the same events:

- An unknown assailant (or assailants) has infiltrated the mail delivery system, resulting in severe illness and death throughout the country. Victims have included children, healthy adults, and older adults. Initial symptoms can be nonspecific, but rapidly progress. If treatment is not begun early, death is a likely result. Anyone who receives regular mail may be at risk. The government has no system in place to detect this threat and the medical community routinely fails to diagnose the conditions early. The long-ignored public health system is not prepared to deal with the huge burden of preventing illness in those who may have been or will be exposed. Tens of thousands of our citizens are taking prophylactic antibiotics â€œjust in case.â€• If you receive any unusual packages or see collections of powder that don't have an obvious explanation, call the police. If you develop a fever, cough, chest pain, or unusual rashâ€”which may not be painful, seek medical attention at once. Tune in to your local news station for more information on this burgeoning threat to our nation's security.
- A small number of individuals in isolated exposure settings have developed illnesses following bioterrorism events. Although the most severe form of this disease was previously thought to have a very high mortality rate, most people have survived these exposures, particularly with early and proper medical care. For the general population, it is estimated that the risk of exposure is about 1 in 200,000,000. The government has developed a case definition and medical experts have disseminated information to assist the medical community and public in the early recognition of symptoms and signs that are consistent with this exposure. Prophylactic treatment within days of exposure of those in high-risk professions, such as mail handlers at major postal sorting facilities, prevents illness. Unfortunately, there have been a

large number of hoaxes and false alarms about possible terrorist events, and a lot of understandable fear in the community about nonspecific symptoms. For additional information, contact your state health department at 211 or go to http://www.bt.cdc.gov/agent/anthrax/needtoknow.asp.

TABLE 124-4. Factors that Alter the Acceptability of Perceived Risk

More Acceptable	Less Acceptable
Natural	Man-made
Associated with a trusted source	Not associated with a trusted source
Familiar	Exotic
Voluntary	Involuntary
Potentially beneficial	Limited or absent potential benefit
Statistical (low harm likelihood)	Catastrophic (high harm likelihood)
Fairly distributed or shared by all	Unfairly distributed (injustice)

Affects adults	Affects children

Modified from Fischhoff B, Lichtenstein S, Slovic P, Derby SL, Keeney RL: *Acceptable Risk.* Cambridge, MA: Cambridge University Press, 1981.

Both of these paragraphs describe the 2001 anthrax bioterrorism events within the United States where a total of 22 people sickened or died from anthrax exposure. The first communication suggests that everyone is at risk and the situation is dire; the communication in the second paragraph is that the risk is isolated (a single individual died who was not in what was recognized as an at-risk setting) and there is a plan and process being developed to respond to the threat. The first is sensationalistic, imparting a helpless, victim role to the reader, although the second provides a framework in which to assess one's personal risk and access to sources of reliable information. Both types of reports were prevalent following the 2001 anthrax attacks. Which report seems more complete, accurate, or useful is determined by the assumptions and perspectives of the reader, in addition to the message the author wishes to deliver or response desired. Some would say that communicating a high degree of risk is important to gain the attention of the reader and to ensure that no one ignores a warning. However, the lack of a risk perspective prevents the reader from

placing this information in context with the myriad other risk communication messages conveyed on a daily basis. In general, those risk communication messages that do not provide a context or comparison to generally familiar activities or risks, are more prone to misinterpretation or misapplication. As biopreparedness moves from infrastructure and surveillance improvement to planning and response drills, appropriate message development

and risk communication to the public become increasingly important.

Summary

High-quality risk assessment and effective risk communication are the hallmarks of a successful interaction between the public and the PC, and between the toxicologist and an individual patient, the media, or the public health community. Adherence to general principles include obtaining the best information possible regarding potential exposures, and conveying as complete as possible a risk characterization of the hazard, likelihood of a completed exposure pathway, possible effects, and treatment options, in an understandable fashion. It is important to clarify the difference between public health standards and individual exposure risks, with an understanding of the many psychosocial issues that influence perception. Information should be provided in a context that allows the individual to prioritize his/her response based on a factual and balanced presentation.

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Chapter 125
Hazmat Incident Response

Frank G. Walter

Hazmat Incident Response

A hazardous material (hazmat) can be defined as any xenobiotic capable of harming people, property, or the environment; therefore, the list of hazardous materials is understandably large.[26, 27]

A hazardous materials' emergency is an uncontrolled or unexpected release of a hazardous material. Hazmat incident response is an area of special expertise within the field of medical toxicology. In general, hazmat incident response focuses on the care of patients exposed to xenobiotics in the prehospital setting, prepares for multicasualty incidents, and emphasizes patient decontamination while at the same time trying to prevent contamination of healthcare providers. The general principles of toxicology apply regardless of whether a patient is at a hazmat incident, in a prehospital setting, or in a hospital setting. Although patient-care resources vary among these treatment settings, the fundamental principles of patient care remain the same.

Because the number of hazardous materials is so large, it is efficient to group hazardous materials according to their toxicological characteristics. Various classification systems have been devised. The International Hazard Classification System (IHCS) is the most commonly used (Table 125-1).[106 , 110] Individual hazmat studies commonly use their own classification systems, emphasizing the toxicodynamic effects of hazardous materials such as systemic asphyxiants or highlighting individual chemicals such as ammonia or chlorine or general classes of chemicals such as acids, bases, or volatile organic compounds.[26 , 27]

Epidemiology

Although the concepts regarding hazardous materials toxicology are centuries old, the systematic study of hazmat epidemiology only began in recent decades. Because the United States Department of Transportation (DOT) regulates transportation of hazardous materials, it has been collecting data on hazmat incidents since 1971. Recent data, spanning a decade, indicate that in the United States the number of transportation incidents has decreased somewhat from 16,105 in 1994 to 15,220 in 2003, although the number of deaths has remained relatively low: 11 in 1994 and 14 in 2003.[105]

For decades, the vast majority of hazmat incidents were thought to occur during transportation because the DOT collected, published, and promulgated data regarding hazmat incidents that occur only during transportation. In the late 1980s, medical science began to focus on the epidemiology of hazmat incidents. There are a limited number of hazmat epidemiology articles in peer-reviewed medical journals.[15 , 16 , 17 , 18 , 19 , 20 and 21 , 26 , 27 and 28 , 30 , 31 and 32 , 34 , 35 , 37 , 38 , 43 , 44 , 45 and 46 , 49 , 53 , 54 , 55 and 56 , 58 , 59 , 60 , 61 , 62 and 63 , 67 , 68 , 69 , 70 and 71 , 73 , 81 , 82 , 92 , 93 , 95 , 98 , 100 , 101 , 109 , 110 , 111 , 112 , 113 and 114 , 117 , 118]

Nevertheless, data from these articles and other US government

sources indicate that the majority of hazmat incidents actually occur at fixed facilities rather than during transportation.[1,2,3,4,5,6,7,8,9,10 and 11,104]

The substances most commonly encountered at hazmat incidents vary from one locale to another and are predominately determined by the major industries in a particular area.[109,110] For example, pesticides are the most commonly encountered class of hazardous materials in Fresno County, whose major industry is agribusiness.[109] Although most hazmat incidents involve only one hazardous material, more than one hazardous material can be encountered at a given incident. One study described 107 hazmat incidents involving a total of 156 materials.[109]

The vast majority of consequential hazmat incidents are caused by gases, vapors, or aerosols. In one study, 4 of the 5 most commonly encountered individual chemicals were ammonia, phosphine, sulfur oxides, and hydrogen sulfide.[27] The important implication for decontamination is that gases do not usually contaminate people secondarily because they do not adhere to patients. Therefore, patients exposed only to gases generally do not require skin decontamination to prevent secondary contamination, and much greater efficiency is possible in patient care at gas, vapor, and aerosol hazmat incidents. Inhalation is the most common route of exposure at hazmat incidents and was the route of exposure at 73% of the hazmat incidents, accounting for 76% of the exposed patients described in one study.[26,27]

The vast majority of hazmat incidents do not result in patient injury. Of 53,142 hazmat incidents, only 4,413 incidents (8%) resulted in patients injury.[62] Most patient-producing hazmat incidents are multicasualty incidents. For example, the 4,413 patient-producing incidents resulted in 17,743 patients.[10,62] Most hazmat patients do not require hospital admission. Of the 8,126 total patients in one study, 51% were transported to and treated at a hospital but were not admitted; 24% were treated on scene but

were not transported; 3% were transported to a hospital and only needed observation; 8% were transported and subsequently admitted to a hospital; and 6% were seen at their physicians' offices within 24 hours of the hazmat incident.[11]

Hazmat incidents can result in fatalities and injuries. Of the 17,743 patients from the 4,413 patient-producing hazmat incidents, 244 (1%) died. One study reported that 63 deaths were caused by

hazardous materials released in 36 fatal hazmat incidents. The majority of these fatal hazmat incidents, 26 of 36 (72%) occurred at fixed-facilities, with 10 of 36 (28%) being transportation-related.[92] Among the 63 total fatalities, 6% were rescue personnel responding to the hazmat incident. Explosions killed 16 of 63 victims (25%).[92] Rescue personnel and healthcare providers must focus on the whole patient and not just poisoning because hazmat victims can also have injuries caused by vehicular crashes, explosions, or thermal burns.[92]

Class 1: Explosives
- Division 1.1: Mass explosion hazard
- Division 1.2: Projection hazard
- Division 1.3: Predominantly a fire hazard
- Division 1.4: No significant blast hazard
- Division 1.5: Very insensitive explosives
- Division 1.6: Extremely insensitive detonating articles

Class 2: Gases
- Division 2.1: Flammable gases
- Division 2.2: Nonflammable compressed gases
- Division 2.3: Poisonous gases
- Division 2.4: Corrosive gases (Canada)

Class 3: Flammable/combustible liquids

Class 4: Flammable solids
- Division 4.1: Flammable solid
- Division 4.2: Spontaneously combustible materials

Division 4.3: Dangerous when wet materials
Class 5: Oxidizers and organic peroxides
Division 5.1: Oxidizers
Division 5.2: Organic peroxides
Class 6: Poisonous materials and infectious substances
Division 6.1: Poison materials
Division 6.2: Infectious substances
Class 7: Radioactive substances
Class 8: Corrosive materials
Class 9: Miscellaneous hazardous materials

TABLE 125-1. International Hazard Classification System

Emergency personnel and equipment can become contaminated at hazmat incidents.[35,70,71,73,109,110,117] For example, in one study, contamination occurred to one ambulance that drove through a puddle of liquid organic phosphorus pesticides that had spilled from a crashed exterminator truck. This ambulance was responding to a call for a â€œmotor vehicle crash.â€•[109]

Hazardous Materials and Hazmat Response

Chemical Names and Numbers

Chemical compounds may be known by several names, including the chemical, common, generic, or brand (proprietary) name.[22,23] A chemical may be the sole substance in a given hazardous material or one of several compounds in a mixture.

The Chemical Abstracts Service (CAS) of the American Chemical Society (ACS) numbers chemicals to overcome the confusion regarding multiple names for a single chemical. The CAS assigns a unique CAS registry number (CAS#) to atoms, molecules, and

mixtures. For example, the CAS# of methanol is 67â€“56â€“1.[88, 89] These numbers provide a unique identification for chemicals and a means for crosschecking chemical names. Identifying a chemical by name and CAS# is critical because one must be as specific as possible about the hazardous material in question. Trade or brand names can be misleading. The material safety data sheet (MSDS) describing a product usually lists the chemical name, the CAS#, and the brand name.[83]

Vehicular Placarding: UN Numbers, NA Numbers, and PIN

Substances in each hazard class of the IHCS (Table 125-1) are assigned 4-digit identification numbers, which are known as United Nations (UN), North American (NA), or Product Identification Numbers (PIN) and are displayed on characteristic vehicular placards. This system is used by the US DOT in the Emergency Response Guidebook.[106] The IHCS assigns a chemical to a hazard class based on its most dangerous physical characteristic, such as, explosiveness or flammability. Other potential hazards of an agent, such as its ability to cause cancer or birth defects, are not considered. This system provides very little guidance in treating poisonings caused by hazardous materials.

National Fire Protection Association 704 System for Fixed Facility Placarding

Fixed facilities such as hospitals or laboratories use a placarding system that is different from the vehicular placarding system. The National Fire Protection Association (NFPA) 704 system is used at most fixed facilities.[84] The NFPA system uses a diamond-shaped sign that is divided into 4 color-coded quadrants; red, yellow, white, and blue. This system gives hazmat responders information about the flammability, reactivity, health effects, and also other

information, such as the water reactivity, oxidizing activity, or radioactivity.

The red quadrant on top indicates flammability; the blue quadrant on the left indicates health hazard; the yellow quadrant on the right indicates reactivity; and the white quadrant on the bottom is for other information, such as OXY for an oxidizing product, W for a product that has unusual reactivity with water, and the standard radioactive symbol for radioactive substances.

Numbers in the red, blue, and yellow quadrants indicate the degree of hazard: numbers range from 0, which is minimal, to 4, which is severe and indicate specific levels of hazard.

Like all placarding systems, this one also has limitations. It does not name the specific hazardous substances in the facility and gives no information about the quantities or locations of the materials.

Substance Identification

Once a hazardous materials emergency has been recognized, responders must know what the material is and its potential health effects. Obviously, exact identification is desirable but not always possible. Information regarding the site of the hazmat incident, the type of business, laboratory, or vehicle,

involved allows hazmat responders to safely search for and identify essential placards or documents. Fixed facility placards, vehicular placards, MSDSs, bills of lading, shipping documents, inventory sheets, verbal information from employees and management, are potential sources of information.

CHEMTREC is a service of the Chemical Manufacturers Association. It has information about shippers, products, and manufacturers. CHEMTREC can be reached at 1â€“800â€“424â€“9300.[39] The internet address for CHEMTREC is http://www.chemtrec.org . CHEMTREC provides information at no charge, 24 hours a day.

Details of an incident are relayed to the shipper's or manufacturer's 24-hour emergency contact, and they, in turn, are linked to hazmat incident responders. Technical data are available on handling the substance(s) involved, including the physical characteristics, transportation, and disposal.

A regional poison center (PC) is another valuable source of information. Other information sources include local and state health departments, the American Conference of Governmental and Industrial Hygienists (ACGIH), the Occupational Safety and Health Administration (OSHA), National Institutes of Occupational Safety and Health (NIOSH), Agency for Toxic Substances and Disease Registry (ASTDR), and the Centers for Disease Control and Prevention (CDC).[1,13,14,88,89,94] If the name of the substance is known before arrival at the scene, then research can begin en route with reviews of the physical, chemical, and toxicologic properties of the material. If the chemical is not known before arrival at the scene, efforts to obtain this information should begin as soon as safely possible. Responder safety is a priority.

Even if the exact identity of the toxic material is not known, hazmat responders may be able to classify the hazardous material into one of several major toxicologic classes by identifying a hazmat toxidrome that allows them to reasonably treat the patient and protect themselves and others; for example, do patients have irritation of the mucous membranes and upper airway caused by a highly water-soluble irritant gas? Do the patients exhibit signs of asphyxia with major central nervous system and/or cardiopulmonary signs and symptoms? Do patients exhibit signs of cholinergic excess caused by organic phosphorus compounds or carbamate poisoning? Do patients exhibit chemical burns compatible with corrosives? Do patients have the odor of solvents with signs of CNS depression and cardiac irritability, compatible with exposure to hydrocarbons or halogenated hydrocarbons? Also, even when the exact identity of the hazardous material is not known, what is usually known is the physical state of the material, that is: solid, liquid, or gas. Airborne

xenobiotics potentially mean many more victims. Airborne xenobiotics include not only gases and vapors, but also the liquid suspensions, fog and mists, and the solid suspensions, smoke, fumes, and dusts.

State

The physical state of a material determines how it will spread through the environment and gives clues to the potential route(s) of exposure for the material.

Unless moved by physical means such as wind, ventilation systems, or people, solids will usually stay in one area. Solids can cause exposures by inhalation of dusts, by ingestion, or rarely by absorption through skin and mucous membranes. Solids that undergo sublimation, changing directly from a solid into a gas without passing through the liquid state, can give off vapors that can cause airborne exposure. Only two commonly encountered solids sublime, dry ice and naphthalene. A vapor is defined as a gaseous dispersion of the molecules of a substance that is normally a liquid or a solid at standard temperature and pressure (STP), that is, 32Â°F (0Â°C = 273Â°K) and 1 atm (760 torr = 760 mm Hg = 14.7 psi). Uncontained liquids will spread over surfaces and flow downhill. Liquids can evaporate, creating a vapor hazard.

Primary and Secondary Contamination

The state of matter will also help healthcare providers determine whether the hazardous material presents a significant risk of secondary contamination and whether decontamination of the skin and mucous membranes is necessary.

Primary contamination is defined as contamination of people or equipment caused by direct contact with the initial release of a hazardous material by direct contact at its source of release. Primary contamination can occur whether the hazardous material is

a solid, a liquid, or a gas.

Secondary contamination is defined as contamination of healthcare personnel or equipment caused by direct contact with a patient or equipment covered with adherent solids or liquids that have been removed from the source of the hazardous material spill. Secondary contamination generally occurs only with solids or liquids. In general, patients or equipment covered with adherent solid or liquid hazardous materials, including chemical, biological, or radiological agents, should be decontaminated before transportation, to prevent downstream contamination of healthcare providers and equipment. An exception to the principles of limited need for cutaneous decontamination for those exposed to gas is the patient whose sweaty skin was exposed to a highly water-soluble irritant gas such as ammonia that dissolves in sweat to produce corrosive ammonium hydroxide. In this case, the primary purpose of decontamination is to prevent or treat the patient's chemical burns caused by the caustic action of aqueous ammonium hydroxide on perspiring skin, rather than preventing secondary contamination of rescuers.

Aerosols are airborne xenobiotics that are not gases. Aerosols are suspensions of solids or liquids in air, such as solid dusts or liquid mists, that can cover victims with these adherent solids or liquids, which can effect secondary contamination. These patients do require decontamination to prevent secondary contamination.

Water Solubility

The water solubility of a hazardous material determines whether water alone is sufficient for skin decontamination or whether a detergent must also be used. The general rule regarding solubility is that â€œlike dissolves like.â€• In other words, a polar solvent, such as water, will dissolve polar substances such as salts. For example, the herbicide paraquat is actually a salt, paraquat dichloride, that is miscible in water. Therefore, if a patient's skin is contaminated with paraquat, copious water irrigation is sufficient for

skin decontamination. A mild liquid detergent is acceptable but is not necessary. On the other hand, a nonpolar solvent, such as toluene, is not water-soluble and is immiscible.[88, 89] Therefore, if a patient's skin is contaminated with toluene, water irrigation alone may be insufficient for decontamination, and a mild liquid detergent is also necessary.[88, 89]

Vapor Pressure

The vapor pressure (VP) is useful to estimate whether enough of a solid or liquid will be released in the gaseous state to pose an inhalation risk. VP is defined essentially as the quantity of the gaseous state overlying an evaporating liquid or a subliming solid. The lower the VP, the less likely the xenobiotics will volatilize and generate a respirable gas. Conversely, the higher

the VP of a chemical, the more likely it will volatilize or generate a respirable gas. Water has a VP of approximately 20 mm Hg at 70Â°F (21Â°C), and acetone has a VP of 250 mm Hg at the same temperature. Therefore, acetone evaporates more rapidly than water and poses more of an inhalation risk. Standard reference texts (*NIOSH Pocket Guide to Chemical Hazards Merck Index*) list vapor pressures for commonly encountered chemicals.[88, 89, 106]

Hot zone
Red zone
Exclusion or restricted zone
Warm zone
Yellow zone
Decontamination or contamination reduction zone
Cold zone
Green zone
Support zone

[a] NIOSH, EPA. Adapted with permission from the Advanced Hazmat Life Support Provider Mannual, 2nd ed. Tucson, AZ, Arizona Board

of Regents, 2000.

Temperature Terminology System[a]	Color Terminology System	Explanatory Terminology System

TABLE 125-2. The Nomenclatures of the Hazmat Control Zones

Hazmat Scene Control Zones

Scene management is a fundamental feature at a hazmat incident. It is almost always necessary to isolate the scene, deny access to the public and the media, and limit access to emergency response personnel to prevent needless contamination. Three control zones are established around a scene and are described either by â€œtemperature,â€• â€œcolor,â€• or â€œexplanatory terminologyâ€• (Table 125-2 and Figure 125-1). NIOSH, the US Environmental Protection Agency (EPA), and most US prehospital and hospital healthcare professionals use the temperature terminology system.[88]

The hot zone is the area immediately surrounding a hazardous materials incident. It extends far enough to prevent the primary contamination of people and materials outside this zone. Primary contamination can occur to those who enter this zone. In general, evacuation, but no decontamination or patient care, is carried out in this zone, except for opening the airway and placing the patient on a backboard with spine precautions. This is because rescuers are generally hazmat technicians who wear level A or B suits that severely limit visibility and dexterity.

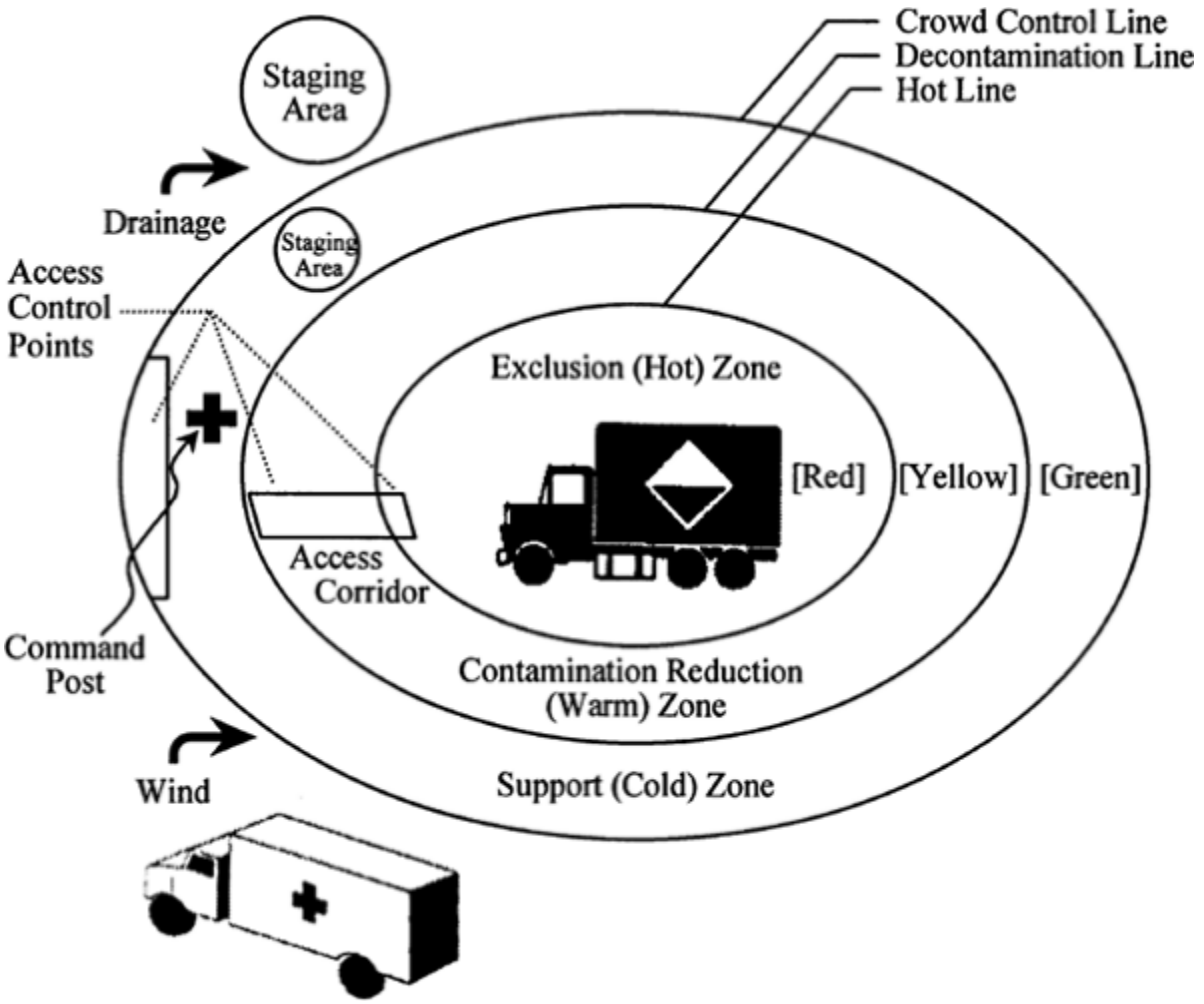

Figure 125-1. NIOSH/OSHA recommended control zones. *(Modified from ATSDR guidelines.) Modified with permission from The Advanced Hazmat Life Support Provider Manual, 3rd ed. Tucson, Az, Arizona Board of Regents, 2003.*

The warm zone is the area surrounding the hot zone and contains the decontamination or access corridor, where victims, the hazmat entry team members, and their equipment are decontaminated. It includes two control points for the access corridor. Many consider initiating therapy at this stage, particularly for chemical weapons events where multiple casualties are involved.

The cold zone is the area beyond the warm zone. Contaminated

victims and hazmat responders should be decontaminated before entering this area from the warm zone. Equipment and personnel are not expected to become contaminated in this zone. This is the area in which resources are assembled to support the hazmat emergency response. The incident command center is usually located in the cold zone, and definitive patient care is conducted here. This zone includes the primary survey and resuscitation with management of airway (with cervical spine control), breathing, circulation, disability, and exposure with evaluation for toxicity and trauma (ABCDE). Definitive care also includes antidotal treatment for specific poisonings.

Personal Protective Equipment

A critical goal of hazmat emergency responders is protecting themselves and the public. Safeguarding hazmat responders includes wearing appropriate personal protective equipment (PPE) to (1) prevent exposure to the hazard and (2) prevent injury to the wearer from incorrect use of or malfunction of the PPE equipment.[77, 90]

Personal protective equipment can create significant health hazards, including loss of cooling by evaporation, heat stress, physical stress, psychological stress, impaired vision, impaired mobility, and impaired communication. Because of these risks, individuals involved in hazmat emergency response must be trained regarding the appropriate use, decontamination, maintenance, and storage of PPE. This training includes instruction regarding the

risk of permeation, penetration, and degradation of PPE. PPE with a self-contained breathing apparatus (SCBA) has a fixed supply of air that significantly limits the amount of time the wearer can operate in the hot zone, usually about 20 minutes.

D

C
+

+

B
+
+
+
+

A

+
+
+
+

[a] Definitions: level A, a self-contained breathing apparatus (SCBA) worn under a vapor-protective, fully encapsulated, airtight, chemical-resistant suit; level B, a positive-pressure supplied-air respirator with an escape SCBA worn under a hooded, splash protective, chemical-resistant suit; level C, an air-purifying respirator worn with a hooded, splash protective, chemical-resistant suit; level D: regular work clothing (offers no protection).

	Protects Respiratory System From:			Protects Skin and Eyes From:	
Level[a]	Select Vapors and Aerosols	Gases, Vapors, and Aerosols	Oxygen-Deficient Atmospheres	Liquids and Solids	Gases and Vapors

TABLE 125-3. Personal Protective Equipment

Levels of Protection

The EPA defines four levels of protection for PPE, levels A (highest) through D (lowest). The different levels of PPE are designed to provide a choice of PPE, depending on the hazards at a specific hazmat incident (Table 125-3).

Level A provides the highest level of both respiratory and skin (clothing) protection and provides vapor protection to the respiratory tract, mucous membranes, and the skin. This level of PPE is airtight, and the breathing apparatus must be worn under the suit.

Level B provides the highest level of respiratory protection but less skin protection. Level B provides skin splash protection by using chemical-resistant clothing. It does not provide skin vapor protection but does provide respiratory tract vapor protection. Some hospitals have specially trained healthcare professionals who wear level B PPE when decontaminating contaminated patients presenting to the hospital, prior to decontamination. However, the majority of hospitals are training their frontline, emergency department (ED) healthcare professionals to wear level C PPE when decontaminating contaminated patients who present to the hospital, prior to decontamination.

Level C protection should be used when the type of airborne substance is known, when its concentration can be measured, when the criteria for using air-purifying respirators are met, and when skin and eye exposures are unlikely. Level C provides skin splash protection, the same as level B; however, level C has a lower level of respiratory protection than either level A or B.

Level D is basically a regular work uniform. It should not be worn

when significant chemical respiratory or skin hazards exist. It provides no respiratory protection and minimal skin protection. Level D was specifically developed to show *what not to wear* for chemical protection.

PPE Respiratory Protection

Personnel must be fit-tested before using any respirator. A tiny space between the edge of the respirator and the face of the hazmat responder could permit exposure to an airborne hazard. Contact lenses cannot be worn with any respiratory protective equipment. Corrective eyeglass lenses must be mounted inside the face mask of the PPE. The only exception to these general rules are the use of hooded level C powered air purifying respirators (PAPRs) that do not require fit testing and allow individuals to wear their own eyeglasses within the hooded PAPR. This is the reason that the majority of US hospitals prefer hooded PAPRs for their ED personnel who must decontaminate contaminated patients who present directly to the ED.

Level A PPE mandates use of a self-contained breathing apparatus. A SCBA is composed of a face piece connected by a hose to a compressed air source. An open-circuit, positive-pressure SCBA, is used most often in emergency response, and provides clean air from a cylinder to the face piece of the wearer, who exhales into the atmosphere. Thus, a higher air pressure is maintained inside the face piece than outside. This affords the SCBA wearer the highest level of protection against airborne hazards, because any leakage will force air out of the face piece and not allow airborne hazards to enter against the higher pressure within the face piece. Disadvantages of SCBA include its bulkiness, heaviness, and a limited time period of respiratory protection because of the limited amount of air in the tank.

A supplied-air respirator (SAR) may be used in level B PPE and differs from SCBA in that air is supplied through a line that is

connected to a source located away from the contaminated area. Only positive-pressure SARs are recommended for hazmat use. One major advantage of SARs over SCBA is that they allow an individual to work for a longer period. However, a hazmat worker must stay connected to the SAR and cannot leave the contaminated area by a different exit.

An air-purifying respirator (APR) may be used in level C PPE and allows breathing of ambient air after inhalation through a specific purifying canister or filter. There are three basic types of APRs: chemical cartridge, disposable, and powered-air (PAPR). Although APRs afford the wearer increased mobility, they can be used only where there is sufficient oxygen in the ambient air. The chemical cartridges/canisters purify the air by filtration, adsorption, and/or absorption. Filters may also be used in combination with cartridges to provide increased protection from particulates such as asbestos.

Hazmat Incident Response Rules and Standards

OSHA and NFPA have developed, respectively, rules and guidelines regarding hazmat incident response.[75 , 84 , 85 , 86 and 87 , 97 , 107] OSHA rules are mandated as law and must be followed.[75 , 97 , 107] Meeting NFPA guidelines will ensure OSHA compliance.[75 , 84 , 85 , 86 and 87 , 97]

The Superfund Amendments and Reauthorization Act of 1986, known as SARA, required OSHA to develop and implement standards to protect employees responding to hazardous materials emergencies. This resulted in the â€œHazardous Waste Operations and Emergency Responseâ€• standard, 29 CFR 1910.120, or HAZWOPER.[107]

NFPA 471, â€œRecommended Practice for Responding to Hazardous Materials Incidents,â€• outlines the following tactical objectives: incident response planning, communication procedures, response

levels, site safety, control zones, personal protective equipment, incident mitigation, decontamination, and medical monitoring.[85]

NFPA 472, â€œStandard on Professional Competence of Responders to Hazardous Materials Incidents,â€• helps define the minimum skills, knowledge, and standards for training outlined in HAZWOPER for 3 types of responders.[86]

Prehospital Hazmat Emergency Response Team Composition, Organization, and Responsibilities

First Responder at the Awareness Level

First responders at the awareness level could be first on the scene at an emergency incident involving hazardous material. They are expected to recognize the presence of hazardous materials, protect themselves, secure the area, and call for better trained personnel. They must take a safe position and keep other people from entering the area. They must recognize that the level of mitigation exceeds their training and call for a hazmat response team. Most emergency medical technician (EMT) basic curricula include this level of first responder training.

First Responder at the Operational Level

These individuals are trained in all competencies of the awareness level and are additionally trained to protect nearby persons, the environment, or exposed property from the effects of hazmat releases. Operational level certified individuals are expected to assume a defensive posture, to control the release from a safe distance, and to keep the hazardous material from spreading. Operational level individuals are trained to perform absorption of

liquids, containment of the spill, vapor suppression, and vapor dispersion. They do not operate within the hot zone.

Hazardous Materials Technician

Hazardous materials technicians respond to hazmat releases, or potential releases, for the purpose of controlling the release. They are trained in the use of chemical-resistant suits, air-monitoring equipment, mitigation techniques, and the interpretation of physical properties of hazardous materials. Technicians are capable of containing an incident, making safe entry into a hazardous environment, determining the appropriate course of action, victim rescue, and cleaning up or neutralizing the incident to return the property to a safe and usable status, if possible. These individuals are trained to operate within the hot zone to mitigate the incident. This certification level includes knowledge of hazardous material chemistry, air-monitoring equipment, tools used within the hot zone, and more.

Advanced Hazmat Components

Advanced Hazmat Providers

Paramedics should be trained in the recognition of signs and symptoms caused by exposure to hazardous materials, and the delivery of antidotal therapy to victims of hazmat poisonings.[75]

The inclusion of such training into a department's hazmat response team is beneficial, not only for the needs of the public but also to protect hazmat technicians who make entry into hazardous atmospheres.[75] Ideally, hazmat technician entry into hazardous atmospheres should not be performed, unless appropriately trained paramedics are standing by, on scene, with resuscitative equipment in place, including a drug box containing essential antidotes for specific hazardous materials.[75]

Medical Control

Obtaining medical control should begin early in the development of the hazmat team. Incidents involving hazardous materials can have far-reaching community implications. The ideal medical director for a hazardous materials team should be a medical toxicologist familiar with the operations and logistics of functioning in the prehospital environment.[75] This physician should be consulted in all aspects of planning for a hazmat response. In addition to developing training curricula and treatment plans for toxic exposures, this physician can work with emergency responders and hospitals to help integrate emergency personnel into the incident command structure and assist with the logistics of decontamination and hospital preparedness for victims of hazmat incidents.[75]

Online, direct medical control plays an important role in caring for hazmat victims.[75] Contact with medical control should be established as soon as possible after deciding that hot zone entry is necessary. This prealert notification allows the physician and hospital staff to be prepared to institute contingency plans when patients are identified who may require transport to a receiving facility.

Medical control should also include consultation with a regional PC, if possible. Field personnel should be familiar with how to access information through the PC. Similarly, the PC should be familiar with the level of training of responding emergency medical services (EMS) personnel.

Patient Care Responsibilities of the Prehospital Decontamination Team and the Hazmat Entry Team

Hazmat responders should identify the entry and exit areas by controlling points for the access corridor (decontamination corridor)

from the hot zone, through the warm zone, to the cold zone (Figure 125-1). This corridor should be upwind, uphill, and upstream from the hot zone, if possible. Hazmat technician entry team members should remove victims from the contaminated hot zone and deliver patients to the inner control point of the access (decontamination) corridor.[33 , 42 , 66 , 72 , 75 , 79 , 80 , 102] Hazmat decontamination team members decontaminate patients in the decontamination (access) corridor of the contamination reduction (warm) zone.[33 , 42 , 66 , 72 , 75 , 79 , 80 , 102] After decontamination, hazmat responders deliver patients to paramedics in the cold zone.[33 , 42 , 66 , 72 , 75 , 79 , 80 , 102]

The primary responsibility of the prehospital hazmat medical sector is the protection of the hazmat entry team personnel. This is accomplished by researching and recording clinically pertinent information about the hazardous material (Table 125-4), remaining available on scene for medical treatment, (Table 125-5) and assessing individuals before entry into, and on exit from, a hazardous environment.[75] Documentation of each assessment should be recorded on a prepared form and compared to the exclusion criteria defined by NFPA 471.[75 , 85] A position in the hazmat medical sector should be held by advanced hazmat trained individuals, preferably with operational level responder competency and ideally with hazmat technician level competency.[86 , 87]

Patient Care Responsibilities of EMS Paramedics at Hazmat Incidents

EMS paramedics who are not part of the hazmat team should report to the incident staging area and await direction from the incident commander. They should approach the site from upwind, uphill, and upstream, if possible.

EMS paramedics should remain in the cold zone until properly protected hazmat incident responders arrive, decontaminate, and deliver patients to them for further triage. Then, EMS paramedics

should evaluate each patient, direct patients without complaints to the

occupant staging area, and take patients with complaints to the patient staging area. An EMS paramedic should stay with the patients in the occupant staging area to continually reevaluate these asymptomatic victims and transfer them to the patient staging area if they do become symptomatic. Patients leaving the occupant staging area should receive instructions regarding potential signs and symptoms that may develop and necessitate their subsequent evaluation at a healthcare facility.

- ❑ Research hazardous material information (use 3 references) and contact poison center
- ❑ Contact most appropriate base hospital
- ❑ Preentry medical evaluation on entry team and backup teams
- ❑ Brief entry and backup teams on signs and symptoms of exposure
- ❑ During entry, be available for immediate treatment and/or transport, following emergency decontamination.
- ❑ Postentry medical evaluation (immediate and 10 minutes postentry, if possible)
- ❑ After incident, update hospital on incident termination

Chemical name: **Synonyms:**

Physical Properties

- ❑ Solid IDLH: _____
- ❑ Liquid VP: _____
- ❑ Gas BP: _____
- FP: _____
- Solubility: _____

Routes of Exposure

- ❑ Inhalation
- ❑ Absorption
- ❑ Ingestion

Hazard Class

- ❑ Corrosive ❑ Poison
- ❑ Explosive ❑ Other: _____
- ❑ Flammable gas
- ❑ Flammable solid UN#: _____
- ❑ Oxidizer CAS#: _____

Toxicology

- ❑ Irritant gas
- ❑ Simple asphyxiant
- ❑ Systemic asphyxiant
  - ❑ Carbon monoxide
  - ❑ Cyanide
  - ❑ Methemoglobin inducer
  - ❑ Sulfide
- ❑ Cholinesterase inhibitor
  - ❑ Carbamate
  - ❑ Organic phosphorus compound
- ❑ Caustic
  - ❑ Acid
  - ❑ Alkali
- ❑ Hydrocarbon or halogenated hydrocarbon
- ❑ Other: _____

Signs and Symptoms

Skin
- ❑ Irritation
- ❑ Chemical burns
- ❑ Thermal burns
- ❑ Fasciculations
- ❑ Diaphoresis

Eyes
- ❑ Miosis
- ❑ Mydriasis
- ❑ Irritation
- ❑ Lacrimation

Respiratory
- ❑ Irritation
- ❑ Laryngeal spasm
- ❑ Bronchospasm
- ❑ Bronchorrhea
- ❑ Depression
- ❑ Hypoxia
- ❑ Crackles

Cardiovascular
- ❑ Tachydysrhythmias
- ❑ Bradydysrhythmias
- ❑ Angina
- ❑ Crackles

Nervous System
- ❑ Excitation
- ❑ Seizures
- ❑ Depression

Other
- ❑ Emesis
- ❑ Salivation
- ❑ Diarrhea
- ❑ Urination

Treatment

Decon

Airway
- ❑ Suction
- ❑ Intubate

Breathing
- ❑ Oxygen
- ❑ Bag valve ventilation
- ❑ β-Adrenergic agonist

Cardiovascular
- ❑ Monitor
- ❑ IV
- ❑ ACLS guidelines
- ❑ Fluids
- ❑ Vasopressors
- ❑ CPR

Nervous System
- ❑ Benzodiazepine

Antidote: _____

Other: _____

Modified with permission from The Advanced Hazmat Life Support Provider Manual, 2nd ed. Tucson AZ, Arizona Board of Regents, 2000.

TABLE 125-4. Hazmat Incident Response Paramedic Worksheet

Under most circumstances EMS patient care takes place in the patient staging area of the cold zone, including medical management of hazmat victims except under certain mass casuality scenarios. Decontamination should not be necessary because EMS paramedics in the cold zone should care only for decontaminated

patients or patients who did not have skin contamination.

Transportation of patients from the hazmat incident is ultimately under the control of the incident commander but is usually delegated to the prehospital hazmat medical sector and EMS paramedics in consultation with a base hospital physician. In general, no victim with skin contamination should be transported from the hazmat site without being properly decontaminated. Before transportation, EMS should notify the base hospital of the number of victims being transported, and their toxicologic history, patient assessments, and treatment rendered. The base hospital physician may have additional orders, either before or after consultation with the PC and/or a medical toxicologist. If a patient is to be transported to a hospital other than the base hospital, the receiving hospital should be contacted.

Atropine
Î²-Adrenergic antagonist, calcium channel blocker, and cardioactive steroids overdoses; muscarinic mushroom (*Clitocybe, Inocybe*) poisoning; organic phosphorus and carbamate insecticide poisoning
Benzodiazepines
Stimulants, organic phosphorus poisoning
Calcium chloride
Calcium channel blocker overdose, hydrofluoric acid
Diphenhydramine
Extrapyramidal reactions from antipsychotics or antiemetics, organic phosphorus poisoning
Glucagon
Î²-Adrenergic antagonists, calcium channel blocker overdoses, hypoglycemia
Oxygen
Carbon monoxide, cyanide, hydrogen sulfide poisoning, organic phosphorus poisoning
Sodium bicarbonate
(1) Cyanide, methanol, ethylene glycol (reversal of metabolic

acidosis)
(2) Salicylates, chlorpropamide, phenobarbital, formic acid, chlorphenoxyherbicides (enhanced elimination)
(3) Cyclic antidepressants, quinine, carbamazepine, type IA and IC antidysrhythmics, cocaine, some phenothiazines (reversal of type IA ECG effects)
[a] Use of medications outside of protocols may not be permissible in some areas, even with on-line medical control.
[b] Table does not include medications such as D_{50} W, thiamine and naloxone primarily intended to be used as standard component of overdose management antidotes for an altered level of consciousness.

Medication Antidotal Use

TABLE 125-5. Antidotes Commonly Employed by Paramedics[a, b]

Emergency Department Responsibilities for Hazmat Victims

Since 2001 many, but not all, hospitals and EDs have dramatically improved their decontamination equipment, fit testing, and training in the safe use of personal protective equipment.[12, 24, 47, 52, 64] It is critical that hospitals be involved with community hazmat planning to ensure that as many hazmat victims as possible are decontaminated in the field before delivery to the hospital.[25, 29, 36, 40, 41, 48, 74, 91] The hospital must have a preestablished protocol by which hospital response teams will decontaminate patients who arrive at the hospital if not previously decontaminated.[25, 51, 57, 65, 74, 76, 96, 99, 103, 108, 115, 116] Hazmat patients who require skin decontamination should be denied entry to the ED until decontaminated by an appropriately trained

and equipped hazmat response team. The emergency physician will determine when the patient is safe to enter the ED after carefully assessing the risks and benefits to the decontaminated patient, the other patients in the ED, and the ED healthcare personnel.

Decontamination

Decontamination has two important functions: altering absorption for the patient and preventing secondary contamination of others. Primary goals at any hazmat incident are protecting emergency responders, preventing secondary contamination, and decreasing morbidity and mortality of hazmat victims.[29, 33, 50, 66, 76, 78, 79, 102, 108] Prompt, adequate skin decontamination is the most important determinant to improve patient outcome with chemical burns.[78]

Exposure solely to gases, such as simple asphyxiants, generally requires no skin or mucous membrane decontamination to prevent secondary contamination of others. However, exposure to highly water-soluble irritant gases, such as anhydrous ammonia, can cause skin and mucous membrane irritation and chemical burns; these are treated with copious amounts of water irrigation. This primarily treats the patient, rather than primarily preventing secondary contamination of healthcare providers.

When indicated by the presence of adherent solids or liquids on a patient, skin decontamination should be performed in the field, in the decontamination zone, if at all possible. If this is not done, these patients must be decontaminated at the hospital, prior to entering the hospital. Decontamination is a 2-step procedure. First remove all clothing, jewelry, and shoes. Bag and tag these possessions. The patient's possessions should be left at the scene, stored, and may need to be disposed of as hazardous waste. Any adherent solid particles should be brushed away from the patient. Gently blot away any obvious adherent liquid. Step two is meticulous washing with large quantities of water. Use a mild liquid

detergent if the adherent solids or liquids are not water-soluble or if the identity of the material is unknown. Most decontamination solutions are made for equipment, not people.[50] Do not use these potentially irritating solutions on people.[50] Pay close attention to all exposed skin and, in particular, the skin folds, the axillae, the genital area, and the feet. Use lukewarm water with gentle water pressure to reduce the risk of hypothermia. Apply water systematically from head to toe, protecting the patient's airway.

Exposed, symptomatic eyes should be continuously irrigated with water throughout the patient contact, including transport, if possible. Remember to check for and remove contact lenses. Use of therapeutic lenses is the most efficient method to decontaminate a patient's eyes, but this requires using an ocular topical anesthetic such as proparacaine.

Role of the Emergency Physician in Collaboration with the Emergency Department Nursing Staff and Hospital Safety Officer

- Provide prehospital medical control as the base hospital emergency physician, if possible.
- Activate the hospital's disaster plan, initiating the Hospital Incident Command, if indicated.
- Contact the PC and/or medical toxicologist or, alternatively, call the hospital's chemical spill coordinator or the hospital's radiation control personnel, if the substance is believed to be radioactive.
- Decide what procedures should be used in the field for decontamination in conjunction with the PC and/or medical toxicologist.

- Advise prehospital EMS personnel on precautions and adequate decontamination procedures.
- Decide if field decontamination procedures are adequate with the help of the PC and/or medical toxicologist.
- Meet the ambulance and decontaminated patients outside of the ED, and reassess for the adequacy of decontamination before patient entry into the ED.
- Deny ED entry to any physician or patient with skin contamination who has not been decontaminated before arrival in the ED, and if necessary, contact dispatch to send a hazmat response team to the ED while the patient waits outside the ED in an area of limited patient traffic.
- Notify hospital security to provide ED security and deny entry of contaminated patients unless the attending emergency physician makes a conscious decision to allow entry after considering the risks and benefits.

- Decide if and how a decontamination room should be used, when necessary, and when available.
- Decide if an additional decontamination area should be prepared outside the ED and, if so, establish the external unit.[25 , 29 , 40 , 41 and 42 , 51 , 57 , 65 , 74 , 96 , 99 , 103]
- Review current ED status and staffing and assign personnel to care for all ED patients.
- Call an appropriate level trauma alert, if the patient has physical injuries.

Summary

Hazmat incident response is an integrated, interdisciplinary approach involving prehospital, hospital, PC, and public health

professionals. Most patients at hazmat incidents are exposed through inhalation of a gas, or a solid or liquid aerosol. Prehospital and hospital healthcare professionals must use appropriate personal protective equipment when caring for patients who have not been decontaminated. Decontamination is critical to alter absorption for the patient and to prevent secondary contamination of downstream healthcare providers and equipment.

The general principles of toxicology apply regardless of whether a patient is at a hazmat incident in a prehospital or hospital setting. Although patient-care resources vary among these treatment settings, the fundamental principles of patient care remain the same: All patients should receive a primary survey and resuscitation, emphasizing airway, breathing, circulation, etc. Additionally, in hazmat patients, goals will include altering absorption of xenobiotics by decontamination; administering antidotes if possible; changing the catabolism of xenobiotics and, also if possible, creating less toxic or nontoxic metabolite; distributing the xenobiotics differently within the body, particularly away from active binding sites, if possible; and enhancing the elimination of xenobiotics from the body, if possible.

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Chapter 126
Chemical Weapons

Jeffrey R. Suchard

On March 20, 1995, during peak morning commuter traffic, a religiously motivated terrorist cult released sarin in the Tokyo subway system. Cult members concealed the nerve agent in plastic bags wrapped in newspape which they placed on 5 subway car floors and punctured with umbrellas l leaving the trains. Fifteen subway stations were filled with a noxious sub resulting in a mass casualty event.[63,67,68] Initial reports suggested an explosion with consequent toxic gas release, and preparations were made receive victims with burns, blast and inhalation injuries, and carbon mon exposure. The first ambulatory victims reached local hospitals 30 minutes the chemical release with complaints of eye pain and dim vision. Ambula began arriving 15 minutes later. Victims denied any explosion, and repor instead that people abruptly began collapsing in the subway stations.[67] S Luke's International Hospital received the largest number of victims, abou patients within the first hour, mostly arriving by private vehicle or on foo [67] Nearly 2 hours after the event, the fire department reported that the causative material was acetonitrile and that victims were suffering from toxicity.[67] Medical teams noted, instead, symptoms more consistent with cholinergic toxicity. Mildly affected victims had ocular complaints related

miosis, rhinorrhea, and mild headache. Moderately ill victims also had dy vomiting, muscle fasciculations, and weakness. The most critical victims seizures, coma, and respiratory or cardiac arrest.[63] Serum cholinesterase were severely depressed in the sickest patients, leading to suspicion of c phosphorus compound poisoning. Sarin was confirmed as the causative ag hours after its release.[67] A total of 5510 people sought medical attention more than 200 hospitals and clinics in the Tokyo area.[84] The majority of patients were either minimally affected, and were discharged home after observation period, or had no demonstrable toxicity. One thousand fifty were at least moderately ill. Eight fatalities occurred the first day, later increasing to 12.[105] Some healthcare workers were symptomatic from se exposure, particularly when the victims were taken directly to poorly ver areas. A survey conducted 4 years after the terrorist attack revealed that majority of victim respondents had persistent physical and psychologic complaints.[103]

Recent years have witnessed an enormous resurgence of interest in chem and biological weapons (CBW). Although â€œunconventionalâ€• warfare chemical and biological agents has been practiced since antiquity, it was until the 20th century that such weapons have been manufactured and us a mass scale. In addition to battlefield use, chemical weapons may appea terrorist groups, in that the technology and financial outlay required to p them is much less than for nuclear weapons, although the potential morb and mortality remain high (Table 126-1).

Chemical weapons clearly fall within the purview of medical toxicology. I unlike the many drugs and chemicals widely studied by toxicologists that incidentally cause poisonings, these compounds were specifically designed kill, incapacitate, or injure. Some agents generally considered nonlethal, tear gas and pepper spray, are therefore also considered chemical weapo Biological warfare agents share many characteristics with chemical agent (Table 126-2) and are covered in Chap. 127 , although the issues commo both chemical and biological weapons are discussed in this chapter.

History

The first well-documented intentional use of chemicals as weapons occurr 429 B.C. when Spartans besieging Athenian cities burned pitch-soaked wo brimstone to produce sulfurous clouds.[28] Chemical weapons were sporad used, or their use considered, up through the 19th century, and in 1854 British Lord Playfair even suggested that asphyxiating enemy soldiers wit poison gases was more humane than killing them with conventional weap

Large-scale chemical warfare began in World War I. On April 22, 1915, th Germans released chlorine from compressed gas cylinders near Ypres, Be A cloud of chlorine gas drifted over Allied lines, killing hundreds and forc 15,000 troops to retreat. The Germans had not anticipated such impressi effectiveness and were unable to fully exploit their tactical advantage.[28] Both sides rapidly escalated the use of toxic gases, released from cylinde by artillery shells, including various pulmonary irritants, lacrimators, ars and cyanides.

The Germans first used sulfur mustard on July 12, 1917, again near Ypres first mustard attack alone caused over 20,000 deaths or injuries and pre new problems.[28 , 53 , 90] Unlike prior war gases, mustard was persistent i environment and vesicated the skin in addition to injuring the lungs and membranes. The Allies soon responded in kind. Sulfur mustard was unequ its ability to incapacitate opponents.[10] Injuries far outweighed fatalities, up manpower and resources to care for the wounded. Although only abou 2â€“3% of 120,000 British sulfur mustard casualties died, only 30% of th survivors could be released from the hospital within 30 days.[54]

Only one major chemical weapon event occurred during World War II. On December 2, 1943, German planes bombed American ships in Bari, Italy. John Harvey was destroyed, releasing the contents of 2000 mustard bom causing over 600 Allied military and an unknown number of civilian casu , 53 , 90

Chemical warfare

Intentional use of weapons designed to kill, injure, or incapacitate on the of toxic or noxious chemical properties

Biologic warfare
Intentional use of microorganisms or toxins derived from living organisms cause death, disability, or damage in humans, animals, or plants
Terrorism
The unlawful use of force against persons or property to intimidate or coe government, the civilian population, or any segment thereof, in furtheran political or social objectives
CW
Chemical warfare or chemical weapon
BW
Biological warfare or biologic weapon
CBW
Chemical and/or biologic warfare, or weapons
NBC
Nuclear, biologic and/or chemical; usually in reference to weapons
WMD
Weapons of mass destruction; nuclear, radiologic, chemical, and/or biolo weapons intended to produce mass casualties

TABLE 126-1. Unconventional Weapons: Definitions and Acronyms

Germany began producing nerve agents just before World War II. Tabun developed in 1936 by Gerhard Schrader when conducting insecticide rese for IG Farbenindustrie.[32 , 87] Tabun was abandoned as an insecticide beca its overwhelming human toxicity, and was instead reported to the govern as mandated for all discoveries of potential military importance. Sarin wa synthesized in 1938, named after its developers: Schrader, Ambrose, Ru and Van der Linde.[32] Between 10,000â€“30,000 tons of tabun and 5â€“10 of sarin were produced during World War II. Soman was synthesized in 1 but no large-scale production facilities were developed. When the Allies discovered these nerve agents at the end of the war, code names were designated based on the order of their development. Tabun was called GA letter G standing for German), sarin was GB, and soman was GD.[32]

- Agents most effectively dispersed in aerosol or vapor forms
- Delivery systems frequently similar
- Movement of agents highly subject to wind and weather conditions
- Appropriate personal protective equipment prevents illness

â€¢

Rate at which attack results in illness

Rapid, usually minutes to hours

Delayed, usually days to weeks

â€¢

Identifying release

Easier because of:

- Rapid effects
- Possible chemical odor
- Commercially available chemical detectors

Harder because of:

- Delayed effects
- Lack of color, odor, or taste
- Limited development of real-time detectors

â€¢

Agent persistence

Variable

- Liquids semipersistent to persistent
- Gases nonpersistent

Generally nonpersistent; most BW degraded by sunlight, heat, desiccatio
(exception, anthrax spores)

â€¢

Victim distribution

Near and downwind from release point

Victims may be widely dispersed by time disease is apparent

â€¢

First responders

EMTs, hazmat teams, firefighters, law enforcement officers

Emergency physicians and nurses, primary care practitioners, infectious
physicians, epidemiologists, public health officials, hospital administrator

laboratory experts (but may be same as CW if release is identified imme
â€¢
Decontamination
Critically important in most cases
Not needed in delayed presentations; less important for acute exposures
â€¢
Medical treatment
Chemical antidotes, supportive care
Vaccines, antibiotics, supportive care
â€¢
Patient isolation
Unnecessary after adequate decontamination
Crucial for easily communicable diseases (eg, smallpox, pneumonic plagu
however, many BW agents are not easily transmissible
Adapted from Henderson DA: The looming threat of bioterrorism, Science
1999;283:1279â€“1282.

Similarities

Differences Chemical weapons (CW) Biologic weapons (BW)

TABLE 126-2. Chemical versus Biologic Weapons: Comparison a
Contrast

In 1952, the British synthesized an even more potent nerve agent while
searching for a dichlorodiphenyltrichloroethane (DDT) replacement. This
substance was given to the United States for military development, and w
named VX, with the letter V presumably standing for venom. A VX leak k
6000 sheep near a military base in Skull Valley, Utah in 1968.[32, 49, 87] I
is believed to have used riot-control agents, mustard, and possibly nerve
in the Yemen War of 1963â€“1967. The United States used defoliants and
control agents in Vietnam and Laos, claiming that these were not forbidde
the Geneva Protocol, which the United States finally ratified in 1975. Iraq
sulfur mustard, tabun, and soman during its war with Iran, and may have
used cyanide against the Kurds.[36, 47, 53, 90]

More recently, terrorist groups have begun to employ chemical weapons. was released twice by the Aum Shinrikyo cult in Japan. The first release occurred in Matsumoto in 1994, killing 7 and injuring over 600.[56, 64] A r highly publicized sarin attack occurred in the Tokyo subway system in 19 killing 12 and resulting in over 5000 persons seeking medical attention.[84] members have also used VX in assassinations.[55, 60]

General Considerations

Nerve Gas, Mustard Gas, Poison Gas

The term â€œwar gasâ€• is generally a misnomer. Sulfur mustard and n agents are liquids at normal temperatures and pressures, and many riot- agents are solids. These weapons are most efficiently dispersed as aeros Some chemical weapon agents (eg, chlorine, phosgene, hydrogen cyanide truly gases, although these agents are generally considered obsolete for battlefield use; they might still be used as improvisational agents, especi terrorist attacks.

Liquid chemical weapons have a certain degree of volatility and may eva into poisonous vapors. Volatility is inversely related to persistence, the t to remain in the environment. Persistent agents, such as mustard or VX c contaminate an area for prolonged periods, denying the enemy free mov and use of material. The toxic hazard from semipersistent agents like sari nonpersistent agents like hydrogen cyanide dissipate more rapidly.

Chemical or biological agent aerosols and chemical weapon gases and va are highly subject to local atmospheric conditions. Less dispersion occurs inversion layers and in the absence of wind, as typically occurs at night o early morning. Enclosed spaces also prevent wind dispersion and even si dilution. Except for hydrogen cyanide, CBW gases and vapors are all more than air and will pool in low-lying areas.

Chemical weapons dispersion in enclosed, low-lying spaces was used in th Tokyo subway sarin attack. The number of fatalities could have been muc

higher had the nerve agent been effectively aerosolized instead of simply allowed to evaporate. Photos from the attack show severely affected or deceased victims in very close proximity to mildly affected, ambulatory individuals. Presumably, sarin concentrations decreased with distance fror source, and only a few victims, if any, were actually contaminated with li After removal from high-concentration areas, the victims' bodies posed le threat to bystanders because of dilution and improved ventilation. Even s some healthcare providers were secondarily exposed, as the victims were even disrobed prior to entering the hospitals. Up to 46% of hospital staff areas with poor ventilation reported symptoms consistent with mild acute poisoning, although cholinesterase levels were not reported.[61, 63, 67] Ab one third of rescue workers in the 1994 Matsumoto sarin incident also de mild toxicity. Rescuers arriving at the scene later were less likely to deve symptoms.[57]

Preparation for CBW Incidents

A rational medical response to CBW events differs from the common resp isolated toxicologic incidents. Healthcare providers must learn new inforr related to unconventional weapons. Fortunately, a multimillion-dollar Do Preparedness Program was funded in 1996 by the Nunn-Lugar-Domenici initiative for weapons of mass destruction (WMD) defense.[62] Medical pro in 120 major US cities are receiving training in the recognition and treatn chemical and biologic casualties.[19, 21]

Healthcare providers must protect themselves and their facilities first, or ultimately no one will receive care. New medicolegal and ethical consider will arise in CBW mass-casualty events that are otherwise infrequently se greatest good for the greatest number of victims may preclude heroic interventions in a few critical patients. Charges of negligence may later a regarding delays in treatment or failure to diagnose subtle signs of disea even if such actions were unavoidable at the time.[19]

The responses to chemical and biological agents will also differ.[30] Chemic weapons, like conventional explosives, generally produce clinical effects seconds to hours, making a â€œsceneâ€• or â€œhot zoneâ€• evident. T

responders for a chemical event will be fire and police authorities, hazma teams, and emergency medical services (EMS). Patients will be brought t area healthcare facilities and the disease process, although perhaps not t specific diagnosis, will be recognized. With biologic agents, the victims wi all present for care at the same time in the same place. First responders local and distant emergency departments (EDs) and primary care offices, highlighting in these specialties the need for further training of healthcar personnel. Currently, there is no standard curriculum for the training of emergency and other physicians about the health hazards related to nucl biological, chemical (NBC) weapons, although progress in this regard is underway.[21, 71] Anesthesiologists and critical care specialists, too, are recognizing their lack of formalized training in preparing for chemical ma casualty incidents.[7, 44]

In preparation for the 1996 Olympic Games in Atlanta, a multidisciplinary force was assembled to detect, identify, and respond to any CBW threat c release of toxic industrial chemicals.[82] Efforts included stockpiling antibi and antidotes, training first-responders, enhancing surveillance, and aug clinical capabilities. The group correctly suspected that the most likely te event was use of conventional explosives; nevertheless, samples from th Centennial Park explosion were rapidly obtained to exclude dissemination CBW agent. Such an intense response to the threat of CBW terrorism wou difficult to maintain for extended periods.

Recommendations for more sustained healthcare facility domestic prepar include, improved training to promptly recognize CBW mass casualty eve efforts to protect healthcare providers, and establishing decontamination triage protocols.[48] Table 126-3 lists specific recommendations. Several fa the response to a CBW event are still being refined, such as the optimal of personal protective equipment, determining who needs decontaminatio by what means, and what is to be done with wastewater produced by mas decontamination.[48]

Communication is always a key issue in disaster management. Preestabli lines of communication and command should be implemented.[150] Outside agencies should also be alerted to CBW incidents, which in the United Sta

should include, at a minimum, the Federal Bureau of Investigation (FBI) a Centers for Disease Control and Prevention (CDC) (Table 126-4).[40] On a level, communication can be severely impaired by personal protective ge which points out the need for loudspeakers or some other form of public address.[48 , 100]

Decontamination

Decontamination serves two functions: (1) to prevent further absorption spread of a noxious substance on a given casualty and (2) to prevent spr other persons. Decontamination is critical for some chemical weapons exposures, but is less crucial for biologic agents. Victims of an occult bio weapon agent release

will not present for medical care until they become symptomatic, usually days later when decontamination will make no difference. Also, chemical agents can be dispersed as liquids, which are more amenable to decontamination than gases or aerosols, and are more likely to spread on person or between persons. Decontamination issues specific to biological weapon agents are discussed in the following chapter.

- Immediate access to personal protective equipment (PPE) for healthc providers
- Decontamination facilities that can be made operational within 2 to 3 minutes
- Triage of victims into those able to decontaminate themselves (decre the workload for healthcare providers) and those requiring assistance
- Decontamination facilities permitting simultaneous use by multiple pe and providing some measure of visual privacy.
- A brief sign-in process where patients are assigned numbers and give identically numbered plastic bags to contain their clothing and valuab
- Provision of food, water, and psychological support for staff, who may required to perform for extended periods
- Secondary triage to separate persons requiring immediate medical tr

from those with minor or no apparent injuries who are sent to a holdi for observation
- Providing victims with written information regarding the agent involv potential short- and long-term effects, recommended treatment, stres reactions, and possible avenues for further assistance
- Careful handling of information released to the media to prevent con or erroneous reports
- Instituting postexposure surveillance studies

TABLE 126-3. Recommendations for Healthcare Facility Respons CBW Incidents

Xenobiotics that are exclusively gases at normal temperatures and press (eg, chlorine, phosgene, or hydrogen cyanide) require only removing the from the area of exposure. Isolated vapor exposures, as from volatilized agents or sulfur mustard, are also terminated by leaving the area and ma require no skin decontamination of victims.[53,85] Japanese experience w sarin suggests that clothing should be removed from victims of nerve age vapor exposure and placed in airtight receptacles, such as plastic bags. S the secondary exposures to sarin were thought to have occurred as nerve that had condensed on the victims' clothing revaporized into the ambient and this caution probably holds true also for sulfur mustard vapor exposu

Chemical weapons dispersed as liquids present the greatest need for decontamination. Because nerve agents are highly potent and have rapid of effects, some victims with significant dermal contamination may not s to reach medical care.[85] Liquid-contaminated clothing must be removed, a able, victims should remove their own clothing to prevent cross-contami

Decontamination should be done as soon as practicable, to prevent prog of disease, and outside of healthcare facilities, to prevent contamination working environment and secondary casualties. Decontamination near the incident scene would be ideal in terms of timeliness, although this will no logistically be possible in many situations. The more likely scenario is tha victims may arrive independently at a decontamination center in proximity

healthcare facility. In mass-casualty incidents, decontamination efforts m benefit from separating victims into those who can remove their own clot and shower themselves with minimal direction and assistance, and the m seriously affected who will require full assistance. The degree of protectiv required by the decontamination personnel cannot be predicted in advanc may not be easy to objectively determine at the time of the incident. Lev gear may be adequate for persons assisting the â€œwalking wounded,â€ although level A gear is appropriate for those decontaminating the most seriously affected (and presumably most seriously contaminated) victims Chemically contaminated victims presenting to a healthcare facility shoulc possible, be denied entrance until decontaminated. Patients who have alı entered a healthcare facility and are only later determined to be a contamination hazard present a more difficult problem. If the situation a such patients should be taken outside for decontamination before returnir the previous care area cordoned off until any remaining safety hazard has eliminated. In a mass-casualty disaster, however, such efforts at remedi may not be practical.

Nerve agents are hydrolyzed and inactivated by solutions that release ch such as household bleach or solutions that are sufficiently alkaline. To av potential dermal and mucous membrane injury, a 1:10 dilution of househ bleach in water (producing a 0.5% sodium hypochlorite solution) has bee recommended, not only for nerve agents, but also for sulfur mustard and biological agents.[48 , 51 , 87] Alternatives include regular soap and water c copious water alone. Rapid washing is more important than the solution u because 15â€“20 minutes is necessary for hypochlorite solutions to inact chemical agents.[48] Care should be taken to clean the hair, intertriginous axillae, and groin.[87]

Decontamination after sulfur mustard exposure is more problematic than nerve agents. First, it is more likely that significantly contaminated victim survive to reach medical care, and they may remain asymptomatic for se hours. Also, the biochemical damage becomes irreversible long before sy develop.

Decontamination within 1â€“2 minutes is the only effective means of limi

tissue damage from mustard.[89] The actual means of mustard decontamir however, are identical to those for nerve agents. Victims must be disrobe thoroughly showered. Dilute hypochlorite solutions (eg, 0.5% sodium hypochlorite, a 1:10 dilution of household bleach) have been advocated t inactivate mustard, but copious water irrigation will also suffice.[53] Sympt victims of mustard exposure should still be decontaminated, even though unlikely to benefit that particular casualty, to prevent the spread of agent others.[89] Lewisite and phosgene oxime must also be decontaminated qui although they produce immediate symptoms, making it more likely that will present promptly when decontamination is most effective.

CDC Emergency Preparedness and Response Branch (770) 488-7100
For advice, or to report a suspected or actual event
http://www.cdc.gov/nceh/emergency
CDC Bioterrorism Preparedness and Response Activity (404) 639-0385
(800)-cdc-info
http://www.bt.cdc.gov
FBI Weapons of Mass Destruction Operations Unit (202) 324-6928
(202) 324-3000 (Public Relations)
http://www.fbi.gov
Department of Justice Domestic Preparedness National Response Hotline
(800) 424-8802
To report a suspected or actual event
CB HelpLine: Office for Domestic Preparedness
(800) 368-6498
Nonemergent planning and information source for civilian emergency responders
CB HotLine: National Response Center
(800) 424-8802
For chemical and biologic weapons emergencies
US Army Medical Research Institute of Infectious Disease (USAMRIID) Ho
(888) 872-7443 (USA-RIID)
To assist in BW threat assessment, diagnosis, and treatment issues
Commander, USAMRIID
(301) 619-2833 (Phone)

(301) 619-4625 (Fax)
For information or diagnostics, medical management, and vaccines
http://www.USAMRID.army.mil/

TABLE 126-4. CBW Phone Numbers/Contacts

Water irrigation is generally recommended for riot control agent exposure because hypochlorite solutions may exacerbate skin lesions.[53] Inadequate decontaminated patients exposed to lacrimator agents can produce secon cases among healthcare providers, so any contaminated clothing should b removed and bagged.

Significant issues remain regarding decontamination measures. The numb people potentially requiring decontamination may easily outstrip capacity. simulation of sarin and sulfur mustard decontamination, the maximum ca was 16 patients per hour.[98] Incidents with hundreds or thousands of vict may need to rely on communal showers and/or selective decontamination Decontamination wastewater should ideally be contained and treated, but facilities have the capability or funds to do this. Wastewater may, howeve minor issue. In biological weapon incidents there is only a temporary risk because of rapid environmental degradation, and in large-scale chemical events the wastewater poses only a small percentage of the total enviro impact.[48]

Risk of Exposure

The actual release of CBW agents can be characterized as a low-probabili high-consequence event.[9,73] Potential sources for civilian exposure incl terrorist attacks, inadvertent releases from domestic stockpiles, direct m attacks, and industrial events. Terrorist may sabotage military or industr stockpiles or directly attack the populace. Experience has shown that ph are much more likely to encounter hoaxes,[13] isolated cases,[77] or limited incidents with a modest number of casualties.[1,99] Riot control agents ar exceptions, in that treating riot control agent and pepper spray victims is routine occurrence in many urban emergency departments.

Technical and organizational obstacles decrease the chance of major CBW terrorist events. Obtaining or producing chemical or biological weapons, although simpler than for nuclear weapons, is only part of the process. E dissemination is difficult if the goal is to maximize casualties. Proper milli biologic agents to produce stable, respirable aerosols requires technical sophistication probably only attainable with governmental research suppo Illustrating this point is the ineffectiveness of the Aum Shinrikyo's biolog weapon releases and the limited number of sarin fatalities, despite large amounts of funds available to support these attacks.[69] Low-technology a such as food contamination, poisoning of livestock, and enclosed-space v dispersal appear more likely to occur than attacks resulting in hundreds, thousands, or millions of casualties.[92] Smaller attacks, or merely threate use of CBW agents, may be equally consequential from a terrorist's pers if they exert the same political influence.

Nevertheless, even inefficiently dispersed agents of sufficient toxicity can produce multiple casualties and terrorize the populace, as occurred in the Matsumoto and Tokyo sarin attacks. Impact estimates of efficiently dispe biological weapons are alarming. Fifty kilograms of anthrax spores disser along a 2-km line upwind of 500,000 people would be expected to kill 95 and incapacitate another 125,000 people: nearly a 50% casualty rate.[20] societal economic impact of bioterrorist attacks range from $477.7 million 100,000 persons exposed for brucellosis to $26.2 billion per 100,000 exp for anthrax.[38]

The chemicals most likely to be used militarily appear to be sulfur mustar the nerve agents. A â€œlow-techâ€• terrorist attack could involve the r of industrial chemicals, such as chlorine, phosgene, or ammonia gas. Alth the list of potential biological weapon agents is long, only a handful of pathogens have credible risk of producing public health disasters by overwhelming healthcare resources and causing high mortality, widespre panic, and massive disruption of commerce.[14] Topping this list are anthra smallpox, and plague, followed by botulinum toxin, hemorrhagic fever vi and tularemia.

Psychological Effects

Either the threat or the actual use of CBW presents unique psychologic stressors. Even among trained persons, a CBW-contaminated environment produce high stress through the necessity of wearing protective gear, po exposure to agents, high workload intensity, and interactions with the dea dying. About 10â€“20% of participants in military training exercises, in w chance of actual exposure exists, experience moderate to severe psycho symptoms.[25] Disorders of mood, cognition, and behavior will be common exposed or potentially exposed victims as a result of the uncertainty, fear panic that may accompany a CBW incident, even a hoax. The psychologic casualties will probably outnumber victims requiring medical treatment. without training, including some healthcare providers, are likely to confus somatic symptoms with true exposure. Medical resources may easily be overwhelmed unless triage can identify those who will benefit most from appropriate counseling, education, and psychologic support. Psychiatrists be enlisted in plans to manage CBW incidents for their expertise in treati anxiety, fear, panic, somatization, and grief.[16]

Experience with actual or threatened exposures to CBW agents have born these concerns. In Israel during the Gulf War, anxiety-related somatic re to missile attacks were reported in 18â€“38% of persons surveyed,[11] and 500 people sought medical attention in emergency departments for anxie Among 5510 people seeking medical attention after the Tokyo subway sa release, only about 25% were hospitalized.[84] Some of the â€œvictimsâ€• presented days or even weeks after the incident,[63, 68] apparently feeling unwell and thinking they had been exposed.[105]

Uncontrolled release of information may compound terror and increase psychologic casualties. Imagine the influx of patients resulting from a new report suggesting that anyone with dizziness or nausea be checked for ne agent toxicity, or that fever and cough indicate infection with anthrax.

The Israeli Experience During the Gulf War

Israel as a country is probably best prepared for CBW disasters. In late 1

the civilian population was supplied with rubber

gas masks, atropine syringes, and Fuller earth decontamination powder.[7
Israeli hospitals conduct chemical practice drills every 3â€“5 years.[100] Th
drills identify several key lessons, including designating specific hospitals
chemical casualties, blocking hospital access to a single guarded entrance
prevent internal contamination, and extending nurses' authority to initiat
treatment by established protocols. The Israeli plan provides two tiers of
The first triage occurs outside of the hospital by protected medical perso
who perform only life-saving interventions, such as intubation, hemorrha
control, and antidotal therapy. Patients are then decontaminated and ente
hospital. Afterwards, patients are triaged again according to severity of i
into separate areas in which dedicated healthcare teams provide the app
interventions.[79 , 100]

Thirty-nine ballistic missiles with conventional warheads were launched a
Israel from Iraq in early 1991, with only 6 missiles causing direct casualt
Many more â€œinjuriesâ€• resulted from CBW defensive measures and
psychologic stress than from physical trauma. Out of 1060 injuries report
from EDs during this time period, 234 persons were directly wounded in
explosions (most injuries were minor), and there were only 2 fatalities fr
trauma.[37 , 74] Over 200 people presented for medical evaluation after sel
injection of atropine, a few requiring admission to the hospital.[4 , 37 , 74] A
540 people sought care for acute anxiety reactions. Some suffocated from
improperly used gas masks, fell and injured themselves when rushing to
sealed against CBW agents, or were poisoned by carbon monoxide in thes
airtight rooms.[2 , 37 , 74] Increased rates of myocardial infarction and
cerebrovascular accidents were also observed.[74] A survey of hospital staf
members found that only 42% would report for duty following a chemical
weapon attack.[80]

Special Populations

Pregnancy does not appear to be a significant factor in the treatment of
victims of chemical weapons. In the Tokyo subway sarin attack, 5 victims

identified at one hospital as being pregnant. These women were only mild affected and were admitted for observation. All had healthy babies, the fi born 3 weeks after the incident.[63 , 65 , 68] In Israel, no obstetric complic occurred among women wearing gas masks during labor and delivery.[22 ,

Children have important differences from adults regarding chemical weap effects and decontamination efforts. Perhaps the most obvious differences that children breathe at a lower elevation above the ground and at a high than adults. Because nearly all chemical weapon gases and vapors are he than air, children will be exposed to higher concentrations than adults in same exposure setting.[76 , 108] Children may also be more susceptible to vesicants and nerve agents than adults with equivalent exposures.[75 , 108] Children have thinner and more delicate skin, allowing for more systemic absorption and more rapid onset of injury with sulfur mustard. The pedia bloodâ€“brain barrier may also be less resistant than in adults and the a of endogenous detoxifying enzymes, such as paraoxonase, is less, allowin greater toxicity with nerve agents. Additionally, children with organic phosphorus compound poisoning less frequently exhibit a muscarinic toxic syndrome than adults, and often present with isolated CNS depression.[75]

The decontamination of children is another feature that requires an age approach. Children have a larger surface area-to-mass ratio and may be likely to carry a toxic or fatal dose of a chemical weapon on their skin. M children will need assistance and supervision during decontamination procedures; keeping a mother or other adult guardian with a child should with both decontamination and thermoregulation.[76] Neonatal incubators been suggested as improvised chemical weapon protective devices for ve young children in the hospital setting.[23] This suggestion from Israel make tacit assumption, however, that the hospital would be experiencing a pot chemical weapon attack, which is more applicable to a warfare scenario th a response to events occurring outside the hospital.

Nerve Agents

Physical Characteristics and Toxicity

Nerve agents (Figure 126-1) are extremely potent organic phosphorus compound cholinesterase inhibitors, and are the most toxic of the known chemical weapons.[53] For example, sarin is 1000-fold more potent in vitro the pesticide parathion.[85] Aerosol doses causing 50% human mortality (L range from 400 mg-min/m^3 for tabun down to 10 mg-min/m^3 for VX, con to 2500â€“5000 mg-min/m^3 for hydrogen cyanide. Dermal exposure LD_{50} nerve agents range from 1700 mg for sarin down to only 6â€“10 mg for V [85] Pure nerve agents are clear and colorless. Tabun has a faint fruity odo soman has been variably described as smelling sweet, musty, fruity, spic nutty, or like camphor. Most subjects exposed to sarin and VX are unable describe the odor.[49 , 85] The G-agents tabun (GA), sarin (GB), and soman are volatile and present a significant vapor hazard. Sarin is the most vola only slightly less so than water. VX is an oily liquid with low volatility and environmental persistence.[49 , 53 , 85] Other G- and V-agents have been developed but are not discussed here in detail, because the clinical effect treatment options are essentially identical.

Pathophysiology

The pathophysiology of nerve agents is essentially identical to that from phosphorus compound insecticides (Chap. 109), differing only in terms o potency and physical characteristics of the toxins. The resultant toxic syn includes muscarinic (salivation, lacrimation, urination, defecation, GI cra emesis, or SLUDGE syndrome) and nicotinic (muscle fasciculation, weakn paralysis) signs, and central effects (loss of consciousness, seizures, res depression).[32 , 83 , 87]

Clinical Effects

Nerve agent vapor exposures produce rapid effects, within seconds to mi whereas the effects from liquid exposure may be delayed as the agent is absorbed through the skin.[51 , 85] Vapor or aerosol exposures have histor been more common, whether through experiments or from unintentional releases in the laboratory[83] or in terrorist attacks.[56 , 68] Aerosol or vapo exposure initially affects the eyes, nose, and respiratory tract. Miosis is

common, resulting from direct contact of nerve agent with the eye, and r persist for several weeks.[83, 87] Other ocular effects include conjunctival injection and blurring and dimming of the vision. Dim vision is often ascri pupillary constriction, but central neural mechanisms also play a role.[85] C spasm produces ocular pain, headache, nausea, and vomiting, often exac by near-vision accomodation.[32] Rhinorrhea, airway secretions, bronchoconstriction, and dyspnea occur with increasing exposures. With a vapor exposure, 1 or 2 breaths may produce loss of consciousness within seconds, followed by seizures, paralysis, and apnea within minutes.[51]

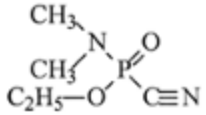
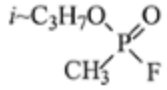
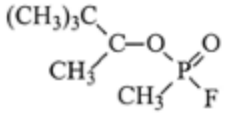
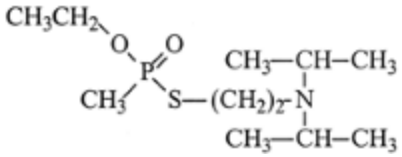
Military Designation	Common Name	Proper Name	Chemical Formula
GA	Tabun	Ethyl-*N,N*-dimethylphosphoramidocyanidate	
GB	Sarin	Isopropyl-methylphosphonofluoridate	
GD	Soman	Pinacolyl-methylphoshonofluoridate	
VX	-	*O*-Ethyl-*S*-[2-(diisopropylamino)ethyl]-methylphosphonothiolate	

Figure 126-1. Nerve agents.

In the 1995 Tokyo subway sarin incident ocular effects were most commc sarin vapor exposure, with miosis (89â€“99% of symptomatic victims), ey dim vision, and decreased visual acuity.[32, 68] Other common complaints cough, throat tightness, nausea, headache, dizziness, chest discomfort, a abdominal cramping.[50, 94] Among 111 patients admitted to one hospital,

most common presenting signs and symptoms were miosis (99%), heada (74.8%), dyspnea (63.1%), nausea (60.4%), eye pain (45%), blurred vis (39.6%), dim vision (37.8%), and weakness (36.9%).[63, 68] Excessive secretions were less common, with rhinorrhea seen in about one quarter patients admitted at one hospital,[68] and in none of 58 patients at anothe Secondary exposures occurred among emergency medical technicians (EM and hospital personnel in both the Tokyo[50, 61, 63] and Matsumoto[56, 57] terrorist sarin releases, apparently from evaporation of nerve agent that condensed on the primary victims' clothing.

Liquid nerve agents can permeate ordinary clothing, allowing for percuta absorption and rendering patients as potential hazards to healthcare per prior to proper decontamination.[27] Mild dermal exposure produces localiz sweating and muscle fasciculations after an asymptomatic period lasting u 18 hours. Moderate skin exposure produces systemic effects with nausea, vomiting, diarrhea, and generalized weakness. Substantial dermal contar will produce earlier and more severe symptoms, often with abrupt onset. toxicity from any route of exposure causes loss of consciousness, seizure generalized fasciculations, flaccid paralysis, apnea, and/or incontinence.[5, 87] Cardiovascular effects are less predictable, as either bradycardia (mu or tachycardia (nicotinic) may occur.[51] In the Tokyo sarin event, tachyca and hypertension were more common than bradycardia.[59, 94] Subtle CNS effects may continue for weeks, but typically resolve if no anoxic brain ir occurred. Neither delayed peripheral neuropathy nor the intermediate sy have been described in humans exposed to nerve agents.[87, 88] Followup have shown persistent neurologic, neurobehavioral, and electrocardiogra changes,[78, 107] although these studies are limited by small numbers and potential for introducing bias. Psychological sequelae included acute stres reactions in one third of admitted patients[68] and posttraumatic stress disorder.[103, 107]

Treatment of Nerve Agent Exposure

Decontamination

In critically ill patients, antidotal treatment may be necessary before or c the decontamination process; but generally, decontamination should occu before other treatment is instituted.

Atropine

Atropine is the standard anticholinergic antidote for the muscarinic effects nerve agents.[18] Atropine does not reverse nicotinic effects but does have central effects and may thus assist in halting seizure activity.[32 , 49 , 85]

Atropine is administered parenterally, either by the intravenous (IV) or intramuscular (IM) route, and the dose is determined by titration to effec standard adult dose determined by the American military is 2 mg, an am expected to produce substantial benefit in reversing nerve agent toxicity that should be tolerated by an unpoisoned adult unintentionally receiving drug.[85] Current recommendations place the minimum initial dose of atrop adults at 2 mg; dosing in children begins at 0.02 mg/kg, with a minimum mg. Severely poisoned adult patients receive an initial dose of 5â€“6 mg. Repeat doses are given every 2â€“5 minutes until resolution of muscarini of toxicity. Therapeutic endpoints are, drying of respiratory secretions

and resolution of bronchoconstriction, bradycardia, and/or seizures (if in present). Reversal of miosis or development of tachycardia are not reliab markers to guide atropine therapy.[32] The total amount of atropine necess treat nerve agent poisoning is often much less than required for organic phosphorus compound insecticide toxicity of similar degree. Typically, less 20 mg is required in the first 24 hours, even in severe cases.[32 , 85 , 87] F than 20% of moderately ill patients admitted to one hospital for sarin po in Tokyo required more than 2 mg atropine.[68]

American troops in the Gulf War were issued 3 MARK I kits for immediate treatment of nerve agent poisoning. Each kit contains two autoinjectors: AtroPen containing 2 mg of atropine in 0.7 mL diluent, and a ComboPen containing 600 mg of 2-PAM in 2 mL diluent (Survival Technology, Rockv MD).[85] These autoinjectors permit rapid IM injections of antidote through protective clothing and are given in the lateral thigh.[18] Treatment algorit

guided the number of MARK I kits to administer. In general, conscious ca not in severe distress self-administer 1 kit (2 mg atropine), moderate to cases receive 3 kits (6 mg atropine) initially, and all receive additional do necessary, every 5â€“10 minutes.[18,53,85]

In a nerve agent mass casualty incident, a hospital's intravenous atropine supplies may be rapidly depleted. Alternative sources include atropine fro ambulances, ophthalmic and veterinary preparations, or substituting alte antimuscarinic agents, such as glycopyrrolate.[32] Atropine might also be s as a bulk powder formulation and rapidly reconstituted for injection when needed.[26,43]

Oximes

Oximes are nucleophilic compounds that reactivate organic phosphorus compound-inhibited cholinesterase enzymes by removing the dialkylphos moiety. The only oxime approved in the Unites States by the FDA is prali (pyridine-2-aldoxime) chloride, or 2-PAM, a monopyridinium compound. O pralidoxime salts are used elsewhere, such as the methanesulfonate salt pralidoxime (P2S) in the United Kingdom and 2-PAM methiodide in Japan. oximes include the bispyridinium compounds trimedoxime (TMB4) and ob (Toxogenin) used in other European countries.[49,68,85] Oximes should b given in conjunction with atropine, as they are not particularly effective i reversing muscarinic effects when given alone. Oximes are the only nerve antidotes that can reverse the neuromuscular nicotinic effects of fascicul weakness, and flaccid paralysis.

Oximes are effective only if administered before irreversible dealkylation, â€œaging,â€• of the organic phosphorus compound-cholinesterase comp occurs. Soman (GD) has an aging half-life of 2â€“6 minutes in humans.[17] unlikely that soman-poisoned victims will reach medical care early enough oxime therapy to be of great benefit. For comparison, tabun (GA) has an half-life of about 14 hours, sarin (GB) 3â€“5 hours, and VX 48 hours.[17] Pralidoxime is effective against sarin and VX in animal studies but not ag tabun because of ineffective nucleophilic attack against that particular ag and not because of aging issues. Obidoxime also is effective against sarin

not against tabun.[49]

The bispyridinium Hagedorn (H-series) oximes, particularly HI-6 and HLÃ have also been studied in the context of nerve agent toxicity.[49] HI-6 app beneficial against soman poisoning (possibly through direct pharmacologi action and/or reactivation of aged soman-inhibited ChE) but is not very against tabun. HLÃ¶-7 has reactivating activity for both soman- and tabu inhibited ChE and may thus represent a universal oxime antidote for nerv agents. Administration of HI-6 and HLÃ¶-7 by autoinjector is difficult bec they are not stable in aqueous solution.

For more details about pralidoxime administration, dosing, and side effec Antidotes in Depth: Pralidoxime . The ComboPen autoinjector in MARK I k contains 600 mg pralidoxime, which produces a therapeutic maximal plas concentration of 6.5 Âµg/mL in average human subjects.[85] When possible however, pralidoxime is optimally administered IV. Repeat pralidoxime do continuous infusions are less likely to be needed for nerve agents than fo organic phosphorus compound insecticides because severe effects are sh lived in properly decontaminated patients.[32]

Anticonvulsants

Severe human nerve agent toxicity rapidly induces convulsions, which pe a few minutes until the onset of flaccid paralysis. Diazepam has beneficia effects beyond other anticonvulsants and simple Î³-aminobutyric acid (GA channel agonism, including effects on choline transport across the blood barrier and acetylcholine turnover.[49] Current American military doctrine is administer 10 mg diazepam IM by autoinjector at the onset of severe tox whether seizures are present or not. Thus, whenever 3 MARK I kits are u victim is given diazepam as well. Additional autoinjectors are given by m personnel as necessary for seizures.[53] The reason for the IM route of dia suggested above is mostly because of issues of timely administration und conditions. If intravenous access is feasible, IV diazepam in 5-mg doses every 15 minutes (up to 15 mg) is recommended.[49] Although diazepam is most well-studied benzodiazepine in the treatment of nerve agent toxicity medications in the same class (eg, lorazepam, midazolam) should have s

beneficial effects.

Pyridostigmine Pretreatment

The first large-scale use of pyridostigmine as a pretreatment for nerve ag toxicity occurred during Operation Desert Storm.[39] Pyridostigmine is a carbamate acetylcholinesterase inhibitor that is freely and spontaneously reversible, whereas nerve agent inhibition is permanent once â€œagingâ€ occurs. Toxicity from rapidly aging nerve agents such as soman (GD) can probably not be reversed by standard oxime therapy in realistic clinical situations. Almost paradoxically, then, a carbamate can occupy cholinest blocking access of nerve agent to the active site, and thereby protect the enzyme from permanent inhibition. Following nerve agent exposure, pyridostigmine is rapidly hydrolyzed from acetylcholinesterase and can als easily displaced by oximes, regenerating functional enzyme. Between 20% 40% cholinesterase inhibition is desired to protect against nerve agents.[1] milligram doses of pyridostigmine bromide reduces cholinesterase activity 28.4% in healthy individuals. Asthmatics taking 30 mg doses had a mean reduction in cholinesterase activity without significant reductions in resp function or in response to inhaled atropine.[72] In animal studies, pyridost confers a benefit against soman and tabun, but not against sarin or VX.[18] it must be recognized that pyridostigmine is not an antidote, but is instea pretreatment adjunct that greatly enhances the efficacy of atropine and therapy.[27 , 87]

American troops in the Gulf War took 30 mg pyridostigmine bromide orall 8 hours when under threat of nerve agent attack. Cholinergic side effects mostly gastrointestinal, were common but rarely required treatment or discontinuing therapy.[39] Israeli soldiers taking the same dose also report range of

mostly cholinergic symptoms but also a high incidence (71.4%) of dry m which may be more related to environmental and psychological stressors. Israeli patients were hospitalized during the Gulf War for acute intentiona pyridostigmine overdoses.[3] All patients recovered fully, including one pat

who self-treated with atropine autoinjectors and presented with anticholi toxicity and another who suffered cardiac arrest, apparently from coinges 4000 mg propranolol.

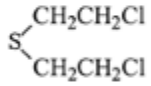
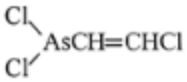
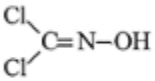
Military Designation	Common Name	Proper Name	Chemical Formula
H, HD	Sulfur mustard	Bis-(2-Chloroethyl) sulfide 2,2'-Dichloroethyl sulfide	
L	Lewisite	2-Chlorovinyldichloroarsine β-Chlorovinyldichloroarsine	
CX	Phosgene oxime	Dichloroformoxime	

Figure 126-2. Vesicants.

Vesicants

Vesicants are agents that cause blistering of skin and mucous membranes (Figure 126-2).

Sulfur Mustard

Sulfur mustard is bis(2-chloroethyl) sulfide, a vesicant alkylating compou similar to nitrogen mustards used in chemotherapy. Nineteenth-century scientists described the compound as smelling like mustard, tasting like and causing blistering of the skin on contact. The Allies of World War I ca Hun Stoffe (German Stuff), abbreviated as HS and later as just H. Distille nearly pure mustard is designated HD. The French called it Yperite, after site where it was first used, and the Germans called it LOST after the two chemists who suggested its use as a chemical weapon, Lommel and Stein was also called â€œyellow crossâ€• after the markings on German artille shells filled with mustard.[10 , 15 , 54 , 89] Sulfur mustard was used by the and Japanese in the 1930s, by Egypt in the 1960s, and by Iraq in the 19

Some Iranian mustard casualties were evacuated to Europe, resulting in a number of recent reports on treatment.[58, 97] Non-battlefield exposures l also occurred among Baltic Sea fishermen while recovering corroding she dumped after WWII[1, 97] and to persons unearthing shells from old battlefields.[77, 89]

Physical Characteristics

Sulfur mustard is a yellow to brown oily liquid with an odor resembling n garlic, or horseradish. Mustard has relatively low volatility and high environmental persistence. Nonetheless, most historical mustard injuries occurred from vapor exposure, a danger that increases in warmer climate Mustard vapor is 5.4 times denser than air. Mustard freezes at 57Â°F (1 so it is sometimes mixed with other substances, including such chemical agents like chloropicrin or Lewisite, to lower the freezing point and permi dispersion as a liquid.[15, 53, 89]

Pathophysiology

Sulfur mustard toxicity occurs through several mechanisms. First, mustard alkylating agent. Mustard spontaneously undergoes intramolecular cycliza form a highly reactive sulfonium ion that alkylates sulfhydryl (-SH) and a NH_2) groups (Figure 126-3).[10, 15, 53, 89] The most important acute manifestation is indirect inhibition of glycolysis. Sulfur mustard rapidly a and crosslinks purine bases in nucleic acids. DNA repair mechanisms are activated, depleting NAD^+ , which in turn inhibits glycolysis, and ultimate leads to cellular necrosis from adenosine triphosphate (ATP) depletion.[10] Mustard also depletes glutathione, leading to loss of protection against o stress, dysregulation of calcium homeostasis, and further inactivation of sulfhydryl-containing enzymes.[89] Sulfur mustard is also a weak cholinerg agonist.[53, 89]

Clinical Effects

The organs most commonly affected by mustard are the eyes, skin, and respiratory tract. During WWI, 80â€“90% of American mustard casualties

cutaneous lesions, 86% had ocular involvement, and 75% had airway inj
Iranian soldiers treated in Europe had more airway (95%) and ocular inju
(92%), and 83% had cutaneous lesions, probably because of the more e
vaporization occurring in the warmer environment.[10 , 89] Incapacitation m
severe in terms of number of lost man-days, time for

lesions to heal, and increased risk of infection. In contrast, mortality is r
low. In WWI, only 2â€“3% of British mustard casualties and fewer than 2
American casualties died. Fatality rates of 3â€“4% were reported from th
Iraq War.[10 , 54] Most deaths occur several days after exposure, either fro
respiratory failure, secondary bacterial pneumonia, or bone marrow supp

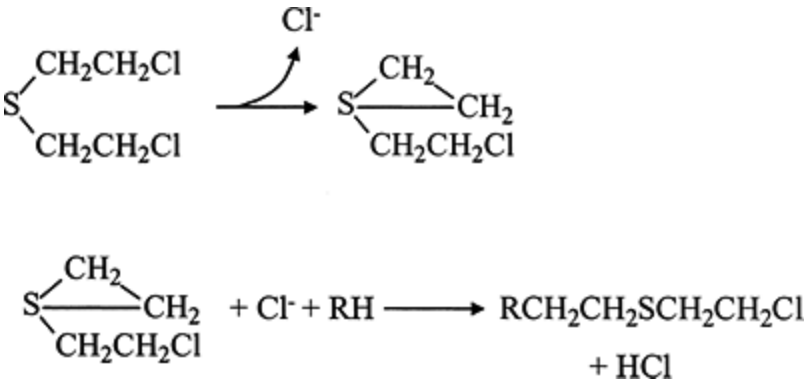


Figure 126-3. Mechanism of sulfur mustard toxicity.

Dermal exposure produces dose-related injury. After a latent period of 4
hours, victims develop erythema that may progress to vesicle and/or bull
formation and skin necrosis. Warm, moist, and thin skin is at increased ri
mustard injury, in particular the perineum, scrotum, axillae, antecubital
and neck. The vesicle fluid does not contain mustard because all chemica
reactions are complete within a few minutes.[54] If decontamination is not
performed immediately after exposure, injury can not be prevented. Late
decontamination may, however, limit the severity of lesions and further
of the agent. Skin exposure to vapor typically results in first- or second-
burns, although liquid exposure may result in full-thickness burns.[89] Mus
easily penetrates normal clothing and uniforms, and many soldiers receiv
gluteal, perineal, and scrotal burns from sitting on contaminated objects.

dermal effects include changes in pigmentation, increased incidence of melanocytic nevi and cherry angiomas, and the development of chronic neuropathic symptoms in mustard burned areas.[15, 24, 89, 97]

Latency of several hours also occurs following ocular and respiratory trac exposures. Ocular effects include pain, miosis, photophobia, lacrimation, vision, blepharospasm, and corneal damage. Permanent blindness is rare, recovery generally occurring within a few weeks. Inhalation of mustard r in a chemical tracheobronchitis. Hoarseness, cough, sore throat, and ches pressure are common initial complaints. Bronchospasm and obstruction fr sloughed membranes occur in more serious cases, but lung parenchymal damage only occurs in the most severe inhalational exposures. Productive associated with fever and leukocytosis is common 12â€“24 hours after exposure, and represents a sterile bronchitis or pneumonitis. Nausea and vomiting are common within the first few hours. High-dose exposures ma cause bone marrow suppression.[10, 15, 53, 89]

Various long-term sequelae have been associated with sulfur mustard. Fa workers chronically exposed to mustard have increased risk of respiratory carcinomas, although no clear association is demonstrated for battlefield exposures.[88] Chronic respiratory sequelae include chronic bronchitis, bronchiectasis, pulmonary fibrosis, interstitial lung disease, emphysema, bronchiolitis obliterans.[5, 96] A delayed keratitis may also occur, sometim many years after ocular exposure, along with the skin changes noted abo Among the approximately 34,000 Iranians with confirmed exposure to su mustard during the war with Iraq, chronic pulmonary sequelae were noted 42.5%, ocular lesions in 39.3%, and dermatologic lesions in 24.5%.[42]

Treatment

Decontamination is essential in treating the sulfur mustard exposures, ev among asymptomatic victims. In addition to previously described decontamination regimens, animal data suggests that topical iodine prep (eg, povidone-iodine ointment) may be beneficial in decontaminating the from sulfur mustard,[106] although human clinical experience is currently l

Further treatment is largely supportive and symptomatic. Military

recommendations are to keep skin lesions clean and to treat with topical antibiotics. Small blisters (<1 cm) need not be dÃ©brided, but larger bul should be unroofed. Fluid losses tend to be less than from thermal burns. healing can take weeks to months, although skin grafting is rarely neces Ophthalmic injuries usually heal completely with routine chemical burn ca Victims may become blinded because of a combination of blepharospasm corneal edema, which completely resolves in most cases; patients should informed that this condition is very likely temporary.[34] Severe eye injurie require topical mydriatics, anesthetics, and petroleum jelly to prevent fo of lid synechiae. Respiratory tract injuries are treated with antitussives, bronchodilators, mucolytics, and oxygen supplementation as needed. An should be reserved until there is confirmation of a bacterial pathogen. Ea intubation should be considered for severe airway involvement to assist i ventilation, provide positive airway pressures, and facilitate bronchoscop removal of pseudomembranes and debris.[10 , 53 , 89] Several antiinflamma and sulfhydryl-scavenging agents have shown benefit in animals as prop therapy (or if given immediately after exposure), but there are no data to support their use after injury has occurred.[89] Mustard-induced neutropenia be treated with granulocyte colony-stimulating factor.[52]

Lewisite

Lewisite (2-chlorovinyldichloroarsine) was developed to avoid some shortcomings in the use of sulfur mustard in World War I. It was difficult stage attacks across mustard-contaminated ground, and a less persistent alternative was desired. US Army Captain W. L. Lewis isolated this chemic pure form in 1918. Lewisite was never used in combat because the first shipment was en route to Europe when the war ended, and it was intenti destroyed at sea. British anti-Lewisite (BAL, dimercaprol) was developed a specific antidotal agent and remains in use for chelation of arsenic and o heavy metals.[49 , 89]

Pure Lewisite is an oily, colorless liquid. Impure preparations are colored amber to blue-black to black and have the odor of geraniums. Lewisite is volatile than mustard and is easily hydrolyzed by water and by alkaline a

solutions such as sodium hypochlorite. These properties increase safety f offensive battlefield use, but make maintaining a potent vapor concentra difficult.

Lewisite toxicity is similar to that of sulfur mustard, resulting in dermal a mucous membrane damage, with conjunctivitis, airway injury, and vesicu An important clinical distinction is that Lewisite is immediately painful, w initial contact with mustard is not. Other differences are faster onset of inflammatory response and healing of lesions from Lewisite, less seconda infection of Lewisite lesions, and less subsequent pigmentation changes.[8] mechanisms of Lewisite toxicity are not completely known, but appear to glutathione depletion and arsenical interaction with enzyme sulfhydryl gr Nevertheless, Lewisite toxicity is qualitatively and quantitatively different the arsenic it contains. Treatment consists of decontamination with copio water and/or dilute hypochlorite solution, supportive care, and BAL. BAL parenterally for systemic toxicity and is also used topically for dermal or ophthalmic injuries. Alternative heavy metal chelators that may be used a Lewisite antidotes include dimercaptopropane sulfonate (DMPS) and succ (2,3-dimercaptosuccinic acid).[49]

Phosgene Oxime

Although classified as a vesicant, phosgene oxime (dichloroformoxime, or does not cause vesiculation of the skin. CX is more properly an urticant o â€œnettleâ€• agent, in that it produces erythema, wheals, and urticaria to stinging

nettles. Phosgene oxime produces immediate irritation of the skin and m membranes. CX has never been used in battle, and little is known about mechanism or effects on humans.[53 , 89]

Cyanides (Blood Agents)

Several cyanides have been used as chemical weapons. During World War French used hydrogen cyanide (HCN) and cyanogen chloride (CNCl), desi as agents AC and CK respectively, without great success; the Austrians

introduced cyanogen bromide (CNBr). Cyanide weapons are relatively in
because of rapid dispersion and their â€œall or nothingâ€• biological ac
An exposed individual either rapidly succumbs to cyanide toxicity, or will
recover with minimal sequelae. Mass casualty events from cyanide CW ag
have been reported during the Iran-Iraq War and from Iraq's suppression
Kurds.[6 , 53]

The cyanides have been called â€œblood agentsâ€• based on the under
early in the 20th century that they were carried in the blood to exert sys
toxicity, whereas the other known chemical weapon agents produced loca
effects. This term is now antiquated because sulfur mustard and nerve a
can be carried in the blood and because the target of cyanide toxicity is
respiration in the mitochondria. The clinical effects and treatment of cyan
toxicity are covered elsewhere (Chap. 121) and do not differ significantly
used as a weapon. Hydrocyanic acid gas persists for only a few minutes i
atmosphere, because it is lighter than air and rapidly disperses. Cyanoge
chloride additionally causes ophthalmic and respiratory tract irritation and
produce delayed acute lung injury in victims who are not rapidly killed.[6 ,

Pulmonary Agents

Both chlorine (agent CL) and phosgene (agent CG) were used as war gase
World War I. Chlorine, phosgene, various organohalides, and nitrogen ox
belong to a group of toxic chemicals designated â€œpulmonary agentsâ€
because they can all induce delayed pulmonary edema from increased al
capillary membrane permeability.[49 , 53 , 101] Although pulmonary agents
not been used militarily since 1918, the risk of chlorine and phosgene ex
remains because of their extensive use in industry, or possibly as a terro
weapon. See Chap. 119 for clinical details, as the remainder of this sectio
highlights mass-casualty issues regarding these agents.

When released on the battlefield, chlorine forms a yellow-green cloud with
distinct pungent odor detectable at levels that are not immediately dange
Phosgene is either colorless or seen as a white cloud as a result of atmos
hydrolysis. Phosgene is reported to smell like grass, sweet newly mown h
corn, or like moldy hay. Although sulfur mustard was known as the â€œki

war gases,â€• [10] phosgene accounted for about 85% of all WWI deaths attributed to chemical weapons.[49] Phosgene produces injury by hydrolysis lungs to hydrochloric acid and by forming diamides that cross-link cell components (Figure 126-4). Battlefield exposure triggers cough, chest discomfort, dyspnea, lacrimation, and the peculiar complaint that smokin tobacco produces an objectionable taste. WWI phosgene fatalities were n develop a mushroom-shaped efflux of pink foam at their mouths from pu edema fluid. Prolonged observation after phosgene exposure is the rule, some casualties have initially appeared well and have been discharged, o return in severe respiratory distress a few hours later.[49 , 53 , 101]

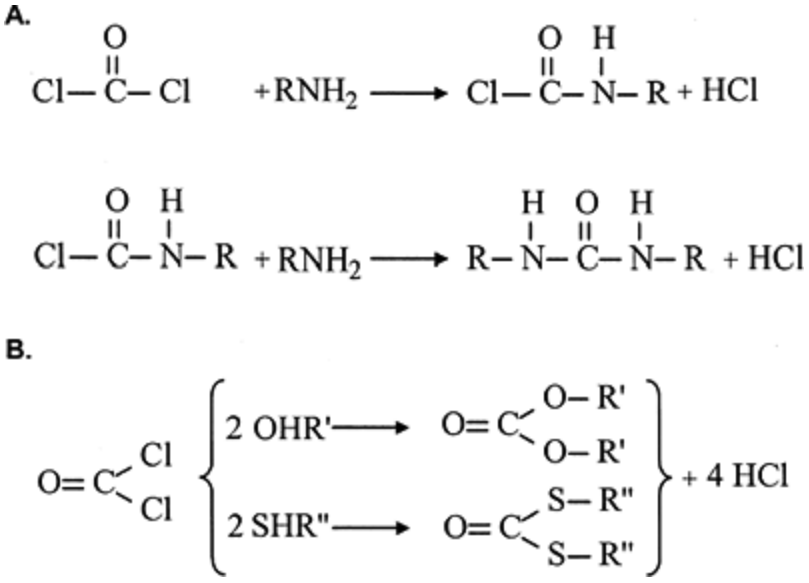


Figure 126-4. Proposed mechanisms of phosgene toxicity. A . Phosgene crosslinks two amine equivalents, forming a diamide and HCI. B . Similar crosslinking reactions occur with hydroxyl and thiol groups.

Riot Control Agents

Riot control agents (Figure 126-5) are intentionally nonlethal xenobiotics temporarily disable exposed individuals through intense irritation of expo mucous membranes and skin. These xenobiotics are also known as lacrin irritants, harassing agents, human repellents, and tear gas.[33] They are s

normal temperatures and pressures, but are typically dispersed as aeroso as small solid particles in liquid sprays. Common characteristics include r onset of effects within seconds to minutes, relatively brief duration once exposure has ceased and the victim is decontaminated, and a high safety (lethal dose vs. effective dose).[49 , 53 , 86]

CN (chloroacetophenone) has been widely used since WWI. CN is the acti ingredient in the Chemical Mace brand nonlethal weapon originally produc 1965 by the General Ordinance Equipment Company, later a division of S Wesson.[93] CS (o-chlorobenzilidene malononitrile) has largely replaced CN because of its higher potency, lower toxicity, and improved chemical stal [, 45 , 86] When used for crowd control, both CN and CS are disseminated a aerosols or as smoke from incendiary devices. Exposed persons develop irritation of the eyes, progressing to conjunctival injection, lacrimation, photophobia, and blepharospasm. Mucous membranes of the upper aero tracts can also be involved. Inhalation causes chest tightness, cough, sn and increased secretions. Dermal exposure may cause a burning sensatio erythema, or vesiculation, depending on the dose. Victims generally rem themselves from the offensive environment and recover within 15â€“30 Deaths are rare from riot control agents, and typically occur from respira tract complications in closed-space exposures where exiting the area is impossible.[49 , 53 , 86]

Personal protective devices dispensing lacrimator substances also cause chemical injuries in the absence of war or civil unrest. Law enforcement agencies and private citizens may have access to products containing CS, and/or OC (oleoresin capsicum, or pepper spray). OC is the essential oil from pepper plants (*Capsicum anuum* species) which contains capsaicin (8-methyl-N-vanillyl-6-noneamide), a naturally occurring lacrimator. Caps activates heat-dependent nociceptors, explaining why exposures are experienced as â€œhot.â€• [12] Severe respiratory tract injuries and fatali occasionally reported from exposures to these devices.[91 , 102]

Chloropicrin (trichloronitromethane or nitrochloroform) is another lacrima previously used as a CW agent that occasionally causes human toxicity by

use as a fumigant and soil insecticide.[95] DM (10-chloro-5,10-dihydrodiphenarsazine, or diphenylaminearsine) is a vomiting agent. Clin effects are delayed for several minutes after exposure, by which time the may have absorbed a significant amount. In addition to upper respiratory ocular irritation, DM causes more prolonged systemic effects with headac malaise, nausea, and vomiting.[53 , 86]

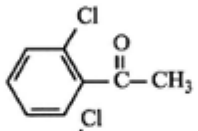
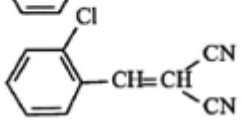
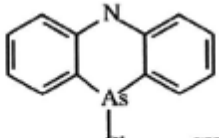
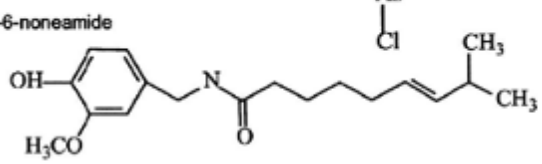
Military Designation	Common Name	Proper Name	Chemical Formula
CN	Chemical mace	1-Chloroacetophenone 2-Chloroacetophenone 2-Chloro-1-phenylethanone	
CS	Tear gas	O-Chlorobenzylidene malonitrile 2-Chlorobenzalmalonitrile	
DM	Adamsite	10-Chloro-5,10-dihydrophenarsazine Diphenylaminechlorarsine	
OC	Pepper spray, capsaicin	*trans*-8-Methyl-*N*-vanillyl-6-noneamide Oleoresin capsicum	

Figure 126-5. Riot control agents.

The primary treatment for all riot control agents is removal from exposur Contaminated clothing should be removed and placed in airtight bags to secondary exposures.[45] Skin irrigation with copious cold water is used fo significant dermal exposures.[8 , 45 , 46] Symptomatic treatments, such as topical ophthalmic anesthetics, nebulized bronchodilators, or oral antihis and corticosteroids, are indicated as appropriate in more severely affecte victims.[8] Capsaicin-induced dermatitis has been treated variably with im in water or oil, vinegar, bleach, lidocaine gel, and topical antacid suspen [, 35 , 93] Cold water produces earlier symptomatic relief, but oil immersion longer-lasting benefit.[35]

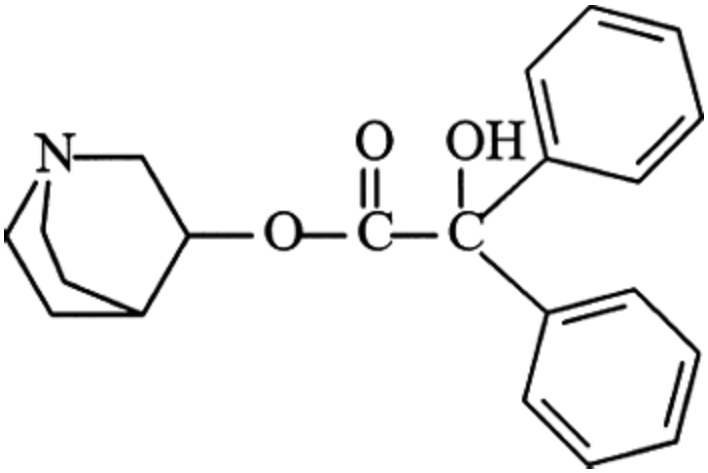


Figure 126-6. Incapacitating agent BZ (3-Quinuclidinyl benzilate, QNB).

Incapacitating Agents

3-Quinuclidinyl benzilate (BZ or QNB; Figure 126-6) is an antimuscarinic compound that has been developed as an incapacitating CW agent. BZ is more potent centrally than atropine, with an ID_{50} (dose that incapacitates of those exposed) of about 0.5 mg. Clinical effects are characteristic for anticholinergics, with drowsiness, poor coordination, and slowing of thou processes progressing to delirium. BZ takes at least an hour to produce manifestations, peaks at 8 hours, continues to incapacitate for 24 hours, takes 2â€“3 days to fully resolve.[41] During the recent Balkan wars, alleg were made that Bosnian Serbs used BZ against civilians, who reported hallucinations associated with attacks by artillery shells emitting smoke.[2]

Ultra-potent opioids may also be used as incapacitating CW agents. In 20 Russian security forces used a fentanyl derivative (possibly carfentanil or remifentanil) to end a 3-day standoff with terrorists in a Moscow theater which Chechen rebels held more than 800 hostages.[104] A â€œgasâ€• wa introduced into the theater ventilation system, which quickly subdued the occupants. Over 650 of the hostages were hospitalized, and 128 died. In news reports suggested the use of BZ, although the clinical findings were consistent with a CNS depressant. Within a few days, Russian officials sta that the agent used was a fentanyl derivative and was not expected to ca

fatalities. The relatively high case fatality rate could be because of multip factors, including variability in dose, displacement of oxygen by rapid introduction of gas into the building, failure to adequately notify healthca teams and supply them with antidotes, and poor physical condition of the hostages.

Lysergic acid diethylamide (LSD) has also been investigated as an incapa agent.[41] Table 126-5 describes the various toxic syndromes that may be from use of CW agents.

P.1787

P.1788

P.1789

Summary

Unconventional weapons of mass destruction continue to pose a threat to safety. Chemical and biologic weapons releases are considered more likely occur than thermonuclear weapons incidents, as CBW agents use resourc subject to less governmental control and requires less sophisticated tech and financial outlay than nuclear weapons. CBW agents are appealing to terrorist groups because the impact in terms of death, disability, econom losses, and panic remain high. The psychological impact of CBW terrorism well exceed that for conventional or nuclear weapons. Although the prob of incidents resulting in widespread public health disasters appears low, t consequences are high, and substantial preparations must be made in ad Smaller CBW incidents, unintentional releases, and hoaxes have occurred will probably continue to occur. Toxicologists and associated healthcare professionals occupy a unique position to impact preparedness and respo through familiarity with chemical hazards and biologic toxins.

Nerve Agents
Tabun (GA),

Sarin (GB) Soman (GD), VX

â€¢
Aerosol/vapor (Mild/moderate exposure)
Rapid (sec-mins)
Miosis, eye pain, dim or blurred vision
Rhinorrhea, â†‘secretions
Dyspnea, cough, wheezing, bronchorrhea
â€”
Headache
Nausea, vomiting, abdominal cramps
â€”
â€¢
Dermal exposure (Mild/moderate exposure)
Delayed (min-hrs)
â€”
â€”
â€”
Localized sweating
â€”
Nausea, vomiting, diarrhea, cramping
Subjective weakness local muscle fasciculations
â€¢
Severe exposure (Any route)
As above (by route)
Miosis
â†‘Secretions
Apnea
â€”
Sudden collapse, seizures
Incontinence
generalized fasciculations, weakness, flaccid paralysis
Vesicants
Sulfur Mustard (H, HD)
Delayed (hrs)
Conjunctivitis, pain, blurred vision, blindness (temporary)

Irritation, hoarseness barky cough, sinus tenderness tracheobronchitis
(More severe exposures) Productive cough, pseudomembrane formation, obstruction
Erythema, vesicles, bullae, necrosis
â€”
Nausea, vomiting
Bone marrow suppression (in severe exposures)
Lewisite (L)
Immediate irritation Delayed vesication
Pain, blepharospasm conjunctivitis, lid edema
(Same as Sulfur Mustard)
(Same as Sulfur Mustard)
Erythema, vesicles
â€”
â€”
Shock (in severe exposures)
Phosgene Oxime (CX)
Immediate irritation Delayed urtication
Pain, corneal damage
Irritation
Acute lung injury
Pain blanching, erythema, urticaria Necrosis
â€”
â€”
â€”
Pulmonary Agents
Phosgene (CG), Chlorine (CL)
Immediate Irritation Delayed ALI
Irritation
Irritation stridor (Chlorine)
Dyspnea, cough Acute lung injury
â€”
â€”
â€”

Chlorine effects more rapid than phosgene
Cyanides
Hydrogen Cyanide (AC)
Rapid (sec-mins)
â€”
â€”
Hyperpnea then apnea
â€”
Anxiety, agitation, sudden collapse, seizures
â€”
â€”
Cyanogen Chloride (CK)
Rapid (sec-mins)
Irritation
Irritation
Hyperpnea then apnea
â€”
Anxiety, agitation, sudden collapse, seizures
â€”
â€”
Riot Control Agents
Lacrimators (CN, CS) Capsaicin (OC)
Immediate
Pain, lacrimation, blepharospasm conjunctivitis
Irritation
Cough, chest pain
Burning pain, erythema Vesiculation severe exposures
â€”
Nausea, retching (may occur with CN/CS)
â€”
Adamsite (DM)
Rapid (min)
Irritation
Irritation, sneezing

Cough, chest pain
â€”
Headache
Nausea, vomiting, abdominal cramps
â€”
Incapacitating Agent
3-quinuclidinyl benzilate (BZ)
Delayed (hrs)
Mydriasis
Dry mouth
â€”
â€”
Anticholinergic delirium
â€”
â€”
Ultra-potent opioids
Rapid (sec-min)
Miosis
â€”
Hypoventilation
â€”
CNS depression
â€”
â€”

		Organ System					
Chemical Weapon	Onset	Eyes	Upper Airways and Mucous Membranes	Lungs	Skin	CNS	GI Tract

TABLE 126-5. Chemical Weapons Toxic Syndromes

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Chapter 127
Biological Weapons

Jeffrey R. Suchard

On March 10, 1998, when employees at a collection agency in Phoenix, A opened an envelope containing a payment for $53.99, some granular ma and a threatening note were found. The letter read, â€œYou S.O.B.!!!! Yo just been exposed to anthrax spores prepare to die â€¦ you better have a ready â€¦ Also a standard pestelence [sic] has been put on you and your â€¦.â€•[86] After a 911 call, police and a fire department hazmat team re to the scene. Little useful information was immediately available regardin kind of decontamination or treatment would be necessary, leading the potentially exposed employees to believe they were destined to develop a rapidly fatal illness. Nine employees and one police officer were quarantir several nearby businesses were evacuated while a decontamination showe constructed at the scene.[87] The victims were transported to a local hospi emergency department (ED), where they were examined, advised to retur they developed influenza-like symptoms, and given prescriptions for ciprofloxacin. However, their clothes, wallets, and purses were still in quarantine, making it difficult for the victims to fill these potentially life- prescriptions. The perpetrator was identified and apprehended from retur address information accompanying the payment. He was indicted 2 days

charges of mailing threatening communications and threatening to use w of mass destruction. Within 4 days, bacteriologic testing of the envelope letter excluded the presence of *Bacillus anthracis* ; the granular material believed to be salt and pepper.[53 , 86]

Expertise in dealing with biological weapons requires specific knowledge the fields of infectious disease, epidemiology, toxicology, and public heal Biological and chemical warfare agents share many characteristics in com including intent of use, some dispersion methods, and initial defense base adequate personal protective equipment and decontamination (see Tables and 126-2). Key differences between biological and chemical weapons h involve a greater delay in onset of clinical symptoms after exposure, that incubation period for biological warfare (CBW) agents is greater than the period for chemical warfare agents, and that decontamination is less cruc victims exposed to BW agents than to CW agents. Additionally, a few BW can reproduce in the human host and cause secondary casualties, and di following exposure to several of these agents can be prevented by the ti administration of prophylactic medications.

Biological weapons may be bacteria, viruses, or toxins derived from microorganisms. Some fungi are listed as potential BW agents, although t none are known to have been developed into weapons.[96] Because toxin w do not contain living organisms, some authorities classify them as chemi rather than biological, weapons. For the purposes of discussion in this ch toxin weapons derived from microorganisms will be considered biological weapons. Of note to toxicologists, most of the bacterial BW agents exert effects through toxins they elaborate.

Most of the diseases caused by biological weapons are either infrequently encountered in modern clinical medicine, such as anthrax and plague, or longer occur naturally, such as smallpox. Physicians and other healthcare personnel therefore require specific training in the recognition and mana of biological warfare victims. Potential BW agents have been categorized risk of mass-casualty outbreaks resulting from deployment and exposure. high-risk agents are easily disseminated or transmitted and may cause hi mortality and potentially a public health disaster; these agents include s

anthrax, plague, botulism, tularemia, and several hemorrhagic fever viru The moderate-risk agents include Q fever, brucellosis, the equine encepl viruses, ricin, and staphylococcal enterotoxin B, all of which are discussed this chapter.

History

Biological warfare has ancient roots. Missile-type weapons poisoned with toxins were used as early as 18,000 years ago (Chap. 1). Recent excava an Egyptian tomb, from about 2100 BC, yielded arrows coated with cardi steroids and paralytic toxins.[68] Around 600 BC, the Athenians used helle and the Assyrians used ergot alkaloids, to poison enemy water supplies.[6] 200 BC, the Carthaginian general Maharbal tainted wine consumed by Af rebel forces with the anticholinergic herb mandragora and then ambushed intoxicated troops. In 184 B.C., Hannibal ordered earthen pots filled with â€œserpents of every kindâ€• hurled onto enemy ships, thereby winning naval battle of Eurymedon against King Eumenes of Pergamon.[28 , 49 , 83] B.C., King Mithridates VI of Pontus was retreating from the Roman Gener Pompey near Trebizond, modern northeast Turkey. At the advice of a ph counselor, Mithridates maneuvered Pompey's troops into a region where honey was contaminated with grayanotoxins from rhododendron nectar. Romans ate the poisoned honey and were effectively ambushed.[52]

From 1344 to 1346 AD, the Tartars besieged the Genoan trade city of Kaf the Black Sea coast. When the Tartars began to die

of bubonic plague, the dead bodies were hurled over the battlements. Wi city, plague forced the Genoans to flee, and they then disseminated the to other trade ports and eventually to the rest of Europe, causing the Bla Death.[98] In 1763, Sir Jeffrey Amherst, the commander of British forces d the French and Indian War, instituted a policy of spreading smallpox to N Americans by giving them contaminated blankets and handkerchiefs.[22 , 7]

During World War I, Germany was the only combatant nation with an acti program. German agents infected Allied livestock with anthrax and gland Eighty years after the capture of a German device used to disseminate a

viable spores were recovered.[75]

Shiro Ishii, a Japanese army doctor, headed an active BW program throu Japan's war with China and World War II.[38] Several centers were founded most famous being Unit 731 in Manchuria, where human experiments on prisoners-of-war and imprisoned civilians occurred. Several field trials wi bubonic plague were performed on Chinese civilians and Russian troops. Soviets Union, Germany, France, Britain, and Canada all started BW rese facilities in the period between the World Wars.

BW research program in the United States was founded at Camp Detrick, Maryland in 1942. Fort Detrick, as it is now known, remains the home of United States Army Medical Research Institute of Infectious Diseases (USAMRIID). Anthrax and botulinum toxin were the foci of weapons deve during WWII; it is estimated that the United States could have manufactu 1,000,000 anthrax bombs and 275,000 botulinum bombs by 1945 had fu production been implemented.[4]

The British BW program was established in 1940 at Porton Down, but mos the field testing of anthrax occurred on Gruinard Island off the northern c Scotland.[66] In 1979, the soil was still found to be contaminated with viab anthrax spores.[54] The island was decontaminated with 5% formaldehyde water, and was deemed safe by the British government in 1988.[1]

During the Cold War, the US military maintained active research into bio weapons, including field trials with bacterial simulants. In 1950, ships in Francisco harbor released aerosols of *Serratia marcesans* and other simu which resulted in a minor outbreak of Serratia sepsis. In 1966, light bulb with *Bacillus subtilis* var *globigii* were shattered in the New York City sub system, confirming the hypothesis that the piston-like action of the subw trains could rapidly disperse the bacterial aerosol throughout the city.[22] , , 78

In London, in 1978, the Bulgarian exile Georgi Markov was assassinated b tiny metal pellet fired from a gun designed to appear like an umbrella. He thought to have died from sepsis until the pellet was found at autopsy.[23] After the fall of the Soviet Union, government officials confirmed that the

used umbrella guns firing ricin pellets to assassinate Markov and others.

In 1979, an outbreak of human anthrax caused at least 66 fatalities in th Russian city of Sverdlovsk. Soviet officials first blamed the outbreak on gastrointestinal anthrax from a shipment of contaminated meat.[55] Autops however, revealed that the deaths were from inhalational anthrax, and epidemiologic investigation demonstrated that almost all of the cases occ downwind from a military facility. These data are consistent only with a of aerosolized anthrax, which has since been confirmed by Russian autho

In the late 1970s and early 1980s, many reports came from Southeast As Afghanistan that Soviet-supported troops were using a biological weapon as Yellow Rain.[39] Some samples of Yellow Rain were found to contain trichothecene mycotoxins, although controversy remains regarding wheth finding represents intentional biological warfare or a naturally occurring phenomenon.[70]

During the 1990s there was a great deal of concern about the use and po stockpiling of weapons of mass destruction by Saddam Hussein in Iraq.[51] part of the WMD program, Iraq had a very active BW research program, investigating at least 5 bacteria, 1 fungus, 5 viruses, 4 toxins, simulants, variety of dispersion methods.[81 , 99] Thousands of liters of anthrax spore botulinum toxin, and aflatoxin were produced and weaponized into bombs payloads for SCUD missiles.

Biological terrorism and the threat of bioterrorism are now recognized as worldwide, growing public health concerns.[40] In the US in 1984, a large outbreak of salmonellosis was traced to intentional contamination of rest salad bars by the Rajneeshee cult in Oregon.[91] The Aum Shinrikyo cult ba Japan investigated the use of cholera and Q fever, unsuccessfully release anthrax spores and botulinum toxin, and even sent members to Africa to the Ebola virus.[71 , 89] The mere threat of biologic agent release can terro city. At the end of the 1990s, there was a huge increase in false anthrax threats, which paralyzed Los Angeles and cities in Indiana, Kentucky, and Tennessee among many others.[11] Because of heightened concern for bioterrorism, even naturally occurring disease outbreaks have raised sus of biological terrorism. In 1999, an outbreak of West Nile-like virus ence

in New York and a case of brucellosis in New Hampshire acquired under suspicious circumstances were investigated as potential BW agent release[76] Similarly, a 1999â€“2000 epidemic of tularemia in war-torn Kosovo wa scrutinized as the potential result of an intentional BW agent release.[37]

General Considerations

Differences Between BW Incidents and Naturally Occurring Outbreaks

Because the clinical effects of bioweapons are delayed, as may be the symptoms, it can be difficult to differentiate occult BW releases from nat occurring disease outbreaks. Several epidemiologic criteria are proposed t in such determinations,[69] at least several of which should be identifiable i incident (Table 127-1).

To avoid early detection, terrorists might choose to release an endemic infection, or a disease that mimics an endemic infection, during its seasor peak incidence. In some areas of the United States, for example, a few ca bubonic plague would not attract notice; that is, until dozens or hundreds cases were identified. An outbreak of inhalational anthrax during the infl season may similarly be hidden amongst patients with identical early syn until an unusually high mortality was evident.[20] By the time the BW outb recognized for what it truly is, the perpetrators could dispose of any phys evidence and flee the area. On the other hand, even a single case of sma (anywhere in the world), Ebola virus infection, or Congo-Crimean hemorr fever (in nonendemic areas) would immediately raise suspicion of a BW a

Preparation

Many BW agents initially produce nonspecific symptoms of diseases, rarely ever seen in clinical practice. Inhalational anthrax

and pneumonic plague, for example, could easily be misdiagnosed as infl or acute bronchitis. Providers in EDs and primary care medicine must be

educated to recognize the signs, symptoms, and clinical progression of d caused by BW agents.[77 , 94] Clear identification, isolation, and aggressive treatment early after exposure within the first 24â€“48 hours are the bes only means of reducing mortality and, in the case of smallpox or plague, preventing secondary or tertiary cases.[27] However, even with increasing awareness and educational efforts, many physicians remain inadequately prepared. As recently as 1999, only 53% of surveyed emergency medicin residencies included formal training in BW issues, with more than 70% of residency directors rating themselves as less than adequate or very poor recognizing BW casualties.[72]

- Large epidemic with unusually high morbidity and/or mortality
- Epidemic curve (number of cases versus time) showing an â€œexplos of cases, reflecting a point source in time rather than insidious onset
- Tight geographic localization of cases, especially downwind of potenti release site
- Predominance of respiratory tract symptoms because most BW agents contracted by aerosol inhalation
- Simultaneous outbreaks of multiple unusual diseases
- Immunosuppressed and elderly persons more susceptible
- Nonendemic infection (â€œimpossible epidemiologyâ€•)
- Unseasonal time for endemic infection
- Organisms with unusual antimicrobial resistance patterns, reflecting E genetic engineering
- Animal casualties from same disease outbreak
- Absence of normal zoonotic disease host
- Low attack rates among persons incidentally working in areas with fil air supplies or closed ventilation systems, using HEPA masks, or rem indoors during outdoor exposures
- Delivery vehicle or munitions discovered
- Law enforcement or military intelligence information
- Claim of BW release by belligerent force

TABLE 127-1. Epidemiologic Clues Suggesting Bioweapons Releas

Decontamination

Biological warfare agents are most effective when dispersed by aerosol. after a known or suspected release of bioaerosols, decontamination is a relatively minor concern, because aerosols sized to reach the lower resp tract (<5 Âµm particles) produce little surface contamination. However, s removal of clothing will eliminate a high proportion of deposited particles, subsequent showering with soap and water will probably remove 99.99% remaining organisms on the skin.[48] Thus, decontamination after BW aero exposure, when needed, is achieved through disrobing and showering wit and water, which can be done on-site or in the victims' homes and away healthcare facilities, thereby reducing strain on disaster response manpov material in multiple-victim exposures.[27 , 40 , 48 , 77] When there is gross, evidence of skin exposure to biological agents, the patient should be decontaminated by thorough irrigation, and, if available, sterilizing the sk a sporicidal/bactericidal solution (eg, 0.5% sodium hypochlorite), and a f water rinse.[48 , 77] After occult bioweapons releases, victims are identified after exposure; decontamination will obviously not be helpful and may or serve to delay care.

Biological Warfare Agents

Bacteria

Anthrax

Anthrax is caused by *Bacillus anthracis* , a Gram-positive spore-forming found in soil worldwide. *B. anthracis* causes disease primarily in herbivor animals. Human anthrax cases generally occur in farmers, ranchers, and workers handling contaminated animal carcasses, hides, wool, hair, and bones.[35] Details regarding the 2001 bioterrorist anthrax outbreak in the

States are given below.

Clinical Manifestations

A few clinically distinct forms of anthrax may occur, depending on the rou exposure. Cutaneous anthrax results from direct inoculation of spores into skin via abrasions or other wounds and accounts for about 95% of endem (naturally occurring) human cases. Patients develop a painless red macule vesiculates, ulcerates, and forms a 1â€“5-cm brown-black eschar surroun edema.[58] The eschar color gave rise to the name anthrax, from the Greek *anthrakos* meaning â€œcoal.â€• Most skin lesions heal spontaneously, a 10â€“20% of untreated patients progress to septicemia and death. Cutan anthrax fatalities are uncommon when treated with antibiotic therapy.

Gastrointestinal anthrax results from ingesting insufficiently cooked meat infected animals. Patients develop nausea, vomiting, fever, abdominal pai mucosal ulcers, which can cause GI hemorrhage, perforation, and sepsis. Mortality from gastrointestinal anthrax is at least 50%, even with antibio treatment.[35 , 62]

Inhalational anthrax results from exposure to aerosolized *B. anthracis* sp Although this form of anthrax is very rare, it is so closely associated with occupational exposures that it has been called â€œwoolsorter's disease.â Inhalational anthrax is also likely to be the form that occurs in a BW atta because the anthrax spores would be most effectively disseminated by a After an incubation period of 1â€“6 days, the patient develops fever, ma fatigue, nonproductive cough, and mild chest discomfort, which may be e mistaken for community acquired pneumonia.[18] The initial symptoms may improve for 2â€“3 days or the patient may abruptly progress to severe respiratory distress with dyspnea, diaphoresis, stridor, and cyanosis. Bacteremia, shock, metastatic infection such as meningitis, which occurs about 50% of cases, and death may follow within 24â€“36 hours. Prior to 2001 bioterrorist outbreak, mortality from inhalational anthrax was expec be nearly 100%, even with antibiotics, once symptoms develop.[31 , 35 , 62] Currently, with appropriate antibiotic therapy and supportive care, 5 of 1 patients with inhalational anthrax died, albeit a high mortality rate, but l

than previously predicted.[44]

Pathophysiology

Inhalational anthrax causes a mediastinitis. Diagnostic imaging typically mediastinal widening from enlarged hilar lymph nodes and pleural effusic although pulmonary parenchymal infiltrates may also be seen.[44] Inhaled are taken up into the lymphatic system where they germinate and the ba reproduce. *B. anthracis* produces three toxins: protective antigen, edema and lethal factor. Protective antigen (PA) is so named because antibodies against it protect the subject from the effects of the other 2 toxins. PA fo heptamer that inserts into plasma membranes, facilitating endocytosis of other two toxins into target cells.[73] Edema factor is a calmodulin-depend adenylate cyclase. Increased intracellular cyclic adenosine monophosphat (AMP) upsets water homeostasis, leading to massive edema and impaired

neutrophil function. Lethal factor is a zinc metalloprotease that stimulate macrophages to release tumor necrosis factor Î± and interleukin-1Î², contributing to death in systemic anthrax infections (see Figure 127-1).[2]

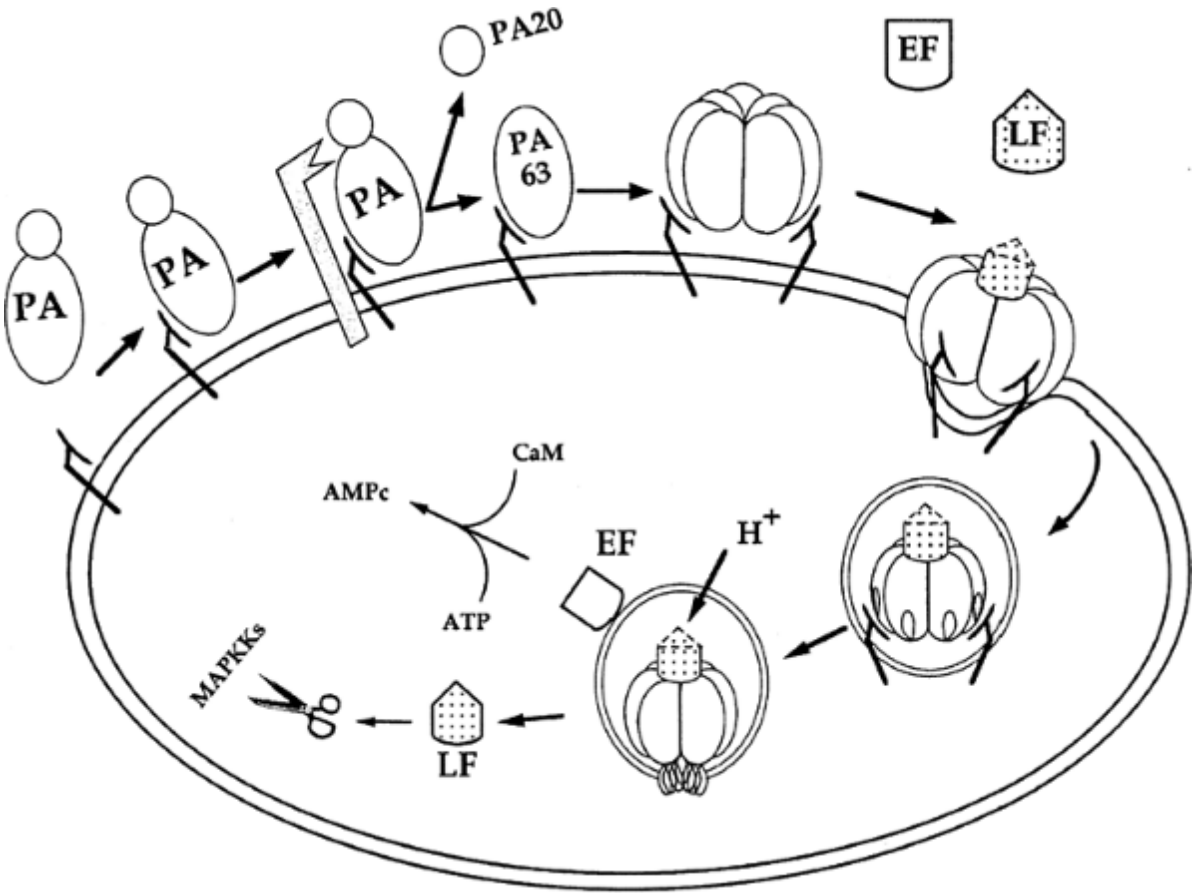

Figure 127-1. Model of action of anthrax toxins. PA = Protective antigen; Edema factor; LF = Lethal factor; CaM = Calmodulin; MAPKKs = Mitogen-activated protein kinases. *(Reprinted with permission from Brossier F, Mo Toxins of Bacillus anthracis. Toxicon 2001;39:1747â€“1755.)*

Treatment

The primary antibiotics recommended to treat anthrax are ciprofloxacin a doxycycline. Although other fluoroquinolones would be expected to have activity against anthrax, only the manufacturer of ciprofloxacin applied fo received a Food and Drug Administration (FDA)-approved indication for us this infection. In a mass-casualty setting or for postexposure prophylaxis should be treated with ciprofloxacin 500 mg PO every 12 hours. Alternate therapies are doxycycline 100 mg PO every 12 hours, or amoxicillin 500 r every 8 hours, if the anthrax strain is proven susceptible.[44] The recomm

duration of therapy is 60 days, stemming from case experience in Sverdl where some patients developed disease several (6â€“7) weeks after the release.[63] Children can also be treated with ciprofloxacin (15 mg/kg; ma 500 mg/dose) or amoxicillin (80 mg/kg/d divided every 8 hours; maximu mg/dose). The relative pediatric contraindication to fluoroquinolones is outweighed by the risk of potentially fatal disease. Cutaneous anthrax is with the same drugs and doses as for postexposure prophylaxis.

Inhalational anthrax should be treated initially with intravenous antibiotic Adults should receive ciprofloxacin 400 mg IV or doxycycline 100 mg IV 12 hours, along with 1 or 2 additional antibiotics with in vitro activity ag anthrax (eg, rifampin, vancomycin, penicillin, ampicillin, chloramphenicol imipenem, clindamycin, clarithromycin). Children should be given ciproflo 10 mg/kg IV (max 400 mg/dose), or doxycycline 2.2 mg/kg IV (max 100 mg/dose), and additional antibiotics as above.[44] In a true mass-casualty however, when resources are strained and inpatient care is not available every victim, oral therapy, as described above, may be instituted. When clinically appropriate, oral antibiotic therapy can be substituted for IV, wi total treatment duration of 60 days. Some patients in the 2001 outbreak specifically treated with antibiotics that inhibit protein synthesis in attem reduce bacterial production of toxins.

Anthrax Vaccine

An effective vaccine against anthrax is available.[36, 60, 61, 79, 100] In th United States, the Bioport Corporation (formerly Michigan Biologic Produc Institute) is licensed by the FDA to produce anthrax vaccine adsorbed (A FDA advisory panel review in 1985 found the vaccine to be safe and effe The vaccine consists of a membrane-sterilized culture filtrate of *B. anthr* V770-NP1-R, an avirulent, nonencapsulated strain that produces protecti antigen, adsorbed to aluminum hydroxide, formulated with benzethonium chloride (preservative) and formaldehyde (stabilizer).[100] In human and a experiments, the vaccine is highly effective in preventing all forms of an (including inhalational), and the vaccine is recommended for workers in h risk occupations. As with any vaccine, local reactions to AVA occur in som

recipients (up to 20% with mild, local reactions), and self-limited system reactions occur more rarely (<1.5%). Serious adverse events are very ra only 22 potentially related cases of serious adverse events from over 1 r doses administered to US armed forces.[36] The dosage schedule for AVA is mL subcutaneously at 0, 2, and 4 weeks and 6, 12, and 18 months, follov yearly boosters.

Undue concern has arisen regarding the safety of anthrax vaccination, an several members of the armed service have been punished or discharged refusing to accept vaccinations.[67]

The 2001 Bioterrorist Anthrax Outbreak

Starting on September 27, 2001 a 63-year-old Florida man developed ma fatigue, fever, chills, anorexia, and diaphoresis. He was admitted to a loc hospital on October 2, after presenting with additional complaints

of nausea, vomiting, and confusion. Chest radiography showed cardiomeg left perihilar infiltrate, small left pleural effusion, and a prominent superi mediastinum. Lumbar puncture revealed hemorrhagic meningitis with ma Gram-positive bacilli. *Bacillus anthracis* was isolated from the cerebrospir after only a 7-hour incubation and from blood cultures within 24 hours. T patient had progressive clinical deterioration and died on hospital day nu 4.[46]

On October 4, the Centers for Disease Control and Prevention (CDC) relea public health message regarding this case, which initially appeared to be isolated, perhaps naturally occurring sporadic event; another case of ant was reported in Texas earlier the same year.[14] Nevertheless, the rarity o inhalational anthrax especially outside of a high-risk occupation, combine increased suspicion in the wake of events on September 11, 2001, led to investigation of a potential bioterrorist event. Within days, epidemiologic investigation suggested workplace exposure to anthrax spores, and perso working in the same building were started on prophylactic ciprofloxacin.[15] October 12, a case of cutaneous anthrax was reported in New York City associated with a suspicious letter opened on September 25.[16] Anthrax c

and environmental contamination were also soon detected in Washington, and in a New Jersey postal facility. The public response to the reports of serious and fatal cases included misuse and hoarding of antibiotics, purc gas masks (often with inappropriate filtering mechanisms for biological weapons), reporting numerous miscellaneous powdery substances, and perpetrating or reporting copycat hoaxes.

By November 7, 2001, a total of 22 cases of anthrax were reported: 10 inhalational and 12 cutaneous.[17] One additional death from inhalational occurred on November 21, 2001,[3] and a case of cutaneous anthrax also occurred in a laboratory worker analyzing samples obtained during the investigation.[19] In two of the fatal cases, no contact with contaminated l could be established.[3, 31, 65] One infant hospitalized in New York City w cutaneous anthrax was initially misdiagnosed as suffering from a brown r spider envenomation.[33] The total number of medical victims of anthrax in Fall of 2001 was 23: 11 cases of inhalational anthrax (with 5 fatalities), a cases of cutaneous anthrax (8 confirmed and 4 suspected).[19]

Although the overall morbidity and mortality from this bioterrorist event relatively low, the psychosocial-economic impact was high. Several hundr postal and other facilities were tested for *B. anthracis* spore contaminatio public health authorities recommended antibiotic prophylaxis be initiated approximately 32,000 persons.[17] Additional indirect costs and effects are difficult to quantify, including the number of persons self-initiating antibi treatment without an evident indication, lost production and wages, environmental and biologic sample testing, decontamination efforts, and international sense of unease.

Published estimates of tens of thousands of deaths from a military-style attack[47] depend on efficient BW agent dispersion. The technically easier letter has clearly proven itself to be a â€œWeapon of Mass Disruption.â€ predicted, the psychological impact far exceeded the actual medical eme and events with a modest number of medical patients are probably more than true mass-casualty BW incidents. On the other hand, prior assumpti regarding the clinical aspects of anthrax were not as reliable. The mortali among the 11 cases of inhalational anthrax was 45%, considerably lower

expected and probably because of earlier diagnosis, improved supportive measures, and a wider choice of antibiotics, compared to historical contr Presentation with fulminant illness, such as sepsis, still appears to be pr of a fatal outcome, yet the initial phase of illness does not necessarily lea death, if treated with appropriate antibiotics.[5 , 46 , 56] Pleural effusions w the most common radiographic abnormality, rather than a widened medi and pulmonary parenchymal infiltrates were seen in 7 patients, whereas teaching had been that pneumonia does not commonly occur with inhalat anthrax.[35 , 46 , 62]

Plague

Yersinia pestis is a Gram-negative bacillus responsible for over 200 millio human deaths and 3 major pandemics in recorded history.[58 , 59] Naturall occurring plague is transmitted by flea vectors from rodent hosts, or by respiratory droplets from infected animals or humans. Plague is a particu frightening BW agent because it can be released as an aerosol to cause a fulminant communicable form of the disease for which no effective vaccin exists. Antibiotics must be initiated early after exposure because once sy develop, mortality is extremely high.

Clinical Presentation

Plague occurs in three clinical forms: bubonic, septicemic, and pneumonic Bubonic plague has an incubation period of 2â€“10 days followed by feve malaise, and painful, enlarged regional lymph nodes called buboes. The i nodes are most commonly affected, because the legs are more prone to f bites.[62] In the United States, 85â€“90% of human plague patients have t bubonic form, 10â€“15% have a primary septicemic form without lymphadenopathy, and about 1% present with pneumonic plague. Secondc septicemia occurs in 23% of patients presenting with bubonic plague.[59] V skin lesions at the site of inoculation (pustules, vesicles, eschars, or pap occur in some patients, although the petechiae and ecchymoses that occu advanced cases may resemble meningococcemia.[58 , 62] Distal gangrene f small artery thrombosis may occur, explaining why plague pandemics are

sometimes called â€œThe Black Death.â€• If left untreated, bubonic pla carries a 60% mortality rate.[58] Bubonic plague could result from an inter release of plague-infested fleas.

Pneumonic plague is an infection of the lungs with *Y. pestis* . Between 5% 15% of bubonic plague patients develop secondary pneumonic plague thr septicemic spread of the organism.[59] Primary pneumonic plague occurs fr inhalation of infected respiratory droplets or an intentionally disseminated aerosol. The incubation period of pneumonic plague after inhalation is 2â days. The onset of disease is acute and often fulminant. Patients develop malaise, and cough productive of bloody sputum, rapidly progressing to dyspnea, stridor, cyanosis, and cardiorespiratory collapse. Plague pneumo almost always fatal unless treatment is begun with 24 hours of symptom onset.[32 , 62]

Diagnosis and Treatment

Plague can be diagnosed by various staining techniques, immunologic stu by culturing the organism from blood, sputum, or lymph node aspirates. gram stained, *Y. pestis* appears as a Gram-positive â€œsafety-pinâ€•-sh bipolar coccobacillus.[31] Chest radiographs in pneumonic plague reveal pa consolidated bronchopneumonia. Leukocytosis with a left shift is common, markers of low-grade disseminated intravascular coagulation (DIC) and elevations of unconjugated bilirubin and hepatic aminotransferases.[32]

Antibiotic treatment options are similar to those for anthrax. In a mass-c setting or for postexposure prophylaxis, adults are

treated with doxycycline 100 mg PO twice daily or ciprofloxacin 500 mg P daily. Children receive doxycycline 2.2 mg/kg or ciprofloxacin 20 mg/kg, u maximum of the adult doses. Chloramphenicol 25 mg/kg PO four times da an alternative. The duration of treatment is 7 days for postexposure prophylaxis, and 10 days for mass-casualty incidents. Patients with pneu plague need to be isolated to prevent secondary cases. Respiratory dropl precautions are necessary in pneumonic plague until the patient has rece antibiotics for three days.[32] In a contained-casualty setting, pneumonic

is treated with parenteral streptomycin or gentamicin; alternative antibic include doxycycline, ciprofloxacin, and chloramphenicol.[43] A killed whole- vaccine effective against bubonic plague is available, but does not reliabl protect against pneumonic plague in animal studies.[58, 61]

Tularemia

Francisella tularensis is a small, aerobic, Gram-negative coccobacillus weaponized by the United States and probably other countries as well. T occurs naturally as a zoonotic disease spread by bloodsucking arthropods direct contact with infected animal material. Tularemia in humans may oc ulceroglandular or typhoidal forms, depending on the route of exposure. Ulceroglandular tularemia is more common, occurring after skin or mucou membrane exposure to infected animal blood or tissues. Patients develop ulcer with associated lymphadenopathy, fever, chills, headache, and mal Typhoidal tularemia presents with fever, prostration, and weight loss wit adenopathy. Exposure to aerosolized bacteria, as employed in BW, will m likely result in typhoidal tularemia with prominent respiratory symptoms s a nonproductive cough and substernal chest discomfort. Diagnosing tulare often difficult, as the organism is hard to isolate by culture and the symp are nonspecific. Chest radiography may demonstrate infiltrates, mediasti lymphadenopathy, or pleural effusions.[24, 29, 31, 61, 62]

Antibiotic treatment options are again similar to those for anthrax and pl In mass-casualty settings, or for postexposure prophylaxis, adults are tr with doxycycline 100 mg twice daily or ciprofloxacin 500 mg orally twice for 14 days; pediatric dosing for doxycycline is 2.2 mg/kg or ciprofloxacin mg/kg (maximum = adult dose) twice daily. When dealing with a limited of casualties, the preferred antibiotics are streptomycin 1 g IM twice daily gentamicin 5 mg/kg IM/IV once daily. Alternatives include parenteral doxycycline, chloramphenicol, and ciprofloxacin.[24]

Brucellosis

Brucellosis could potentially be used as an incapacitating BW agent, becau causes disease with low mortality but significant morbidity. Brucellae (*Bru*

melitensis , *abortus* , *suis* , and *canis*) are small, aerobic, Gram-negative coccobacilli that generally cause disease in ruminant livestock. Humans c brucellosis by ingesting contaminated meat and dairy products or by aero transmission from infected animals. The United States weaponized *B. suis* other countries are also believed to have developed brucella bioweapons. Brucellosis commonly presents with nonspecific symptoms such as fever, and malaise, with either an acute or insidious onset. Because brucellae a facultative intracellular parasites that localize in the lung, spleen, liver, C bone marrow, and synovium, organ-specific signs and symptoms may occ Diagnosis is made by serologic methods or culture. Because single-drug treatment often results in relapse, combined therapy is indicated. Treatm choice (adult doses) are doxycycline 200 mg/d orally, plus rifampin 600â mg/d orally for 6 weeks, or doxycycline 200 mg/d orally for 6 weeks with streptomycin 15 mg/kg twice daily IM or gentamicin 1.5 mg/kg IM q8h fo first 10 days.[31 , 42 , 61 , 62]

Q Fever

Q fever was first described by Edward Derrick in 1937, and was given its nameâ€”Q for â€œqueryâ€•â€”because the causative organism was not known. Q fever occurs naturally as a self-limited febrile, zoonotic disease contracted from domestic livestock. Q fever is now known to be caused b *Coxiella burnetti* , a unique rickettsia-like organism that can persist on inanimate objects for weeks to months and can cause clinical disease with inhalation of only a single organism. These features are of obvious benefi use as a potential BW agent. After a 10â€“40-day incubation period, Q fe manifests as an undifferentiated febrile illness, with headache, fatigue, a myalgias. Patchy pulmonary infiltrates on chest radiography that resembl or atypical bacterial pneumonia, occur in 50% of cases, although only hal patients have cough and even fewer have pleuritic chest pain. Uncommon complications include hepatitis, endocarditis, meningitis, encephalitis, an osteomyelitis. Patients are generally not critically ill, and the disease can long as 2 weeks. Treatment with antibiotics will shorten the course of acu fever and can prevent clinically evident disease when given during the incubation period. Tetracyclines are the mainstay of therapy, and either

tetracycline 500 mg PO q6h or doxycycline 100 mg PO q12h should be giv 5â€“7 days.[9 , 31 , 62]

Viruses

Smallpox

Smallpox is caused by the variola virus, a large DNA orthopoxvirus with a range limited to humans. Prior to global World Health Organization (WHO efforts to eradicate naturally occurring smallpox by immunization, recurre epidemics were common and the disease carried roughly a 30% fatality ra unvaccinated populations.[41 , 57] Smallpox is highly contagious. Outbreaks the 1960s and 1970s in Europe often resulted in 10â€“20 secondary cases index case. One German smallpox patient with a cough, isolated in a sing room, infected persons on three floors of a hospital.[41] The overwhelming majority of secondary infections, however, occur among close family con especially those sleeping in the same room or even in the same bed.[26]

In 1980, the United Nations' WHO certified that smallpox had been eradi from the world, and recommended ceasing vaccinations and either destro transferring remaining stocks of variola virus to one of two designated b level 4 facilities: the CDC in Atlanta, or the Russian State Research Cente Virology and Biotechnology (VECTOR).[7] All remaining known variola stock scheduled for destruction in 1999; however, before this was done, a WHO resolution called for a delay based on an Institute of Medicine report con that live virus should be retained to develop new antiviral agents or vacci protect against any potential future release of smallpox.[82] The Soviet Uni known to have weaponized smallpox, and other countries are believed to maintain stocks of variola virus. Until very recently, worldwide stocks of smallpox vaccine were considered inadequate for mass inoculations, if necessary. However, in addition to the known stockpiles of smallpox vacc millions of stored doses were discovered in the United States, and experi have determined that the administration of diluted vaccine successfully immunizes recipients.[34] Additionally, new methodologies for smallpox va production are being developed. Smallpox vaccination

for military personnel was reinstated in 2002 and was made available for civilians in 2003.[20 , 21]

Pathophysiology

Transmission of smallpox typically occurs through inhalation of droplets o aerosols, but may also occur through contaminated fomites. The infectiou is not known, but is probably only a few virions. After a 12â€“14-day inc period, the patient develops fever, malaise, and prostration with headach backache. Oropharyngeal lesions appear, shedding virus into the saliva. T three days after the onset of fever, a papular rash develops on the face a spreads to the extremities. The fever continues while the rash becomes vesicular and then pustular. Scabs form from the pustules and eventually separate, leaving pitted and hypopigmented scars. Deaths usually occur the second week of the illness. Vaccination before exposure, or within 2â days after exposure, provides almost complete protection against smallpo disease most likely to be confused with smallpox is chickenpox (varicella) Although the individual lesions of smallpox and varicella are physically indistinguishable, the person infected with smallpox may still be differen clinically. The lesions of smallpox should all appear at the same stage of development, whereas chickenpox lesions occur at varying stages. Small lesions tend to be found in a centrifugal distribution (face and distal extremities), whereas chickenpox lesions are more centripetal and tend t appear first on the trunk.

Two antiviral drugs commercially available in the United States, cidofovir ribavirin, are effective in vitro against variola.[61] Current evidence sugges however, that although cidofovir may prevent smallpox when given within days of exposure, it is unlikely to be effective once symptoms develop.[41] single case of smallpox should be considered a potential international hea emergency and immediately reported to the appropriate public health authorities.

Smallpox Vaccination

Rapid postexposure vaccination confers excellent protection against smal
The smallpox vaccine employs a live vaccinia virus (derived from cowpox
vaccine) rather than the actual variola virus that causes smallpox. Althou
contracting smallpox from the vaccine is therefore impossible, other adve
reactions may occur. The two most serious reactions are postvaccinal
encephalitis and progressive vaccinia. Postvaccinal encephalitis occurs in
3 cases per million primary vaccinees. Forty percent of cases are fatal, a
some survivors are left with permanent neurologic sequelae. Progressive
vaccinia can occur in immunosuppressed individuals and is treated with v
immune globulin (VIG). Because smallpox was eradicated before the eme
of HIV, there is limited clinical experience with smallpox vaccination in A
patients, who theoretically are at increased risk of progressive vaccinia.[4
However, among 10 individuals with undiagnosed HIV at the time of rece
smallpox vaccination, none developed complications.[90] Routine vaccinatio
contraindicated in the immunosuppressed, persons with a history or evide
eczema and other chronic dermatitis, close household or sexual contacts
patients with these contraindications, and during pregnancy. Because the
vaccine is a live virus, it can be transmitted from the vaccinee to close c
Thirty secondary and tertiary cases of vaccinia were reported resulting fr
recent US military vaccinations.[20] The number of serious adverse events
modern smallpox vaccination is very low.[21] However, two confirmed and
suspected cases of myopericarditis occurred among over 450,000 vaccine
After a true exposure to variola, most authorities would agree that the o
absolute contraindication to smallpox vaccination is significant impairment
systemic immunity. Concomitant administration of VIG would be recomm
for pregnant women and persons with eczema.[57]

Viral Hemorrhagic Fevers

Several taxonomically diverse RNA viruses produce acute febrile illnesses
characterized by malaise, prostration, and increased vascular permeability
can result in bleeding manifestations in the more severely affected patie
Viral hemorrhagic fevers (VHF) are all highly infectious by the aerosol ro
making them candidates for use as BW agents. These agents include the
causing Lassa fever, dengue, yellow fever, Crimean-Congo hemorrhagic f

and the Marburg, Ebola, and Hanta viruses. Clinical features, such as the of renal, hepatic, and hematologic involvement, vary according to the in agent, but they all carry the risk of secondary infection through droplet aerosols. Ribavirin has been used for some VHFs, but supportive care is t mainstay of therapy.[6 , 31 , 45]

Viral Encephalitides

Three antigenically related alpha viruses of the *Togaviridae* family pose r BW agents: western equine encephalitis (WEE), eastern equine encephali (EEE), and Venezuelan equine encephalitis (VEE). Birds are the natural r of these viruses, and natural outbreaks occur among equines and humans mosquito transmission. Eastern equine encephalitis infections are the mo severe in humans, with a 50â€“70% fatality rate and high incidence of neurologic sequelae among survivors. WEE is less neurologically invasive, severe encephalitis from VEE is rare, except in children. Adults infected w usually develop an acute, febrile, incapacitating disease with prolonged recovery. The equine encephalitides have many properties helpful for weaponization, in that they can be produced in large quantities, they are relatively stable and highly infectious to humans as aerosols, and a choice available between lethal or incapacitating infections.[84]

Venezuelan equine encephalitis is considered the most likely BW threat a the viral encephalitides. After a 1â€“5-day incubation period, victims exp the sudden onset of malaise, myalgias, prostration, spiking fevers, rigors severe headache, and photophobia. Nausea, vomiting, cough, sore throat, diarrhea may follow. This acute phase lasts 24â€“72 hours. Between 0.5% 4% of cases develop overt encephalitis, with meningismus, seizures, com paralysis, which carries up to a 20% fatality rate. The diagnosis is usually established clinically, although the virus can sometimes be isolated from or from throat swabs, and serologic tests are available. The white blood c count often shows a striking leukopenia and lymphopenia. Treatment is supportive. Person-to-person transmission can theoretically occur from c nuclei. Recovery takes 1â€“2 weeks.[31 , 62 , 84]

Toxins

Several toxins derived from bacteria, plants, fungi, and algae could theo be used as BW agents, if produced in sufficient quantities. Because of the potency, only small amounts of these agents would be needed to kill or incapacitate exposed victims. Fortunately, obstacles in manufacturing weaponizable amounts limits the number of toxins that are practical for u biological weapons. Discussion here is limited to those toxins known or h suspected to have been weaponized. Toxins themselves are not living or and therefore can not reproduce; for this

reason, they are arguably equivalent to chemical weapons. But because t weapons are derived from living organisms, they are categorized here as biological weapons.

Botulinum Toxin

Botulinum toxin has been developed as a biological weapon in the United and other countries.[2 , 71 , 81 , 99] The two most likely means of employin botulism as a BW agent are by food contamination or by aerosol. Either r would result in the clinical syndrome of botulism (Chap. 46), characterize multiple bulbar nerve palsies and a symmetric descending paralysis, endir death from respiratory failure. Inhalation botulism from laboratory incider occurred rarely in humans and has also been investigated in animal experiments.[64] Onset of symptoms of botulism can occur as early as 24â hours, or may take several days. The mainstay of therapy is supportive c with ventilation if necessary. Serotype-specific antitoxin should halt prog of disease, but does not reverse established neurologic deficits. In the U States, the CDC produces and distributes antitoxin against the botulism serotypes commonly found in food poisoning, either a bivalent equine an against types A and B or a trivalent antitoxin against serotypes A, B, and US Army maintains a â€œdespeciatedâ€• equine heptavalent antitoxin a serotypes A through G. In animal experiments, these $F(abâ€²)_2$ fragments protective against inhalation botulism if given prior to onset of symptoms Prophylaxis for persons at high risk, usually laboratory personnel, is

accomplished by vaccination with a pentavalent toxoid for botulinum serc Aâ€“E. This toxoid was given to approximately 8,000 service members du the Gulf War and caused self-limited, local symptoms similar to tetanus immunization.[62 , 64]

Ricin

Ricin, one of the most toxic and easily produced plant toxins, derived fror castor bean plant, *Ricinus communis* . Although ricin has never been used battle, it has attracted the attention of domestic extremists and terrorists has been used in politically motivated assassinations.[23 , 30 , 50] Ricin inh protein synthesis at the ribosome. Clinical toxicity will vary depending on dose and route of exposure. Inhalation of aerosolized ricin results in incr alveolar-capillary permeability and airway necrosis following a latent phas 4â€“8 hours. Ingestion causes gastrointestinal hemorrhage with necrosis liver, spleen, and kidney. Intramuscular administration produces severe necrosis with extension into the lymphatics. In the absence of specific immunologic testing, differentiating ricin poisoning from sepsis may be c because of the presence of leukocytosis and fever. Vaccination of laborat animals with an investigational toxoid is protective.[30 , 62]

Staphylococcal Enterotoxin B

Staphylococcal enterotoxin B (SEB) is 1 of 7 enterotoxins produced by *Staphylococcus aureus* . SEB is recognized as a â€œsuperantigen,â€• be of its profound activation of the immune system on exposure to even to quantities. As a BW agent, SEB could be ingested through contaminated f water, resulting in acute gastroenteritis identical to classic staphylococcal poisoning. If inhaled as an aerosol, SEB produces fever, myalgias, and a pneumonitis after a 3â€“12-hour latent period. SEB inhalation can be fata more often would simply be incapacitating for several days to weeks. Tre is supportive.[62 , 93]

Trichothecene Mycotoxins

The trichothecene mycotoxins are low molecular weight (250â€“500 dalto

nonvolatile compounds produced by filamentous fungi (molds) of various
including *Fusarium* , *Myrotecium* , *Trichoderma* , and *Stachybotrys* .
Trichothecene mycotoxins are unusual among potential BW agents in that
toxicity can occur with exposure to intact skin. Naturally occurring tricho
toxicity results from ingesting contaminated grains or by inhaling toxin
aerosolized from contaminated hay or cotton. Outbreaks of ingested
trichothecene toxins result in a clinical syndrome called alimentary toxic
characterized by gastroenteritis, fevers, chills, bone marrow suppression
granulocytopenia, and secondary sepsisâ€”a syndrome similar to acute r
poisoning. Survival beyond this stage is characterized by the development
and upper airway ulceration, and intradermal and mucosal hemorrhage.
Trichothecene toxins are potent inhibitors of protein synthesis in eukaryo
cells, producing widespread cytotoxicity, particularly in rapidly proliferati
tissues. Exposure to any mucosal surface results in severe irritation. Der
exposure can produce inflammatory lesions lasting for 1â€“2 weeks,
vesiculation, and, in higher doses, death.[62 , 85 , 95]

Several reports from the 1970s and 1980s suggested that Soviet support
forces were using trichothecene mycotoxins, particularly the toxin T-2 (Fi
127-2), as BW agents. Aerosol and droplet clouds called â€œYellow Rain
were associated with mass casualty incidents in Afghanistan, Laos, and
Kampuchea.[39 , 95] Yellow Rain attacks have also been reported in the Ira
War.[77] Such attacks would involve multiple routes of exposure, with skin
deposition likely being the major site. Early symptoms included nausea,
vomiting, weakness, dizziness, and ataxia. Diarrhea would then ensue, at
watery and then becoming bloody. Within 3â€“12 hours victims would de
dyspnea, cough, chest pain, sore mouths, bleeding gums, epistaxis, and
hematemesis. Exposed skin areas would become intensely inflamed, with
appearance of vesicles, bullae, petechiae, ecchymoses, and frank necrosi

Nonetheless, evidence that trichothecene mycotoxins were used as BW a
was mostly circumstantial. Although T-2 toxin was found in victims' blood
urine, it was also found in samples from unexposed individuals, probably
baseline ingestion of contaminated foods. Environmental samples contain
Yellow Rain droplets were inconsistently found to contain mycotoxins.
Eyewitness accounts of Yellow Rain attacks varied widely (including

various descriptions of the alleged agent's color), and, despite the large of such attacks, no contaminated ordinance or dispersal device was ever recovered.[80] It was also discovered that Yellow Rain droplets were comp mostly of pollen grains. Supporters of the Yellow Rain as BW theory reto that pollen grains would be an ideal carrier for biotoxins, given that their ideal for aerosolization. However, the pollen in Yellow Rain samples did n contain protein, similar to pollen that has been digested by bees. Further distribution of pollen species found in Yellow Rain was indistinguishable fr contents of feces of the Asian honeybee, and mass bee defecation resulti showers of yellow droplets has been observed.[70 , 80] The Yellow Rain as feces theory assumes that any mass casualty incidents were from endem disease outbreaks, other CBW agents not yet identified, or a combination both. Whether Yellow Rain was intentional biological warfare or a comple natural phenomenon, trichothecene mycotoxins remain a potentially effe dermally active BW agent.

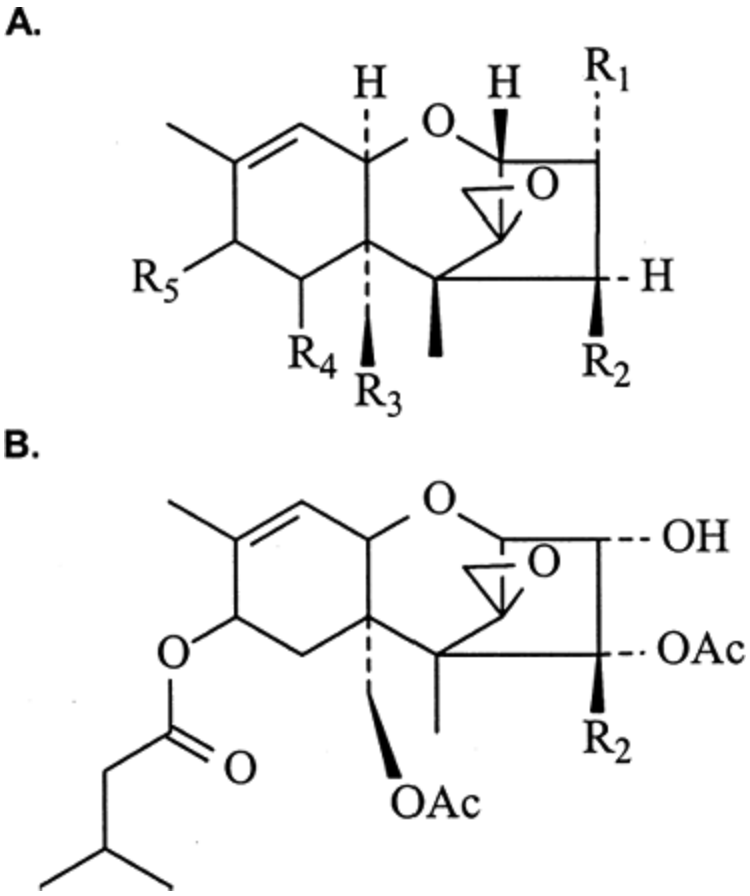

Figure 127-2. Trichothecene mycotoxins. A. Tetracyclic trichothecene n
B. T-2 toxin.

Summary

Although biological weapons have been used intermittently for centuries,
recently has their danger in potentially causing mass casualties been con
recognized. Even with multinational bans against their development and u
threat of biological weapons remains because the financial outlay in deve
biological weapons is low compared to other weapons of mass destruction
because even the threat of their use may aid some parties in furthering t
political goals. Currently, the risk of a medical catastrophe from BW agen
producing thousands or millions of victims appears low, with inhalational
or smallpox being the most likely agents in such a scenario. Nevertheless
incidents with limited numbers of casualties, or just threats of employing

agents, can have significant social impact.

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Chapter 128
Radiation

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A 16-year-old boy broke open an illuminated exit sign, when the liquid contents spilled onto his clothing. He then discovered a radioactive caution sticker on the back of the frame, told his parents who were concerned about potential radioactivity, and called 911. On arrival to the emergency department (ED), the radiation safety officer was notified. The patient was disrobed, his skin was washed with lukewarm water and soap, and his clothing was placed in a sealed plastic bag. The patient's vital signs and clinical examination were normal. A portable dosimeter measured 28 ÂµCi of radioactivity in his urine sample from the isotope tritium (^{3}H), the radioactive source in the exit sign. Intravenous crystalloid fluids were administered to increase urine output, and the patient remained asymptomatic. He was discharged from the hospital the next day. Routine blood work remained normal several days later.

Over the last century, radiation injuries and the nature of radiation itself have been vigorously studied as a result of its expanding role in our society. Today, radionuclides are used for a wide variety of

medical and nonmedical purposes ranging from detecting smoke to diagnostic testing to powering spacecraft. Although useful, radionuclides can present a danger to humans both through their metallic nature and through the process of radioactive decay. This ionizing radiation may cause injury to multiple cellular structures and critical molecules, such as DNA, resulting in mutations, neoplasms, or cell death. The particles of radiation, their sources, and the mechanisms by which they pose a health risk are the subjects of the following discussion.

Historical Exposures

Radiation became a concern for scientists as a toxin only a year following the discovery of x-rays by Wilhelm Roentgen in 1895.[87] Soon after, Thomas Edison reported corneal injuries in several of his workers conducting experiments using his newly invented x-ray generator. Eight years later, Clarence Dally, one of Edison's most dependable assistants, became the first radiation-related death in the United States.[29] Fortunately, the medical community recognized the utility of Edison's fluoroscope and began to use x-ray machines to help diagnose various illnesses. For example, the British army developed and used mobile x-ray machines to find bullets and shrapnel in wounded soldiers in Sudan in the early 1900s.

Over the next 10â€“15 years, radioactive substances also found their way into society as objects of fascination and as a means of alternative medical therapies. Aggressively marketed as cure-alls, advertisements for products such as the Revigator and Radithor enticed people to drink water â€œchargedâ€• with radon or radium. These products ushered in 20 years of â€œhealthâ€• products containing radioactive materials.[57,58]

In 1915, the British Roentgen Society, recognizing the potential hazards of radiation, proposed standards for radiation protection of workers, which included shielding, restricted work hours, and medical examinations. However, no dose limits were implemented because

dose quantitation was unavailable.

The opening of the Radium Luminous Materials Corporation in Orange, New Jersey in 1917 represented the first of several companies to profit from the novelty and popularity of radium's bluish glow. In an industry that employed over 4000 workers at its peak, nearly all of whom were female, the radium was hand-painted onto watch and instrument dials. These young women were instructed to obtain a fine tip on their paintbrushes using a technique called â€œlip pointing,â€• which meant using their lips and tongues to shape their paintbrushes. Unaware of the danger, some of these women also painted their nails, lips, and eyelids with the radioactive paint. By 1927, about 100 of them died from osteosarcoma of the jaw, brain tumors, and developed other noncancerous lesions of the mouth, all related to radium exposure.[60,72]

The only occasion a nuclear bomb was used against a human population occurred in August 1945 when the United States dropped a bomb on Hiroshima and on Nagasaki, Japan.[27] One contained a uranium core and liberated energy equivalent to 12,500 tons of TNT. The other contained a plutonium core and liberated an energy equivalent to 20,000 tons of TNT. Estimates of dead and injured for both cities are well over 200,000.[35] Most of the deaths were from the bomb blast, but many thousands died from acute radiation syndrome (ARS) and subsequently from radiation-induced cancers. In addition to the people of those cities who were victims of the bombs, at least 20,000 men and women from Britain, Australia, New Zealand, and India who formed the British Commonwealth Occupation Forces (BCOF) were also exposed to residual radiation as they were involved in security and clean-up tasks. Published memoirs even include photographs of Australian soldiers playing football on the flattened hypocenter of Hiroshima. Data concerning the health effects of the BCOF in postwar Japan are less well known than those reported by the British Nuclear Tests Veterans Association (BNTVA). The BNTVA is a group of 20,000 men who were required to attend United Kingdom nuclear weapons tests in Australia and at Christmas

Island between 1952 and 1963. Over two thirds of this cohort died of neoplasms at ages of 50â€“65 years, irrespective

of the individual's age at the time of the witnessed explosion.[79,80] Since that time there have been thousands of nuclear bomb tests around the world in the atmosphere, underground, and underwater.

With the beginning of the nuclear age also came unintentional criticality events of varying kinds in which individuals were exposed to large amounts of radiation. Criticality refers to the chain reaction of fissionable atoms that results in the release of energy. It is the basic operating principle behind fission bombs and nuclear reactors and is an efficient means of generating energy. Two criticality events occurred in Los Alamos in the 1940s during experiments in which scientists performed what was called â€œtickling the dragon.â€• In that era, determining the amount of fissionable material necessary to precipitate a chain reaction was not precisely defined mathematically. Harry Daghlian and Louis Slotin, two scientists involved in the development of the first atomic bomb, were to bring subcritical amounts of fissionable material together to see if a reaction would occur. Both men died of first use acute radiation sickness (ARS) following exposure to high levels of radiation released during these experiments. Since 1945, there have been numerous criticality events, the most recent occurring in Tokaimura, Japan in 1999. In that instance, workers making fuel for nuclear reactors allowed excess uranium to enter the reaction container. The criticality event that resulted killed one worker and caused the evacuation of all the people living within 350 meters of the manufacturing plant.

During the late 1920s, radiologists used a thorium-containing contrast agent called Thorotrast. During that time when imaging modalities were limited, this opacifying agent, provided intravascularly in a colloidal suspension, provided essential medical information during the early development of angiography. Unfortunately, physicians did not appreciate the dangers of this

agent and only later discovered its very slow elimination rate and propensity to accumulate in hepatic tissue. Because of emission of Î± particles, cases of thorium-induced hepatic carcinomas and angiosarcomas, led to its eventual discontinuance in 1952.

Although many nuclear reactor incidents have occured around the world, the most serious occurred at Chernobyl in the Ukraine in 1986. In this instance, a series of errors led to a fire at the reactor core, several explosions, and a meltdown of the reactor. Over the first 10 days following the incident, a cloud carrying radioactive material (predominantly ^{131}I and ^{137}Cs) spread to the Baltic States, Scandinavia, and Europe. In addition to the 31 people who died of ARS in the first few weeks following the event, nearly 250 others in the surrounding area were hospitalized, and an unknown number suffered other long-term sequelae.[28,33,45]

Not all radiation events occur at nuclear facilities. In September 1987 in GoiÃ¢nia, Brazil, two men scavenged the contents of an abandoned medical clinic and unwittingly handled a source of ^{137}Cs. As in the early part of the century with radium, the fascinating bluish glow contributed to many radiation exposures, some of them quite extensive. In the end, the government monitored approximately 113,000 individuals and found nearly 250 contaminated individuals. Forty-six patients were treated with a chelating agent, 19 were found to have localized radiation burns, and 4 died in the month following the initial exposure with another dying several years afterward from radiation-induced injuries.[67]

The Principles of Radioactivity

Dating from the 15th century, radiation is defined as energy sent out in the form of waves or particles. Although considered by physicists as incomplete, the particle-wave theory remains a useful model by which to understand the toxic aspects of radiation. Despite the strong nuclear force that holds the basic building blocks of atoms together, many isotopes are unstable. Several other forces, most

notably the electroweak force, may tip the balance toward instability and an isotope will transform. This process may be intentional, as with the criticality events in a nuclear reactor or nuclear bomb, but mainly occurs spontaneously in nature as the process called radioactive decay.

Radioactive Decay

In 1900, Marie Curie discovered that unstable nuclei decay or transform into more stable nuclei (daughters) via the emission of various particles or energy. Radioactive decay occurs through five mechanisms: emission of Î³ rays, Î± particles, Î² particles, positrons, or capture of an electron. It is the emission of these various particles that makes radioactive decay dangerous because these particles form ionizing radiation. These emitted particles are released with specific decay energies depending on the isotope undergoing the process.

The terminal half-life ($t_{1/2}$), a term first used by Ernest Rutherford in 1904, is the period of time it takes for a radioisotope to lose half of its radioactivity. Every radioisotope has a characteristic half-life. Some isotopes exist for millionths of a second, whereas others last billions of years. In every case, the activities of radioactive isotopes diminish exponentially with time. The equation $R = R_0e^{-Âμ}$ describes radioactive decay, in which R is the activity, R_0 is initial activity, t is time, and Î» is the decay constant. Each radioisotope has its own decay constant (Table 128-1).

Photons are massless particles that travel at the speed of light and mediate electromagnetic radiation. Depending on the energy of the particles, and therefore their wavelength, the radiation has different names. Radiation having the lowest energy and the longest wavelength are called radio waves. As photons become more energetic and have shorter wavelengths, they are called, sequentially, microwaves, heat or infrared, visible light, and ultraviolet rays. Î³ Rays and x-rays have greater energy than ultraviolet rays and can penetrate deeply into the body, which makes

them both deadly and beneficial as radiation therapy.

TABLE 128-1. Physical Properties of Common Radioisotopes

Isotope	Half-Life	Mode of Decay	Decay Energy (MeV)[1]
^{47}Ca	4.53 days	Î²-	1.979
^{14}C	5730 yrs	Î²-	0.156
^{137}Cs	30.23 yrs	Î²-	1.176
^{51}Cr	27.8 days	electron capture	0.752
^{57}Co	270 days	electron capture	0.837
^{67}Cu	61.8 hrs	Î²-	0.576
^{3}H	12.26 yrs	Î²-	0.02
^{123}I	13.3 hrs	electron capture	1.4
^{131}I	8 days	Î²-	0.970
^{40}K	1.28 Ã— 10^{9} yrs	Î²-/Î²+ electron capture	1.35/1.505
^{32}P	14.3 days	Î²-	1.710

^{222}Rn	3.8 days	Î±	5.587
^{85}Sr	64 days	electron capture	1.11
^{201}TI	73 hrs	electron capture	0.41
^{238}U	4.51 Ã— 10^{9} yrs	Î±	4.268
^{133}Xe	5.27 days	Î²-	0.427
^{1}MeV = mega-electron volts			

Î³ Rays and x-rays are essentially the same and are only distinguishable by their source. Î³ Radiation is emitted by unstable atomic nuclei in the process of radioactive decay. A given Î³ ray will have a fixed wavelength depending on the energy that formed it; the greater the energy of the decay, the smaller the wavelength of the Î³ radiation. X-rays come from atomic processes outside the nucleus. For example, an x-ray machine generates x-rays by accelerating electrons through a large voltage and colliding them into a heavy metal target. The rapid deceleration of electrons in the target generates x-rays. In general, the higher the voltage, the greater the energy of the x-rays generated along a spectrum of wavelengths. X-rays and Î³ rays may have the same energy. Once an x-ray and Î³ ray of the same energy leave their respective sources they cannot be distinguished from one another. They behave in exactly the same way, including the types of biological effects they may cause. Because of their nature, high-energy Î³ and x-rays can penetrate several feet of insulating concrete.

Î²--*Particles* are also called electrons. They are emitted during Î²-decay from an unstable radionuclide, which is an atom that disintegrates by emitting a particle, electromagnetic radiation or both. Positrons, positively charged electrons, may also be emitted during decay processes. Because of their mass, electrons have less penetration than Î³ radiation but may still pass several centimeters into human skin.[86] For this reason, Î² particles cause health problems chiefly through incorporation into living organisms, which occurs when a radionuclide is inhaled, ingested, or deposited on a wound.[5]

Î±-*Particles* are helium nuclei (2 protons and 2 neutrons) stripped of their electrons. These relatively massive particles are emitted during Î± decay. These particles are the most easily shielded of the emitted particles mentioned and are stopped by a piece of paper, skin, or clothing. Like Î² particles, Î± particles principally cause health effects only when they are incorporated.

Neutrons are primarily released from nuclear fission, although high-energy photon beams used in radiotherapy may also produce them. The natural decay of radionuclides does not include emission of neutrons. This is mainly a health hazard for workers in a nuclear power facility or victims of a nuclear explosion. Unique among the particles of radioactivity, when neutrons are stopped or captured they can cause a previously stable atom to become radioactive.

Cosmic rays complete the group of various kinds of radiation to which an individual may be exposed. Cosmic rays are streams of electrons, protons, and Î± particles thought to emanate from stars and supernovas. They rain down on the earth from all directions only to give up their energy as they strike the nuclei of oxygen and nitrogen in the upper reaches of the earth's atmosphere. By the time it reaches the earth, the energy of cosmic radiation is reduced by several orders of magnitude. Traveling or living at altitude where the atmosphere shields relatively less cosmic radiation naturally means greater exposure to cosmic rays but in general is not considered a

toxic threat to humans.

Ionizing Radiation Versus Nonionizing Radiation

Ionizing radiation refers to any radiation with sufficient energy to disrupt an atom or molecule with which it impacts. In this interaction, an electron is removed or some other decay process occurs, leaving behind a changed atom. Depending on the specifics of the interaction, these atoms may now be ionized or highly-reactive free radicals. Hydroxyl free radicals, formed by ionizing water, are responsible for biochemical lesions that are the foundation of radiation toxicity.

The space between collisions of ionizing radiation and their target molecules varies with the particle type and its energy. A heavy charged particle, such as an Î± particle, loses kinetic energy through a series of small energy transfers to other atomic electrons in the target medium, such as tissues. Most of the energy deposition occurs in the infratrack, a narrow region around the particle track extending about 10 atomic distances. The energy loss per unit length of particle track is called the linear energy transfer (LET), which is expressed in kiloelectron volts per micrometer (keV/Âµm; see Table 128-1). Heavy charged particles, such as Î± particles, are referred to as high LET radiation, whereas x-rays, Î³ rays, and fast electrons are low LET radiation.

Because of its large size, collisions along the path of an Î± particle are clustered together, limiting its ability to penetrate tissue. By comparison, collisions along the path of Î³ rays are spread out, increasing their ability to penetrate tissue. It is this ability to penetrate tissue and transfer energy that accounts for the relative dangers of the forms of radiation and tissue susceptibility.

For a source of radiation to pose a threat to tissue, the ionizing particle must be placed in close proximity to vital components of

tissue that can sustain damage. High-energy photons penetrate deeply and so pose a similar risk whether they come from an external source or from an incorporated source. As noted above, Î± and Î² particles have much more limited tissue penetration and thus radionuclides that radiate these particles must first be incorporated to pose a threat to tissue.

Nonionizing radiation spans a wide spectrum of electromagnetic radiation frequencies. Generally, nonionizing radiation consists of relatively low-energy photons and is used safely in cell phone and television signal transmission, radar, microwaves, and magnetic fields that emanate from high-voltage electricity and metal detectors. Although these are all considered radiation in that they are all energies released from a source, these photons lack the necessary energy required to cause ionization and cellular damage.

Radiation Units of Measure

The amount of radiation to which an object is exposed, that is, the amount emitted from a source that falls on an object, is given in units called roentgens (R). A roentgen is a unit for measuring the quantity of Î³ or x-radiation by measuring the amount of ionization produced in air. It may be loosely defined as the amount of x-radiation that produces 1 electrostatic unit of charge in 1 cubic centimeter of air at standard temperature and pressure. As an example, an individual standing at a given distance from the x-rayâ€“generating tube of a particular x-ray machine is exposed, on the skin, to a particular number of roentgens of x-rays (Figure 128-1).

Not all roentgens to which an individual is exposed pose a risk for cellular damage. Much of the radiation passes through the body and does not cause harm. Only the fraction is absorbed by the tissue has a probability of causing cellular damage. The unit that describes absorbed radiation is the rad (radiation absorbed dose), which corresponds to an absorption of energy in any medium of 100 ergs/g.

The units of the International System (SI), first introduced in the 1970s, have largely replaced the older units. The gray (Gy) is the corresponding SI unit to the rad and is equivalent to 100 rads.

Not all radiations produce the same effects at the tissue level. For example, a given number of Gy of x-rays produce less cellular damage than the same number of Gy of Î± particles when all other conditions are equal. To predict the degree of damage that radiation of any type may cause, other units of measure are needed to normalize the different potencies in terms of their risk. The rem (roentgen equivalent

man) and the Sv (sievert, in SI) are the units that allow these calculations. These units are useful for comparing the effects of different radiations or evaluating the danger of a mixture of radiations, such as in radioactive decay, in which some isotopes emit more than one kind of radiation at a time (eg, Î² and Î³). In defining rem, x-rays are the standard radiation for comparison. One rem may be defined as the dose of radiation that produces damage equivalent to one rad of x-rays (or 0.01 Sv). Thus, for x-rays, one Sv is equivalent to 100 rem. To perform the normalization, the dose in grays is multiplied by a relative biologic effectiveness-dependent quality factor (Q). This factor Q multiplies the amount of radiation by 1 for x-rays, Î³ rays, and Î² particles, 2 for Î± particles, and by 5 or more for neutron radiation. Thus, 1 Sv is equivalent to 1 Gy of x-rays. As a very coarse reference point, a regular chest radiograph imparts about 20â€“40 mrem or 0.2â€“0.4 mSv to an individual, but it must be remembered that this radiation dose is delivered very quickly to a limited portion of the body and is quite different from a similar amount delivered over a longer period of time to a worker through an occupational exposure.

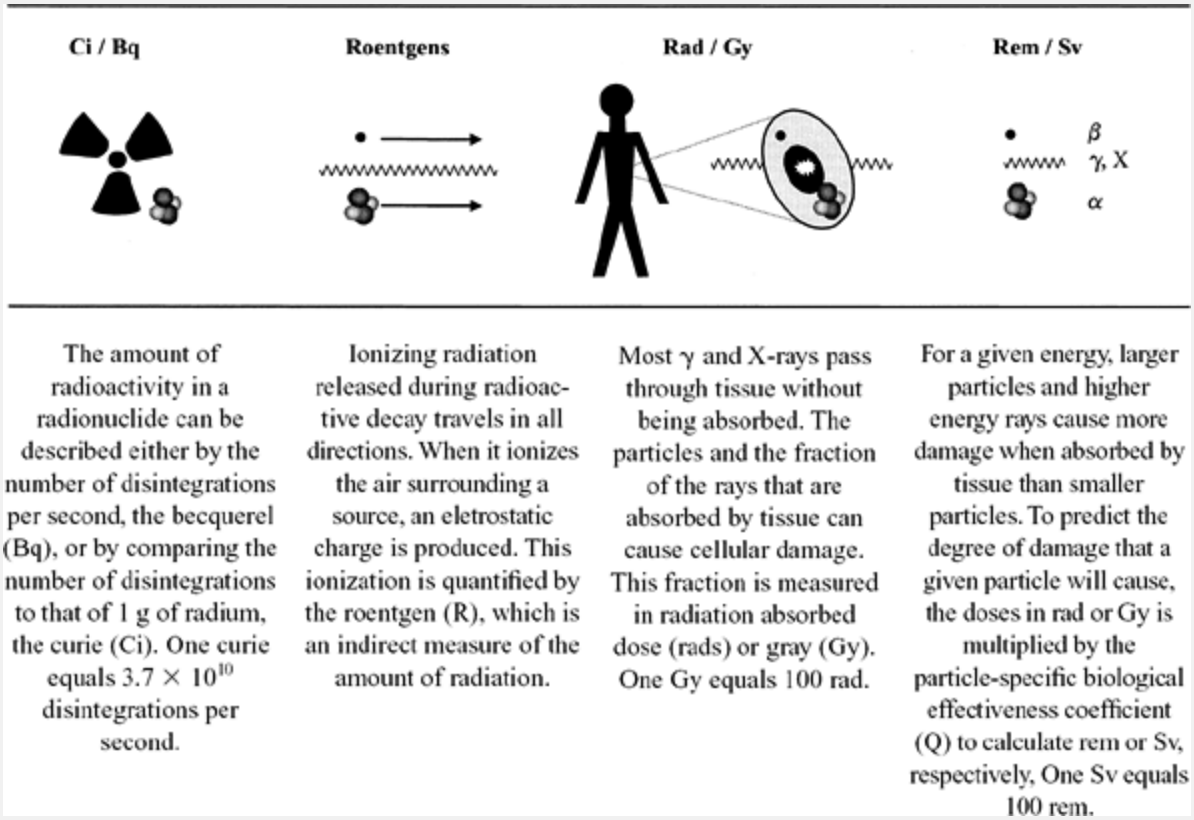

Figure 128-1. The definitions associated with radiation. Both curie and bequerel describe a quantity of radionuclide in terms of the number of disintegrations rather than mass. Roentgens describes the amount of air ionized by either gamma (Î³) or x-rays, which indirectly quantifies the amount of radiation in the air around a source. Rad and gray describe the fraction of radiation that actually interacts with cellular material and potentially causes injury. Roentgen equivalent man (Rem) and sievert (Sv) calculate the effective dose taking into account the different particles. For example, a 100 keV alpha (Î±) particle causes more damage to cellular material than a 100 keV beta particle (Î²).

In 1910, the curie (Ci) became the unit defining the activity of

radioactive decay, although it does not give information regarding what is released or the risk of exposure. One curie equals 3.7 Ã— 10^{10} disintegrations per second, based on the decay of 1 g of radium. The SI unit is the becquerel (Bq), named for Antoine Henri Becquerel, who in 1896 first reported invisible emanations from naturally occurring minerals that fogged photographic plates. One becquerel is equivalent to 1 disintegration per second. Thus, 1 Ci is equivalent to 3.7 Ã— 10^{10} Bq. This number corresponds to an amount of radioactivity in a source. For example, following the Chernobyl incident, 1.2 Ã— 10^{7} TBq (terabecquerel, 1.2 Ã— 10^{19} disintegrations per second) of radioactive material was released into the atmosphere. By comparison, the men who removed the source of ^{137}Cs in GoiÃ¢nia found 50.9 TBq (50.9 Ã— 10^{12} Bq or 13.7 Ã— 10^{5} mCi) of cesium. A thallium stress test uses 111 Ã— 10^{6} Bq (3 mCi) of ^{201}Tl, and the average indoor concentration of ^{222}Rn in the United States is 55 Bq/m^3 (14.8 Ã— 10^{-6} mCi). To illustrate further, a stress test's dose of ^{201}Tl provides a dose of 0.018 Gy (1.8 rad) and 0.018 Sv (1.8 rem).

Irradiation, Contamination, and Incorporation

An object that is irradiated is exposed to ionizing radiation. This type of exposure includes handling radioactive isotopes, medical diagnostic imaging modalities such as x-ray machines and CT scanners, and rare exposures to criticality events. These sources of ionizing radiation can generate high-energy photons, which penetrate tissue well and cause tissue damage. A whole-body irradiation is one in which the entire body is exposed at once, whereas more commonly shielding devices, such as lead aprons, and collimation techniques used in radiotherapy limit the amount of exposed tissue to the intended target. The risk of tissue damage depends on the total amount of radiation and the tissue type because different tissue types have their own intrinsic resistance to radiation damage. An

irradiated object does not become radioactive itself, unless exposed to neutrons.

The Food and Drug Administration (FDA) approved irradiation of wheat and flour in 1963. They have concluded from 40 years of study that irradiation is a safe and effective process for many foods to control bacteria such as *Escherichia coli*, *Salmonella*, and *Campylobacter*. The FDA states that irradiation does not make food radioactive, compromise nutritional quality, or noticeably change the taste, texture, or appearance of food, as long as it is applied properly to a suitable product. Organizations that support irradiation of food include the American Medical Association (AMA), the Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO).

Contamination occurs when a radioactive substance covers an object completely or in part. Several examples include a laboratory or industrial worker who unintentionally spills a radioactive nuclide on clothing or skin or a victim of a radiologic dispersing device, a â€œdirty bomb,â€• in which a radioisotope is packaged with a conventional explosive and the resultant explosion disperses the radionuclide. In these similar cases, the source of radiation is the nuclide undergoing its normal decay process, and the individual is exposed to particles such as those mentioned in Table 128-1. The risk for tissue damage from the radiation particles is usually quite low, assuming that the contamination is detected and appropriate measures for decontamination are instituted.

Incorporation occurs when a radionuclide assimilates into a patient's body tissue. It generally follows exposure via the inhalational, enteral, or parenteral route, but may occur via any route that permits a radionuclide to enter the body. This principle is used in many diagnostic and therapeutic procedures such as a thallium stress test, bone scan, gallium scan, liver and spleen scan, and ^{89}strontium therapy. Depending on the dose and type of radionuclide,

incorporation may lead to tissue damage, as was the situation for many people following the event at Chernobyl. In this instance, inhalation and subsequent absorption of ^{131}I allowed this radionuclide access to the thyroid, resulting in an increase in thyroid cancer among children and adolescents in the most contaminated regions of Ukraine and Belarus.[9,43,92]

Regulation and Reporting

The Nuclear Regulatory Commission (NRC), the Environmental Protection Agency (EPA), and many state governments share the responsibility of licensing and regulating radioisotopes in the United States. The individual states regulate radioactive substances that occur naturally or are produced by machines, such as linear accelerators or cyclotrons. The FDA regulates the manufacture and use of linear accelerators, but the states regulate their operation. The NRC regulates medical, academic, and industrial uses of nuclear materials generated by or from a nuclear reactor.

The Oak Ridge Institute for Science and Education's (ORISE) Radiation Emergency Assistance Center/Training Site and the International Atomic Energy Agency (IAEA) both maintain radiation incident registries that track US and foreign radiation incidents. However, recognizing that both these registries are limited in their data collection regarding individual patients' clinical conditions and their therapy, the Moscow Ulm Radiation Accident Clinical History Database (MURAD) was formed in 1990. The International Computer Database for Radiation Exposure Case Histories (ICDREC) succeeded MURAD and seeks to gather as many cases of ARS as possible to develop research and management strategies for the scientific community.[15]

Exposures to man-made sources of radiation are not required to be reported to poison centers and in general do not result in significant morbidity. However, the American Association of Poison Control Centers Toxic Exposure Surveillance System (AAPCC-TESS) reported

a total of 2636 exposures to radioactive isotopes over the last 10 years, increasing from 166 in 1993 to 320 in 2003. This increase in reported exposures was commensurate with the overall increase in reports to poison centers. Of the 2003 reported cases, 287 (90%) were unintentional, and 26 (8%) involved children younger than 6 years of age. There were no deaths reported to poison centers from exposure to radioisotopes over the last 10 years (Chap. 130).

Epidemiology

Everyone is exposed to radiation in one form or another each day (Table 128-2). There are naturally occurring sources of radiation in the earth's crust that make the largest annual contribution to man's radiation exposure, and man-made sources of radiation, which make a relatively smaller contribution to our average annual exposure.

Natural Sources of Radiation

A wide variety of natural sources expose humans on a daily basis to ionizing radiation. In the United States the estimated annual dose equivalent of radiation is 3.6 mSv, and natural sources contribute about 80% of that annual dose.[12,29] Terrestrial sources of radiation originate from radionuclides in the earth's crust that move into the air and water. These primordial radionuclides, so named because their physical half-lives are comparable to the age of the earth, include uranium, actinium, and thorium. Geographic areas vary regarding the content of these radionuclides.

Radon, a radioactive noble gas, accounts for most of the human exposure to radiation from natural sources. This gas, a natural decay product of uranium and thorium, enters homes and other buildings from the building materials themselves or through microscopic cracks in the building's structures. With a relatively short half-life of 3.82 days, ^{222}Rn poses a health risk if decay occurs while in the

respiratory space and deposits on respiratory tissue as one of its daughter isotopes, which are solids. These radon daughters emit Î± particles as they decay and are the principle causes in the associated increased incidence of lung cancer in those exposed to radon.[74]

TABLE 128-2. Average Effective Annual Ionizing Radiation Dose Equivalent in the United States

Source	Dose[1] mSv[2]	%
Natural		
Cosmic	0.27	8
Internal	0.39	11
Radon[3]	2.0	55
Terrestrial	0.28	8
Subtotal	2.94	82
Man-Made		
Consumer products	0.10	3
Nuclear medicine	0.14	4

Occupational	<0.01	<0.3
X-ray diagnostic imaging	0.39	11
Subtotal	0.63	18
Total	3.6	100

[1]All doses are averages and contain some variability within the measurement.
[2]mSv = millisieverts
[3]Average effective dose to bronchial epithelium

Additionally, radon daughters are charged and can attach to larger aerosols to be inhaled primarily. Radon daughters can also remain unattached to aerosols and form smaller sized aggregates, enabling them to penetrate to smaller airspaces. There is a complex relationship between exposure to radon progeny and dose to target cells. Influencing physiologic factors include tidal volume, minute ventilation, mucus thickness, and mucociliary clearance.

The risk of lung cancer is increased in heavy smokers who additionally expose their lungs to 200 mSv from ^{210}Po (a radon daughter) that is naturally found in tobacco smoke. Areas of New York, New Jersey, and Pennsylvania, called the Reading Prong, have particularly high levels of radon as a result of a richer concentration in the earth's crust of primordial radionuclides that liberate radon. The EPA has recommended household level intervention when ambient radon levels exceed 147 Bq/m^3 (4 pCi/L). Individuals can test their own homes for radon with either short-term (less than 90 days) or long-term (greater than 90 days) commercially available measurement devices.

The second largest natural source of radiation originates from ingested radionuclides, of which ^{40}K, a naturally occurring isotope, is the most abundant. Together with other primordial radionuclides in our diet, this source of internal radiation accounts for about 12% of the annual dose of absorbed radiation.

Man-Made Sources

As mentioned earlier, man-made sources of radiation can be found in many consumer products and in many different types of industry (Table 128-3). The National Council on Radiation Protection and Measurements (NCRP) estimates the annual number of workers occupationally exposed to radiation to be nearly a million.[29] On average, those occupations with the highest exposures (about 12 mSv/yr) are uranium miners, nuclear power operators, and sailors in close proximity to nuclear reactors. Those with lesser additional exposures (about 1â€“2 mSv/yr) include physicians, x-ray technologists, nuclear fuel processing workers, and workers in other industries that use radionuclides.

Medical occupational exposure principally includes physicians, nurses, and x-ray technologists, who receive an additional annual effective dose of about 1 mSv. This dose can range up to 17 mSv with certain techniques such as fluoroscopy but are only partial body exposures because of the appropriate use of lead aprons and other protective barriers. Medical procedures also account for substantial annual exposure to man-made radiation for patients. In 1989, the NCRP estimated the annual number of various diagnostic procedures involving radiation in the United States to exceed 250 million, although the number has increased quite rapidly over the last decade. Medical sources of exposure to patients account for about 0.5 mSv or 15% of the average annual exposure.

Exposures have been studied in emergency physicians, orthopedists, and interventional cardiologists.[30,42,95,100] Each of these fields uses different modalities of radiation, which pose different risks to the

individual performing the procedure. Two studies examining exposure to physicians assisting in cervical spine radiographs found the calculated whole-body exposure ranged up to 0.027 mSv per procedure, or 0.75% of the estimated annual dose equivalent of radiation in the United States.[42,100] This exposure annualized over a year neared the NCRP upper limits of safety, which might be exceeded if the number of procedures were to increase. Two other studies examined physician exposure to radiation by fluoroscopy used in interventional cardiology and orthopedic procedures. These doses ranged from 0.05â€“0.3 mSv per procedure. In each of these four studies, appropriate shielding was used, and dosimeters measured individual areas of exposed body parts such as extremities and the head. Radiation was undetectable beneath a lead apron. Estimated whole-body exposures to these procedures were considered not to exceed the limits established by OSHA of 50 mSv per year. Although the likelihood of exceeding established radiation limits is low regardless of the procedure, and even assuming a reasonable increase in the number of procedures performed, appropriate shielding and safety training are emphasized to minimize the risk of exposure.

TABLE 128-3. Uses of Radioisotopes

^{241}Americium:	Used in smoke detectors, to measure lead levels in paint, steel, and paper production
^{109}Cadmium:	Analyze metal alloys
^{47}Calcium:	Biomedical research of cell function and bone formation

^{252}Californium:	Inspect luggage for explosives, gauge moisture content of soil and silo materials
^{14}Carbon:	Pharmaceutical research, radiometric dating
^{137}Cesium:	Measure dosages of radioactive pharmaceuticals, oil industry to measure flow in pipelines
^{51}Chromium:	Red blood cell survival studies
^{57}Cobalt:	Nuclear medicine
^{67}Copper:	Chemotherapy
^{244}Curium:	Mining industry
^{123}Iodine:	Diagnosis of thyroid disorders
^{129}Iodine:	Used to check some radioactivity counters in vitro diagnostic testing
^{131}Iodine:	Treatment of thyroid disorders
^{192}Iridium:	Test the integrity of pipeline welds, boilers, and aircraft parts
^{55}Iron:	Analyze electroplating solutions

^{85}Krypton:	Indicator lights, textile industry
^{63}Nickel:	Detect explosives, voltage regulators, surge protectors
^{32}Phosphorus:	Molecular biology and genetics research
^{238}Plutonium:	Power source for NASA spacecraft
^{210}Polonium:	Photographic film production
^{147}Promethium:	Thermostats, textile industry
^{226}Radium:	Lightning rods
^{75}Selenium:	Protein studies
^{24}Sodium:	Industrial pipelines integrity
^{85}Strontium:	Study bone formation and metabolism
^{99}Technetium:	Nuclear medicine
^{201}Thallium:	Cardiac imaging
^{232Th}Thoriated tungsten:	Electric arc welding

^{229}Thorium:	Fluorescent lights
^{230}Thorium:	Coloring and fluorescence in colored glazes and glassware
^{3H}Tritium:	Basic science and pharmaceutical studies, for self-luminous signs, luminous dials, gauges and wrist watches, luminous paint
^{234}Uranium:	Dental fixtures
^{235}Uranium:	Fuel for nuclear power plants and naval nuclear propulsion systems, fluorescent glassware, colored glazes, and wall tiles
^{133}Xenon:	Nuclear medicine

Various medical scans use radioactive nuclides to study various disease processes (Table 128-4). Other radionuclides used in

medical diagnostics include ^{111}In, ^{67}Ga, and ^{51}Cr. Other scientific research uses tritium (^{3}H) and ^{32}P. These nuclides decay through Î²-particle capture or emission. In general, unintentional topical exposure to these radionuclides in this setting is not considered hazardous because skin and clothing provide adequate barriers against the poorly penetrating particles emitted. In the case of unintentional incorporation, it is highly unlikely that the amount infused will be sufficient to cause a serious health risk.

TABLE 128-4. Diagnostic Imaging Procedures: The Type and Amount of Radionuclide or Radiation

Test	Radionuclide	Amount
Whole Body Bone Scan	^{99}Tc	25mCi(9.25 Ã— 10^8Bq)
Radionuclide Cerebral Angiogram	^{99}Tc-DTPA	15mCi(5.55 Ã— 10^8Bq)
Cardiac Ejection Scan (MUGA)	$^{99}TcO_4$	20mCi(7.4 Ã— 10^8Bq)
DISIDA/Hepatobiliary Scan	^{99}Tc-DISIDA	5mCi(18.5 Ã— 10^7Bq)
Ventilation/Perfusion Scan	^{133}Xe	10mCi(37 Ã— 10^7Bq)
	^{99}Tc	4mCi(14.8 Ã— 10^7Bq)
Thyroid Scan	^{123}I	0.2mCi(0.74 Ã— 10^7Bq)
Myocardial Perfusion Scan (Exercise)	^{201}TI	3mCi(11.1 Ã— 10^7Bq)

	^{99}Tc	20mCi(7.4 Ã— 10^8Bq)
Strontium Therapy	^{89}Sr	4mCi(14.8 Ã— 10^7Bq)
Venogram	^{99}Tc	20mCi(7.4 Ã— 10^8Bq)
Chest radiograph	60 mrad or 0.06 mGy in a collimated field[1]	
Abdominal radiograph	100â€“1500 mrad or 1â€“5 mGy in a collimated field	
CT-Head	1â€“2 rads or 0.01â€“0.02 Gy per slice[2]	
CT-Body	1 rad or 0.01 Gy per slice[2]	
[1]Collimation is the act of restricting the size of the useful x-ray field to the region of clinical interest. These skin-entry doses are approximations dependent on equipment and technique. [2]The dose per each examination is about the same as the dose per slice and not the sum of the slices.		

Depleted uranium (DU) is used by the United States military and by several other governments as an armor piercing alloy ammunition. Munitions made of this material are favored because it is pyrophoric, sharpens on impact, has a high density (about 1.7 times that of

lead), and is less expensive than tungsten, which was used for this purpose until 1973. DU can be obtained from the enrichment process of natural uranium in the development of nuclear fuel, the reprocessing of spent nuclear fuel, or developed directly for military purposes. DU is mainly ^{238}U, but contains approximately 0.2% of other isotopes of uranium and several other transuranic elements as well depending on its origin. Consequently, DU's Î± and Î² activity is about 40% less radioactive than naturally occurring uranium. When DU munitions strike a hard target, it is dispersed as an aerosol and contaminates a limited area. Radiation exposure is derived from incorporation of the aerosolized material.[31] Thus, as a radiation hazard, exposure to solid ^{238}U is considered to be negligible although currently many studies are investigating the potential link between DU and the incidence of leukemias, other cancers, and birth defects.[4,11,18,24,41,62,63,69,70,73] One study examined a cohort of over 50,000 service personnel from the United Kingdom who served in the Gulf War but found no increase in the incidence of any cancers over 6 years following the end of the war.[56]

Exposure Limits

The various agencies involved in regulating radiation exposures to both workers and the public include OSHA, the NRC, and the Department of Transportation (DOT). The NRC has established â€œStandards for Protection against Radiation,â€• which regulates radiation exposures using a 2-fold system of dose limitation: doses to individuals shall not exceed limits established by the NRC, and all exposures shall be kept as low as reasonably achievable (ALARA). The total effective dose equivalent may not exceed 50 mSv/yr to reduce the risk of stochastic effects (see Stochastic Versus Deterministic Effects of Radiation). The dose to the fetus of a pregnant radiation worker may not exceed 5 mSv over 9 months and should not substantially exceed 0.5 mSv in any one month, although this amount is not carefully defined.[40,82]

Pathophysiology

Ionizing radiation causes damage to tissue by several mechanisms depending on its energy. Radiation with high LET predominantly causes direct damage, which is when incoming radiation impacts a target molecule directly. This occurs because high LET radiation, such as an Î± particle, has a high statistical probability of impacting an important molecule, such as DNA.[29] If this occurs, a mutation may arise, which may then result in alteration of a germ line, development of a neoplasm, or cell death. The risk of these consequences overall, however, is low because of the relative paucity of DNA within a cell and the even smaller percentage of active DNA within a given cell.

Low LET radiation, x-rays, Î³ rays, and fast electrons, predominantly cause indirect damage. The likelihood that radiation will cause cell damage is a function of its LET and reaches a peak at about 100 keV/Âµm. At this energy, the average separation between ionization events coincides with the diameter of the DNA helix and allows for the greatest probability of double-strand breaks, which is the basis for most biologic effects. Greater or lesser energies correlate to a lower probability of DNA impacts, and so the rest of the cell media becomes the energy absorber.[37]

Indirectly, radiation impacts a molecule and creates a reactive species, which then chemically reacts with organic molecules in cells, altering their structure or function. These radiation-induced ions are quite unstable, however, and usually convert to free radicals. Most importantly, radiation may impact a water molecule, which is in great abundance, to generate a hydroxyl radical (OHÂ·).[29] The hydroxyl radical diffuses only a short distance through the cell because of its highly reactive nature and itself causes molecular damage.

The bystander effect refers to cellular damage in unirradiated cells that neighbor irradiated cells. As early as the 1940s, there were reports of inactivation of cells by ionization of the surrounding

medium. Today, with the use of a single-particle microbeam, a device that can fire a predefined exact number of Î± particles through a particular cell nucleus, cultured cells that were not hit by radiation have increased chromosome damage, rearrangement, and rate of death. The bystander effect is demonstrated using proton beams and x-rays, and in cells cultured with DU.[64,75] Communication from cell to cell via gap junctions is an important factor in cell death and mutations, which are observed in these experiments. In one experiment, when 10% of cells on a dish were exposed to two or more Î± particles, the resulting frequency of induced oncogenic transformation was indistinguishable from that when all the cells on the dish were exposed to the same number of Î± particles.[84]

Genomic instability is when a gene responsible for the stability of the genome and the consistency of replication is altered, resulting in a cascade of other mutations and the subsequent development of

a neoplasm. Several studies demonstrate that, in addition to direct radiation damage to genetic material, radiation causes perturbations in intracellular oxidation-reduction reactions and far outlast radiation-generated hydroxyl radicals, which exist only for fractions of a second. These changes in oxidation-reduction reactions in turn cause other changes in signaling pathways leading to apoptosis, transformation, and other bystander effects that manifest as delayed or lethal mutations and chromosomal instability. Studies are ongoing that investigate specific causes of cellular injury and the precise mechanisms that may be responsible.[37,55]

Although any molecule may be damaged in a variety of ways that may lead to cell injury of varying severity, double-stranded breaks in DNA are the type of damage most likely to cause chromosomal aberrations or cell death. The cell's radiosensitivity is directly related to its rate of proliferation and inversely related to its degree of differentiation.[44,78] Thousands of these types of lesions occur daily in the human body from natural environmental radiation.

For this reason, there are several mechanisms that protect and repair damage that may result from either direct or indirect means of radiation damage. It is estimated that up to 90% of all chromosomal breaks heal by adhesion in a process known as â€œrestitution.â€• All that is required for DNA to heal is oxygen and time, which forms the basis for fractionated radiation therapy. This therapy takes advantage of the inefficient repair mechanisms of cancerous cells compared to normal cells. Thus, by giving the radiation dose over several sessions, radiation damage will accumulate in cancer cells during radiation therapy, and more cancer cells are killed. Sulfhydryl-containing molecules, such as glutathione, and other scavengers provide protection against free radicals. These molecules react with free radicals and inactivate them quickly, thus limiting the damage they can cause. Following a large radiation exposure, however, both restitution and the protection provided by free radical scavengers may be overwhelmed, and damage may occur.

Stochastic Versus Deterministic Effects of Radiation

The radiation damage just described has two consequential results: it kills cells or it alters cells and causes cancer. Injuries that do not require a threshold limit to be exceeded include mutagenic and carcinogenic changes to individual cells where DNA is the critical and ultimate target. This is the stochastic effect of radiation. Theoretically, there is no dose of radiation too small to have the potential of causing cancer in an exposed individual.[13] Theories suggesting that a single dose of radiation can cause a change in the genome that potentially alters the structure of a protooncogene, control of an oncogene, or activates oncogenic viruses in hosts are supported by a growing body of work investigating bystander effects and genomic instability.[34] These effects may take several months to years to manifest, as happened with Japanese survivors of the nuclear bombs who suffered a spectrum of malignancies many years

after the event.

Whereas the stochastic effects of radiation may follow less severe exposures, such as prolonged exposure to low-level radon gas, the deterministic effects of radiation usually follow a large whole-body exposure, such as a Chernobyl- or Tokaimura-type event. In terms of cell death, a relatively large number of cells of an organ system must be killed before an effect becomes clinically evident. This number of killed cells constitutes a threshold limit that must be exceeded, and this is what is known as the deterministic or nonstochastic effects of radiation.

To illustrate the differences between stochastic and nonstochastic effects consider a single alpha particle from ^{210}Po incorporated in a radon-contaminated household may impact an active segment of DNA in a patient's respiratory tract, ultimately giving rise to a cancerâ€”the stochastic effect. In Tokaimura, the most severely injured worker received 17 Sv of neutron and Î³ radiation and experienced so much cell death across so many systems in his body that he died well before any injured yet surviving cells could develop into a cancerâ€”the deterministic effect.

Acute Radiation Syndrome

The Army Medical Corps first described ARS in 1946 when victims of the explosions at Hiroshima and Nagasaki were admitted for treatment at Osaka University Hospital.[47] Understanding the features of ARS is essential for managing a patient who is exposed to massive whole-body irradiation, generally considered to be 1 Gy (250 times the average annual exposure) or more. In many cases, a reliable estimate of the radiation dose is difficult, thus making it more practical to focus on the clinical features of radiation injury and their prognostic utility.

The acute radiation syndrome involves a sequence of events that varies with the severity of the exposure.[26,93,99] Generally, more

severe exposures lead to more rapid onset of symptoms and more severe clinical features. There are four classic clinical stages described, which begin with the early prodromal stage of nausea and vomiting. These symptoms begin anywhere from hours to days postexposure. Although the time to onset postexposure is inversely proportional to the dose received, the duration of the prodromal phase is directly proportional to the dose. That is, the greater the dose received, the more rapid the onset of symptoms, and the longer their duration, except in cases in which death follows rapidly.[78] The latent period follows next as an apparent improvement of symptoms during which time the patient appears to have recovered and has no clinically apparent difficulties. The duration of this stage is inversely related to dose and may last from several days to several weeks. The third stage usually begins in the third to fifth week after exposure and consists of manifest illness described below. If one survives this stage, recovery, the fourth stage, is likely, but may take weeks to months before it is completed. Those exposed to supralethal amounts of radiation may experience all the phases in a few hours prior to a rapid death.

These four stages describe the clinical manifestations that may be observed as a result of massive exposure, but the various systems of the body manifest their own injuries, which constitute several subsyndromes.[26,99] These subsyndromes are not mutually exclusive of one another and may overlap as cell death or damage progresses.

The cerebrovascular syndrome describes the manifestations of injury to the central nervous system following massive irradiation. This syndrome, following exposure to doses of about 15â€“20 Gy or greater, is characterized by rapid or immediate onset of pyrexia, ataxia, loss of motor control, apathy, lethargy, cardiovascular shock, and seizures. The mechanism of this injury may be a combination of radiation-induced vascular lesions and free radicalâ€“induced neuronal death and cerebral edema.

Despite autopsy evidence of some radiation-induced inflammatory

changes to the heart, animal experiments show this organ to

be relatively resistant to high doses of radiation. Cardiovascular shock is more likely because of systemic vascular damage, which may later compound shock resulting from other subsyndromes should the patient survive to that point. A â€œvascular radiation subsyndromeâ€• might be considered to help explain the changes in hemodynamics a patient experiences following a massive dose of radiation. Once these subsyndromes are manifest, they may never resolve.[20,26,78,83]

The gastrointestinal syndrome begins following an exposure to about 6 Gy or more where there is gastrointestinal mucosal cell injury and death. Symptoms include anorexia, nausea, vomiting, and diarrhea. As the mucosal lining is sloughed, there is persistent bloody diarrhea, hypersecretion of cellular fluids into the lumen, and a loss of peristalsis, which may progress to abdominal distension and dehydration. Destruction of the mucosal lining allows for colonization by enteric organisms with ensuing sepsis.

The hematologic changes that occur following an exposure to about 1 Gy or greater are called the hematopoietic syndrome. Hematopoietic stem cells are highly radiosensitive, in contrast to the more mature erythrocytes and platelets. Lymphocytes are also radiosensitive and can die quickly from cell lysis following an exposure. This contrasts with granulocytes, which endure radiation better. In addition to stem cell death and white cell depletion with immunodeficiency, platelets are consumed in gingival and gastrointestinal microhemorrhages. The main effect of radiation-induced hematopoietic syndrome is pancytopenia leading to death from sepsis complicated by hemorrhage. A lymphocyte nadir typically occurs 8â€“30 days postexposure, with higher doses achieving earlier nadir.[14,25]

The pulmonary system is not spared injury from irradiation. Pneumonitis may occur within 1â€“3 months following a dose of 6â€“10 Gy. This may lead to respiratory failure, pulmonary fibrosis,

or cor pulmonale months to years later.

Dose Estimation

Determining the dose received by an individual who was irradiated is important in providing appropriate therapy and establishing a prognosis. However, estimating the dose received is difficult for a number of reasons, such as the absence of a radiation-monitoring device, exposure to radiation of mixed form (such as Î³ and neutron radiation), and partial shielding of various body parts.[83]

In cases of whole-body irradiation, it is the ARS itself that allows for an estimate of the radiation dose received. The Biological Assessment Tool available at the Armed Forces Radiobiology Research Institute's web site, and guidelines from the International Atomic Energy Agency (IAEA), use clinical signs and symptoms, including the time to onset of vomiting after an exposure to radiation, to calculate the exposure dose and may be the clinician's best dosimeter.[78] Use of this kind of timing may be limited, however, because most exposures can not be perceived by human senses.

As previously mentioned, the component of the hematopoietic syndrome that manifests as lymphopenia is common following an exposure to 1 Gy or more. The observed predictability of this lymphopenia has led to the development of several models for biodosimetry. It is important to note that dosimetry models account for changes in lymphocyte count because of other reasons, such as trauma and burns, and have been validated. However, discrepancies between the models suggest that more than one element of dosimetry be used whenever possible.[99]

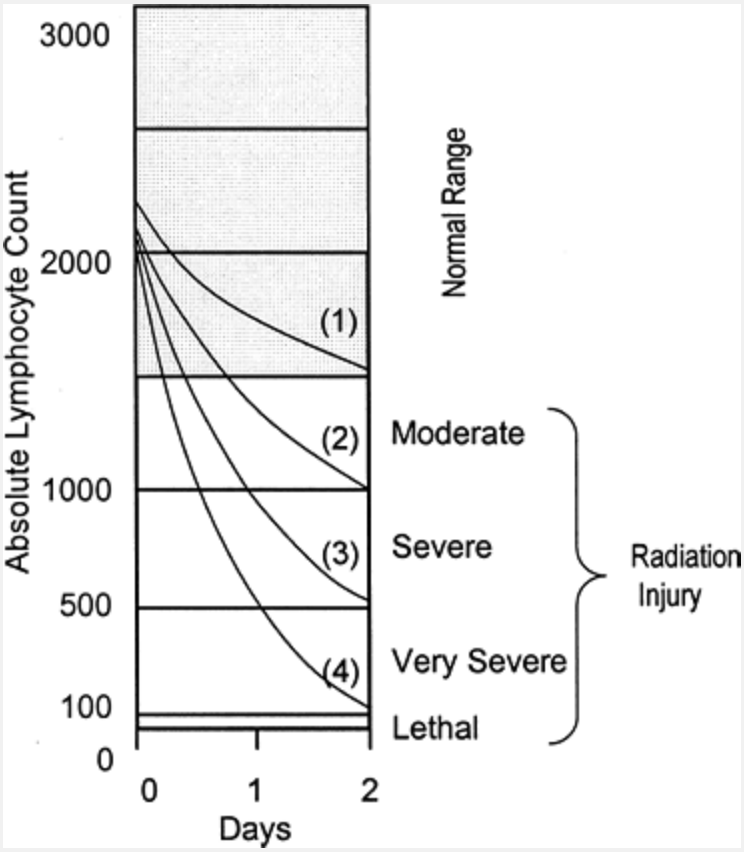

Figure 128-2. Classic Andrews lymphocyte depletion curves with accompanying clinical severity curves. Curves 1â€“4 correspond to whole body exposures of 3.1, 4.4, 5.6, and 7.1 Gy, respectively. *(From Goans RE, Holloway EC, Berger ME, Ricks RC: Early dose assessment following severe radiation accidents. Health Phys 1997:72:513â€“518.*

The broad ranges of radiation dose that correlate with lymphocyte count are described in the classic Andrews nomogram of 1965 (Figure 128-2). Using historical data from exposed patients, one author calculated a lymphocyte depletion constant using the equation:

$$L(t) = L_0 e^{-K(D)\ t}$$

in which L(t) is the lymphocyte count at time t, L_0 is the lymphocyte count prior to the exposureâ€”the population mean taken as 2.45 Ã— 10^9 cells/L, K(D) is the rate constant for a given dose of radiation, and D is the dose of radiation. Solving for K(D) will allow for an accurate estimate of a rapidly delivered, whole body exposure[32] (Table 128-5).

The standard criterion for biodosimetry are chromosome aberration bioassays. Introduced in 1966, this technique analyzes the number of dicentric chromosomes that occur following an exposure to radiation. An exposure to radiation can cause breakage of

the DNA molecule in two nonhomologous chromosomes and produce â€œsticky endsâ€• that recombine end-to-end. In metaphase, these appear as a single chromosome with two centromeres and are called dicentric. The number of dicentrics in lymphocytes correlates reliably with a given dose of radiation. Additionally, if the number of dicentric chromosomes follow a Poisson distribution, a uniform exposure can be assumed (see Table 128-5).[1,50,76]

TABLE 128-5. Biodosimetry Tools[99]

Dose Estimate (Gy)	Time to Onset of Vomiting (Hours)	Rate Constant for Lymphocyte Depletion	Dicentric Chromosomes in Human Peripheral Blood Lymphocytes (per 1000 Cells)
0	n/a	â€”	1â€“2
1	>24	0.126	88

2	4.5	0.252	234
3	2.5	0.378	439
4	1.75	0.5	703
5	1.25	0.63	1024

Even though there is no currently accepted standard for performance, analysis of dicentric chromosomes in peripheral blood lymphocytes is the only method routinely used in biodosimetry. However, because proliferative death of cells containing aberrant chromosomes reduce the number of such cells available for analysis over time, and the migration of lymphocytes into tissue and the lymphatic system, there is a limited period available to use this test to perform dose calculations retrospectively.[46,49] A recent development in molecular biology, the fluorescence in situ hybridization (FISH) chromosome-painting technique, has opened the possibility for accurate recognition of translocations and thus retrospective determination of dose. Unlike dicentrics, complete translocations persist in cell division and enable dose estimation over years following exposure.[48] In fact, this technique was employed to evaluate the radiation dose experienced by clean-up workers at Chernobyl. These authors concluded that it is likely that recorded doses for these cleanup workers overestimate their average bone marrow doses, perhaps substantially.[52] Unfortunately, these techniques are not widely available, require incubation times of 48â€“72 hours, and can not assess for doses greater than 5 Gy, although new methods for high-exposure assessments are being developed.

Prognosis

The prognosis of those exposed to radiation will vary with the amount of the exposure, the type of medical care received, and the number of casualties in a given exposure scenario. Survival is inversely proportional to the radiation dose absorbed, and even the relatively radioresistant cell types can be killed by high amounts of radiation. For these reasons, an acute dose of 20 Gy or more is considered supralethal.[86] Historically, those who were exposed to greater than 10 Gy died despite care. This includes one worker at Tokaimura who was exposed to 17 Gy who died 3 months postexposure, and 20 of 21 workers who were exposed to radiation in the 6â€“16-Gy range at Chernobyl. Some authors suggest that those exposed to 10 Gy or greater be given supportive and comfort care only because their survival is considered to be unlikely.[99]

Within the group exposed to 5â€“10 Gy, depending on the dose received, there may be milder forms of CNS and cardiovascular syndromes that last for a longer time. A severe GI syndrome in which high fever and persistent hematochezia are present suggests a poor prognosis. This syndrome may overlap with a severe form of the hematopoietic syndrome in which damage to bone marrow stem cells is so severe that bone marrow function may not recover for weeks or months. These patients will likely require bone marrow transplantation and multiple transfusions of platelets and red blood cells, optimal supportive care, and infection control to survive.

Patients exposed to radiation in the range of 2â€“5 Gy will likely survive with medical care. Although the median lethal dose of radiation for humans is estimated to be 4.5 Gy, the manifestations of ARS will be similar to those noted above but will likely be delayed and less severe. Many patients will survive without bone marrow transplantation if supportive care optimizes fluid and electrolyte replacement and controls bleeding and infection.

Survival is expected for those patients acutely exposed to less than 2

Gy with little medical intervention necessary. Mild forms of GI and hematopoietic syndromes may occur in delayed fashion compared to more severe exposures.

Carcinogenesis

There are good data to support that radiation increases the incidence of specific cancers in humans. One of the most important sources of these data is life-span studies of atomic bomb survivors in Japan.[19] This group of people is extensively studied over the last half-century, and although the relative risks assigned to specific cancers are modified over the years and subject to interpretation, there is a general agreement that the incidences of leukemia (except chronic lymphocytic leukemia, CLL), female breast carcinoma, and thyroid cancer increase following a sufficient exposure. This risk is largely extrapolated from models of high-dose exposures, but is also supported by data for persons exposed to radon.[19] These cancers usually do not appear until years after the exposure. Because of technical and logistic difficulties in performing appropriate epidemiological studies, there is difficulty in quantifying the cancer risk from exposure to low-dose (less than 10 mSv) radiation.[7] For those exposed while they are young, the excess incidence of cancer occurs only when they are at the age when those cancers otherwise appear in the unirradiated population, as was discussed earlier with the British Nuclear Tests Veterans Association (BNTVA) group.[29,80]

Pulmonary exposure to radon has been studied extensively in the last few years. Both uranium miners and household residents in areas with high ambient radon concentrations, such as New Jersey and Sweden are at increased risk for developing lung cancer from exposure to radon gas. A cohort of nonsmoking uranium miners showed a 12-fold increased risk of lung cancer over controls, which is similar to the estimates of the increased risk of lung cancer caused by radiation exposure in atomic bomb survivors.[12,81] The increased risk of lung cancer from exposure to radon gas is modified by

concurrent cigarette smoking, which may have a multiplicative effect rather than an additive effect.[71]

Commonly Encountered Radionuclides

Most exposures that come to medical attention are not large, whole-body irradiations but are rather small spills in the laboratory or inadvertent exposures from one of many products that are commercially available. With the notable exception of a well-known case of massive americium contamination in Oak Ridge, Tennessee and the cesium exposure in GoiÃ¢nia, Brazil, the vast majority of these types of cases are not reported in the medical literature.[25,91]

Americium (symbol Am, atomic number 95, and atomic weight 243) was discovered in 1946 in Chicago during the Manhattan Project. Its most stable isotope, ^{243}Am, has a half-life of over 7500 years, although ^{241}Am, with a half-life of 470 years, was the first isotope to be isolated. It decays by Î± activity and Î³ emissions and will accumulate in bone if incorporated.[53] It is used to test machinery integrity, glass thickness, and in smoke detectors, where

it ionizes the air between 2 electrodes and generates an electric current that soot may impede. Î±- Particles from these detectors are easily absorbed within a few centimeters of the surrounding air and pose little risk. One g of americium dioxide provides enough americium for more than 5000 smoke detectors. Useful chelators include diethylenetriaminepentaacetic acid (DTPA, now FDA-approved) and linear tetrahydroxypyridinone (LIHOPO). In 1976, a worker at the Hanford Plutonium Finishing Plant, suffered a large ^{241}Am contamination in an explosion at the site. One hundred g (500,000 smoke detectors worth) of ^{241}Am was involved, contaminating the victim's face with 70MBq, but there was likely some inhalational exposure as well. He was treated with long-term DTPA, and despite some leukopenia from the radiation, he survived for 11 years before dying from unrelated cardiac disease.[91]

Cesium (symbol Cs, atomic number 55, and atomic weight 132): Bunsen discovered Cs spectroscopically in 1860. It decays by Î² activity and Î³ emissions and tends to follow the potassium cycle in nature, providing a whole-body dose if incorporated. It is used as a radiation source in radiation therapy and as a radionuclide source for atomic clocks. Cesium, the nuclide of the GoiÃ¢nia incident, comes in the form of a powder, which would make dispersal relatively easy if used in a dirty bomb. Insoluble Prussian blue was recently approved by the FDA as a chelator for patients contaminated with cesium (see Antidotes In Depth: Prussian Blue).[17,51]

Cobalt (symbol Co, atomic number 27, and atomic weight 58.9) was discovered in 1735 by Brandt. ^{60}Co is an artificially made isotope and is an important source of Î³ rays for radiotherapy, and detecting weld seam integrity. ^{60}Co was the source of a significant radiation incident that took place in North America in 1983.[59] A radiotherapy source containing 16.65 (10^{12}Bq (450 Ci) of ^{60}Co in the form of thousands of millimeter-sized pellets was opened and spilled onto a truck in a junk yard in Juarez, Mexico. At least 200 people were exposed to the contaminated truck and the materials subsequently made from the contaminated scrap metal in the junk yard.

Iodine (symbol I, atomic number 53, and atomic weight 126.9): Courtois discovered iodine in 1811. There are 23 isotopes of iodine; ^{127}I is the only one that is stable. ^{125}I is used in thyroid studies and decays by Î³ emissions. ^{131}I is used in metastatic thyroid surveys and decays by Î² activity and Î³ emissions. ^{129}I and ^{131}I are also products of fission in nuclear reactors that may be released into the environment during an event. These isotopes will accumulate in thyroid tissue if incorporated and can cause local damage to thyroid tissue. It is this potential for incorporation that prophylaxis with potassium iodide (KI) is indicated in the event of a large exposure.

Phosphorus (symbol P, atomic number 15, and atomic weight 30) was discovered in 1669 by Brand. ^{32}P has a half-life of 14 days and decays by Î² activity. The maximum range of decay particles in air is

20 feet, and in tissue, 1/3 inch. For soluble ^{32}P compounds, bone receives approximately 20% of the dose following ingestion or inhalation. Shielding for ^{32}P and other Î² emitters should be made of material with atomic numbers of less than 13 (aluminum) to reduce the generation of x-rays, electromagnetic radiation produced by the rapid change of velocity of a fast moving particle as it approaches an atomic nucleus and is deflected.

Radon (symbol Rn, atomic number 86, and atomic weights range from 204 to 224) was discovered in 1900 by Dorn, and was first called *radium emanation*, then *niton*, and finally radon in 1923. Radon is the heaviest noble gas. Radon is also a decay product of radium and a decay product of thorium and actinium, where it is also called thoron and actinon, respectively. ^{222}Rn decays by Î± activity and Î³ emissions. Exposure of radon gas to the pulmonary epithelium is associated with an increased incidence of lung cancer in both uranium miners and in those who dwell in residences with increased levels of radon. Damage to bronchial epithelium results from radon's Î± emissions and radiation from radon daughters that precipitate as solids and remain in the lungs. Good enclosed space ventilation, abstinence from cigarette smoking, and monitoring of radon levels will help to minimize this risk.

Technetium (symbol Tc, atomic number 43, and atomic weight 98.9) was discovered in 1937, and it was the first element to be produced artificially. Tc does not exist in terrestrial materials but does seem to exist literally among the stars. ^{99}Tc is used in testicular, bone, and thyroid scans and has a half-life of 6 days. Tc decays by Î² activity and Î³ emission. Chelation may be accomplished with DTPA.

Thallium (symbol Tl, atomic number 81, and atomic weight 204): Crookes discovered thallium spectroscopically in 1861. ^{201}Tl is used for cardiac imaging, has a half-life of 73 hours, and decays by electron capture and Î³ emission. Chelation can be accomplished with Prussian blue (see Antidotes in Depth: Prussian Blue).

Tritium is an isotope of hydrogen whose nucleus contains 1 proton

and 2 neutrons, and its symbol is ^{3}H.[98] Tritium decays by Î² activity and is used in basic science research as a radioactive label, and for luminous dials. Tritium has a half-life of 12.25 years. When ingested as tritiated water, tritium tends to follow the water cycle in humans, providing a whole-body dose if incorporated. However, its biological half-life is 10â€“12 days, which can be decreased by increasing urine output, greatly limiting its potential toxicity.

Xenon (symbol Xe, atomic number 54, and atomic weight 131): Ramsay and Travers discovered Xe in 1898. There are 31 isotopes of Xe, 22 of which are unstable. ^{133}Xe is used in ventilation/perfusion scans. Its half-life is 5.27 days, and it decays by Î² activity and Î³ emission.

Management

Initial Assessment

The initial management of patients exposed to radiation will obviously depend on a number of different factors, including the amount of radiation in the exposure and the number of casualties in the event. These important factors will describe to a great extent the amount of resources, such as hospital beds or relatively rarely used medications, that will be required in managing those who were exposed. In a mass-casualty event, established prehospital plans should be followed to best manage the large numbers of variously injured given that the radiation exposure may also be accompanied by an explosion of potentially catastrophic size.

All patients should have stabilization of their airway, breathing, and circulation. Field triage protocols, according to the kind of event, will designate patients as minor, delayed, immediate, or deceased depending on their burns or physical trauma and will not be altered because of their radiation exposure. Decontamination should proceed in the field taking care not to contaminate prehospital providers or

equipment. Prehospital personnel should use personal protective equipment and Geiger counters.

Initial Emergency Department Management

When one or more patients who have been exposed to massive irradiation present to the ED, attention must first be paid to the more conventional injuries that may also be present.[78,93,99] Many times

radiation exposures occur with fires or explosions, and patients may have burns, smoke inhalation injuries, or traumatic injuries. This scenario would be the same for the explosion of the â€œdirty bomb,â€• a conventional explosive designed to disperse a radionuclide. Most survivable radiation injuries require prompt treatment but are not life threatening in the first few hours postevent. Thus, there is time to determine if the nature of the exposure was an irradiation or contamination by a radionuclide. Routine considerations of airway, breathing, and circulation take priority for these patients as with all others. If a patient should require surgery, the Armed Forces Radiobiology Research Institute (AFRRI) recommends that surgery proceed immediately because of the delayed and impaired wound healing associated with irradiated tissue.

For large-scale radiation incidents, it is likely that a number of individuals will be involved in developing the best management plan for the casualties. Locally, the radiation safety officer, the medical toxicologist, and the medical oncologist will lend their expertise to the emergency physician to determine the risk of the contaminant, begin appropriate testing to determine the biological effect, and lastly to initiate medical therapy if warranted. Additionally, the local or regional Department of Health should be notified. Larger or complex exposures may require the expertise of the Radiation

Emergency Assistance Center based in Oak Ridge, Tennessee (865-576-3131 Mondayâ€“Friday 8amâ€“4:30pm EST, after hours call 865-576-1005), which can provide valuable support.

Smaller-scale exposures to radiation still require at least a brief evaluation for burns and trauma, depending on the circumstances surrounding the nature of the exposure. Calls to the poison center from a residence require referral to emergency services for an expert evaluation of the level of contamination of the site and appropriate decontamination measures. Exposures in the laboratory or nuclear medicine suites require referral to the radiation safety officer in the building for a similar evaluation.

Decontamination

Patients exposed to radionuclides may be contaminated with radioactive material either externally or internally or both. Historically no medical personnel have ever developed ARS through exposure to a contaminated patient, although caution must be exercised when performing decontamination to minimize exposure to care providers. Unless there is active ongoing radiation, many authors recommend decontamination at the site of exposure to minimize the spread of radioactive materials.[78] All clothing should be removed, and patients should be thoroughly washed with soap and water. In the past, green soap, phosphate-based detergents, and chelating agents such as ethylenediaminetetraacetic acid (EDTA) and DTPA were used.[83] This can remove up to 95% of radioactive material from the patient. Open wounds should be carefully scrubbed to minimize the risk of internal contamination. A portable dosimeter may assist in external decontamination. If the patient was exposed to neutron radiation such as from a nuclear reactor, blood samples testing for induced ^{24}Na by $\hat{I}^3$-spectrophotometric analysis may help as an additional indicator of total dose received. Collected emesis and feces may also be analyzed, if desired, to help estimate total body dose. All clothing and liquid used to decontaminate must be

collected and be clearly marked as radioactive waste. Obviously, there should be no eating, drinking, or smoking at the scene of decontamination.

For patients with smaller exposures to radionuclides, such as laboratory workers, decontamination is often the only management technique required to limit injury. Portable dosimeters will identify contaminated areas, which may be sealed off to limit spread of exposure, especially if the radionuclide is in gaseous form. As with larger exposures, contaminated clothing must be removed and collected. Contaminated skin must be washed with lukewarm soap and water, repeatedly if needed, with care taken not to abrade intact skin and risk inadvertent incorporation. Washing may also be guided by a portable dosimeter. The cesium-exposed patients in GoiÃ¢nia received repeated baths in warm water and neutral soap over the first 2 days of their hospitalization, as did the Hanford americium patient.[91] If the patient is still contaminated after repeated washing, it is recommended to use a cream hand cleaner that contains no abrasives. Some of the GoiÃ¢nia patients habitually walked barefoot and had developed hyperkeratosis. The palms and soles that were heavily contaminated were treated with titanium dioxide mixed with hydrated lanolin. The paste was rubbed into the contaminated area and then gently abraded to try to remove more cesium.[67]

In evaluating an area in which a spill of radioactive material has occurred, a judgment must be made regarding the severity of the incident so that appropriate steps are taken. If a major incident has occurred involving large amounts of radioactive material, a large contaminated area, airborne radioactivity, or spread of radiation outside an authorized area, evacuation, notification of the radiation safety officer in an institutional setting, and calling local or regional emergency response are recommended. Minor incidents involve small amounts of radioactive material where the individual knows how to clean the site, has appropriate decontamination material on hand, and can clean the area in a reasonably short time. Several different decontaminating agents are commercially available from general

stores and many scientific suppliers. These agents come in the form of concentrated detergents or foaming sprays where a small spill is quickly wiped clean and disposed of in an appropriate container.

Triage

It is critical for patients exposed to a large dose of radiation to be triaged according to the dose so that a management plan can be created for them. There are many proposed stages of the various subsyndromes of ARS to help with this dosimetry, but in general we may consider three groups: exposure to less than 2 Gy, 2â€“4 Gy, and greater than 4 Gy. Those exposed to less than 2 Gy may experience some of the hematopoietic syndrome, but may be followed as an outpatient with or without cytokine therapy. Between 2 and 4 Gy, the hematopoietic syndrome is likely and may be severe, but at this dose the GI syndrome is not likely to be a major complication. Hospitalization is recommended at least initially for more accurate dosimetry and supportive care, including the early initiation of cytokine therapy. Exposure to greater than 4 Gy will mean a severe hematopoietic syndrome and likely a severe GI syndrome as well. These patients will likely require an intensive care setting and substantial supportive care for their survival.

Medical Management

In the ED, after airway and breathing have been managed appropriately, intravenous access should be established. As with thermal burns, peripheral IVs are more prone to infection, and central venous access is recommended. Fluid replacement may begin with crystalloid solution where the rate will be modified by recorded inputs and outputs and assessment of surface area burns if any.

Emergency management of emesis and pain may be difficult in those patients who received a high dose of radiation. Many types of

antiemetics are used to control an irradiated patient's vomiting. The 5-HT_3 antagonists, ondansetron and granisetron, are particularly effective in this setting. Mild pain may be managed with acetaminophen, but nonsteroidal antiinflammatory medications are not recommended, as they may exacerbate gastric bleeding in a patient for whom bleeding may soon become difficult to control. Morphine is recommended for the management of more severe pain, which may develop within a few hours after the injury from burns, mucositis, and other complications. As with burn patients, prophylactic use of antibiotics is not recommended.

In the ED it is important to obtain a complete blood count as soon as possible after exposure to begin biodosimetry estimation, and for blood typing. The timing of prodromal signs, such as vomiting, and calculation of the rate constant for lymphocyte depletion help to estimate the dose of radiation to which the patient was exposed. Ideally, a CBC is obtained 3 times a day for the first 2â€“3 days following exposure. Some authors recommend initiation of cytokine therapy as soon as possible if the estimated exposure dose is 3 Gy or greater. A threshold of 2 Gy may be used for children younger than 12 years and adults older than 60 years since these patients may be relatively more sensitive to the toxic effects of radiation. Blood typing early is important because the patient may require transfusions of red blood cells and platelets. Use of irradiated cells is recommended to avoid graft-versus-host disease.

For patients who survive the acute period, sepsis is the leading cause of death. To maximize survival, patients with a severe radiation exposure should be treated as other severely burned or immunocompromised patients regarding their risk of infection. Rigorous attention must be paid to the proper use of H_2 antagonists, antibiotics, antifungals, antivirals, and cultures of body fluids.

Special Management Techniques

Some patients may require supportive measures to boost their

immune system and decrease the risk of infection.[78,99] The colony-stimulating factors, granulocyte colony-stimulating factor, and granulocyte macrophage colony-stimulating factor prime neutrophil microbicidal activity and accelerate neutrophil recovery. Spared hematopoietic stem cells in patients with significant whole body or partial radiation exposures can be stimulated to proliferate in this manner. Although these cytokines only have approval by the FDA for treatment of myelosuppression resulting from cancer treatments, the rationale for their use in the setting of radiation-induced myelosuppression is based on positive results obtained in treating cancer patients and a small number of radiation incident victims and experiments with nonhuman primates.[21,22,99] Colony-stimulating factors were used successfully at GoiÃ¢nia and decreased the period of leukocyte depression while raising the nadir. Although there is no conclusive evidence that early administration is critical for best outcome for these patients, colony-stimulating factor therapy should be initiated as early as possible following the diagnosis of a 3 Gy exposure or greater. These factors should be continued until the absolute neutrophil count exceeds 1000 cells/mm^3. However, in the setting of a mass casualty event, it may be prudent to withhold these resources from those with large dose exposures or those with significant concurrent traumatic injuries.

Following Chernobyl, 13 patients received bone marrow transplantation for hematopoietic support until their irradiated bone marrow could recover.[1,78] Unlike patients who undergo bone marrow suppression for clinical reasons, patients involved in a radiation exposure may have incomplete exposure and are usually partially shielded, which may allow for survival of some stem cells. Eleven of these bone marrow transplantation patients at Chernobyl died, complicating the interpretation of the efficacy of transplantation. Bone marrow transplantation does not change the mortality risk from the other subsyndromes of ARS. The ability of bone marrow transplantation to improve the clinical course of an irradiated patient depends on how likely the patient was to die from hematopoietic

syndrome alone. Some authors consider that there is limited indication for stem cell transplantation when there is also severe radiation injury to organ systems other than the hematopoietic system.[15] This remains a controversial mode of treatment for irradiated patients.

Probiotics is the introduction of selective nonpathogenic strains of *Lactobacillus* and *Bifidobacteria* into the gastrointestinal tract to suppress the number of pathogens.[78,94] Experimentally, this technique increases survival in canine and rodent models. Probiotics was also used in Chernobyl on 3 men whose survival time was prolonged, although it was not statistically significant when compared respectively to case controls.

Incorporation of radionuclides presents a challenge to the treating physicians in which the goal is removal of an internal store of the radioactive material. Beginning in 1966, experiments with beagle dogs treated with DTPA showed decreased incidences of bone cancer when exposed to ^{241}Am.[53,54] Both Ca-DTPA and Zn-DTPA were approved in August 2004 by the FDA for human use for decontamination of plutonium, americium, and curium, although both are also considered useful in the elimination of soluble uranium salts (nitrates and chlorides not oxides) as well. The FDA recommends Ca-DTPA to be given first, ideally within 6 hours of exposure. Because its potency as a chelator is greater than its zinc counterpart, it poses a greater risk in long-term treatment because of loss of essential minerals. For this reason the FDA recommends using Zn-DTPA if treatment is to continue past 24 hours postexposure.[18] Zn-DTPA is poorly absorbed via the gastrointestinal tract. Both drugs may be administered intramuscularly, intravenously, or via nebulizer if a pulmonary exposure is suspected. Currently, Oak Ridge Associated Universities (ORAU) distributes DTPA under contract with the US Department of Energy (DOE). Additionally, rat experiments with LIHOPO demonstrate decreased retention of plutonium and uranium even after incorporation into bone.[18,97]

Prussian blue, ferric hexacyanoferrate, has been used for many years to treat thallium poisoning. Because it absorbs cesium ions, it is used in fission product recovery and is therefore useful in chelation therapy for patients contaminated with cesium. The two forms of Prussian blue, soluble and insoluble, have been used somewhat interchangeably as antidotes for thallium. However, it is the insoluble form that has the advantage when increasing elimination of cesium from the body (see Antidotes in Depth: Prussian Blue).[17,90,96]

As was mentioned earlier, ^{131}I is one of the key fission products that may be released from a nuclear power facility in an accident such as happened at Chernobyl. Additionally, much discussion is currently devoted to the potential for a terrorist attack either on a nuclear power facility or using a radiological dispersal device (a.k.a. â€œdirty bombâ€•) in which there could be environmental dispersal of radioactive iodine, although the 8-day half-life of ^{131}I theoretically limits its utility as an effective environmental contaminant. The increase of thyroid cancer observed in atomic bomb survivors and in those contaminated from the Chernobyl event prompted

the International Atomic Energy Agency (IAEA) to establish intervention criteria for a radiation emergency of an effective dose equivalent of 100 mSv.

TABLE 128-6. Potassium Iodide Regimen

Age	Dosage
>18â€“40 years	130 mg
3â€“18 years	65 mg
1 monthâ€“3 years	32 mg
Newbornâ€“1 month	16 mg

For children 18 years and younger, when there is prolonged risk for inhaled radioactive iodine, it is recommended that the indicated dose be repeated daily until the risk is considered past. This recommendation applies to lactating mothers.
For adults younger than 40 years, repeated dosing is not indicated in favor of controlling food intake, eg, abstention from drinking milk during the time of contamination.
For adults older than 40 years, the risk of radiation-induced cancer is so low that iodide prophylaxis is not indicated, unless the radiation amount is on the order of 5 Gy, but this is unlikely.

Supplying stable iodide to the thyroid, which acts as a blocking agent, reduces the uptake of ^{131}I.[89] This treatment, which should begin as soon as the environmental contamination has occurred, will limit the deterministic and stochastic effects of radioactive iodine uptake in thyroid tissue, particularly in children. The WHO, the CDC, the NRC, and the FDA all recommend similar dosing regimens based

on age for the prophylactic use of KI if an iodine-involving radiation incident threatens a population. KI is FDA-approved as a nonprescription drug and is available as 130-mg tablets that can be either split or dissolved in liquid for the smaller doses (Table 128-6). Several studies have also demonstrated that iodine can be absorbed transdermally when applied as tincture of iodine and povidone iodine to block thyroid uptake of radioiodine.[65,66]

Pregnancy and Radiation

In the normal course of events, uncertainty exists regarding the normal viability of the fertilized ovum, and there is a naturally high rate of embryo loss during the early weeks of pregnancy. When exposure to radiation via medical examination is possible, pregnant women and physicians have exhibited extreme concern over its potential teratogenic effects, even though maternal exposures to less than 0.05 Gy (5 rad) is considered not to be teratogenic.[3,36,77] Additionally, risk of direct harm to the fetus from cosmic radiation during casual airline travel is thought to be negligible.[2] Unfortunately, there is little direct information concerning the effects of radiation in early human pregnancy. Experimental data using rats and mice show increased mortality rates both in vitro and in vivo following irradiation and a dose-response curve that depicts incremental increases in radiation dose corresponding to increasingly greater effects in causing malformations.[88] Experimental human data from the 1930s show increased lethality and induction of abortion when pregnant women were exposed to 3.6 Gy and 5 Gy for a therapeutic abortion by x-ray.[39,61]

The most important sources of information concerning the teratogenic effects of fetal irradiation are the survivors of the nuclear bomb blasts of World War II. The three principal risks to a fetus following radiation exposure are congenital abnormalities, severe mental retardation, and the late development of a neoplasm. The embryo is at particular risk because of its rapid development,

and there are several periods of particular sensitivity so that irradiation at specific times is associated with increased risk of specific problems. Roughly speaking, uterine absorption of 0.1â€“0.15 Sv during the first 2 weeks postconception risks fetal lethality. During the third to seventh weeks postconception, uterine doses of 0.05â€“0.5 Sv risks congenital abnormalities, growth retardation, and small head size that may be accompanied by mental retardation. During the time between weeks 8 and 25 postconception, the risk is severe mental retardation, that decreases at the 16th week.[23,85,88]

Accurate specification of the risks from fetal doses is difficult especially at doses less than 0.2 Sv. Different models consider dose-response relationships for developmental complications and cancer development as linear or linear-quadratic, and with or without a threshold limit. A risk of congenital abnormalities of 5% following exposure to 0.2 Sv compares to a widely accepted average incidence for congenital abnormality of 6% for newborns throughout the world.[88] Patients receiving various diagnostic procedures in the hospital may be exposed to these doses.[38] Clearly, pregnant women who are exposed to radiation are at some risk for a fetal complication, although that risk may be difficult to quantify at the low doses expected with routine radiologic procedures.[10] That low-level intrauterine exposure to radiation increases subsequent cancer risk is not the question, but rather the etiologic significance of the radiation. For many years, studies have been plagued with incomplete data, biological implausibility, and other problems that confound an explanation.[6] Consideration should always be given to the potential maternal benefit of the radiologic procedure and the potential risk to the fetus.[82] However, the vast majority of routine diagnostic imaging procedures imparts less than 0.05 Sv to the fetus and so is considered to be of negligible risk.

Pediatrics and Radiation

The use of CT scanning in children has markedly increased over the last 20 years. One hospital's survey showed a 92% increase in abdominal and pelvic CT examinations from 1996 to 1999 for children younger than 15 years old. Although it is difficult to estimate the increased incidence of cancer rates because of LET radiation, there are reports that attribute a greater lifetime risk for cancer mortality resulting from CT examination in children. This risk is compounded by the tendency not to adjust the radiation dose given to a child during a CT examination from the amount given to adults. Together, these trends may mean increased radiation-induced mortality over the lifetime of the patient resulting from medical evaluation.[8,16,68]

Summary

The danger of ionizing radiation to humans is through the disruption of cellular structure and function. Cell death and mutagenesis are the destructive consequences of an exposure to radiation. Fortunately, large exposures of radiation to the general population are rare outside of the setting of an armed conflict, and most contaminations that occur are small and easily controlled.

In general, recognition of the exposure and thorough decontamination are the critical steps to minimizing the potential toxicity of an exposure. Careful attention to storage of radioactive waste and contaminated materials and good supportive care are usually all that are required to care for most patients.

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Chapter 129
Poison Prevention and Education

Lauren Schwartz

Preventing poisonings and improved access to poison center (PC) services are both national public health issues. Healthy People 2010 is a federal document that presents health goals for the nation. This document reflects the input of public health individuals and organizations and consists of 28 areas with objectives to reach two main goalsâ€”increasing quality and years of healthy life and eliminating health disparities. Two objectives in the Injury and Violence Prevention section relate to poison prevention. Objective 15-7 is to reduce nonfatal poisonings and Objective 15-8 is to reduce deaths caused by poisoning. Objective 1-12 in Access to Quality Health Services focuses on national access to PCs and recommends establishing a single toll-free telephone number for access to PCs on a 24-hour basis throughout the United States.[18] This objective was achieved in 2002. Community-based public education programs at PCs are designed to help meet these public health objectives.

Legislation and Poison Prevention

As discussed in Chap. 1, because the first PC was established in 1953, a number of legislative events have improved poison prevention and awareness efforts and reduced the number of unintentional poisonings in children. Public education programs at PCs have been influenced by these federal measures.

National Poison Prevention Week

In 1961, President John F. Kennedy signed Public Law 87-319, designating the third week of March as National Poison Prevention Week (PPW) to raise awareness of the dangers of unintentional poisonings. During PPW, PCs and other organizations around the country organize events and activities to promote poison prevention. The American Association of Poison Control Centers (AAPCC) (http://www.aapcc.org) publicizes PPW nationally through joint efforts with the Poison Prevention Week Council and the Consumer Product Safety Commission (CPSC).

Child-Resistant Packaging Act

In 1970, the Poison Prevention Packaging Act was passed. This law requires that the CPSC mandate the use of child-resistant containers for toxic household substances. In 1974, oral prescription medications were included in this requirement. A review of mortality data in children younger than age five shows a significant decrease in deaths after enforcement of the child-resistant packaging legislation.[44,53]

Toll-Free Access to Poison Centers

In 2000, the Poison Control Center Enhancement and Awareness Act was enacted with a goal of nationwide access to PCs. A toll-free number (1-800-222-1222) was established access for all US

PCs. Callers are connected to a regional PC based on the area code and telephone number exchange. The AAPCC operates the toll-free number through a Cooperative Agreement with the Centers for Disease Control and Prevention (CDC) and Health Resources Services Administration (HRSA).[5] Figure 129-1 displays the national logo incorporated into educational efforts to support and promote the new national number for US PCs.

The Role of Public Educators in Poison Centers

Nationally, PCs employ approximately 100 public educators; 40% of whom are full-time.[20] Educators encompass a range of educational background including nurses, pharmacists, health educators, and teachers. The primary goals of public education programs at PCs are to teach poison prevention techniques (primary prevention) and to raise awareness about available services should a poisoning occur (secondary prevention).[8,20,31] Public educators at PCs provide community-based programs by developing print materials, videos, and awareness campaigns through public service advertising using radio, television, print, and mass transit venues. Additionally, the use of the Internet has provided a new medium for educators to

provide information and materials that can be downloaded without cost. Educators participate in community health coalitions, work in conjunction with other injury prevention groups such as National Safe Kids coalitions, and collaborate with a wide range of community health agencies. Caregivers of children younger than age six are often deemed the most important group to reach with education programs. Educators often work with national programs for families including Women, Infant and Children (WIC), Head Start, and the Red Cross. Additionally, programs for seniors and grandparents offer an educational opportunity to reach this large

high-risk population. Collaborative programs with American Association of Retired Persons (AARP), senior centers, and Department for the Aging offer an opportunity to provide programs focused on medication safety and poison prevention for older adults.

Figure 129-1. National toll-free number logo.

The membership of the AAPCC's Public Education Committee (PEC) includes the educators from PCs across the United States and Canada. A Chair, Co-Chair, Secretary, and seven Steering Committee members represent the leadership of the committee. The mission of the PEC is to provide poison prevention awareness programs, in an effort to reduce morbidity and mortality associated with poisoning.[4] The PEC provides education sessions at the North American Congress of Clinical Toxicology each year. PEC workshops focus on program development, evaluation, grant writing, strategic planning, and other topics of interest to PC educators.[20]

Needs Assessments

To develop successful poison education programs, educators must analyze demographic data, call volume rates, cultural issues, language, and barriers to calling a PC. Geographic information systems (GIS) software offers a way for PCs to visually map demographic data. The use of this type of software is increasing in public health and can be applied to PC efforts. The coordination of data retrieval from various data entry programs and the use of GIS software by PC staff provides access to call rates by zip codes, counties, census tracts, or congressional districts to be used for planning programs. Health and social services for the targeted community may also be presented using GIS maps. Using GIS for population-based programs is recommended for developing social marketing campaigns, health education programs, outreach efforts, and coalition building.[43] The study of geographic areas with low call rates enhances the potential for educational targeted programs.

Focus groups provide a useful qualitative method for PC educators to identify caregivers' and seniors' perceptions about calling the PC. Barriers frequently cited by low-income English- and Spanish-speaking mothers include: preference for calling 911 rather than the PC, fear of being reported to child welfare agencies, confidentiality issues, language difficulties, lack of direct contact with health providers, low self-efficacy, and concerns regarding cost for the call are identified as issues regarding PC utilization.[1,7,9,22,47] In one study, 51% of caregivers interviewed in a low-income urban pediatric clinic said that they would immediately take their child to the emergency department (ED) after a possible poisoning exposure.[45] Each of these barriers must be considered when planning new programs for reaching caregivers of young children.

Focus groups conducted with seniors show that the majority does not perceive the PC as a service appropriate for their concerns; rather as a service for children and parents. Additionally, the participants expressed a very narrow view of what was considered

a poison such as bleach and household products. Similar to caregivers of children, seniors repeatedly state that they would call 911 in an emergency.[10]

Follow-up surveys are an additional way to analyze factors related to PC access. English- and Spanish-speaking caregivers in Texas were contacted after an ED visit related to a child's poisoning exposure. Findings showed that more than half had spoken to PC staff prior to the hospital visit. Of those who did not call the PC, 68% claimed prior knowledge of the PC, yet failed to use it. Significant demographic variables associated with a failure to call the PC were Hispanic (schooled in Mexico) and African American.[24] Findings from an ethnographic study of 50 Mexican mothers with children younger than five years demonstrated that none had the PC number in their home.[35]

Poison Education Programs

Of the two million annual calls to PCs nationally, more than one million involve children younger than age six.[54] As a result, programs to teach caregivers about primary and secondary prevention techniques have been the focus of education efforts. Typically, these programs focus on teaching poison prevention tips (Table 129-1) and raising awareness of PC services. Historically, seniors have not been a priority population for PC education resources. However, this group represents the majority of fatalities reported nationally to PCs.[20,54] Poison education programs designed to reach individuals (caregivers, pediatricians, children, and seniors) through community-wide interventions are reported in the literature. Interventions have reported an increase in knowledge about PC messages and poison prevention.[23,30] Those programs that targeted communities using mass mailing[6,27,57] were shown to be less

effective in raising awareness than programs that combined

mailing with media campaigns.[1,50]

TABLE 129-1. Poison Prevention Tips

[check mark]Identify poisons inside and outside the home
[check mark]Keep poisons out of reach in a locked cabinet
[check mark]Keep products in their original containers
[check mark]Never keep food and nonfood items together
[check mark]Install carbon monoxide detectors in sleeping areas
[check mark]Keep plants out of reach of children and pets
[check mark]Use child-resistant containers
[check mark]Post the poison center number on all telephones

Interventions Targeting Health Behavior

Unintentional poisonings frequently happen when children are left unattended for a brief period of time (<5 minutes) and a toxic product in use or recently purchased is left within reach of the unattended child.[37] Retention of knowledge and change in behavior measured through telephone surveys after a poison prevention intervention revealed that caregivers are more likely to have the PC number posted in the home.[23,55]

Interventions may be conducted with caregivers after a potential poisoning exposure occurs. The ED presents an opportunity for poison education programs to work with families to prevent further exposure situations.[14] An injury prevention program provided to caregivers of young children after a home injury was shown to be effective, particularly regarding poison prevention information and

the use of safety devices.[39]

The effectiveness of a poison prevention education for families that called the PC following a potential exposure in a young child was also studied. Poison prevention instructions, telephone stickers, a cabinet lock, and a coupon for syrup of ipecac were sent to the family one week after the initial call. Follow-up telephone interviews showed that intervention group recipients reported a higher use of the cabinet lock (59%) and were significantly more likely to post the telephone number for the PC (78%) than those in the control group who did not receive any poison prevention materials within two weeks of the incident. However, families receiving the intervention were not more likely to store syrup of ipecac in the home.[55] Similar results were found during follow-up telephone calls made to WIC participants receiving a free cabinet lock and telephone stickers after an educational workshop.[46]

Poison education programs developed to address caregiver barriers have also been evaluated. To address barriers, a video targeting low-income and Spanish-speaking mothers was developed and evaluated. Results showed increased knowledge about the services, staff, and appropriate use of the PC compared with a control group that attended the regularly scheduled WIC class. After the intervention, changes in attitudes about calling the PC and an increase in the number of participants with the PC number posted at home were reported.[23]

Instructor training programs have been designed by a number of PCs to reach leaders or educators of community-based organizations to incorporate poison education into their roles for the general population. Working with community-based services such as WIC presents an opportunity to reach the target population. Pre- and posttests administered to WIC staff and public health nurses showed increased understanding about poison prevention and increased awareness of PC services.[40]

Focus group participants identified pediatricians as a trusted source of health information for parents.[47] The American Academy of Pediatrics (AAP) includes a poison prevention counseling recommendation as part of The Injury Prevention Program (TIPP). TIPP is a safety education program for parents of children newborn through age 12. The TIPP Age-Related Safety Sheets includes poison prevention advice for parents of children 6â€“12 month olds, 1â€“2 years, and 2â€“4 years.[3] In each, parents are encouraged to call the toll-free number for PCs if the child ingests a potentially poisonous product. It is important that the AAP continues its support for efforts by PCs to prevent childhood poisonings.[31] In another study, family practitioners and pediatricians were surveyed with respect to poison prevention counseling for parents. Although more than 80% of both groups reported that this was an important topic, family practitioners were less likely to provide poison information during a visit.[17]

Education programs are designed for school-age curricula. The effectiveness of MORE HEALTH, a program to teach kindergarten and third-grade students about poison prevention was studied.[30] Posttests administered 1â€“2 weeks after the intervention, showed increased knowledge in the intervention group of children. Parents of children in the intervention group also reported their homes were more likely to be â€œpoison-proofed.â€• The population at highest risk for poisoning fatalities is older adults. As mentioned previously, there is a paucity of poison education programs targeting this group. Recommendations have been made to educate older adults about potential problems with medication use, storage of products, and the services of the PC.[20,29,49] Efforts to teach nursing home staff about potential poisoning exposures is also recommended.[29] There has been a shift in the priority of poison education programs to address this target population. An ED study of patients older than 65 years old showed that seniors had poor knowledge of their current medications. Patients taking more medications were less likely to know the proper dose, name,

and purpose.[12] An evaluation of the effectiveness of PC education programs is necessary to measure changes in knowledge, attitudes, and behavior as a result of interventions with seniors.

Community-Wide Interventions

In a recent review of pediatric literature focusing on community-based poisoning prevention programs, only four studies could be found using poisoning rates as the outcome measure. There is a need for more studies to measure community-based poison prevention efforts.[36]

Mass mailing campaigns have been evaluated as a relatively inexpensive way to raise awareness and increase PC call volume. In most instances, this technique has not been found to be effective.[16,27] On follow-up surveys, only 50% of mailing recipients remembered ever receiving PC materials.[16] When compared with the prior year, a mass mailing effort did not result in increased call volume for exposure or information calls.[27] Likewise, a distribution of textbook covers with the national logo and PC information to elementary and secondary schools in low utilization counties was also not an effective method for increasing PC call volume.[57] However, overall call volume increased by 11.2% after more than one million pieces of literature containing the toll-free number were distributed in a mass mailing effort.[26]

An increased number of information calls to the PC was attributed to a campaign developed to raise community awareness.[50] Media provide a venue for conducting educational activities. Direct mail, radio, television, newspapers, and magazines were incorporated into a media campaign developed to raise awareness in a particular Latino community. A telephone survey conducted with families of children younger than 6 years old in the targeted area showed an increase in awareness about the PC.[1] Developing this type of program is often costly compared with other education efforts, however the potential audience is extensive. Mass media

campaigns are powerful tools used in health promotion and disease prevention efforts. Research shows that media campaigns combined with community-based interventions are successful at changing health behaviors and raising awareness. Creating a supportive

environment for the action required is essential for short- and long-term behavioral changes.[41] News stations often provide a way to broadcast poison prevention messages through the media during PPW and during periods associated with perceived increased risks to a community. Free and confidential services at poison control centers provide caregivers with access to general information or a response to emergencies.

Multilingual Populations

Language and culture must be addressed when planning community-based programs. Quantitative and qualitative research examining Latino communities and calls to the PC have been conducted. Two studies examined the call rates in communities with significantly Latino populations. These areas had lower call rates than comparable areas with high Caucasian populations.[13,52] Furthermore, a number of studies demonstrate that Spanish speaking caregivers are less likely to call the PC because of concerns including confidentiality and language barriers.[1,7,13,22,35] In a study conducted with 100 Mexican mothers of children younger than age five, 32% reported that a doctor or nurse would be the initial contact for health advice. Other sources include friends and family (29%), mother, grandmother, mother-in-law (21%), and spouses (17%). The majority of mothers (81%) acknowledged the use of home remedies to treat their children's illnesses.[33] Caution should be used when planning programs based on census data for demographic information as this may not reflect the specific component under study in community-based programs. If ethnicity information is not collected when callers contact the

PC, there are severe limitations to the value of the data.[13,48]

Qualitative research can help to identify cultural issues when planning targeted education efforts. Monolingual Spanish mothers were more likely to report poor storage of household products and plants.[1] Mexican-born mothers of children younger than five were interviewed in their homes about poison prevention techniques. Safe storage was clearly a problem in these homes with 64% of homes (32/50) having bleach stored within reach of children. Housing made up of multiple families living in the same home further impedes safe storage practices. In this study, families stored all personal products including medications and cleaners with them in their bedroom rather than common areas such as the bathroom.[35]

It is important to consider employment of bilingual staff as public educators when trying to expand public awareness. The benefits include the ability to provide programs directly to the audience and eliminate the need for a translator. A lack of bilingual providers was the most significant barrier identified for Latina women interviewed about injury prevention techniques.[19] Health education programs including mass media campaigns, designed to accurately reflect the cultural identityâ€”language, beliefs, rolesâ€”of the targeted population are more likely to be accepted. Field testing concepts and materials is important for the development and distribution of appropriate information for multicultural populations. Further work is needed to examine cultural beliefs related to poison prevention and an individual's use of and access to the PC. It is important to address cultural beliefs related to use of herbal medicine and complementary medicine use.[33] New education programs are needed to reach targeted populations including Latino and Asian communities across the country. Programs may be more successful if individuals trust and view a source as credible, particularly when cultural attitudes and beliefs closely resemble their own.[28]

Literacy/Health Literacy

Literacy is another area of consideration when designing poison education programs. Health literacy is defined as â€œthe degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions.â€• [42] This encompasses the ability to read, understand, and discuss medical information.[38] It is estimated that approximately 90 million Americansâ€”half the adult populationâ€”have limited literacy skills and are often unable to understand health information and complete the tasks required by the healthcare system. Older adults, minority groups, immigrants, and low-income individuals are at highest risk for low health literacy.[25] People with low functional health literacy abilities are less likely to understand written and verbal health information, medicine labels, and appointment information.[56] This type of health information is often written at reading levels of at least 10th grade or higher.[15] Inability to read labels because of eyesight or the inability to read English often contributes to unintentional poisoning exposures associated with dosing errors for prescription and nonprescription medications. Identification of products may rely on brand recognition along with label reading.[34] Older adults are at particularly high risk because of their extensive use of medications.[49] The inability to read warning labels in English presents a literacy issue for those who are not native English speakers regardless of age.[35] Improvements for labels of both nonprescription and prescription medications are needed to address the actual reading abilities of the adult population. When designing written health materials, the recommended reading level is sixth grade. The majority of Americans are able to understand medical information at this level.[15] In addition to reading level, use of graphics, font style, color, type size, and layout are important components when developing print material. Recommendations for nonprint methods for communicating health information include audiotapes, visuals (posters, fotonovelas,

pictographs), action-oriented activities (role-play, theater, story telling), and audiovisuals (videos, CDs).[2,15,38,56]

Applying Health Education Principles to Poison Education Programs

Health education involves planning, implementing and evaluating programs based on theories and models. These models offer direction for educators with health promotion planning.[32] There is a need to increase the number of poison educational programs incorporating health education principles. This includes education efforts designed to reach individuals through community-based programs and media campaigns.

Both the Health Belief Model (HBM) and Social Cognitive Theory (SCT) incorporate the concept of self-efficacy and are applicable when designing poison prevention interventions and mass media campaigns. Self-efficacy is the individual's belief that he or she will be able to accomplish the task requested.[6,15,21] It is often believed that self-efficacy is necessary for changing health behaviors. The SCT suggests that individuals, the environment, and behavior are intimately and inextricably interrelated.[6] The HBM suggests that individuals are more likely to make health behavior changes based on perceived risk susceptibility, severity, potential barriers, and self-efficacy. Again, decisions are made when actions are seen as potentially more beneficial to the individual than the perceived risks associated with surmounting the current barriers.[21]

One project to conduct focus groups used the HBM approach as a framework for poison prevention and for the assessment of barriers to PC use. Questions for participants were developed based on the principles of HBMâ€”that is perceived susceptibility, severity, benefits, barriers, and self-efficacy related to the health

action requested. The majority of mothers viewed poisoning as an emergency and felt it was a health concern for their children. Cues to action are also a component of the model and involve discussions about poison prevention or related information. Participants recommended using community-based venues and culturally appropriate information to expand awareness about poison prevention and the poison control center.[9]

The HBM and SCT approaches were used to develop the questions for focus groups in both English and Spanish. These questions addressed issues related to poison prevention (severity and susceptibility), the services of the PC (including barriers), and suggestions for education. Focus group participants suggested the use of modeling to reinforce real-life scenarios in which a mother handles the poisoning emergency with the staff at the PC with a positive outcome.[22] As a result, a video was developed addressing these ideas. Two poisoning situations in which a mother calls the center are depicted. One involves home management (ingestion of bleach) and the second involves taking the child to the emergency department (swallowing grandmother's antihypertensive pill). The video is available in English and Spanish along with teaching guides.[23]

A Spanish-language instrument was developed and tested that addresses home safety beliefs using the HBM framework. Low-income monolingual Spanish-speaking mothers of children younger than 4 years of age were interviewed about perceived susceptibility, severity, barriers, and self-efficacy factors affecting unintentional home injuries including poison prevention measures. Barriers identified include literacy skills and access to bilingual health information. Additionally, it is important to develop questionnaires that will be accepted and understood by the target population.[19]

The HBM supports the idea that a â€œteachable momentâ€• may be the right opportunity to present poison prevention

interventions.[39] People may be more open to health information after experiencing a traumatic experience.[11] Events, such as an unintentional poisoning exposure, may motivate individuals to behavioral change. Applying HBM principles suggests that individuals will make changes in terms of poison prevention when or if they view the severity and susceptibility of a poisoning to be high in the home.

Summary

Poison center public education efforts encompass needs assessments, program development, implementation, and evaluation. Two populations, children younger than six years and the elderly, are at highest risk for unintentional poisoning exposures. Focus groups with caregivers of young children conducted across the country have consistently identified barriers to calling poison control centers. These include calling 911, fear of being reported to child welfare agencies, and lack of confidence in handling poisoning emergencies. Using health education theories and models, programs should be developed that address these barriers and encourage caregivers to use the services of the PC appropriately. Education programs focusing on the needs of seniors addressing multigenerational living conditions should be designed. Cultural, health literacy, and language needs of target populations are important considerations when planning poison education programs.

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Chapter 130

Poison Information Centers and Poison Epidemiology

Robert S. Hoffman

History

In 1950, the American Academy of Pediatrics (AAP) created a Committee on Accident Prevention to explore methods to reduce injuries in young children. A subsequent survey by that committee demonstrated that injuries resulting from unintentional poisoning were a significant cause of childhood morbidity. Simultaneously came the realizations that a source of reliable information on the active ingredients of common household xenobiotics was lacking and that there were few accepted methods for treating poisoned patients. In response to this void, the first poison center (PC) was created in Chicago in 1953.[64] Although initially designed to provide information to healthcare providers, both the popularity and the success of this center stimulated a PC movement, which rapidly spread across the country. The myriad of new PCs not only offered product content information to healthcare providers but also began to offer first aid

and prevention information to members of the community.

Approximately 50 years have passed, and in that short time, countless achievements have been realized by a relatively small group of remarkably altruistic individuals. Throughout this time, poison services have remained free to the public, highlighting their essential role in the American public health system. Many of these legislative and educational accomplishments, which are chronicled in Chap. 1, have directly reduced the incidence and severity of poisoning in children.[63,67,71] Concurrently, the number, configuration, and specific role of PCs has shifted in response to public and professional needs.[26,78] Regional centers are staffed by highly trained and certified health professionals who are assisted by extensive information systems. Support is provided by 24-hour access to board-certified medical toxicologists and consultants from all disciplines of medicine and from industry.

The PC of today is charged with many of the same mandates as the original centers. These responsibilities include maintaining a database, providing information to public and health professionals, collecting epidemiologic data on the incidence and severity of poisoning, preventing unnecessary hospitalizations following exposure, and educating healthcare professionals on the diagnosis and treatment of poisoning. However, a crucial test of the utility of PCs will be their ability to demonstrate a reduction in poison related mortality. Although this is an idealistic analysis, surrogates such as ICU admissions, length of stay in hospitals, and total healthcare expenditures might serve as additional indicators of PC success. This chapter explores some of these critical roles and offers a vision of the future.

Maintaining a Database on Product Contents and Poison Management

The first toxicology database created in the United States was a set of

cumbersome 5 Ã— 8 inch index cards produced in the 1950s by the US National Clearinghouse of Poison Control Centers.[64] When it grew to include more than 16,000 cards, the sheer volume of space required to store this information, and the extensive time necessary to manually search these cards, created the necessity of a central repository, such as a PC. As available information grew, a rapid expansion of information technology occurred, and the unwieldy index card database was privatized and transformed into microfiche. Although this resource was physically smaller, specialized equipment was required, and a search was still time-consuming. Numerous encyclopedic and clinical textbooks were written to supplement the database and provide resources for the office or the bedside. With the growth of the computer age and the Internet, the product known as POISINDEX was established as the major source of data on the contents of innumerable household and industrial products, drugs, and plant and animal xenobiotics. POISINDEX also provides uniform management strategies for many potentially toxic exposures.

With this evolution of information technology, PCs are no longer perceived as the sole guardians of toxicology information. Although these services are still essential for the public at large, and those professionals away from their computers, a predictable decline in PC utilization has paralleled this growth in availability of information. A 1991 study in Utah demonstrated that 82.6% of emergency physicians who had POISINDEX available in their institutions no longer routinely consulted the PC.[12] A similar 1994 New York State study suggested that 76% of physicians who had POISINDEX in their emergency departments (EDs) perceived that this decreased their own use of their PC.[76]

An initial analysis might suggest that this is an acceptable trend in that it both allows physicians to respond more rapidly to patient needs and for PCs to be more available to those individuals who do not have access to this information system. However, this practice of â€œnot callingâ€• not only undermines the efforts of PCs to gather

epidemiologic data (see below), it also creates an understanding gap. In other words, the interpretation of the data may be more essential than the data itself. For example, some commonly used sources of toxicology information such as the Physicians' Desk Reference (PDR) and material safety data sheets (MSDS) occasionally provide information that is frankly inaccurate, potentially misleading, or significantly limited.[30,59] Likewise, two recent reviews of drug interaction programs designed for personal digital assistant devices demonstrate significant variability between individual programs.[4,62] Although POISINDEX routinely provides more accurate information regarding overdose, it fails to adapt to ongoing epidemiological trends (such as regional variations in substance use) and is only updated periodically. Essential new information can only be obtained from skilled professionals who specialize in poisoning. Also, because most databases are designed to provide information about known entities, they perform poorly when dealing with unknown and unclear scenarios. For example, consider the case of a clinician caring for a lethargic child whose only medication is Zantac syrup. After the other causes of altered mental status have been excluded, the clinician considers drug toxicity. Consultation with standard references suggests that altered consciousness would not be expected with use of this medication. However, a certified poison information specialist at a regional PC recognized the potential for drug error and had the physician review the syrup bottle in question and call the pharmacy where the drug was provided. Although the prescription was written for Zantac (ranitidine), the bottle actually contained Zyrtec syrup (cetirizine) which could account for the child's symptoms.

Thus, although originally designed as providers of information, PCs must now be considered valued consultants, with staff who not only provide content information but also interpret clinical material and link both to appropriate management strategies. This goal is achieved only through rigorous training and certification criteria designed to provide a valued interaction with healthcare professionals.[2] Access to computer programs cannot be considered a substitute for a thoughtful

human analysis. Computers do not recognize anxiety, inappropriate questions, and other subtle issues that can only be appreciated with a human interface. Another illustrative example of the value of PCs can be drawn from the use of flumazenil for benzodiazepine overdose (Chap. 72). Although it may easily be determined by anyone capable of using an index that flumazenil is an antidote for benzodiazepine overdoses, many subtle characteristics of the patient or the overdose often contraindicate its use. A prospective study determined that when flumazenil was used before consultation with the PC, contraindications were present in 10/14 (71%) cases, resulting in one serious adverse event.[11] In the study mentioned earlier, although physicians with access to Poisindex were less likely to call the PC, 86.7% still felt that using the PC to gain access to a physician toxicologist was a valued resource.[12] Many PCs are linked with centers for poison treatment (CPT), which are healthcare facilities that can provide both bedside consultation and unique diagnostic and therapeutic interventions for a subset of patients with severe or complex poisoning.[1] Preliminary data suggest that direct bedside consultation and care help reduce length of hospital stay and healthcare costs.[20]

Collecting Poison Epidemiology Data

Recent data demonstrate that poisoning is the third leading cause of injury-related fatalities, ranking behind motor vehicle crash and firearm use.[27] Understanding the evolving trends in poisoning is essential to the development of enhanced surveillance, prevention, and education programs designed to reduce unintentional poisoning. Although data can be analyzed from numerous sources such as death certificates, hospital discharge coding records, and PCs, it is essential to recognize the biases that are inherent in each of these reports. Because not all significant poisoning results in either hospitalization or fatality, data from PCs appear to offer a unique perspective.

Unfortunately, the term â€œpoisoningâ€• is often defined differently

and therefore may be confusing. For the purposes of this text, â€œpoisoningâ€• is any exposure to any xenobiotic (drug, toxin, chemical, or naturally occurring substance) that results in injury. Yet the data collected and disseminated by PCs is defined by the term â€œexposures.â€• [47,48,49,50,51,52 and 53,72,73 and 74] Many exposures are of no consequence because of the properties of the xenobiotic involved, the magnitude or duration of the exposure, or uncertainty regarding whether an actual exposure has occurred; therefore, data collected by PCs represent a limited and ill defined measure of poisoning.

The situation is further confounded by multiple biases that are introduced by the actual reporting process, which first and foremost is voluntary and passive. Because the majority of calls concern self-reported data that come from the home and are never subsequently confirmed, a significant percentage of existing data may actually represent potential or possible exposures, with the potential for resultant large statistical errors introduced into the database. Also, current events, hoaxes, and media awareness campaigns all may influence self-reporting rates.[54] Furthermore, to report, a caller must have a telephone and probably speak English. Although telecommunications devices for the hearing impaired and translation services exist, they are rarely used. Enhancement of technology to facilitate the accurate exchange of information between poison information specialists and either hearing impaired callers or those who do not speak English is essential to the future success of PCs. Another would be to entertain more active reporting systems automatically triggered by hospital laboratory values.

Under the present passive system, when hospitals report to the PC, a comparison of the hospital chart with the PC record shows good agreement, demonstrating an accurate exchange of information.[35] Unfortunately, a reporting bias similar to that described above is well recognized regarding professional utilization of poison information centers and has been called the â€œPollyanna phenomenon.â€• [31] For example, in the spring of 1995, PCs in the northeast United States

began to receive numerous reports of severe psychomotor agitation and other manifestations of anticholinergic syndrome in heroin users. In the initial phase of the epidemic, most of the callers requested assistance in establishing a diagnosis, determining possible etiologic agents, and raised questions regarding treatment with physostigmine.[32] Although the epidemic continued for many months, once the media announced that the heroin supply was tainted with scopolamine, and clinicians became familiar with the indications and administration of physostigmine, call volume decreased. Stated simply, healthcare professionals are less likely to call the PC regarding

issues with which they are familiar, are of little clinical consequence, or are not recognized as being related to a poison. Thus, a bias is introduced that results in overreporting of new and serious events and underreporting of the familiar or very common, the extremely rare or unrecognized poisoning, and those exposures or poisonings that are apparently inconsequential. Numerous comparisons support this contention. Thus, investigators who rely on published data from PCs as a sole source of epidemiological information demonstrate a failure to understand the complexity of poisoning data and the aforementioned consequential limitations of PC-derived data.

Fatal Poisoning

A 4-year study compared deaths from poisoning reported to the Rhode Island medical examiner with those reported to the area PC.[46] Not surprisingly, the medical examiner reported many more deaths: 369 compared to 45 reported by the PC. Although the majority of the cases not reported to the PC were victims who died at home, were pronounced dead on arrival to the hospital, or those in whom poisoning was not suspected until the postmortem analysis, 79 patients who subsequently became unreported fatalities were actually admitted to the hospital with a suspected poisoning. In 10 of these cases, the authors concluded that a toxicology consultation might have altered the outcome. Examples of interventions that, if

recommended and performed, might have resulted in a more favorable outcome included the proper use of antidotes such as naloxone, *N*-acetylcysteine for acetaminophen poisoning, the cyanide antidote kit, sodium bicarbonate for a tricyclic antidepressant overdose, and hyperbaric oxygen for carbon monoxide poisoning and hemoperfusion for a theophylline overdose and hemodialysis for a lithium overdose. Likewise, when medical examiner data were analyzed in Massachusetts, over 47% of poison fatalities had not been reported to the PC.[66] A California study evaluating 358 poisoning fatalities reported to the medical examiner showed that only 10 PC fatalities had been reported over a similar time period, demonstrating a comparable reporting gap.[6] Once again in this study, whereas the majority of underreporting was with respect to prehospital deaths (68%), only 5 of 113 hospitalized patients who ultimately died were reported to the PC. Additionally, a cross-sectional comparison of national mortality data with PC data for agricultural chemical poisoning demonstrated a similar trend of underreporting to PCs of seriously poisoned admitted patients who became fatalities.[42] Furthermore, when data for an entire year from the National Center for Health Statistics (NCHS) were compared to the same year of data from the American Association of Poison Control Centers Toxic Exposure Surveillance System (AAPCC-TESS), it was apparent that TESS captured only about 5% of annual poison fatalities.[34] More recent analyses have highlighted a remarkably frightening trend. When 11 states evaluated trends in poison related mortality from 1990â€“2001, an average increase of 145% was noted.[13] A more comprehensive investigation of the Centers for Disease Control and Prevention's (CDC) Web-based Injury Statistics Query and Reporting System (WISQAR) database, demonstrated at 28% reduction in death rates from suicidal poisoning, but confirmed the above noted increase in fatalities from unintentional poisoning. Overall, poisoning fatalities have increased by 56%.[36] In fact, only fatality rates in small children (younger than 9 years old) and older adults (older than 70 years old) have decreased. Focusing on PC data alone would produce the

erroneous assumption that poisoning-related fatalities were not a significant public health concern. In actuality, poisoning is a significant concern in that other programs designed to reduce deaths from motor vehicle crashes and firearms have been largely successful.

It is logical to assume that similar disparities exist regarding reporting of nonfatal poisonings. The resultant gap in public health needs to be addressed through improved definitions, epidemiology, reporting, and analysis of poison-related data systems. This inequity has developed through a long-standing tradition of PCs to focus attention and concentrate on the largely benign exposures in children. The emphasis needs to be redirected toward seriously ill poisoning, ICU utilization, and other markers of actual poisoning rather than healthcare utilization for benign events.

Nonfatal Poisoning

An outreach study in Massachusetts determined that hospitals geographically close to a PC reported their cases almost twice as often as hospitals remotely located (46% vs. 27% of total cases).[14] Additionally, the authors noted that private physicians were less likely to report cases than residents in training. A 1-year retrospective review demonstrated that only 26% (123/470) of poisoned patients who were treated in a particular ED were reported to the PC.[33] Interestingly, only 3% of inhalational exposures were reported, compared with 95% of cyclic antidepressant ingestions. The authors also noted, as suggested above, that reporting decreased when comparable exposures occurred over a short period of time. Finally, in the physician survey study cited earlier, physicians reported that they would â€œalmost neverâ€• contact the PC for asymptomatic exposures (62.9%), chronic toxicity (50.4%), or simply to assist in establishing a reliable database (90.2%).[12]

Occupational Exposures

Xenobiotic exposure occurs commonly in the workplace. As a result of the long-recognized association between occupational exposure and illness, a number of federal and state government-funded agencies, such as the National Institute for Occupational Safety and Health (NIOSH), Occupational Safety and Health Act (OSHA), and the Agency for Toxic Substances and Disease Registry (ATSDR), exist to prevent occupational illness, to educate the public, and to collect data on exposures to occupational xenobiotics. Legislation provides for mandatory reporting in some instances and offers workers job protection for voluntary reporting. PCs also provide information on occupational exposures and collect data. Once again, there are discrepancies between poison information data and the data collected by governmental agencies. A 6-month survey in California noted that only 15.9% of the occupational cases reported to the PC were captured by a state reporting system.[8] These cases tended to underrepresent dermatitis, the most common occupational toxicologic illness. A follow-up study by the same authors demonstrated that over a third of calls came directly from the individual worker, 70% of whom were unaware of the link between their occupation and their symptoms.[7] Although these data suggest that PCs can provide substantial assistance following occupational exposures, one author expressed concern, noting in a followup study that the PC failed to provide an adequate epidemiological assessment in that it did not identify an average of 12 other people per workplace who were also potentially exposed in addition to the index case.[10] A 1999 survey of PCs concluded that PCs' â€œresponses to work-related calls are inadequate,â€• and suggested that written protocols might be helpful.[9]

Adverse Drug Events and Medication Errors

Although the actual numbers are a source of controversy, data

suggest that a striking number of adverse drug events (ADEs) occur each year in the United States, with many resulting in death.[17,45] The ease of 24-hour telephone access, combined with the ability to consult with a health professional, make PCs ideal resources for reporting of ADEs.[18] Yet, over 76% of physicians surveyed stated that they would â€œalmost neverâ€• contact the PC regarding adverse drug events.[12] Moreover, 30/56 (53.6%) PCs surveyed stated that they had not submitted any of their ADE data to the FDA's MedWatch program.[16] Many of the other centers reported only partial compliance with the MedWatch system.[68]

Prescription drug errors are another area of potential poisoning. Retrospective review of PC data suggest that many of these errors are reported. In one report, the PC provided valuable feedback to pharmacists and physicians about these errors. Ideally, reporting to the state board of pharmacy would ensure that proper surveillance and counseling continue. The PC seems to be an ideal institution to perform this function.[65]

Drugs of Abuse

PCs also collect data on exposures to drugs of abuse and misuse. These data consist largely of calls for information from the concerned public and reports of overdose requiring healthcare intervention. Although ethanol, tobacco, and caffeine are the most common xenobiotics used in society, these cases are rarely reflected in poison information data, with the exception of unintentional exposures in children. In fact, because most substance abuse does not result in immediate interactions with the healthcare system, other databases such as the National Institute of Drug Abuse (NIDA) Household Survey (now referred to as the Monitoring the Future Study) might better reflect substance abuse trends.[22] Yet even this database has significant limitations.[5,29] However, because PCs are more focused on immediate healthcare effects of exposures, it could be argued that only those cases in which healthcare interaction is required are of

value in the database. Whereas PC data is collected passively, the Drug Abuse Warning Network (DAWN) provides an active surveillance system of a sample of hospital visits and deaths that relate to substance abuse. Unfortunately, because DAWN data uses hospital chart â€œmentions,â€• which are infrequently validated, the data have been significantly criticized.[69] As such, it is clear that none of these three systems accurately encompasses the scope of the substance abuse problem.

Grossly Underreported Xenobiotics

As discussed above, there is little doubt that alcohol and tobacco are the most common xenobiotics intentionally used and misused in our society. Although their toxicologic manifestations can be acute and severe, chronic subclinical poisoning often goes unnoticed for many years. Similarly, more than one million American children have lead levels above 10 mcg/dL and elevated levels of polychlorinated biphenyls (PCBs) can be found in countless adults and children. We must remain cognizant of these facts when we read that plants, cleaning products, and cosmetics comprise the most common exposures to xenobiotics.[72] These are the most common â€œreportedâ€• exposures.

Using the Existing Data

With the current limitations of the TESS data, it should be clear that neither the numerator nor the denominator of poisoning can be easily appreciated. Analysis of these data for trends may be more useful because the inherent biases involved in TESS reporting are probably consistent over many years. Efforts should be directed to encourage reporting by such enhanced access methods as web-based forms for passive reporting, a direct interface between laboratory and hospital databases that actively transmit data to PCs. Additional resources should be directed at improved case definitions (distinguishing asymptomatic exposure from poisoning) and integration with other

essential databases such as MedWatch and the National Center for Health Statistics (NCHS).

Despite its limitations, TESS data have significant utility. It is often an exposure rather than an actual poisoning that provides the impetus for contact with healthcare. For those exposures that are unlikely to be consequential, the PC can intervene to prevent potentially harmful attempts at home decontamination and costly unnecessary visits to healthcare providers. Interactions with parents at a time of perceived crisis also provides a â€œteachable momentâ€• (Chap. 129) that may help prevent a more consequential exposure in the future. For those exposures that may result in poisoning, the period of time immediately following exposure is an ideal moment to initiate first aid measures designed to prevent or lessen the severity of poisoning. Thus, the cost, benefits, and efficacy of PCs especially regarding home calls must be measured in terms of exposures and not poisonings.

Preventing Unnecessary Hospitalizations Following Exposure

When visits to pediatric EDs for acute poisoning were analyzed, one study demonstrated that 95% of parents had not contacted the PC before coming to the hospital.[15] Sixty-four percent of those children required no hospital services. In contrast, when parents called the PC first, fewer than 1% sought emergency services. When 589 callers to one PC were surveyed, 464 (79%) stated that they would have used the emergency care system if the PC was unavailable.[39] TESS data confirm that approximately 75% of exposures that originate outside of healthcare facilities can be safely managed on site with limited telephone follow-up (TESS). Suggesting simple techniques or reassurance can successfully reduce hospital visits for patients in the TESS population, which as defined, may only represent a potential exposure. Unfortunately, this approach is less applicable to adults and the population as a whole. Many barriers prevent a person from calling a PC, including a lack of familiarity, intellectual and cultural

factors, language difficulties, and confidentiality concerns.[19,40] Epidemiological studies demonstrate that areas of increased population density with high percentages of minority inhabitants have lower utilization of PC services.[70] Also, a recent survey demonstrated additional barriers such as the absence of caregiver comfort with the hands-on contact provided by the healthcare system and a concern regarding implications of child abuse or neglect when reporting to agencies such as PC, many of which have governmental ties.[54] Although it is clear that the institution of a single nationwide toll-free access number has increased calls to PC,[44] it has yet to be determined if this has altered the patterns of use.

The national average cost to the PC for a single human exposure call is less than $35.[78] A federally funded study concluded that in one year, PCs reduced the number of patients who were treated and not hospitalized by 350,000 and reduced hospitalizations by an additional 40,000 patients.[58] Each call to a PC prevented at least $175 in

subsequent medical costs, providing strong theoretical evidence to support the cost efficacy of PCs. In fact, two natural experiments support these calculations: In 1988, Louisiana closed its state-sponsored PC. During the year that followed, the cost of emergency medical services for poisoning in Louisiana increased by more than $1.4 million. This additional expenditure represented a greater than 3-fold increase above the operating cost of that center.[41] Similarly, because of financial disputes in California, direct access to the San Francisco PC was electronically restricted for one major county, with a recording referring callers instead to the 911 system for assistance.[61] The result of each blocked call was to increase healthcare costs by approximately $33. Moreover, these calculations can not account for the unmeasured benefits to society from PC interventions that reduce waiting times for ambulances and hospital treatments because of lower volumes, money saved by the prevention or reduction of injury from early intervention, or lives saved by enhancing access to or utilization of the healthcare system for seriously poisoned patients.

Providing Education for the Public and Health Professionals

PC staff work closely with physicians, community health educators, community support groups, and parent-teacher associations to develop poison prevention activities.[55] Table 130-1 lists common strategies advocated to prevent poisoning. PCs are also actively involved in enhancing training programs for paramedics,[25] medical students,[38] pharmacy students,[21] and resident physicians[21,60] and form an integral part of postgraduate training programs in medical toxicology fellowships.

As stated previously, there is an inherent risk in both enhanced public and professional education programs. Currently, decreased telephone utilization of a PC could equally be the result of a decrease in the incidence of exposure or poisoning or an enhanced understanding of the prevention, diagnosis, and treatment of poisoning. Although education should never be viewed as detrimental, programs must include an emphasis on the continued use of poison information centers to ensure access to current information in a rapidly changing discipline. In actuality, as a result of the ongoing analysis of incoming calls, the knowledge base has the potential to change as rapidly as the calls are reported. Thus, additional emphasis should be applied to routine utilization of the PC as a public health tool to improve the accuracy of epidemiological data. Reporting of rare or suspected events can serve as sentinel efforts that help identify consequential adverse drug opportunities long before normal postmarketing surveillance tools identify areas of concern.

TABLE 130-1. Common Strategies Advocated to Help Prevent Poisoning

All xenobiotics should be kept in their original containers. Food and drink containers should never be used for the excess of a xenobiotic.
Never store xenobiotics in unlocked cabinets under the sink.
Apply locks to medicine cabinets that are within the reach of a child.
In the absence of a lock, the more toxic xenobiotics should be stored on the highest shelves.
Xenobiotics should never be left in the glove compartment of the family car.
Parents should buy or accept medication only if it is in a child-resistant container.
Medication should be considered as medicine, not a plaything and certainly not candy.
Adults should not take their medications in front of children: This will limit exposure to drug-taking role models that may become objects of imitative behavior.
Unused portions of prescription medications should be discarded by flushing the excess down the toilet at the completion of drug therapy. Activated charcoal should be readily available in the home for use if directed by a poison information specialist or clinician. Since it should be anticipated that about 10% of children who have ingested a poison will do so again within a year, these children should receive an enhanced level of supervision.

However, outreach programs that advise the public to access free services for inconsequential events have the ability to overwhelm the already stressed ability to respond to incoming calls in an appropriate

time frame. Public education and public health must cooperate to assure that PCs are staffed with the appropriate number of skilled individuals to respond not only to daily events, but also to address surges in calls that might result from true epidemics or media awareness. Increasing calls to demonstrate increased utilization offers no public health advantage if the utilization is inappropriate or if seriously ill or potentially ill callers lose access to timely responses.

Development of Public Health Initiatives

The initial public health efforts of poison information centers focused on attempts to alter product concentration and to enhance product labeling and packaging. These clearly beneficial endeavors should continue and must evolve. However, current events have also increased PC activities in preparedness for disasters resulting from radiologic, biologic, and chemical terrorism.[28,43] Additional links with governmental agencies such as the CDC and ATSDR will expand the role of medical toxicology in community health.[75] The need for 24-hour rapid access to centralized information, existing data entry and retrieval systems, and links to experts in medical toxicology and emergency medicine helps to place PCs in critical roles in both local and national initiatives. Recent contributions have included development of triage and treatment protocols and assessments of antidote supplies.[23,24]

Summary

Poison centers provide unique benefits to society. Public education efforts help reduce the likelihood of exposure. Provision of first aid advice helps to diminish the consequences of a poisoning once an exposure has occurred. Reassurance and proper first aid help to curtail unnecessary utilization of expensive healthcare. Interactions with healthcare professionals streamline the care of poisoned patients and improve access to toxicologically specific antidotes and the services of medical toxicologists. Data on exposures are used

effectively to create legislation to further limit poisoning by altering contents or improving packaging or labeling.

Recent successes include the establishment of a single nationwide toll-free number to assure easy access to poison services, the development of near real-time surveillance system, and the creation of a stable stream of federal funding. Goals for the continued success of PCs must involve maintaining a uniformly high quality of service, and working to improve the accuracy of the TESS database, a shift in emphasis toward active reporting, reduction of critical services such as ICU admissions, prevention of fatal poisoning,

and prevention of medical error. Many experts believe that part of this success will be through development of uniform practice guidelines, which has already begun.[3,56,57,77] Poison information centers must publicize the need for reporting all poisonings including ADEs and strive to improve systems of active surveillance. Barriers to utilization and reporting must be identified and overcome. TESS reporting must be integrated with other databases so that the true numerators and denominators of poisoning can be understood and so that a concerted response to poisoning and poison prevention can be made. Finally, the causes of the dramatic rise in poison-related deaths must be identified and addressed. Table 130-2 summarizes these and other initiatives, which are also discussed extensively in a recent report from the Institute of Medicine.[37]

TABLE 130-2. Goals for Improving Poisoning Epidemiology Data

Identify and remove barriers to reporting
Create multiple methods of reporting:
Telephone, Facsimile, Internet based or e-mail
Simplify communications devices for the hearing impaired

Allow rapid access to translation services
Enhance awareness of the public health role of PCs
Enhance education of caregivers and healthcare professionals
Establish public health legislation requiring professional reporting of exposures
Distinguish possible exposures from actual exposures to improve the integrity of the database
Create a category for unconfirmed exposures in the database and encourage its use
Divide confirmed exposures by certainty:
  Confirmed by history
  Confirmed by physical examination
  Confirmed by quantitative and qualitative laboratory analysis
Integrate TESS with other databases (such as the ICD and â€œEâ€• code systems) and utilize a standardized data collection instrument
Automatically interact with hospital and commercial laboratories
Uplink pharmacy ADE reports, hospital discharges, public health department reports (similarly available with lead screening programs), fire departments and hazardous materials responders, industry workplace exposures, death certificates, and drug abuse monitoring systems
Provide real-time analysis of incoming data
Enhance the speed of data collection and reporting
Analyze data as it is reported to identify emerging trends
Mandate the use of accepted epidemiological and statistical analyses of data
Provide rapid and regular feedback to primary reporters
Issue timely analyses and reports

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Chapter 131

International Perspectives in Medical Toxicology

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Poisoning is a worldwide problem. The goal of this chapter is to describe what is known about the epidemiology of acute poisoning globally and some of the international efforts that aim to address these problems. The mortality and morbidity attributable to chronic environmental or occupational exposure to xenobiotics in the developing world is beyond the scope of this chapter. Detailed clinical information about individual xenobiotics can be found in the corresponding chapters of this textbook.

Major trends in poisoning epidemiology are highlighted in Table 131-1, which compares poisoning patterns between one hospital in the industrialized world (Bellevue Hospital Center, New York City, United States), and two hospitals in the developing world (Anuradhapura and Polonnaruwa, North Central Province, Sri Lanka). Although these data were not specifically collected to compare poisonings in New York and rural Sri Lanka, major trends in poisoning patterns can be

appreciated (Chap. 130). Utilizing different data sets and rough approximations, the incidence of poisoning is similar in rural Sri Lanka (0.97%) and New York City (0.96%). The most important contrasts between these two environments, are in terms of the classes of xenobiotics that are most common, the overall number of poison-related deaths and the differences in case fatality rates. In Sri Lanka, pesticides account for 50% of all cases of poisoning and are responsible for 75% of poisoning deaths. At Bellevue Hospital in New York City, pesticides are not responsible for any deaths and exposure is uncommon. At Bellevue Hospital, pharmaceutical products account for about 70% of all reported poisoning cases and 95% of poisoning deaths, whereas in Sri Lanka, pharmaceuticals account for about 70% of poisoning cases and only 1.4% of poisoning deaths. Botanical products, yellow oleander in particular, account for about one third of all poisoning cases and nearly 1 in 5 poisoning deaths in Sri Lanka. Botanicals did not cause any deaths at Bellevue Hospital over the same time period. There were 8 poisoning deaths at Bellevue Hospital in New York City, whereas there were more than 30 times the number, 252, in two rural hospitals in Sri Lanka. Finally, in rural Sri Lanka the case fatality rate is 8.1%, which is approximately 10 times more than that at Bellevue Hospital (0.87%). The contrast in poisoning mortality observed in developing versus industrialized countries is not explained by differences in the types of poisons ingested alone, but also reflects profound disparities in healthcare resources. Much of the mortality in Sri Lanka could be dramatically reduced with adequate antidote availability, increased access to intensive care facilities, and public education campaigns.

The 1993 World Development Report divided the world into industrialized and developing countries. The developing world was defined as those countries that were neither recognized to have an established market economy nor are part of the former socialist economies of Europe (eg, the former Soviet Union and its immediate neighbors).[290] This definition is inadequate to describe global poisoning patterns and assumes that healthcare delivery systems and

economies develop in parallel. In fact, while many countries with market economies have rudimentary healthcare delivery systems, there are resource poor countries that provide universal healthcare.

More importantly, variations in poisoning patterns within any given country may be significant, especially when comparing wealthier urban centers with agrarian, often poorer, rural areas. Although the majority of healthcare and academic resources are concentrated in urban centers, it is in the countryside in which much of the mortality from acute poisoning occurs. The accessibility of pesticides to rural people, and their lethality, has a profound influence on global poisoning patterns. This chapter focuses on acute poisoning patterns in countries outside of the United States, Canada, Australia, and Western Europe.

Throughout the world access to evidence-based information is limited, either because of a lack of educational opportunities or because such information simply does not exist.[42] Public health education about poisons and laws limiting access to the most highly toxic chemicals are practically absent in much of the world. Rudimentary public health infrastructures often make the western model of a toxicology consult service impractical. Treatment guidelines designed for poisonings in the industrialized world are often prohibitively resource intensive in healthcare systems that are already overburdened. Many rural healthcare facilities have little in the way of resources beyond the individual physician and a limited pharmacopoeia. Life-saving, yet basic, resources such as mechanical ventilation, antidotes, and antivenoms in are in particularly short supply.[213,271,285] Cultural factors also contribute to the patterns of acute poisonings in individual countries such that countries that are geographically adjacent or linguistically similar may have

very different poisoning patterns. Finally, poisoning patterns change over time and are influenced by the spectrum of available xenobiotics, trends in popular culture and the general level of awareness of the dangers of poisons. It is important to develop a

flexible and dynamic approach to local poison control efforts to ensure that the few resources that are available are used most effectively.

TABLE 131-1. Comparison of Poisoning Patterns Between Bellevue Hospital* (USA) and Anuradhapura and Polonnaruwa Hospitals** (Sri Lanka) 2004

Hospital	Bellevue*	Anuradhapura and Polonnaruwa**
Location	New York City	North Central Province
	Urban	Rural
Annual Census	95,000	320,000
Poisoned Patients	916 (0.96%)	3115 (0.97%)
(% annual census)		
Male (%)	65%	â€“
Adults (>12 years)	93%	â€“
Pharmaceuticals***	70%	10%

Nonpharmaceuticals	30%	90%
Pesticides	0%	50%
Botanicals	0%	31%
Other xenobiotics	â€“	9%
Total Deaths (%)	8 (0.87%)	252 (8.1%)
Pharmaceuticals	75%	1.5%
Nonpharmaceuticals	25%	98.5%
Pesticides	0%	75%
Botanicals	0%	18%
Other xenobiotics	25%	5.5%

*Bellevue Hospital data is abstracted from the AAPCC-Toxic Exposure Surveillance System (TESS) 2004 and represents voluntarily reported cases.

**No emergency department per se exists in these hospitals. Census data represents all hospital admissions in 2004.
***Percentages are approximate, (â€“) indicates that complete data is not available

The PC model, which has been so widely accepted in the industrialized world, has yet to be fully embraced throughout the developing world. Such centers collect and analyze epidemiologic data, provide clinical and public policy consultation, and train indigenous experts. Additionally, PCs may reduce unnecessary emergency department (ED) visits by providing reliable and expert telephone consultation to the public.[192] Although the various functions of a PC may be disseminated throughout the public health system, for the poisoned patient to receive timely and effective care it is necessary that these responsibilities be integrated into a cohesive unit. Much debate exists, however, regarding the utility of a PC within healthcare systems that lack the resources to act on its recommendations. Many of the resources which are integral to the functioning of a PC, such as phone lines and the Internet, are not reliable in the rural areas of the world in which the majority of acute poisoning deaths occur. Furthermore, inpatient care of poisoned patients is not as financially demanding as it is in the United States and other industrialized nations. Hence, reducing ED admissions may not be a compelling argument in favor of PCs in the developing world. A 20-year review of the medical literature found only 7 developing-world countries that had published PC data, perhaps reflecting the difficulties of creating and maintaining PCs[96] (Chap. 130).

The challenges of treating acute poisoning are complex and will require a coordinated effort between governments, academic centers, and individual toxicologists. In countries in which one of these elements is not functional, efforts should be directed toward supporting the existing infrastructure pending the development of other key resources. In particular, treatment guidelines should be evidence based whenever possible. When this is not possible, guidelines should be designed with local experiences and resources in mind. Ultimately, indigenously trained toxicologists will form the foundation for any sustainable poison control program.

Numerous governmental and nongovernmental organizations support

initiatives to provide toxicology information, education, and training internationally. The world wide web has facilitated levels of communication and access to information that were previously not possible.[87,151,161,168,218,229,234] Thus, highly sophisticated and technical information may be easily obtained in many urban centers throughout the world, and clinicians may consult with toxicology experts in academic and governmental centers with a speed and economy that was heretofore unimaginable. Unfortunately, it is unlikely that this technology will become available to rural practitioners in the near future and it remains to be seen if advances in information technology will translate into improved patient care in urban areas. In most cases the challenges faced by practitioners in the developing world are not diagnostic in nature, but relate to the availability of evidence-based treatment guidelines and resources, such as antidotes and ICU facilities. Hence, information alone is unlikely to significantly impact patient care in the developing world.

The Global Health Burden of Poisonings

Although a number of large population poisonings have been widely publicized, the scope of toxicological problems worldwide remains largely unknown. In 1984 in Bhopal, India an industrial error released a cloud of methyl isocyanate, resulting in thousands of deaths [93,127,243,279] More recently, mass arsenic poisoning secondary to contaminated drinking water in rural Bangladesh has been widely reported.[13,120,199,237,248,257] Although these cases of mass poisoning raise public awareness, defining the true burden of disease attributable to mass poisonings is difficult. What is certain is that the mortality attributable to deliberate self-poisoning is extremely high in the developing world: In 1990 the results of several small studies were extrapolated to suggest that there were 2 million episodes of deliberate self-poisoning with pesticides annually in the Asia-Pacific region alone and that the mortality rate was 10%, thus producing 200,000 deaths annually.[143] In the industrialized world, reported mortality rates from intentional ingestions range from

0.5â€“1.0%.[142,226] Occupational or unintentional exposure to pesticides in the same region was estimated to effect 1 million people acutely, and as many as 25 million subacutely. Only 20,000 annual deaths, however, were attributed to unintentional pesticide exposure (mortality rate: 0.8â€“2.0%).[144]

The Global Burden of Disease (GBD) project, administered by the World Health Organization (WHO), attempts to estimate global trends in mortality by cause. Data is divided by region, age of the deceased, and by primary cause of death. Injuries are subdivided into

unintentional injuries, which include poisonings, and intentional injuries, which include intentional self-harm and suicide.[202] The GBD study estimated that at least 75% of world-wide deaths attributed to deliberate self-harm occurred in the developing world: In 1990, 786,000 such deaths were recorded, placing self-harm as the 12th leading cause of death worldwide. The GBD study authors also used several statistical models to project global mortality through 2020: In this study self-inflicted injuries rose to the 10th leading cause of death in 2020, placing them above malaria (29th), perinatal disorders (16th), cirrhosis (12th), measles (27th), and war (15th).[200] In 2000, WHO statistics placed poisoning within the top 15 causes of death worldwide for persons age 5â€“44 years old.[216] Unfortunately, injury surveillance systems are in their infancy in most parts of the world. Global and regional injury statistics are frequently estimates based on data from a minority of countries and tend to overrepresent the experiences of a relatively small group of investigators, potentially introducing significant observer bias into these data.[166]

When examining fatal poisonings alone, some authors have reported that 99% of all worldwide deaths occur in the developing world.[27] In China suicide is now the fifth leading cause of death, where it accounts for 3.58% of all deaths, slightly less than pneumonias.[223] In women aged 15â€“44, self-harm (primarily pesticide ingestions) accounted for nearly 1 in 4 deaths.[201] Whether these data represent a newly emerging epidemic of self-poisoning, or simply reflect

increased reporting of such deaths is unclear. A study of 28,998 injury-related deaths in Bangladeshi women between the ages of 10 and 50 years old found that 60% of injury-related deaths were attributed to poisoning (14% of all deaths in this age group). The majority of these events were intentional ingestions of pesticides, which compares to 2% of all deaths that were attributed to traffic crashes. Married women under the age of 30 were at highest risk for death from self-harm (unadjusted mortality rate: 15 per 100,000).[297]

Unfortunately, self-poisoning is not limited to adults. A 20-year retrospective case series from Northern India examined 217 poisonings in children 0â€“15 years old: 50 of 62 ingestions by children 11â€“15 years of age were intentional, and intentional ingestions accounted for 78% of 27 deaths.[255] Another study of 1188 poisonings in children younger than age 18 from Turkey found that the 12.8% of ingestions were intentional.[131] The intentional ingestion of a xenobiotic should be considered in all children above 6â€“8 years of age.

The terms deliberate self-poisoning or intentional ingestion are preferable to suicidal gesture, as numerous studies have documented that these patients frequently do not actually wish to die nor are they depressed (in this chapter the terms â€œself-poisoningâ€• and â€œintentional ingestion of poisonsâ€• are used synonymously).[96,130,220] Patients in the industrialized world who fatally harm themselves are likely to be male, depressed, middle-aged, or older adult.[43] They are also socially isolated and frequently have alcoholism as a prominent comorbidity. In contrast, patients who complete a fatal self-poisoning in the developing world are more likely to be married or within a family structure, live in a rural area, and be young adults. Depression is present in a minority of patients and alcohol is not frequently cited as a contributing factor.[6,27,41,102,143,183,184 and 185,224] Anecdotal experience, however, suggests that alcohol contributes to despondency and impulsivity, especially in men. This demographic pattern is similar to

that of nonfatal self-poisoners in the industrialized world, where female sex, youth and impulsivity, or personality disorders are risk factors. The main distinction is in terms of mortality, which is low in the industrial world because self-poisoners ingest substances that are less lethal. Thus, assessment tools for depression are unlikely to be useful in the developing world and it is difficult to identify patients at risk for self-poisoning within the general population.

TABLE 131-2. Major Themes in Poisoning in the Developing World

1. Deliberate self-poisoning is a major cause of mortality
2. Pesticides are the most common poisons used in fatal self-poisonings
3. Young, otherwise healthy, people are at high risk for self-poisoning
4. Healthcare resources are frequently inaccessible to rural peoples
5. Lack of healthcare resources, especially intensive care, contributes to higher case fatality rates in the developing world
6. Lack of specific antidotes and antivenoms in the developing world is of major concern

The reasons why intentional ingestion of poisons in the developing world is becoming a public health emergency are multifactorial (Table 131-2). The single most important factor contributing to the high case fatality rate associated with self-poisoning in the developing world is the easy availability of highly toxic xenobiotics in the home. Inadequate pesticide storage practices, unclear labeling and the intrinsic lethality of these compounds are also contributory factors. The reasons that young people intentionally ingest poisons are likely

similar to those found in the industrialized world: Impulsivity and emotional distress combined with economic hardship are commonly cited as the reasons for the ingestion.[129,130] A study of 268 self-poisoners in Sri Lanka found that more than 50% of patients ingested the poison within 30 minutes of deciding to harm themselves, emphasizing the importance of impulsivity in acts of self-poisoning.[104] In contrast to violent means of self-harm, such as jumping from height, hanging, or self-immolation (setting oneself on fire), the danger of intentional ingestion of pesticides may be poorly understood by the public. In a study of 97 self-poisoned patients in Sri Lanka, less than half of the patients were aware of the potential lethality of the pesticide they had ingested.[129] Other cultural factors, such as disputes over dowry and women's roles in society are also important.[145]

Epidemiology of Acute Poisoning Globally

Pesticides: (Chaps. 104,105,106,107,108,109,110,111,112)

Recent work shows that pesticides are the most commonly used poisons in fatal intentional ingestions in the Asia-Pacific region, and that such ingestions have reached epidemic proportions. Although many classes of pesticides are implicated in fatal self-poisonings, organic phosphorus (OP) compounds are responsible for the majority of pesticide-related deaths (Table 131-3).[96,102] In particular, reports from Sri Lanka and India have highlighted this public health emergency.[7,121,128] China also is an area in which this phenomenon is also increasingly reported.[146,223,231] Although many case series come

from the Asia-Pacific region, pesticide ingestion is hardly an

exclusively Asian phenomenon. Case series have also been reported from South America,[79,83,90] Central America,[23,186,281,282,284] the Caribbean,[204] Africa,[95,152,158,287] and the Middle East.[2,4,176,193]

TABLE 131-3. Pesticide Classes Commonly Used in Self-Poisoning in the Developing World

1. Organic phosphorus compounds
2. Organic chlorine compounds
3. Carbamate compounds
4. Paraquat and diquat compounds

Deliberate self-poisoning with OP pesticides puts a high cost on the healthcare system. In a study examining the experience in Sri Lanka, OP pesticide poisoning was responsible for 943 of 2559 (36%) hospital admissions for poisoning. The mortality rate for OP poisoning was 21%, and pesticide-poisoned patients occupied 41% of all medical intensive care beds.[102] In another study of 187 consecutive pesticide poisoned patients in Taiwan the mortality rate was 23%.[249] In all likelihood, such studies underestimate the mortality associated with intentional pesticide ingestion as they are hospital-based and do not include patients who die prior to arrival.

In contrast, a 40-year retrospective study of poisoning in England and Wales found that OP pesticides were responsible for only 68 of 87,385 deaths (0.0007%).[48] Similarly, although more than 80,000 exposures to OP or carbamate pesticides were recorded by the American Association of Poison Control Centers (AAPCC) between 1998 and 2002, an average of only 8 deaths occurred annually

(Chap. 130). The dramatic differences between mortality rates documented in the industrialized world, where pesticide exposures are relatively rare events and primarily unintentional, and the developing world, where massive intentional ingestion is commonplace, highlight the profound differences in terms of epidemiology and resources between these environments.

Factors that contribute to the high mortality in self-poisoning with pesticides in the developing world include the intrinsic lethality of many pesticides and healthcare systems that are poorly prepared to handle such critically ill patients (Table 131-4). Pesticides are easily available, and in highly concentrated preparations, in rural communities throughout the developing world. Inadequate pesticide storage systems are an issue, particularly in unintentional ingestions in children. The ease of drinking liquid pesticides is also a factor facilitating massive intentional ingestions. The extraordinarily high human, economic, and social costs of pesticide-related mortality in the developing world reinforce the importance of developing strategies specifically designed to care for acutely poisoned patients in resource-poor environments. Treatment protocols, such as one recently instituted in Sri Lanka, should be simple, economical, and evidence-based.[98]

The organic chlorine insecticides, such as endosulfan and endrin, are widely reported in South Asia,[50,74,242,252,259] and in Sri Lanka.[240] Although organic chlorine compounds are metabolized rapidly and most patients with minor exposures are expected to do well with supportive care, significant mortality is reported. One report from rural India, where old pesticide containers were used to store food, describes an epidemic of new onset seizures. Thirty-five people were affected, and three children died, before the cause was discovered.[92] Deliberate self-poisoning with organic chlorine pesticides results in significant mortality.[241]

TABLE 131-4. Factors Contributing to High Mortality from Self-Poisoning with Pesticides in the Developing World

1. Ease of access in rural, agrarian households
2. Poor storage practices
3. Inadequate labeling of lethal products
4. High potency
5. Lack of evidence-based practice guidelines appropriate for resource poor areas
6. Lack of clear treatment guidelines

Aluminum phosphide is converted to phosphine gas when it comes in contact with water.[75,170] The product is sold in 3-g tablets, thus facilitating easy ingestion by adults and children. Aluminum phosphide has emerged as a major cause of death in Northern India, where it is reported to be the most common fatal ingestion: Of the 720 cases presented in 4 studies, 439 people died (case fatality rate 61%).[1,15,26,122,157] In a study of 217 poisoned children in Northern India, 58% of all aluminum phosphide patients died and this agent accounted for 62% of all deaths.[255]

Thallium poisoning is reported in the developing world, primarily secondary to homicidal acts using thallium-containing rodenticides, and deliberate self-harm. Reports of poisoning with thallium-containing products is reported in Asia, Africa, the Caribbean, and throughout Latin America.[20,22,113,132,134,178,180,182,196,219,246,277] In a case series of 50 patients reported from Mexico, one patient died after developing pneumonia, whereas another suffered optic nerve atrophy.[236]

Dipyridyl herbicides, such as paraquat and diquat, are used in agricultural regions throughout the world (Chap. 111). These

herbicides are classically characterized by being relatively benign when used as directed, as they rapidly become inert after contact with soil microbes, but extremely toxic when ingested or when massive dermal exposure occurs. Thousands of deaths have been attributed to intentional ingestion of 20% paraquat and diquat concentrates since the introduction of these agents in the early 1960s: Fatalities attributed to these agents have been reported from virtually every country where they are available.[114] Mortality is reported to be greater than 70% in cases of intentional ingestion in the developing world.[128,221] This compares to a 20% mortality rate for paraquat ingestions reported in the United Kingdom, although the amount and formulation of paraquat ingested may have differed in these studies.[215] Because there is no specific antidote to paraquat, and supportive care has little impact on patient outcome, the amount and the concentration of paraquat ingested are the primary predictors of mortality.[114]

In particular, high rates of fatal paraquat poisoning are reported in the Caribbean, the South Pacific, and Korea.[10,19,37,138,221] In Trinidad and Tobago, for example, paraquat ingestion was reported to be the most frequent cause of poison-related death in 1992, although this phenomenon appears to be waning.[137] A Korean study of 154 patients presenting to the Institute of Pesticide Poisoning found that the majority of ingestions were intentional (>75%) and the mortality was greater than 50%.[138] Other sources of fatal exposure include unintentional ingestion, massive dermal exposure, and prolonged occupational spraying.[283]

Ingestion of glyphosphate-surfactant herbicide has been reported in case series from Taiwan. Despite the fact that the mechanism of action of glyphosphate is ostensibly plant-specific, toxicity and death are reported in humans. In a Taiwanese study describing 93 patients who ingested glyphosphate-surfactant herbicide the majority of patients had minor symptoms. The mortality rate in cases of deliberate self-poisoning, however, remained significant at approximately 10%.[270,273]

Recently propanol pesticide self-poisoning, which produces methemoglobinemia and hemolytic anemia, has been recognized in Sri Lanka. In a 4-year retrospective study of 16 severely poisoned patients, 9 deaths were reported. Interviews with local doctors suggested that the case fatality rate was 5â€“10%.[101]

Caustics (Chap. 100)

Caustic chemical compounds (Chap. 100) are common in the developing world in both industry and in the home. Caustic chemical poisoning is distinct from other common poisonings in two respects:

- Gastric lavage and administration of activated charcoal (AC), mainstays of the basic management that may be available in the developing world, are generally contraindicated because of direct damage to the oropharynx, esophagus, and stomach.
- Unlike most xenobiotics, if the acute phase of caustic poisoning is survived, there is a high rate of late complications, primarily esophageal strictures. Late complications may require surgical intervention, balloon dilatation of the esophagus (bougienage), or feeding tube placement. These treatments are expensive, require significant hospital resources and also have inherent morbidity and mortality. A study of 110 caustic poisoned patients from Sri Lanka found that all patients required either bowel resection, reanastomosis surgery, or bougienage. Four patients died during the acute phase of poisoning, however an additional 7 patients died as a result of complication from surgery or bougienage.[96]

In Taiwan, self-poisoning with hydrochloric and sulfuric acid is a major problem. In two reports that describe the experience of 274 patients, the mortality rate was 12%. The majority of these cases resulted from deliberate self-harm (>75%) and more than half of the patients ingested HCl. All severely ill patients who were treated

conservatively and 19 of 27 severely ill patients who went to the operating theater died.[169,262] Another Taiwanese study of 325 caustic poisoned patients, primarily deliberate HCl acid ingestion, reported only 5 deaths in 28 patients who required operative management. Unfortunately, the number of patients too ill to go to surgery was not reported.[292] In contrast, no deaths were reported in a retrospective study of late complications in 75 caustic poisoned patients. This Taiwanese group described outcome as â€œgoodâ€• in 90% of cases. All caustic ingestions in adults (62 patients) were intentional.[291]

Formic and acetic acids are used in the manufacture of rubber, and case series are reported from areas surrounding rubber factories in India and Sri Lanka.[96,235] Because these acids are highly concentrated when used industrially, mortality may be significant. Of 53 formic acid poisoned patients presenting to Trivandum hospital in southern India, there were 15 deaths (28%).[235]

Concentrated acetic acid is also sold for dilution to make vinegar. In Surinam, it was an important means of self-harm prior to 1980 when its sale was banned.[88] In Curacao, 112 cases of acetic acid poisoning were reported during a 4-year period in the 1970s.[235] â€œRubnigneâ€• is a domestic cleaning product commonly found in households in the Caribbean that contains hydrofluoric acid and ammonium diflouride. In 23 cases admitted to the hospital over 3 years in Cayenne, the case fatality rate was 21%.[136]

Ingestion of acid from car batteries is reported in Africa, Papua New Guinea, and the Caribbean. Fatalities have been reported and late complications such as esophageal stricture formation were common in survivors.[85,222,225,289] In a case series of 27 patients reported from South Africa, the majority of patients stated that they ingested the car battery acid because they were aware of its potential harm and the car batteries were easily accessible in unelectrified homes where they are used to provide power.[289] Although no patients died, four required surgical intervention.

Industrial Xenobiotics

Although many toxic xenobiotics are used in industrial processes, a complete review of such xenobiotics or occupational exposures is beyond the scope of this chapter. However, several products commonly used in self-poisoning require mention. Copper sulfate causes direct damage to the GI tract, hepatorenal failure, and hemolysis. It was widely used for self-poisoning in South Asia, especially in the 1960s and 1970s.[77,250,254,255] More recently, in Bangladesh there has been a resurgence in self-poisoning with copper sulfate. In a report of 123 patients seen over six years in the Rajshahi region of southern Bangladesh there were 31 deaths.[11]

Cases of fatal cyanide self-poisoning have been reported in Korea, Taiwan, and India.[35,172,295] In a 4-year autopsy case series from Korea, 121 fatalities were attributed to cyanide poisoning, accounting for 61% of the cases reported.[174] Another autopsy study that compared cause of death in Koreans between the 1930s and the 1960s did not report any cases of cyanide poisoning, suggesting that this is a recent phenomenon.[173] Case reports of self-poisoning with industrial chemicals have been reported from throughout the world including turpentine,[217] chromic acid,[179,275] ethylene dibromide,[227,244,253] ethylene chloride,[67] sodium hypochlorite,[177] ferric chloride, and xylene.[3] As the world becomes increasingly more industrialized, particularly in countries that are considered developing, laws to regulate access to industrial chemicals and ensure safe labeling of xenobiotics have lagged behind the expansion of exposure to these agents. Furthermore, industrial factories are often placed in urban areas, or the areas around factories are rapidly urbanized, placing large numbers of people at risk of poisoning from industrial errors and facilitating easy access to poisons in cases of intentional ingestion.

Domestic Xenobiotics (Chaps. 98 *and*

102)

Domestic products include kerosene used for lighting, household cleaning agents such as chloroxylenol (Dettol), bleach, NaOH-containing cleaners, and strong acids such as HCl used for drain cleaning. Patterns of self-harm using domestic products appear to have significant country to country variability. In one large case series from Zimbabwe, the majority of exposures were unintentional ingestions in children younger than age 6 (61% of all cases). Self-harm was cited in just 19% of cases: kerosene was the most frequently used xenobiotic, followed by rodenticides, bleach, and oven cleaners containing NaOH.[208] Another prospective study from Jordan reported on unintentional ingestion of kerosene in 120 children. Only one patient died, whereas the remaining patients were discharged without complications. Poor storage of kerosene, typically in soda or water containers, and in easily accessible locations was cited as a major factor.[5] Paraffin oils is reported to be a cause of morbidity in Africa.[108] Both kerosene and paraffin cause harm through aspiration and subsequent pulmonary insufficiency.

In contrast, in Hong Kong significant morbidity is associated with self-poisoning with domestic products. â€œDettolâ€• products contain 4.8% chloroxylenol, pine oil, and isopropyl alcohol. When large quantities are ingested, coma and cardiopulmonary depression may occur.[64,148] The risk of pulmonary aspiration is reported to be 8%.[63] Renal failure and direct GI damage are also reported, but appear to be rare.[58,64] Upper airway obstruction is also reported.[150] In one case series of 187 patients from Hong Kong, 95% of ingestions were intentional self-harm, primarily of Dettol-type products. Two deaths were associated with aspiration of Dettol or other detergent solutions; inadequate airway protection and gastric

lavage were identified as risk factors.[60,63] In another Hong Kong study of adolescents, Dettol or detergent products such as cetrimide were cited in more than 50% of cases.[53,76]

Another domestic cleaning product, potassium permanganate, is reported in Hong Kong.[214,296] Death results from hepatorenal insufficiency. Domestic cleaning products containing NaOH are reported to be a common method of self-harm in Malaysia.[24] In Korea, NaOH was reported to be the most common method of self-poisoning in the 1930s and 1960s, although it has now been replaced by other agents such as paraquat and cyanide.[24,172]

Although cosmetics are not cited as a major source of poisoning in the developing world, there are numerous case reports from the Middle East, Africa, and India of hair dye (paraphenylenediamine) poisoning.[191,260,294] During the 1990s, hair dye was reported to be the leading cause of poisoning deaths in Morocco.[29] Forty-six cases of hair dye poisoning were reported from Khartoum and Casablanca. Acutely, patients presented with severe facial and neck edema and depressed level of consciousness. Because of airway compromise and the risk of aspiration, tracheotomy was frequently required. In severe poisoning, multiple organ failure ensued, leading to death (case fatality rate 18%).[38,107,293,294] Barium sulfide, arsenic sulfide, and calcium oxide are contained in many traditional hair removal preparations (darou or nefazat). Ingestion of hair removal products is reported in India and Iran, where it became a popular and dangerous method of self-poisoning after a widely publicized suicide.[9,96]

Animal Envenomations (Chaps. 115,116,117)

Snakebites and envenomations by other animals represent a significant cause of morbidity and mortality in the developing world. Venomous snakes are found on all continents, with the exception of Antarctica, although the majority of species are found in equatorial, tropical, or sub-tropical environments. The health impact of snakebites is determined by the species of snake in a given area, the lethality of venom from these species, snake behavior and human activities. Snakebites from members of the Elapidae and Viperidae

families are responsible for the vast majority of deaths, although several other families are medically important (Colubridae and Atractaspididae species, in particular).[285]

In the United States, snakebite victims are frequently curious children, intoxicated young males, reptile collectors, and snake handlers. In contrast, snakebite may be considered an occupational hazard of working in the rural tropics. Victims are just as likely to be women as men, reflecting rural farming practices. Working in large plantations and subsistence farms places rural people in frequent contact with venomous snakes. With simultaneous changes in global climate and expansion of human settlements, it is likely that the range of venomous snakes will enlarge to include urban areas and regions previously considered too temperate to support them.[133,207]

Few countries mandate the reporting of animal bites, making it difficult to estimate snakebite incidence, severity, and outcome. Because the majority of rural people in many parts of the developing world first consult traditional healers, hospital based studies of mortality and morbidity associated with snakebites may underestimate the scope of the problem.[72,258] A study of rural Philippine rice farmers found that only 8% of cobra (*N. naja philippinensis*) bite victims reached a hospital.[278] The World Health Organization (WHO) estimates that there are 5 million snakebites each year, about half of which result in potential envenomation. Although some disagreement among experts exists, poisonous snakebites are responsible for at least 125,000 deaths annually.[71] In contrast, less than 100 snakebite deaths per year are estimated to occur in Europe, the United States, Canada, and Australia combined.[71] In Australia, an area where venomous snakes are endemic, only 18 deaths were reported over a 10-year period and in the United States, a 20-year retrospective review identified only 97 deaths associated with reptile envenomations.[197,265]

The majority of worldwide deaths from snakebite occur in the Asia-Pacific region, where an estimated 100,000 deaths occur annually.

The incidence of snakebite ranges from 3 per 100,000 in temperate areas of Australia to 526 per 100,000 in Papua New Guinea.[71,82] It is important to understand local trends in snakebite epidemiology because species-specific antivenom should be used whenever possible. There is considerable variation between Asian-Pacific countries in terms of the predominant species responsible for human deaths. In Sri Lanka Russell's viper (*V. russelli*) and the common cobra (*N. naja*) are responsible for 75% of deaths. In Malaysia more than half of hospitalized patients are bitten by the Malayan Pit Viper (*C. rhodostoma*). In India, the case fatality rate is reported to reach 20%, primarily from the carpet viper (*E. carinatus*), Russell's viper (*V. russelli*), and the common cobra (*N. naja*).[71] In Mayanmar, Russell's viper (*V. russelli*) accounts for 70% of venomous snake bites, although this may simply reflect the impact of mandatory reporting laws.

Throughout Africa, snakebites are a source of considerable morbidity and mortality: The incidence of snakebite ranges from 48â€“603 envenomations per 100,000 inhabitants and the case fatality rate ranges from 1â€“28%.[71] The burden of poisonous snakebites on local resources is substantial. During the rainy season in Benin, snakebites account for up to 20% of all hospital admissions. The mortality rate is estimated to be 3.1â€“5.9%. In this region, the incidence of snake bites ranges from 200 annual envenomations per 100,000 in rural villagers to 1,300 envenomations per 100,000 in sugar cane plantation workers (average of 440 envenomations per 100,000 inhabitants).[72] One study conducted in Nigeria in the late 1970s noted an incidence of 497 per 100,000 and a 12.2% mortality rate (primarily because of envenomations by the carpet viper, *E. carinatus*).[232] In another study from rural Kenya, snake bite was estimated to be responsible for 0.7% of all deaths annually.[258] A slightly different pattern emerged in studies of 1069 cases of snakebite in Zimbabwe: the majority of snakebites occurred at night and were not specifically work-related. Although the mortality was relatively low (1.8%), the cost of caring for these patients was

substantial ($225 USD per day, not including the cost of antivenom).[153,209] In Central and South America *Crotalus* spp. are responsible for the majority of deaths. In Brazil, approximately 20,000 snakebites are reported annually. In the tropical Amazon region, the case fatality rate is 1.3%, compared to 1% in more urban areas of the country.[71] In Mexico approximately 4,000 snake bites are reported annually, primarily from *Crotalus* spp.[49]

Several diagnostic and treatment approaches have been developed for snakebites.[34,70,82,165,285] The mainstay of effective therapy is antivenom: Antivenoms must be safe, effective, economical, and widely available.[73] The currently available antivenoms are either prohibitively expensive, ineffective, or have a high rate of adverse reactions. Equally important, many antivenoms must be refrigerated making them impractical therapies in the developing world. The most important challenge to treating snakebites is the lack antivenom availability. Critical evaluation of existing antivenoms and development of new products are desperately needed.[28,171,271,285]

After snakebites, the second most common cause of mortality and morbidity from venomous animals is scorpion stings. Medically important scorpion species are widely distributed throughout the

tropics, being particularly common causes of morbidity in North Africa, Mexico and Brazil.[30,89,105,116,118,238] The total number of medically significant scorpion stings that occur annually is unknown. In Mexico, for example, 240,124 scorpion stings and no deaths were reported for 2003, although antivenom therapy is standard of care throughout the country.[49,89] Mortality rate was reported to reach 8% in areas of the Middle East prior to widespread use of antivenom.[106,139] The majority of these deaths occur in older adults and infants in rural areas where access to healthcare and antivenom is limited. The role of antivenom therapy is widely accepted in many countries, although evidence for its efficacy is scant and there is some debate among experts.[119,140] In reports of 20,000 scorpion stings treated with primarily with antivenom in Saudi Arabia, the rate

of adverse drug reactions was low (1.7â€“13.9%), there were no cases of anaphylaxis and only one death.[139,141]

Other venomous insects, such as Arachnida (spiders) and Hymenoptera (bees, ants, and wasps) are rarely sources of significant mortality on a global level. Most deaths are associated with anaphylactic reactions to Hymenoptera venom. There is morbidity associated with venomous insects, in particular necrotic arachnidism caused by *Loxosceles* ssp. (recluse spiders), which are common throughout the Americas (Chap. 115). Effective antivenom is available to widow spiders (*Lactrodectus* spp), the Brazilian banana or armed spider (*Phoneutria* spp), and the Australian funnel spider (*Atrax robustus*).[285]

Medications

Poisoning with pharmaceutical products is reported throughout the world. In general, the use of pharmaceuticals is more common in urban areas in which access is easier and there are more people with the financial means to buy medications. The pharmacopeia available in the developing world is smaller than in the industrialized world, with the exception of drugs to treat tropical diseases that may indigenous to a particular area. Overall, medications with CNS activity are the most common medications used in self-poisoning in the developing world: This pattern, however, largely reflects the urban experience.[8,55,155,175] In rural areas, pesticides remain the most important cause of poisoning fatalities. In the 1970s, barbiturates were a very common means of self-poisoning and several large case series exist.[83,123,167] Recently, benzodiazepines have grown in popularity, presumably because of their increased availability and a perception amongst lay people that they are dangerous in overdose.[155] Case series also cite tricyclic antidepressants and anticonvulsants, such as carbamazepine.[59,124,193,254,266]

Overdoses of analgesic preparations, such as acetaminophen and

aspirin, are reported from many countries.[40,55,62,286] Intentional overdoses are rare, however, and may reflect that the potential toxicity of these medications is not as widely recognized as in the industrialized world, where such intoxications are commonplace. The majority of these reports are from urban center in which analgesics were less common than either barbiturates or benzodiazepines.[12,52,54,56,57,59,68,69,193,195,261]

Important exceptions to this trend are the antimalarial drugs, chloroquine in particular, which are widely available throughout the developing world and more commonly prescribed in rural areas in which malaria is more prevalent.[78,117,190] A retrospective review of poisoning with pharmaceuticals at 8 referral hospitals in Zimbabwe found that antimalarials accounted for 53.1% of admissions, with chloroquine accounting for 96% of these cases.[25] Fatalities from chloroquine self-poisoning are reported from Africa, Asia, and the Pacific region.[25,81,91,163,181,187,194,205,206,211,230,233,239,247,251,276,288] A report of 29 cases of chloroquine poisoning from Zimbabwe found that 11 patients had at least 1 episode of cardiac arrest and that the fatality rate was 20%.[187] In a more recent study from Zimbabwe the fatality rate was lower, 5.7%. The authors noted that chloroquine self-poisoning was significantly associated with pregnancy, suggesting that it is used as an abortifacient.[25] Self-poisoning with other antimalarial drugs such as quinine is also reported.[45,80,115,164,210,228]

Dapsone is a second-line therapy for *pneumocystis carini* pneumonia in the industrialized world, but a first-line agent for leprosy in the developing world. A review of the medical literature from 1950â€“1993 found just 32 cases of poisoning worldwide.[274] Isoniazid, used to treat tuberculosis, is also reported, although it does not appear to be a common method of self-poisoning nor a major cause of mortality.[263,269]

Herbal and Traditional Medicines (Chaps. 43 *and* 114)

Much is known about the use or the potential toxicity of traditional medicines in the developing world. Large schools of traditional medical theory and practice exist throughout China and India (Ayurvedic medicine). In other countries, traditional medical theory is learned through an apprenticeship process. In Mexico, for example, the National Ethnobotanical herbarium catalogues more than 14,000 different plants used in traditional medical practices.

Although traditional medicinal preparations have been tested by generations of practitioners and the concentrations of active ingredients are generally low, both intentional and unintentional poisonings are common.[65,159,160,267] Because traditional medicines are frequently used by immigrants from the developing world, it is reasonable to ask all immigrant patients if they take any non-physicianâ€“prescribed remedies. As general rule, immigrants should be assumed to have full access to the traditional pharmacopeia of their country of origin.

Toxicity from traditional Chinese medicines is increasingly reported, although the reasons for this phenomenon are not clear (increased use, increased reporting, or increased use in Western cultures). A review of traditional Chinese medicines found 2788 reports of adverse drug reactions, representing 40% of all products (herbs and pharmaceuticals). The most commonly reported agents were *Aconitum* spp, followed by *Triperygium wilfordihoo f.*, and *Isatis tinctoria L.*[160] Adulterants are also common in traditional Chinese medicines, particularly synthetic pharmaceuticals and heavy metals.[61] A Taiwanese study of 2609 samples found that 23% were adulterated with pharmaceutical products (primarily caffeine, nonsteroidal antiinflammatory drugs [NSAIDS], acetaminophen, and diuretics).[135] The seeds of Cycas species contain cyanogenic glycosides and are used in traditional Chinese medicine. A report of

21 symptomatic cases of poisoning in Taiwan noted elevated cyanide level, although not in the toxic range.[66]

Plants (Chaps. 43 *and* 114)

Poisonous plants have been used therapeutically and for harm throughout human history. Typically, they are used to induce abortion, for recreational intoxication, in homicidal acts, or for self-harm. Plants have also been the source of unintentional poisoning, either through direct toxicity or because of a toxic contaminant. This section highlights toxic plants that are commonly used in self-poisoning or have caused epidemic poisoning in the developing world.

Yellow oleander (*Thevetia peruviana*) grows throughout the tropics and contains cardioactive steroids in its sap, leaves, and seeds.[100] Yellow oleander has been used for abortion, homicide, and suicide throughout India. In Sri Lanka, thousands of cases intentional ingestion occur each year.[97,245] A recent report, which did not include patients treated with anti-digoxin Fab, noted that 43% of patients presented with severe dysrhythmias and 6% died.[97] In Latin America, yellow oleander is widely used as an appetite suppressant. Sporadic cases of fatal poisoning are reported throughout Latin America, although most of these cases appear to be unintentional.

Oduvan (*Clistanthus collinus*) leaf contains the glycosides clistanthin A and B, which produce severe hypokalemia and cardiac dysrhythmias.[18,110] Over 500 cases were reported in a series from Tamil Nadu, India.[17] Mortality is significant: in two Indian case series of 77 patients, 24 deaths were reported (case fatality rate of 31%).[264,272]

Ackee tree fruit (*Blighia saphia*), which contains hypoglycin when unripe, is widely consumed as a food source. Epidemics of unripe Ackee fruit poisoning are reported throughout the Caribbean and in Africa.[51,109,189,198] In a report from Jamaica, the mortality was 25%.

In Burkina Faso, the deaths of 29 preschool children over a 5-month period were attributed to consumption of unripe Ackee.[188]

The Superb lily (*Gloriosa superba*) and Meadow saffron (*Colchicum autumnale*) contain colchicine alkaloids. Cases of deliberate self-poisoning are reported from India and Sri Lanka.[14,16,147] It is likely that colchicine-specific Fab would be effective therapy, although no studies are currently available.

Numerous plant species contain atropine-like alkaloids, causing an anticholinergic syndrome when ingested. Most often jimsonweed or thorn apple (*Datura stramonium*) or Peruvian apple (*Datura sanguinea*) are ingested. Reports of intentional ingestion of Datura species have been reported throughout Africa, in Asia, and in Latin America.[36,94,125,156,212,268] Most commonly, the seeds are ingested as a recreational drug for their hallucinatory effects, or as part of traditional medical preparations, where it is often used to treat asthma.

Ingestion of *Karwinskia humboldtiana* (buckthorn, coyotillo in Mexico, wild cherry, or tullidora) causes a demyelinating polyneuropathy, clinically similar to Guillain-BarrÃ© syndrome.[32] The plant grows wild in semi-arid areas throughout the United States, Central and South America, and the Caribbean; poisonings are reported throughout its range.[33,44,46,47] The berries of this shrub are attractive, especially to children, and unintentional ingestions are common. Epidemic poisoning are reported in Central America and Mexico.[21,47] One report from Mexico describes a family that ate the fruit: all patients that ate buckthorn berries developed symptoms, and 3 of 11 patients died.[31]

Castor beans (*Ricinus communis*) are commonly used as purgative agents for weight loss in Mexico, Central and South America. Poisoning by castor beans, or other lectin-containing plants such as Jatropha ssp. (African purging nut), is also reported in Africa and South Asia.[112,126,149] These small, mottled, beans are attractive and widely available. Ricin, the toxic component, produces cytotoxicity

with prominent gastrointestinal symptoms. A few masticated beans contain enough ricin to cause death, although it is rare because GI absorption is poor.[39,280]

Reducing Poisoning Mortality Globally

Recognition of the fact that self-poisoning with pesticides is responsible for the majority of poisoning deaths worldwide compels us to act to reduce the mortality associated with these xenobiotics. Ironically, some programs to remove the most environmentally persistent and toxic chemicals have inadvertently replaced them with chemicals that are highly toxic to humans; for example, the replacement of persistent organic chlorine compounds with carbamates in malaria control programs. The opposite has also occurred when pyrethroids replaced organic phosphorus pesticides in an effort to reduce human toxicity.[162] Strategies to reduce the health effects of pesticides should take into account concerns regarding both environmental and human toxicity, and anticipate which pesticides will replace the most highly toxic chemicals as they are phased out of use. A strategy based on industrial hygiene models of hierarchy of controls has been proposed by several authors (Table 131-5).[241] Although this approach is appealing, it does not specifically address how to reduce intentional ingestions or how to improve hospital care for the individual poisoned patient.

TABLE 131-5. Hierarchical Strategies to Reduce Pesticide Poisoning Mortality in the Developing world

Most Effective

1. Eliminate the most highly toxic compounds
2. Substitute with less toxic, equally effective alternatives
3. Reduce use through improved equipment
4. Isolate people from the hazard
5. Label products and train applicators in safe handling practices
6. Promote use of personal protection equipment
7. Institute administrative controls

Least Effective

Adapted from Roberts DM, Karunarathna A, Buckley NA, et al. Influence of pesticide regulation on acute poisoning deaths in Sri Lanka. Bull World Health Organ 2003;81:789â€“798.

Four basic strategies have been proposed to limit the health impact of the most hazardous chemicals worldwide (Table 131-6).[162] Voluntary interventions include international policy statements and industrial pesticide initiatives. In 1985, the Food and Agriculture Organization (FAO) of the United Nations issued a strongly worded document, the Code of Conduct on the Distribution and Use of Pesticides.[111] The pesticide industry has also worked in cooperation with the FAO to remove or destroy large stockpiles of obsolete or banned pesticides in the developing world. CropLife International is an industry sponsored initiative that claims to reduce the health burden of pesticide poisoning through Safe Use and Integrated Pest Management (IPM) programs (http://www.croplife.org/default/aspx, 2005). The cost effectiveness of industry sponsored Safe Use of

Pesticides programs, however, is questionable.[203] Voluntary initiatives, unfortunately, suffer from a lack of resources, a shortage of political will, and nonexistent enforcement mechanisms.[162]

Integrated Pest Management Programs (IPM) increase productivity and profitability of farms, reduce or eliminate pesticide reliance

and reduce exposure of farmers to pesticides.[154,256] Restricting access to pesticides, however, is the key step in reducing the number of cases and the mortality of intentional ingestions. National programs that remove specific WHO class I and class II pesticides demonstrate this effect on mortality.[86] In Somoa, for example, suicide rates climbed after the introduction of paraquat; when paraquat became less available because of financial constraints, combined with a public education campaign, poisoning case fatality rates returned to previous levels.[37] Similarly, when parathion was recognized to be responsible for more than 90% of pesticide deaths in Jordan, it was banned, resulting in a dramatic reduction in poisoning deaths.[4]

TABLE 131-6. Strategies to Reduce Pesticide Availability in the Developing World

1. Voluntary guidelines, safe use initiatives, and international policy instruments;
2. Changing farming practices: integrated pest management (IPM) and plant biotechnology
3. Direct restriction of pesticide use
4. A minimum pesticide list

Adapted from Konradsen F, van der Hoek W, Cole DC, et al: Reducing acute poisoning in developing countiresâ€"options for restricting the availability of pesticides. Toxicology 2003;192:249â€“261.

A minimum pesticide list, based on the WHO essential drug list initiative, has been proposed.[99] Such a list would provide policy makers and small farmers with a source of unbiased information, and remove the most dangerous and obsolete pesticides from everyday use. Programs to restrict the availability of pesticides reduce mortality, although careful consideration of alternative self-harm agents is necessary to prevent the public from simply switching to another, equally deadly, agent.[4,241]

International Resources

Through the collaboration of the Society of Toxicology (USA) and the European Society of Toxicology, the International Union of Toxicology (IUTOX) was established in 1980 with the goal of fostering international cooperation in the field of toxicology. The IUTOX, which was initially formed by 8 national toxicology organizations, now includes more than 40 member societies from around the world. The IUTOX is a membership organization of toxicology professionals and functions to facilitate cooperation between toxicology societies. In addition to organizing the International Congress on Toxicology every 3 years, IUTOX has also sponsored the Congress of Toxicology in

Developing Countries, which provides opportunities for collaboration between the organizations and individuals in the developing world and their counterparts in industrialized nations.

The International Programme for Chemical Safety (IPCS) provides extensive information via the world wide web and numerous publications. The IPCS is supported by the WHO, the International Labor Organisation, and the United Nations Environment Programme, with many national organizations contributing useful information and resources. The Poisons Information Monographs provide extensive peer-reviewed information on chemicals, pharmaceuticals, poisonous plants, and poisonous and venomous animals. Although this information is not specifically evidence-based, this internationally reviewed document represents consensus opinion from poison control centers around the world. The IPCS materials are available in French, English, Spanish, and Portuguese.

The World Federation of Associations of Poisons Centres and Clinical Toxicology Centres produces a directory of poison centers, called YellowTox, which is a listing based on country. This resource identifies both organizations and individuals with recognized expertise in toxicology (Table 131-7 lists public access web sites that provide toxicology information).

Outside of the United States, numerous governments directly support toxicology information services. The benefit of such programs is that they may provide language appropriate information that is not available from Anglo-American sources.

TABLE 131-7. Examples of Open Access Web Sites That Provide Toxicology Information

1. The International Programme for Chemical Safety (WHO) http://www.who.int/ipcs/en/
2. International Union of Toxicology http://www.iutox.org/index.asp
3. The American Academy of Clinical Toxicology http://www.clintox.org/
4. TOXNET, National Library of Medicine (USA) http://www.toxnet.nlm.nih.gov/
5. The Canadian Network of Toxicology Centres (Canada) http://www.uoguelph.ca/cntc/
6. VIASALUS Toxicology, in Spanish and Catalan (Spain) http://www.viasalus.com/vs/B2P/cn/toxi/index.jsp
7. Centers for Disease Control (USA) http://www.cdc.gov/
8. YellowTox (WHO), a global directory of toxicologists http://www.who.int/ipcs/poisons/centre/directory/en/

Summary

Poisoning is a common cause of death throughout the developing world. Although many different xenobiotics exist in the developing world, pesticides are the most important source of mortality. In particular, paraquat, organic phosphorous compounds and aluminum phosphide are responsible for a disproportionate number of deaths. Conservative estimates suggest that at least three million cases of pesticide poisoning occur annually, resulting in at least 220,000 deaths.[143] The majority of deaths occur in the context of acts of deliberate self-poisoning. It is estimated that at least five million snakebites occur annually, producing at least 125,000 additional

deaths.[71]

Deliberate self-poisoning is a phenomenon that is increasingly reported in the developing world. Although the majority of these patients do not actually wish to die, the availability of highly lethal compounds in homes throughout the developing world leads to the remarkably high case fatality rates. Restricting access to the most dangerous compounds has been shown to reduce mortality, and implementing safe storage programs may further reduce the opportunities for impulsive acts of self-harm.

Epidemiologic information about regional and local poisoning patterns is needed to guide public health interventions. At present, poisoning epidemiology represents estimates derived from a minority of developing world countries. Assumptions regarding the generalizability of these data may not be true. Efforts to develop epidemiologic surveillance systems and establish harmonized definitions of poisonings will yield a more complete picture of global poisonings.

Lack of evidence to support many treatment interventions hinders public health policy in the developing world. Randomized controlled trials need to be conducted to critically evaluate accepted toxicology dogma, especially in the area of pesticide poisoning.[42] Economic analysis must also be conducted prior to recommending expensive, yet unproven, therapies.[103] Pending the implementation of such studies proven therapies, such as atropine for organic phosphorus pesticide poisoning and snake antivenoms, should be made available and affordable. In the case of pesticide poisoning, a coordinated international effort to restrict access to the most lethal agents is of paramount importance.[99]

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Chapter 132

Principles of Epidemiology and Research Design

Kevin C. Osterhoudt

In 1963, Reye and Johnson described a series of patients with encephalopathy and fatty degeneration of the liver.[25,37] Further anecdotal observation of similar patients allowed the development of a hypothesis that aspirin may be an etiologic factor in Reye syndrome (RS).[15] Given such a common exposure as salicylate therapy and such a rare disease as RS, how would researchers investigate whether an association between salicylate and RS truly exists?

In 1976, a case series suggested that enteral erythromycin given to neonates might predispose to infantile hypertrophic pyloric stenosis.[38] How might this association be confirmed given that pyloric stenosis typically occurs in approximately 1 of every 500 infants, but intake of erythromycin is unusual among this group? Gastric emptying has a long tradition as a method of gastrointestinal decontamination to treat patients after acute oral overdose. Hyperbaric oxygen therapy (HBO) is considered as a

therapy to prevent delayed neurologic sequelae from carbon monoxide (CO) poisoning. How can it be determined if these treatments actually offer a patient benefit? Advances in clinical medicine are usually achieved through a typical scientific method. First, astute clinicians make interesting observations. These observations lead to the generation of hypotheses. Research questions are analyzed with epidemiologic investigation, and initial studies are examined with methodologic scrutiny. Initial analytic techniques are improved, and confirmatory studies are performed. Ultimately, models relating cause to effect are formulated.

The field of medical toxicology is rapidly transitioning from a descriptive discipline to one of rigorous scientific exploration. New associations between toxic xenobiotics and diseases are being explored every year. Recent high-profile associations include those between thimerosal vaccine preservatives and childhood neurodevelopmental disorders, and insecticide exposures and childhood cancers and Parkinson disease. An understanding of basic principles of research design and epidemiology is required to interpret published studies and to lay the groundwork for future investigation in toxicology.

Epidemiologic Techniques Available to Investigate Clinical Problems

Table 132-1 lists different study formats.

Observational Design: Descriptive

A staggering array of xenobiotics are able to injure people, necessitating reliance of toxicologists on good descriptive data regarding toxic outcomes. The Toxic Exposure Surveillance System (TESS) of the American Association of Poison Control Centers (AAPCC) now has a database of over 36 million human poison exposure cases.[45] Descriptive case reporting serves a valuable

purpose in describing the characteristics of a medical condition or procedure and remains a fundamental tool of epidemiologic investigation. A case report is a clinical description of a single patient or procedure with respect to a situation. Case reports are most useful for hypothesis generation. However, single case reports are not generalizable, as the reported situation may be atypical. A number of case reports can be grouped, on the basis of similarities, into a case series. Case series can be used to characterize an illness or syndrome, but without a control group they are severely limited in proving cause and effect. In the now classic paper, Reye described 21 children with encephalopathy and fatty degeneration of the liver that characterized the syndrome that now bears his name.[37] Further descriptive data collection suggested that use of aspirin might be associated with RS,[15] but analytic study would be required to support that hypothesis. Published annual reports of TESS data state that their descriptive data are meant to â€œidentify hazards early, focus prevention education, guide clinical research, and direct training.â€•[45] In these roles, descriptive data are often underappreciated.

Cross-sectional studies assess a population for the presence or absence of an exposure and condition simultaneously. Such data often provide estimates of prevalenceâ€”the fraction of individuals in a population sharing a characteristic or condition at a point in time. These studies, particularly helpful in public health planning, have been extremely useful in monitoring common environmental exposures, such as childhood lead poisoning, or population-wide drug use, such as occurs with tobacco, marijuana, and alcohol. The US National Health and Nutrition Examination Survey investigations demonstrated that the percentage of children with blood lead levels >10 Âµg/dL decreased from 88.2% to 4.4% between 1976 and 1991, with the highest rates of plumbism among African American, low-income, or urban children.[5] An *analysis of secular trends* is a study type that compares changes in illness over time or geography to changes in risk factors. These

analyses often lend

circumstantial support to a hypothesis; however, because of the ecological nature of their design, individual data on risk factors are not available to allow exclusion of alternative hypotheses also consistent with the data. A prime example of an analysis of secular trends is Arrowsmith's finding that reports of RS declined between 1980 and 1985, coincident with a fall in sales of, or physician recommendations of, children's aspirin products.[3] This investigation added further confirmation to the etiologic role of aspirin in the development of RS but could not exclude alternative hypotheses such as a change in viral epidemic patterns.

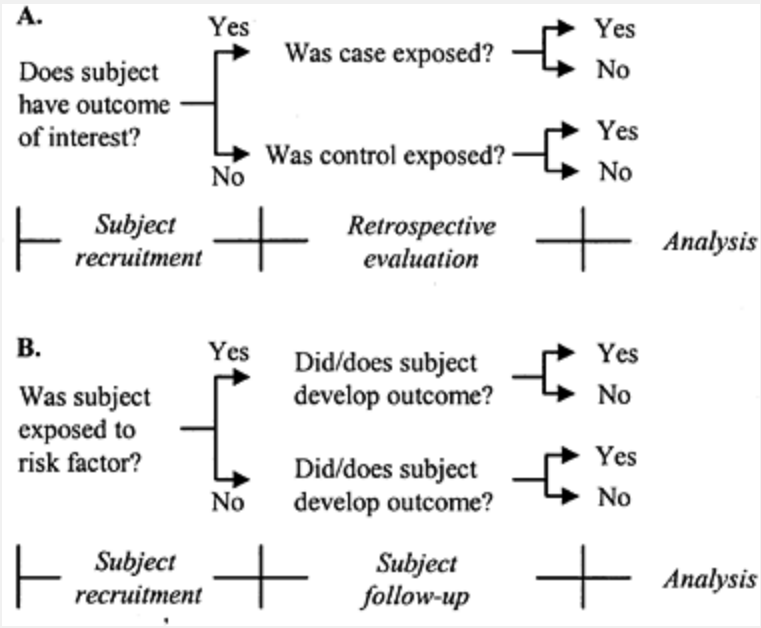

Figure 132-1. A. Schematic representation of the case-control study design. Subjects with an outcome or condition of interest are selected, along with control subjects, and then are evaluated for previous exposure to a risk factor of interest. B. Schematic representation of the cohort study design. Subjects are recruited based on the presence or absence of a risk factor

or exposure, then followed to see if they develop an outcome.

TABLE 132-1. Types of Epidemiologic Study Designs[a]

Experimental
Clinical trial
Observational: Analytic
Cohort
Case-control
Observational: Descriptive
Analysis of secular trends
Cross-sectional
Case series
Case report

[a]Study designs are listed in descending order from the design that offers the best epidemiologic evidence for association to that which offers the least.

Observational Design: Analytical

Hypotheses generated by theoretical reasoning or anecdotal association require analytic testing. Case-control studies and cohort studies are analytic techniques that use observational data, and each technique has its own advantages and disadvantages (Table 132-2). *Case-control studies* compare affected, treated, or diseased patients (cases) to nonaffected patients (controls) and look for a difference in prior risk factors or exposures (Figure 132-1A). Because subjects are recruited into the study based on prior presence or absence of a particular outcome, case-control studies

are always retrospective in nature. They are especially useful when the outcome being studied is rare, and they enable the investigation of any number of potential etiologies for a single disease.

RS is an illness well suited to case-control study. The incidence of RS peaked in the United States in the mid-1970s, and clustered together with viral epidemics of influenza A, influenza B, and varicella. Based on anecdotal observations in a series of patients, a hypothesis was formulated that salicylate may be an etiologic factor in RS.[15] Other putative contributory factors were also proposed, including viral infections, aflatoxin, pesticides, antiemetic drugs, and valproic acid. Exposures to salicylates were common in the 1970s, but the incidence of RS was less than 10 cases per million persons younger than age 18. In the epidemiologic investigation that served as a foundation for decades of research to follow, seven children diagnosed with RS were compared to 16 control children who were matched on the basis of age, gender, time, and viral symptoms.[40] Families were interviewed regarding the types and quantities of medications taken by the children. Salicylates were the only exposure found to be statistically different between cases and controls, and this became the first case-control study to identify increased odds of developing RS after aspirin therapy. Larger subsequent case control studies added confirmatory evidence to the association between salicylate use and RS.[17,23,44]

TABLE 132-2. Advantages of Case-Control versus Cohort Study Designs

Case-control study
Smaller sample required when outcome is rare
Reduced bias in outcome data
Can study many exposures simultaneously
Allows estimation of relative risk
May obviate need for long followup period
Cohort study
Provides more robust evidence of association
Reduced bias in exposure data
Can study many outcomes simultaneously
Allows direct calculation of incidence
Allows direct calculation of relative risk

Cohort studies compare patients with certain risk factors or exposures to those patients without the exposure, then follow these cohorts to see which subjects develop the outcome of interest (see Figure 132-1B). In this respect, they allow the comparison of *incidence* (the number of new outcomes occurring within a population initially free of disease over a period of time) between populations who share an exposure and populations who do not. They may be retrospective or prospective and enable the study of any number of outcomes from a single exposure. They are particularly well-suited to investigations in which the outcome of interest is relatively common. In circumstances when an outcome of interest is very uncommon, such as the case with RS, the large number of study subjects required might make a cohort study impractical. A suggested association between oral erythromycin administration to newborn infants and increased risk of idiopathic hypertrophic pyloric stenosis, which typically affects up to 3

individuals per 1000 live births, remained unstudied until a 1999 cohort study. Investigators analyzed a patient population in which 157 out of 282 infants born at a hospital in a 2-month period were treated with erythromycin prophylaxis because of a pertussis exposure.[20] Investigators separated

these patients into cohorts based on exposure to erythromycin and looked at the differences of pyloric stenosis rates between the 2 groups. Neonates treated with erythromycin were found to be at significantly greater risk of pyloric stenosis than untreated controls. Perhaps the most famous and ambitious cohort study was the Framingham Heart Study in which 5209 residents of Framingham, MA, ages 30â€“62 years have been followed for over 50 years. This study provided a useful tool for studying the incidence of lung cancer, stroke, and cardiovascular disease in those exposed to cigarette smoke[13] and other hazardous agents.

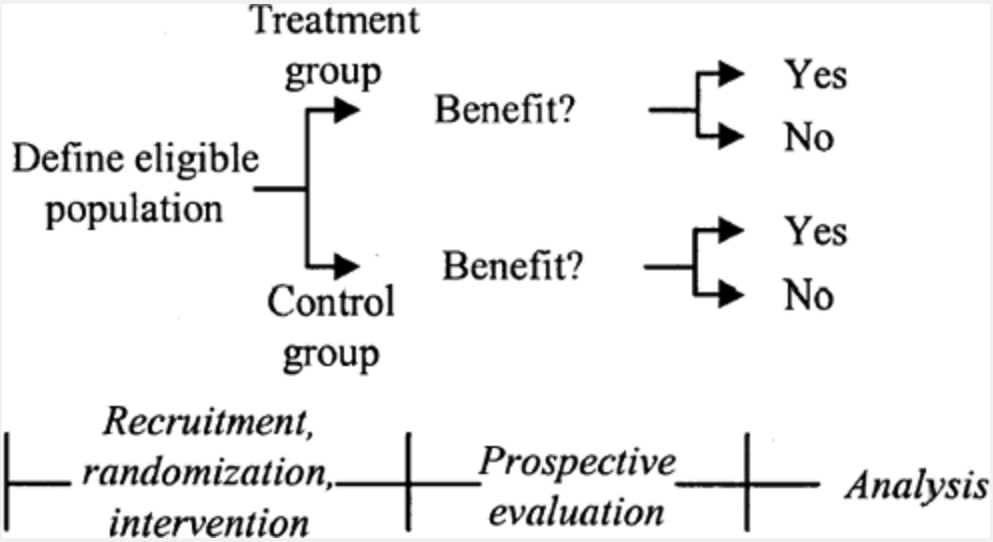

Figure 132-2. Schematic representation of the design of a randomized clinical trial.

Experimental Design

Experimental studies are those in which the treatment, risk factor, or exposure of interest can be controlled by the investigator to study differences in outcome between the groups (Figure 132-2). The prototype is the randomized, blinded, controlled clinical trial. Among epidemiologic study types, these provide the most convincing demonstration of causality. Clinical trials are used to measure the *efficacy* (the treatment effect within a controlled experimental setting) of treatment regimens and to draw inferences about the *effectiveness* of a treatment applied to the general population. Unfortunately, interventional studies are the most complex to perform, and several questions must be addressed by investigators before performing a clinical trial (Table 132-3). Human clinical trials have been especially difficult to apply to the practice of toxicology. Indeed, between 1992 and 1996, one author found only three such randomized clinical trials.[41] Table 132-4 lists characteristics of poisoned patients, which hamper attempts at clinical trials. Volunteer studies, using nontoxic drugs or subtoxic drug doses, are often used to circumvent many of the problems in controlling human poisoning studies; but it is typically difficult to apply results from these studies to the actual physiology of toxic overdose.

TABLE 132-3. Considerations in Designing a Clinical Trial

What is the question of interest?
What is the target patient population?
How will the safety of subjects be assured?
What is a suitable control group?
How will outcomes be measured?
What difference in outcomes between groups is considered important?
What is the analysis plan?
How many subjects will be required?
How will randomization and blinding be achieved and maintained?
How long a followup period will be required?
How will loss of study subjects be handled?
How will treatment compliance be evaluated?

TABLE 132-4. Difficulties in Applying Clinical Trials to Human Poisoning

It is unethical to intentionally â€œpoisonâ€• subjects.
Poisoned patients represent a broad spectrum of demographic patterns.
A wide variety of poisons exist.
Exposures to any single poison are usually limited.
A limited number of poisoned patients are available at any one study site.
Uncertainty often exists as to type, quantity, and timing of most poison exposures.
Poisoning typically results in a relatively short course of illness.

Perhaps the best way to demonstrate an etiologic association between salicylate use and RS would be to perform a randomized, double-blinded, controlled clinical trial. Patients with influenza and fever could be randomly treated with salicylate or placebo, and the incidence of RS in both treatment groups could be determined. However, with such a strong association noted from case-control studies, and with suitable alternative antipyretic medications available, such a study would be unethical. As toxicologists strive to find evidence for, or against, the traditions of clinical practice, several important clinical trials have been published. Among them are many important examples and lessons in epidemiologic study design.

One trial attempted to evaluate whether or not corticosteroids might be beneficial in preventing esophageal strictures secondary to circumferential caustic injury of the esophagus.[2] Because of the inherent difficulty in recruiting eligible patients from a single institution, only 60 patients with esophageal injury were recruited over an 18-year period. These patients were randomized to therapy with or without corticosteroids and followed for the development of stricture. Ten of the 31 patients treated with

corticosteroids developed strictures in comparison to 11 of 29 control patients. The authors concluded that there was no apparent benefit from the use of corticosteroids to treat children who have ingested a caustic substance. A second study challenged our notions of gastrointestinal decontamination and randomized 876 acutely poisoned patients with respect to gastric emptying procedures.[35] Outcomes measured were clinical course, length of hospital stay, and complications. The investigators concluded that routine use of gastric emptying did not provide additional therapeutic benefit beyond that offered by the use of the antidote, activated charcoal. A third representative study demonstrated benefit from HBO therapy regarding the prevention of delayed neurologic sequelae after CO poisoning.[42] Sixty patients with acute CO poisoning were randomized to either ambient pressure or HBO, then followed for the occurrence of neurologic dysfunction. The conclusions of each of the three aforementioned studies have encountered tremendous academic dissection and debate. Certain concerns with the methodology and analysis of these studies are examined later in this chapter to illustrate epidemiologic concepts. Additionally, each of these studies is described in more detail in the relevant chapters of this text (Chaps. 100, 8, and 120).

Measures Used to Quantify the Strength of an Epidemiologic Association

The objective of analytic studies is to define and quantify the degree of statistical dependence between an exposure and an

outcome. Such associations are ideally represented by the relative risk of developing an outcome if exposed in comparison to being unexposed. Thus, the *relative risk* can be defined as the incidence of outcome in exposed individuals compared to the incidence of outcome in unexposed individuals. The relative risk can be

calculated directly from cohort or interventional studies. However, in a case-control study, an investigator chooses the numbers of cases and controls to be studied, so true incidence data are not obtained. In case-control studies an *odds ratio* can be calculated, and the odds ratio will provide an estimate for relative risk in situations in which the outcome is rare, such as when the outcome occurs in fewer than 10% of exposed individuals. Figure 132-3 demonstrates the calculation of relative risk or odds ratio from analytic studies.

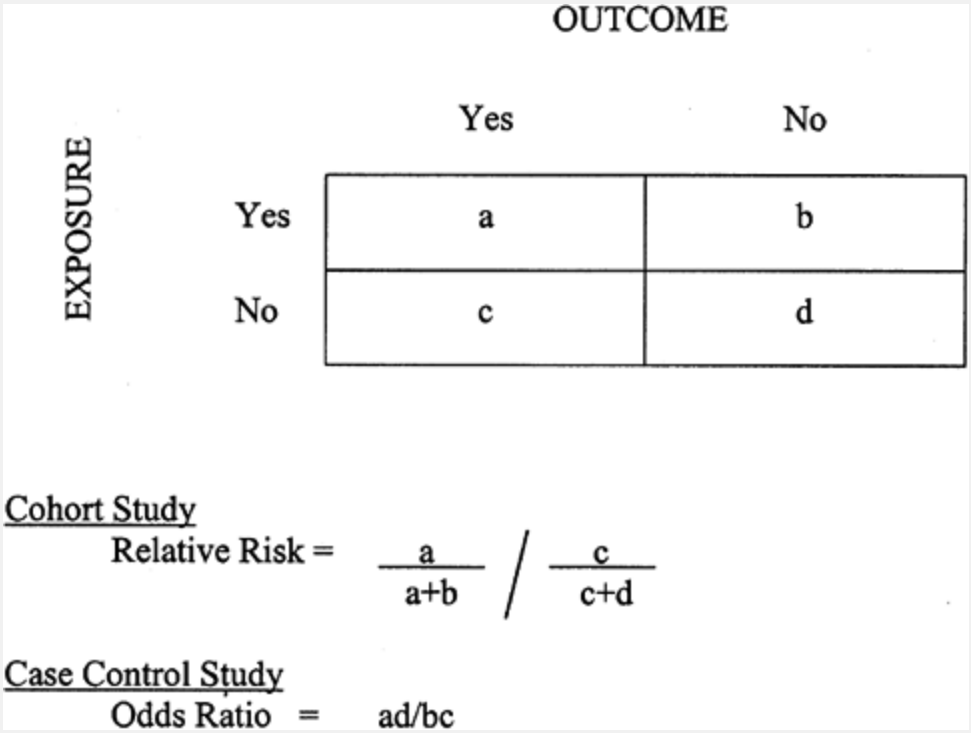

Figure 132-3. Use of a 2 Ã— 2 table to calculate or estimate relative risk from analytic studies. In cohort studies, study subjects are selected on the basis of exposure. In case-control studies, subjects are selected on the basis of outcome. The letters a, b, c, and d represent the number of subjects either exposed or unexposed to a â€œrisk factorâ€• or treatment, with or without the outcome of interest. The odds ratio

estimates the relative risk if the outcome of interest is rare.

A relative risk of 1.0 signifies that an outcome is equally likely to occur whether an individual is exposed or not and implies that no association exists between the exposure and the outcome. A relative risk approaching 0 suggests that an exposure is a marker of protection regarding the outcome, and a relative risk approaching infinity suggests the exposure predicts a tendency toward the outcome. In the previously described case-control investigation of the link between salicylate use and RS, all of the 7 case subjects had used aspirin compared to only 8 of 16 controls.[40] The odds ratio calculated from these data approaches infinity and suggests a strong association between exposure and outcome. In the described clinical trial of therapeutic corticosteroids (the â€œexposureâ€•) in the prevention of esophageal strictures (the â€œoutcomeâ€•), 10 of 31 treated patients developed strictures compared to 11 of 29 untreated patients.[2] This relative risk calculation approximates 1 and seemingly demonstrates little benefit from corticosteroid therapy.

Measures Used to Quantify the Significance of an Epidemiologic Association

Analytic studies are performed to test hypotheses, typically that an exposure is associated with an outcome. The presence of such association in any given study has a number of possible explanations, as detailed in Table 132-5. The goal of statistical analysis is to determine the degree to which chance can be excluded as the true reason the results of the study were obtained. By convention, statistical analysis typically tests the *null hypothesis*â€”the hypothesis that there is no association between exposure and outcome.

Because analytic studies involve only a sample of the total population, they contain two types of inherent error. *Type I error*, also referred to as alpha (Î±) error, is the likelihood that an investigator may conclude that an association exists when none truly does. *Type II error*, or beta (Î²) error, is the possibility that an investigator will be unable to find an association when one is really present. The most commonly reported measures of type I error in published toxicology studies are the *p*-value and the confidence interval (CI). Statistical significance has customarily, but not necessarily, been defined as having less than a 1 in 20 chance of conducting a false-positive study. Therefore, a type I error of less than 5%, which corresponds to a *p*-value of less than 0.05, is usually deemed â€œstatistically significant.â€•

Perhaps a more informative description of the significance of an association is provided through the CI. The CI not only provides a test of statistical significance, it also offers information pertaining to the degree (and possible range) of differences observed. In an unbiased study, the 95% CI provides a range between which, if the study could be repeated an infinite number of times, the observed magnitude of effect would lie 95% of the time. One study reported that no toddlers ingesting 1 or 2 calcium channel antagonists became seriously ill, but a subsequent analysis of the CI around this small set of data demonstrated

that the true incidence could be as high as 18%.[32] A CI around a relative risk or odds ratio is not statistically significant if it includes 1.0, and the narrower the CI the more precise the estimate of the magnitude of effect.

TABLE 132-5. Types of Associations between Exposures and Outcomes That May Be Found with a Clinical Study

No Association	The outcome is independent of exposure.
Artifactual Association	
Chance	The association demonstrated by the study resulted from random error.
Bias	Systematic error in the study led to the noted association.
Indirect Association	The association is real, but not truly cause and effect (confounding).
Causal Association	The outcome is dependent on the exposure.

TABLE 132-6. Considerations in Choice of Sample Size

	Sample Size	
	Large	Small
Pros	• Able to detect associations of small magnitude • Less susceptible to some biases • More robust analysis	• Less work • Less cost
Cons	• More work and more cost	• Might not detect associations of small magnitude • More susceptible to biases associated with patient differences

The likelihood that a study will find a difference if one truly exists is termed statistical *power* and relates to the likelihood of a false-negative study (type II error). Power is usually artificially set by an investigator before a study is performed and is typically set at 80% or 90% to practically limit the number of study subjects needed. Table 132-6 lists considerations applicable to choice of sample size. The sample size of a study is determined by the frequency of the exposure and outcome within the study population, the strength of association deemed clinically relevant, and the amount of error deemed acceptable in the study. Because

power is often set relatively low, it is difficult to state that an association does not exist. It is more appropriate to state that a study was unable to reject the null hypothesis to find an association. In the ongoing controversy regarding the utility of HBO in the treatment of acute CO poisoning, three early randomized studies had alleged benefit,[11,28,42] and two had no benefit.[36,39] Conventional parameters for statistical significance suggest that, if unbiased, the positive studies met a greater burden of evidence than did the negative studies. A more recent multicentered clinical trial found HBO to protect against CO induced cognitive sequelae at 6 weeks (odds ratio 0.45 [95% CI: 0.22â€“0.92]), and at 12 months.[46]

Differentiation Between Clinical Significance and Statistical Significance

The finding of a low *p*-value indicates a statistically high level of confidence that a difference between study groups exists but offers no indication that the difference is clinically important. The interpretation of statistical versus clinical significance is often facilitated through calculation of confidence intervals. Small actual differences between two groups can become statistically significant if large numbers of subjects are studied. Likewise, impressive associations of cause and effect can seem trivial if few subjects are in a study. The clinical significance of an association is left to the judgment of the individual interpreting a study. Ideally, a working definition of clinical significance is developed before a study is performed.

In the noted study of corticosteroids and corrosive injury of the esophagus, 64% of control subjects required esophageal replacement versus 40% of treated subjects.[2] The investigators' calculation of the *p*-value for this comparison is greater than 0.05.

Many would interpret a reduction in esophageal replacement by approximately one-third to be potentially clinically important, yet it is unlikely that this study had statistical power to find such an association. Likewise, in a study suggesting no benefit from gastric emptying after acute overdose, when patients presenting within 1 hour of overdose were examined, 15% of treated patients showed improvement versus 4% of controls.[35] Again, statistical significance was not achieved, but the clinical significance of these data is subject to speculation.

Methodologic Problems Found Within Clinical Studies

Calculation of a *p*-value or confidence interval does nothing to assess the adequacy of study design. These measures are used to quantify the influence of random error, or chance, on research findings. Clinical research involving patients is particularly susceptible to *bias*, which can be defined as systematic error in the collection or interpretation of data. Because such error can lead to an inappropriate estimate of the association between an exposure and an outcome, careful evaluation of potential biases affecting a clinical study is of paramount importance.

Selection bias refers to error introduced into a study by the manner in which subjects are selected for inclusion in the study. This type of bias is most problematic for retrospective studies in which exposures and outcomes have both occurred at the time of subject recruitment. Selection bias may be introduced into a prospective clinical study if the study fails to enroll potential subjects, or if potential subjects refuse to participate, on a systematic basis. Selection bias may even influence the results of clinical trials. In the 1995 trial that found no difference in outcome between acutely poisoned patients treated with gastric emptying and patients from whom gastric emptying was withheld, all patients presenting to the emergency department (ED) after acute

overdose were enrolled.[35] Because most patients with poisoning exposure are likely to do well with minimal support,[45] selection of patients on this basis might be expected to bias this study to find no effect. Reasoning suggests that the patients most likely to benefit from gastric emptying are those with life-threatening toxic ingestion presenting within the first hour after overdose. As mentioned previously, subgroup review of the results of this paper suggests clinical benefit within this group of patients, but without conclusive power.

Information bias refers to error introduced into a study as a result of systematic differences in the quality of data obtained between exposed and unexposed groups, or between those with and without the outcome of interest. Several distinct types of information bias may exist. Affected and nonaffected individuals may have differential memories regarding exposures, so recall bias is a concern in retrospective studies. The potential for *recall bias* is frequently cited as criticism of early retrospective case-control studies of aspirin as an etiologic factor for RS, in which families were asked to recollect their children's aspirin use history. Critics suggest that the parents of children affected by RS might be more vigorous in their recall of exposures than the parents of unaffected children. Similarly, *interviewer bias* may occur if study personnel differ in how they solicit, record, or interpret information as a result of knowledge of the subjects' status regarding exposures or outcomes.

Prospective studies may be troubled by loss to follow-up, especially if subjects are lost from the study for reasons relating to either exposure or outcome such as when subjects withdraw from a study because they are feeling better, or are â€œlostâ€• because they die. *Misclassification bias* occurs when investigators incorrectly categorize subjects with respect to exposure or outcome. In a retrospective study of 378 children regarding the predictability of caustic esophageal injury from clinical signs and

symptoms, it was found that 11 of 80 asymptomatic children had significant burns.[14] There is a possibility that this â€œasymptomaticâ€• child was misclassified because of lack of rigorous written documentation of symptoms or signs within the medical charts.

Bias is best minimized through careful study design. It is important to precisely define the study question and the population at risk and to carefully define rigorous inclusion and exclusion criteria. The outcome should also be defined precisely. During data acquisition the best way to reduce bias may be to keep study personnel gathering exposure data blinded to outcome, and vice versa. Often, it may also be advisable to keep study subjects unaware of their status within a study to the extent that it is ethical (thus, â€œdouble-blindedâ€•â€”neither investigators nor subjects are aware of the subjects' status within a study). Use of placebos or â€œsham treatmentsâ€• is a way to facilitate blinding. One of the strongest criticisms of a 1995 trial of HBO for the prevention of delayed neurologic syndromes after CO poisoning[39] has been the failure to blind patients and investigators to the treatment in question,[30] a flaw that was corrected in a follow-up study published in 2002.[46] It is inevitable that some degree of potential bias will be present in any clinical study. Such bias should be reviewed in analysis, and estimations of its magnitude and direction (bias toward or away from rejection of the null hypothesis) should be considered.

Unlike selection and information biases, which are errors introduced into studies primarily by the investigators or subjects, confounding is a special type of problem that may occur within a study as a result of interrelationships between the exposure of interest and another exposure. *Confounding* is a bias wherein an observed association is not a product of cause and effect but instead results from linking of the exposure of interest to another associated exposure. Studies pertaining to adverse effects of drugs of abuse are especially prone to confounding by variables

such as concomitant caffeine use, alcohol use, tobacco use, nutritional deficiency, and/or psychiatric illness. Analytic studies may restrict characteristics of enrolled subjects or match subject characteristics between comparison groups in an effort to reduce confounding. Accordingly, it has been suggested that future studies on delayed neuropsychiatric manifestations following CO poisoning control for potential confounding from depression and cyanide exposure.[27] Randomization is an important method to assure that unsuspected confounding factors are equally distributed between treatment groups within interventional studies. During data analysis, confounding can often be controlled through stratification of data into subgroups or through multivariate analysis techniques.

Biases Inherent in Studies Using the American Association of Poison Control Centers Database

The TESS database of the AAPCC is an ambitious effort to catalog and describe the epidemiology of poisoning in the United States and Canada. These data serve to help identify new poisoning epidemics, focus prevention and education efforts, guide demographic and economic poisoning analyses, and guide implementation of public health policies. It is a desirable goal to use this database in defining the scope of toxicity for particular xenobiotics and as a clinical research tool. In this regard, it is important to understand the biases inherent in the current database.

It has been suggested that selection bias might exist within poison center (PC) data if poisoning is unrecognized as a cause of illness or if a caregiver has no questions pertaining to the management of a recognized poisoning.[18] Indeed, a survey of 170 emergency physicians in Utah found that 53% admitted to using a PC for

symptomatic acute overdoses, and only 10% contacted PC for the purposes of reporting cases to the national database.[9] Such selection might result in a bias of PC data toward more severe cases. On the other end of the spectrum, investigation has found selection bias in PC data suggesting that fatal poisonings may be severely underrepresented.[21] It is interesting to note that in a 2004 report of the Institute of Medicine,[24] the estimated range of annual fatal poisonings in the United States was from approximately 1000, derived from AAPCC data, to over 30,000, derived from other databases. A study of potential spectrum bias in PC utilization found that one ED reported 95% of cyclic antidepressant overdoses, 33% of venomous snakebites, and only 3% of inhalation exposures.[19] Further complicating the interpretation of PC data are the findings that such data may also be biased regarding geographic distribution of callers,[1] age,[34] ethnicity,[1,10,34,43] and socioeconomic status.[43]

Knowledge of information bias within TESS data is less well-characterized. Phone interviews of callers, many under duress, by PC personnel is certain to be subject to recall and interviewer bias. A comparison of rural hospital chart data to the TESS database demonstrated deficiencies in PC reporting and in clinical information transfer to the TESS database.[22] Loss to follow-up remains a problem for many PC, and misclassification of poisonings by healthcare providers inadequately trained in medical toxicology remains too common.

Despite the large volume of descriptive poisoning data available, it has proven difficult to derive valid, clinically useful conclusions from either the TESS database or from published case reports.[6] One suggested means through which to minimize information bias in descriptive toxicology is through the use of improved data collection charts.[7] Other researchers have found it useful in clinical studies to transform PC data collection from a passive to an active process through use of specific research instruments.[29] Further efforts are required to reduce and to quantify the impact

of selection, interviewer, recall, misclassification, and information biases within PC data to optimize the value of this important resource.

Evidentiary Criteria Used to Link Cause and Effect

As was illustrated in Table 132-5, association of an exposure to an illness does not necessarily equate to cause and effect. In assessing causation it must be determined if bias is present in the selection or measurement of exposure or outcome. If a study is unbiased, the role of chance in the occurrence of the observed association must be explored. If an association is unbiased, unlikely to result from random error, and is not subject to confounding, then assumptions

regarding to causation can be derived. Table 132-7 provides a list of evidentiary criteria that are often used to support causation.

TABLE 132-7. Criteria Supporting Causation

Study design	Was the association demonstrated in a well-designed study?
Temporality	Does the cause precede the effect?
Strength	What degree of relative risk was demonstrated in the analysis?
Dose response	Does an increased presence of risk factor correlate togreater or more frequent

	effect?
Consistency	Does the cause and effect hold true in different studies, locations, and populations?
Plausibility	Is the association in accordance with current scientific knowledge?
Specificity	Does the effect occur without the cause in question, orvice versa?

Many toxicologists deem clinical trials indicating a lack of benefit from gastric emptying, or indicating a therapeutic benefit of HBO therapy for CO intoxication, unconvincing because of the degree of bias present in all relevant published clinical trials. Study design flaws such as bias and confounding are problematic for any epidemiologic study, and after decades of investigation, they still raise skepticism regarding the causative role of salicylates in RS. A wealth of evidence exists to support an etiologic relationship for salicylates regarding RS. Salicylate administration in the prodromal phase of a viral illness was temporally related to the development of RS. The strength of association, as measured by the odds ratio from case-control studies, was enormous in epidemiologic terms. A study by a US Public Health Service Task Force determined that the adjusted odds ratio for an increased risk for RS if exposed to salicylate in the prodromal illness was 40.[23] Because of the rare nature of RS, this measure approximates that salicylate-exposed individuals were at 40 times greater risk of developing RS than those not exposed to salicylate. Concerns of bias in early analytic studies were addressed in further studies,[12] and the association between salicylate use and RS was consistent in refined analysis. Data from a number of studies suggested a

dose-response correlation between salicylate use and RS.[23,40] Finally, the association was consistent throughout different studies performed in different populations. After reviewing the strong epidemiologic evidence linking salicylate use to RS, in 1986 the US Food and Drug Administration (FDA) required labeling of aspirin warning of the possible association. Further evidence supporting the results of earlier case-control studies was the observation that the incidence of RS has fallen dramatically in apparent parallel to a decline in salicylate use.[4,16]

However, in medical toxicology it is virtually impossible to prove causal relationships beyond any doubt. The goal is to build empiric evidence so that associations can be confirmed or refuted with conviction. To some physicians the link between salicylate therapy and RS remains a matter of debate. A recent review of 49 cases of diagnosed RS in Australia found that most of the cases were able to be reclassified as other medical conditions such as inborn errors of metabolism.[31] Advances in medical technology, and a lack of absolute diagnostic criteria that could be applied to all possible RS patients, suggest that significant misclassification bias exists in most of the early RS research. Additionally, it has been suggested that antigenic shift within influenza B and varicella viruses may be an uncontrolled confounding variable in RS research.[26] Despite these dissenting views, the overwhelming majority of evidence suggests that the association between salicylate therapy and development of RS is an important one. Of note, aspirin was taken by millions, and yet the peak incidence of RS was less than 10 cases per million. It remains unsolved whether salicylate use can cause RS in physiologically normal children with viral illness or, perhaps, whether there exists an unidentified metabolic abnormality that may place a specialized population at risk.

Evaluation of Diagnostic Tests and Criteria

In clinical practice it is often useful to have a test, which may be a laboratory result or clinical paradigm, to help arrive at a diagnosis or predict an outcome. For instance, historical questionnaires, capillary blood lead levels, and venous blood lead levels might all be used to identify children at risk of neurocognitive injury from plumbism.[8] However, each of these approaches is likely to have certain disadvantages in terms of effort, cost, discomfort, and/or accuracy. Targeting lead evaluation and therapy at children on the basis of exposure history is expected to be easy and inexpensive, but may not identify some children with significant poisoning; thus, the test may be susceptible to being falsely negative. Capillary blood testing is more costly and uncomfortable and may be susceptible to false-positive test results because of environmental lead dust present on fingertips. The possibility of false-positive or false-negative results must be considered with any diagnostic test (Figure 132-4).

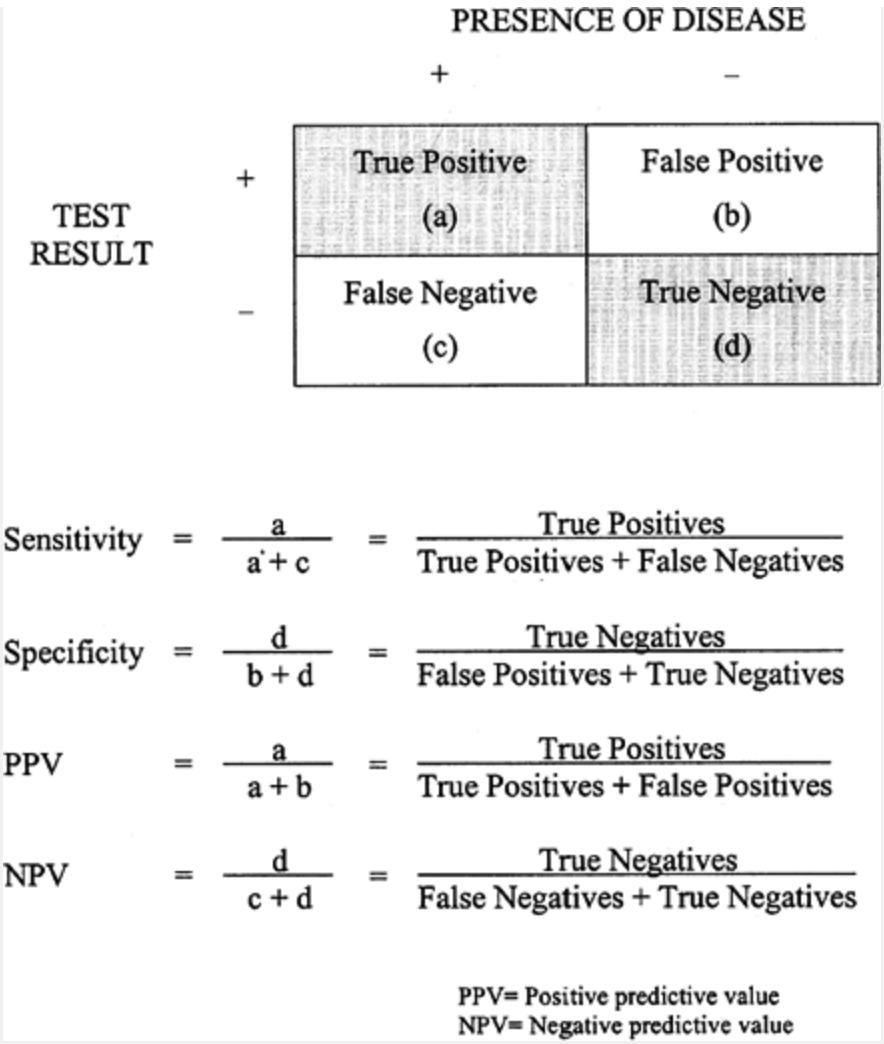

Figure 132-4. Possible results of diagnostic testing and the statistical characteristics used to describe the utility of diagnostic tests. The letters a, b, c, and d represent the numbers of tested individuals with or without the disease of interest.

The utility of diagnostic testing is often described in terms of sensitivity, specificity, predictive value of a positive test (PPV), and predictive value of a negative test (NPV). A cross-sectional

design is often used to study diagnostic tests, as we seek to determine the prevalence of positive tests among the diseased (*sensitivity*), and the prevalence of negative tests among the healthy (*specificity*). A perfect test would be highly sensitive and specific, but this is seldom possible in medical toxicology. A highly sensitive test is often used in screening programs because they rarely lead to false-negative diagnoses. Specific tests are typically used to â€œrule-inâ€• a diagnosis, as they rarely yield false-positive results. Whereas sensitivity and specificity are inherent properties of a diagnostic test applied to a given population; the probability of disease, based on the results of a test, is highly dependent on the prevalence of disease within the population being tested. The PPV is the probability of having disease in a patient with a positive test; the NPV is the probability of not having disease when the test result is negative. A number of studies have tried to examine the utility of vomiting, leukocytosis, hyperglycemia, total iron-binding capacity, and radiographic findings in predicting toxicity after acute iron overdose. In a retrospective assessment of 40 adults with oral iron overdose, vomiting was found to predict a serum iron level above 300 Âµg/dL with a sensitivity of 84%, specificity of 50%, NPV of 44%, and PPV of 87%.[33] This suggested that the presence of vomiting should raise concern for iron toxicity but that the lack of vomiting was not particularly reassuring. Figure 132-4 illustrates the calculation of the sensitivity, specificity, PPV, and NPV. It is important to remember that these calculations, too, are subject to bias and that these calculations are best presented with confidence intervals.

Summary

Medical toxicology has embraced the vision of incorporating â€œevidence-based, or literature-based, medicineâ€• into practice. Randomized clinical trials, although a noble goal, are rare and have proven difficult to perform within the discipline. As toxicologists move beyond descriptive data reporting, there

remains great potential for scientific advancement in the field of toxicology via observational, hypothesis-testing, clinical research. Clinical investigators are charged with the imperative to perform studies based on sound epidemiologic principles. All studies, by nature of population sampling, are at the mercy of chance, but such random error can be quantified using statistical techniques. Systematic error (bias) can be limited, but not entirely excluded, through careful study design. Clinicians interpreting published toxicologic research need to thoroughly evaluate a study's research objectives, design, data acquisition, analysis, and conclusions before applying the results to patient care (Table 132-8). Future epidemiologic investigation should allow more valid conclusions to be drawn regarding the associations between exposures and outcomes, or regarding the value of treatments for poisonings, discussed in the preceding chapters of this text.

Galen, an influential physician from the second century, remarked of his clinical trial, â€œAll who drink of this remedy recover in a short time, except those whom it does not help, who all die. Therefore, it is obvious that it fails only in incurable cases.â€• Unfortunately, error in contemporary clinical investigation of poisoning tends to be more insidious than the error in logic in Galen's conclusion, and skillful scrutiny of published research remains an important endeavor.

TABLE 132-8. Questions to Consider when Evaluating a Study

Research objectives
What is the study question?
What is the studied population?
Study design
What type of study was performed?
How were subjects recruited and enrolled?
Why were subjects excluded?
What was the nature of the comparison group?
Data accrual
How were the data collected?
Are the exposures and outcomes clearly defined?
Are the observations reliable and reproducible?
Was randomization and/or blinding used?
Were subjects lost to followup?
Analysis
Are the results statistically significant?
Are the results clinically significant?
Are potential confounding variables controlled?
Was the study powered to detect important differences?
Conclusions
Are the conclusions justified by data?

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Chapter 133

Adverse Drug Events and Postmarketing Surveillance

Louis R. Cantilena Jr.

A 57-year-old man was brought to the emergency department (ED) by ambulance with a history of 3â€“4 days of progressive weakness, sore muscles, and 1 day of dark colored urine. The patient had been well until the onset of these symptoms. There was no history of illicit drug use, recent surgery or infection, or significant exercise or trauma. His past medical history was significant for mild hypertension, hypercholesterolemia, and smoking. The patient was treated with lovastatin for hypercholesterolemia for 2 years and was switched 9 days earlier from hydrochlorothiazide to mibefradil for hypertension during a routine office visit to his physician. Physical examination revealed a slightly lethargic, well developed male in no distress, blood pressure 110/65 mm Hg, pulse 53 beats/min, respirations 20 breaths/min, and temperature 100.4Â°F (38.0Â°C). Laboratory evaluation showed the CBC to be within normal limits, potassium 6.1 mEq/L, serum bicarbonate 13 mEq/L, BUN 22 mg/dL, and creatinine 5.2 mg/dL. A serum CPK returned

elevated at 65,100 IU. The urine analysis was positive for myoglobin.

A working diagnosis of probable drug-induced rhabdomyolysis was established, all medications discontinued, and the patient was admitted for further treatment of acute renal failure associated with rhabdomyolysis. The Î²-hydroxy-Î²-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitor lovastatin, one of several statin drugs available for the treatment of hypercholesterolemia was suspected as the offending agent as this adverse drug event (ADE) had been previously associated with the statins. What puzzled treating physicians at the time of admission however was the fact that the patient had been treated with the same dosage of lovastatin for 2 years without prior evidence of adverse effects. Attention turned toward the newly started medication, mibefradil, a calcium channel blocker (CCB) approved as an antihypertensive agent by the Food and Drug Administration (FDA) in August 2001. With the assistance of a clinical pharmacology and medical toxicology consultation service, a working hypothesis was developed that mibefradil interfered with the metabolism of lovastatin, raising the serum lovastatin concentration leading to â€œstatin-inducedâ€• rhabdomyolysis. Since the inhibition of cytochrome oxidase by mibefradil was described in its FDA approval, a specific warning regarding a potentially serious metabolism-based drug interaction with certain statins was added to the mibefradil drug label.

This case demonstrates an ADE associated with a specific drug that was not fully appreciated at the time of drug approval and marketing and was not identified until approximately 4 months following the drug's approval. In fact, numerous case reports of suspected drug-drug interaction problems were reported to the FDA within a few months of the initiation of marketing of the agent. The mibefradil drug label was modified and â€œDear Doctorâ€• letters were sent out to warn of these newly discovered drug interactions.[10] The list of known drug interactions for mibefradil grew rapidly to well over 30 agents in a short period of time. Because of this expanding list of potentially serious drug interactions and the availability of alternative therapies for the cardiovascular indications of the agent, mibefradil was withdrawn from the market less than 1 year

after approval.

This chapter focuses on drug-induced disease resulting from adverse drug events (ADEs) caused by both inherent drug toxic effects and as a consequence of unintentional drug interactions. The topics covered in this chapter include a discussion about the diagnosis of drug-induced disease, an overview of the FDA process for drug approval, postmarketing surveillance of ADEs, and the role of the medical toxicologist in the discovery, reporting, and prevention of ADEs.

ADEs are defined as an untoward effect or outcome associated with use of a drug. In this chapter, the word â€œdrugâ€• will be used for a pharmaceutical product and includes prescription and nonprescription products, and dietary supplements.

In the United States, all prescription and nonprescription products must be approved by the Food and Drug Administration (FDA) prior to marketing and sale. For complex reasons, dietary supplements fall outside of this legal requirement. Regulation of these products is discussed later in this chapter and in Chap. 43 .

History of the United States Drug Approval Process

Today in the United States, approvals of new therapeutic agents are occurring at an unprecedented rate. The evolution of the system that currently exists for review of drug applications and approval of new therapeutic agents is the result of relatively recent changes in the US drug approval law. The US drug approval law was closely linked to a series of medical product disasters that occurred during the 20th century in the United States. Before 1900, there was no legal requirement for a company to test a product for safety or efficacy or even to

make valid claims in the drug label. Products such as aspirin-containing heroin were sold as cough syrup. Wine with cocaine was marketed to enhance sales of the alcoholic beverage. Further, there was no legal

requirement for systematic testing of products to determine content or the presence of possible adulterants in product formulations. The Food and Drug Act of 1906 required pharmaceutical manufacturers to meet a standard for the concentration and purity of the drugs they marketed. However, the burden of proof was on the FDA to show that the drug was incorrectly labeled or that the advertising or label was false or misleading.

The Food, Drug and Cosmetic Act of 1938 resulted from a tragedy in which more than 100 patients (mostly children) died from poisoning by a excipient of an oral solution of sulfanilamide. A pharmaceutical company, in an attempt to improve the palatability of a sulfanilamide product for pediatric formulations, introduced the solvent diethylene glycol into the formulation. Diethylene glycol is a sweet-tasting but nephrotoxic hydrocarbon. Only after almost a full year of marketing were cases of renal failure and death reported in sufficient numbers to alert authorities to the extremely toxic nature of the product. The Food Drug and Cosmeti Act of 1938 accomplished the following:

- Required companies to list the ingredients of the product on the product label.
- Required companies to provide the known risks concerning use of the product to physicians or pharmacists.
- Made illegal the misbranding of food or medical products.
- For the first time required companies to test their products for safety before being sold.

Drugs already marketed before 1938 were exempt from the requirement (Chap. 1).

An application in the early 1960s for the approval of Î±-*N* - phthalylglutaramide (Thalidomide), a sedative that had already been marketed in Europe, was submitted to the FDA. The sedative drug had a rapid onset and short duration of action, did not affect ventilation, did no

cause a morning-after effect, and was inexpensive. A medical officer at the FDA (Dr. F. Kelsey) delayed approval by asking the sponsor to clarify several issues in the reportedly poorly organized new drug application (NDA). In the interim, an unusual teratogenic effect, phocomelia, or limb misdevelopment, was linked in Europe to the use of thalidomide. Congressional hearings resulted in the Kefauver-Harris Act of 1968, whicl required a drug manufacturer or sponsor to do the following:

- File an investigational new drug application (IND) before beginning a clinical study with a drug in humans.
- Demonstrate that the drug was effective for the condition that it was being marketed to treat.
- Provide adequate directions for safe usage of the drug.

Once again, the act did not exempt drugs that were already on the market.

Subsequent US laws that affect the FDA's review and approval of product include the following:

- The Orphan Drug Act of 1983, which provides financial incentives to drug manufacturers to develop drugs for the treatment of rare diseases and conditions (see http://www.fda.gov/orphan/designat/recent.htm for a list of drugs that have been approved under the Orphan Drug Act.).
- The Prescription Drug User Fee Act (PDUFA) of 1992, which required manufacturers to pay user fees to the FDA for NDAs and supplements to enable the FDA to hire additional reviewers and accelerate the review process.
- The Dietary Supplement Health and Education Act (DSHEA amendment) of 1994, which removed from FDA the authority to require proof of safety or efficacy prior to marketing of products considered dietary supplements (including herbal remedies). Only

when a specific health claim is made by the product's manufacturer does the FDA have premarketing approval authority. Furthermore, rather than placing on the manufacturers the burden of proof for safety and efficacy of a product, the FDA is required to determine tha a product is unsafe to prevent sale and distribution in the United States.

- Section 112 of the FDA Modernization Act of 1997, allowed for an accelerated drug approval process for agents to treat life-threatening illnesses such as AIDS and cancer if the agent has the potential to address medical needs unmet by currently available drugs. Many of the accelerated drug approvals rely on efficacy results derived from surrogate markers linked to the ultimate indication for the drug. For example, the protease inhibitors were approved on the accelerated track for the treatment of AIDs because of their ability to reduce HIV viral load.
- The Pediatric Research Equity Act of 2003 requires manufacturers to study the pediatric population drugs being submitted for approval for a claimed indication. As a result more data from children is being provided to guide therapeutic use of medication in this patient group.

A complete listing of the laws and statues enforced by the FDA is found on the FDA web site.[12]

A current area of controversy is whether or not changes to FDA law resulting in shorter review times for NDAs have led to an increase in the need to withdraw unsafe medications.[13 , 27 , 33] Recent drug product withdrawals of cyclooxygenase-2 (COX-2) inhibitor antiinflammatory agents have resulted in congressional hearings on the review practices and monitoring of drug safety by the FDA. Depending on the safety signa generated and the specific nature of the ADE, it is possible that in some cases there may be as much as a 10â€“15-year lag in the postmarketing surveillance system, particularly for rare or difficult to diagnose ADEs. Figure 133-1

shows data summarized to 2003, which thus far does not indicate an increase in the percentage of drug withdrawals after PDUFA implementation. The next several years will likely determine whether or not there is an association between the increased rate for drug approval and the rate of safety-related drug withdrawals.

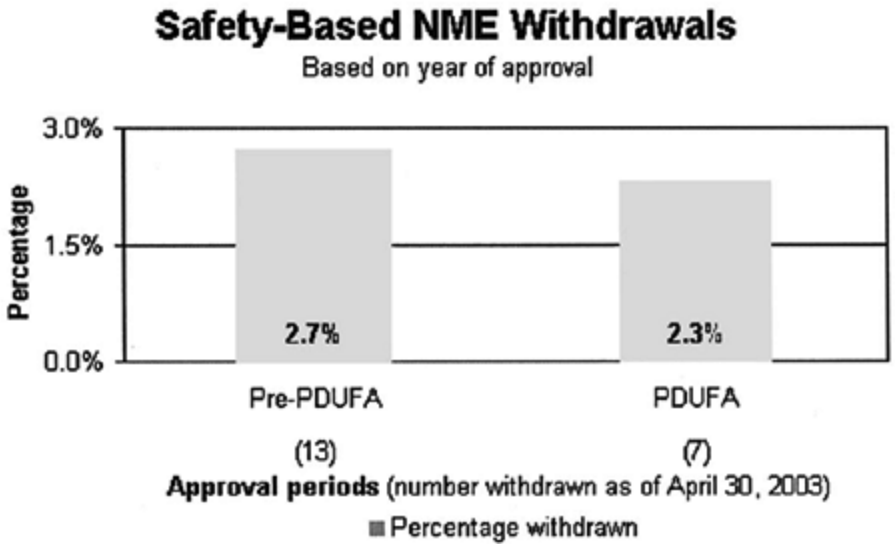

Figure 133-1. Rate of safety based new molecular entity (NME) withdrawals from before and after (to 2003) implementation of the Prescription Drug User Fee Act (PDUFA). (From http://www.fda.gov)

The Drug Development Process

Figure 133-2 shows a schematic overview of the process for drug development of a new molecular entity (NME). The process begins with the preclinical evaluation of the candidate drug. During this evaluation, toxicologic testing is performed in more than one animal species and other testing including stability of the product, manufacturing methods, purity, and initiation of testing for possible carcinogenicity. Dose-response relationships in animal models and in vitro receptor binding or surrogate marker effects are often determined at this time in the program. Also, this is the time when many manufacturers determine the drug's metabolism in animal and in vitro human systems. Following this

preclinical testing, the sponsor submits an IND application to the FDA for approval to initiate human testing. This application contains all relevant data concerning animal and in vitro toxicology testing, product manufacturing and purity, and a protocol for using the drug in initial human investigation. Within 30 days, the FDA must review the IND application and either allow the proposed human study to proceed or inform the sponsor that additional data or preclinical work is required before clinical testing of the candidate drug can begin.

The clinical study of new medications is divided into four basic phases. Phase 1 clinical testing involves a relatively small number of subjects wit the primary aim of determining the safety and toxicity of the drug. Many phase 1 studies will also determine the human pharmacokinetics and metabolism of the drug. Phase 1 studies are normally conducted in 20â€“100 healthy volunteer subjects with the notable exception of phase 1 studies for cancer chemotherapeutic agents, which only enroll patients with cancer.

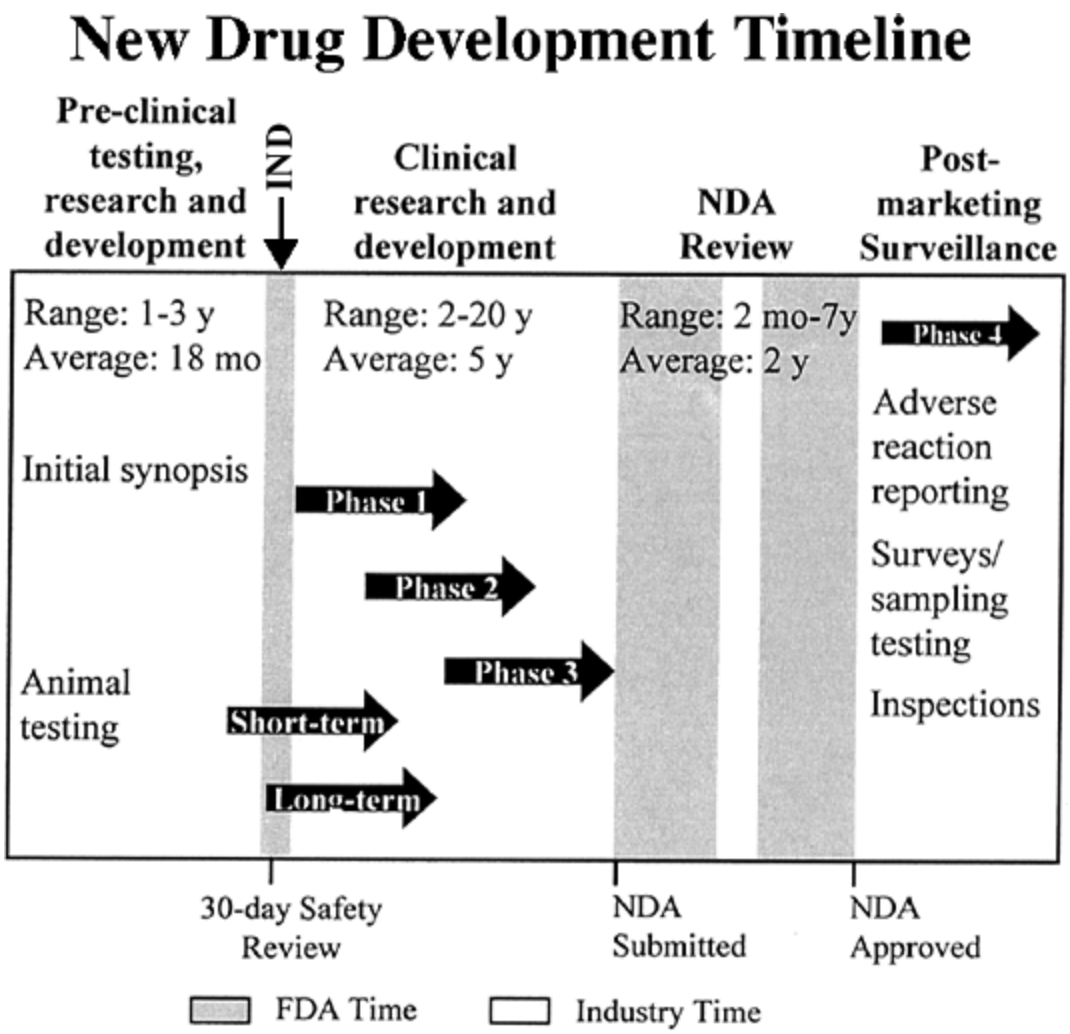

Figure 133-2. Schematic representation of new drug development. (Fror http://www.fda.gov .) NDA = New Drug Application.

Phase 2 clinical testing is designed to determine the potential efficacy of the drug product in humans and sometimes explores the range of effective drug dosages. In this phase, approximately 100â€“300 subjects are usually studied. In phase 2 clinical trials, subjects generally have the diseases for which the drug is intended or are capable of demonstrating the appropriate, validated, biologic surrogate marker to indicate response to the drug.

Phase 3 clinical drug studies usually involve large-scale clinical trials in the actual population for which the drug is intended to be used. Typically

this phase of a drug's development will involve testing a treatment cohor of several hundred to several thousand patients who have the target disease, depending on both the prevalence of the disease and effectiveness of the drug. The primary goal of phase 3 studies is to determine the safety and efficacy of the candidate drug in the actual patient population it will be used in, under conditions close to the anticipated medical use. A candidate drug completing phase 1, 2, and 3 can thus be approved for marketing after study in only 2000â€“4000 patients. In the setting of a fast-track approval or under the Orphan Drug regulations, substantially fewer patients will receive the drug before its approval for marketing. The next phase of drug development is discussed separately below.

Phase 4 Drug Development: Postmarketing Surveillance

The approval of every drug or medical device for marketing always carrie with it some potential risk.[7] If society required that only â€œcompletelyâ€• safe drug products were allowed to be marketed, the drug approval process would likely take decades and fewer drugs would be made available. The FDA and the drug industry therefore significantly relies on postmarketing surveillance for further safety data regarding the toxicity of a drug after approval. There are systems in place to monitor post approval drug safety that are intended to detect instances in which the safety profile of an approved agent may appear to be different after marketing. These systems fall under the category of post marketing surveillance. Individual pharmaceutical manufacturers are responsible for monitoring the safety of their products and reporting to the FDA, on a regular basis, any ADEs that were reported to them. The FDA's postmarketing surveillance (MedWatch Program) for all medical products is a parallel system in place to monitor drug and medical device safety. Because manufacturers are required by law to report ADEs associated with use of their products to FDA, eventually the FDA database contains one complete data set called the Adverse Event Reporting System (AERS

database). These reporting systems are passive in nature. The reports are sent in spontaneously and not actively obtained or pursued by the FDA or manufacturers. Health professionals contribute the majority of reports to the ongoing passive surveillance of drug safety.

Phase 4 clinical studies are sometimes conducted and may include marketing-type studies comparing the new drug to a competitor or studies to evaluate potential safety issues with a drug. The enhancement of safety information is the primary goal of most phase 4 studies. The methods by which phase 4 safety studies are conducted are primarily observational and epidemiologic studies. Main sources of data for the pos approval monitoring of the safety of a drug are the spontaneous reports gathered by both the pharmaceutical manufacturer and FDA. The fields of pharmacovigilance

and pharmacoepidemiology are typically employed in the conduct of phase 4 studies.[21] Until 1993, the FDA used the spontaneous reporting system (SRS) to gather information regarding ADEs occurring in patients using the approved drug. In 1993, this system was renamed and promoted as the MedWatch system.[17] This system relies on spontaneous reports by healthcare professionals or patients regarding the occurrence of deleterious effects associated with the use of a medical product. The primary goals of the MedWatch system are the following:

- To increase awareness of drug- and device-induced disease.
- To clarify what should (and should not) be reported to the agency.
- To make it easier to report adverse effects by creating a single system for health professionals to use in reporting ADEs and product problems to the agency. (4) To provide regular feedback to the healthcare community about safety issues involving medical products.[20]

Currently, the MedWatch program is supported by over 140 organizations representing health professionals and industry, that have agreed to be

MedWatch Partners to help achieve these goals.

Medical product manufacturers that are regulated by the FDA are required to report ADEs occurring in association with the use of their products. Healthcare professionals are encouraged (but not required) to report ADEs. An adverse event is any undesirable experience associated with the use of a medical product in a patient. The MedWatch system has tried to make reporting by healthcare providers easier. A MedWatch report can be made by either facsimile, telephone, mail, or Internet. Establishing causality for a specific medical product is not required before submission of a MedWatch report. The FDA is primarily interested in the report of a serious adverse event, or an ADE previously not associated with the drug being administered, whether or not a causal relationship is established. An event is serious and should be reported when the patient outcome is one of the following:

- Death, and the death is suspected to be a direct result of the adverse event.
- Life-threatening, if the patient was considered to be at substantial risk of dying at the time of the adverse event or the use or continued use of the product would result in the patient's death. (Examples include gastrointestinal hemorrhage, bone marrow suppression, pacemaker failure, and infusion pump failure that permits uncontrolled free flow and results in excessive drug dosing.)
- Hospitalization (initial or prolonged) if admission to the hospital or prolongation of a hospital stay resulted from the adverse event. (Examples include anaphylaxis, pseudomembranous colitis, or bleeding causing or prolonging hospitalization.)
- Disability, if the adverse event resulted in a significant, persistent, or permanent change, impairment, damage, or disruption in the patient's body function/structure, physical activities, or quality of life. (Examples include cerebrovascular accident caused by drug-induced coagulopathy, toxicity, and peripheral neuropathy.)

- Congenital anomaly, if there are suspicions that exposure to a medical product before conception or during pregnancy resulted in an adverse effect on the child. (Examples include vaginal cancer in female offspring from exposure to diethylstilbestrol during pregnancy or limb malformations in the offspring from thalidomide use during pregnancy.)
- Requires intervention to prevent permanent impairment or damage if use of a medical product is suspected to result in a condition requiring medical or surgical intervention to preclude permanent impairment or damage to a patient. (Examples include acetaminophen overdose-induced hepatotoxicity requiring treatment with *N* -acetylcysteine to prevent permanent damage, burns from radiation equipment requiring drug therapy, or breakage of an orthopedic screw requiring replacement of hardware to prevent malunion of a fractured long bone.[20])

Physician reports are given priority for review by the FDA in the MedWatch system. A well-documented case of a serious adverse event is a significant and useful contribution to the MedWatch system.

Reports of serious ADEs to the FDA or to the manufacturer can evolve into an epidemiologically detectable signal that can catalyze subsequent, more detailed investigations (examples of cases where this has occurred are provided later in this chapter). On occasion serious ADEs detected in the AERS database have led to the withdrawal of products from the US market without conducting additional studies.

Reporting serious ADEs has periodically been encouraged by various healthcare groups in conjunction with the FDA. With the introduction of the MedWatch system and MedWatch partner programs, medical societies and organizations such as the American Medical Association (AMA), the American College of Medical Toxicology (ACMT), and the American Academy of Pediatrics (AAP) have encouraged their members to report to the MedWatch system. As a requirement for hospital accreditation, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO)

mandates hospitals to collect, analyze, and report significant and unexpected ADEs to the FDA.

The primary limitation of the MedWatch system is the exclusive reliance on spontaneous reporting of ADEs. Significant underreporting is known to occur in such systems. Current estimates are that fewer than 10% of ADEs are reported.[14, 23, 26] The true incidence of the reported ADE is almost never obtainable because the denominator, which is the number o actual exposures to the drug, is rarely accurately known. Despite these limitations, the MedWatch system is capable of detecting significant ADEs The relatively small number of patients or subjects exposed to the drug before approval (phases 1â€“3) is one reason why relatively uncommon ADEs are frequently not detected until the post approval marketing phase. For example, to detect an uncommon ADE occurring in approximately 1 of 5,000 individuals exposed to a drug with 95% probability that the ADE resulted from exposure to that drug, approximately 15,000 patients would have to be exposed to the drug.[11] In a balanced (equal numbers of drug and placebo recipients) placebo-controlled clinical trial, 30,000 subjects would need to be enrolled. Premarketing clinical studies (phase 1, 2, and 3) may not be able to detect rare ADEs, ADEs that are incorrectly diagnosed, or ADEs that result from a drug interaction that may not have been tested in the development program. An example of a rare ADE not detected until postmarketing involves the drug felbamate, which was approved by the FDA in September 1993 and subsequently found to be associated with aplastic anemia during postmarketing surveillance. Felbamate-induced aplastic anemia had not been detected during the drug development program for the

agent. By July 1994, 9 cases had been reported from an estimated 100,000 patients exposed to felbamate in the United States. Most of the aplastic anemia cases occurred in patients who had taken the drug for less than 1 year. The 9 cases represented an approximate 50-fold increase in aplastic anemia over the expected rate in the population with the very low background rate of 2â€“5 cases per million per previous

year[1 , 29] allowing the FDA to attribute this rare condition to exposure to felbamate.

A primary role of the MedWatch system is to generate a â€œhypothesisâ€• for a potential association of an ADE with a specific drug. Attributing a serious ADE to a drug solely from MedWatch reports does occur but less commonly than does the AERS database producing a signal suggesting a possible drug-related safety problem. An example of this â€œhypothesis generationâ€• function of MedWatch is the question of whether phenylpropanolamine (PPA) causes hemorrhagic stroke in patients using nonprescription diet suppressants or cough and cold preparations containing PPA. In the early 1990s, the Spontaneous Reporting System (SRS, now AERS) detected a potential association of hemorrhagic stroke and nonprescription use of PPA. An industry-sponsored prospective, case-controlled study resulted, to determine if such an association existed. The multicenter study demonstrated that an association did exist, especially for women ages 18â€“49. The Nonprescription Drug Advisory Committee (NDAC) of FDA reviewed this study and the associated MedWatch data in the fall of 2000 and decided that the evidence supported such an association. The committee advised the FDA to remove PPA from the market, which occurred a short time later. Although the entire process of signal identification from MedWatch to presentation of results from the prospective epidemiologic study required nearly a decade for PPA, the process demonstrates the value of the hypothesis-generating ability of the MedWatch system.

1. Was the timing of the adverse event appropriate relative to the exposure to the drug?
2. Has the effect noted, which is the suspected ADE, been reported before?
3. Is there evidence of excessive exposure to the drug?
4. Are there other more likely etiologies responsible for the condition suspected as being an ADE?
5. What is the patient's response to dechallenge?
6. What is the patient's response to rechallenge?

TABLE 133-1. Questions to Consider When Establishing the Diagnosis of an Adverse Drug Event

Establishing the Diagnosis of Drug-Induced Disease

The recognition and diagnosis of a drug-induced disease, or an ADE, is an essential skill for practitioners, including medical toxicologists and clinical pharmacologists. The diagnosis of an ADE is typically established as a result of a systematic medical evaluation. One approach to establishing the diagnosis of drug-induced disease involves consideration of six related questions concerning the patient's clinical presentation and available medical data, as shown in Table 133-1 .

The first question concerns the timing of the onset of the adverse event in relationship to the reported exposure to the drug. Perhaps because of publicity or word of mouth, ADEs are sometimes reported to the FDA MedWatch system even when the onset of the adverse event occurs before the first exposure to the suspect drug. A careful reconstruction of the time course of drug exposure and onset of adverse effects is extremely important in assessing causality. The time course differs considerably for different adverse clinical events. An anaphylactic reaction to a drug occurs within minutes of exposure, whereas renal insufficiency caused by a drug is not likely to be clinically detectable for up to several days after the exposure. A drug that causes cancer (a carcinogen) may not produce a clinically detectable effect for decades. Establishing a time course is an essential first step in the process of making the diagnosis of drug-induced disease.

The second question is whether or not this adverse effect has been reported previously for the suspect drug. An adverse drug effect that occurs commonly is likely to be known before the approval of the drug and is therefore usually found on the initial drug label. For example,

respiratory depression and mental status changes were well known before the approval of fentanyl, an opioid agonist. Less common ADEs for drugs that have been on the market for a period of time are sometimes reported in the literature, included in various medical databases, and in some cases will appear in a revised drug label for the medical product. Previous reports linking the observed adverse effect to drug exposure are very helpful to the physician trying to establish a significant level of probability for causality in the setting of an ADE.

However, in the setting of a newly approved drug or a previously unreported possible ADE, neither previous reports, the medical literature nor the drug label will help establish causality. In this setting, the clinician must rely more on what is known of the pharmacology, the pharmacokinetics, and the anticipated pharmacodynamics of the suspect drug and the timing of the appearance and observed time course of the adverse event. It is important to put â€œdrug-induced diseaseâ€• in the differential diagnosis for most patients presenting for medical care. Someone has to be the first to report what is ultimately recognized as an adverse effect for every xenobiotic. Appropriate vigilance for the possibility of a new ADE significantly increases the probability that a finding can be made early after introduction of a new drug to prevent more widespread drug-induced morbidity or mortality.

The next question to consider is: â€œIs there evidence of excess exposure to the drug?â€• The majority of ADEs that occur are predictable on the basis of the known pharmacology of the specific drug. Such ADEs are referred to as â€œtype Aâ€• ADEs.[3] For example, antihistamines such as diphenhydramine are known to cause significant anticholinergic effects. When a patient presents with mental status changes and clinical findings consistent with the anticholinergic toxidrome after significant exposure to an antihistamine-containing product, the observed effects are consistent with an ADE attributable to the antihistamine. Occasionally, proof of drug excess can come from measurement of the drug in plasma. In the case of the patient with a history of manic-depressive illness, who exhibits hyperreflexia and tremors, the measurement of an elevated lithium plasma concentration

supports the diagnosis of lithium toxicity or an ADE attributable to lithium. In either case, knowing the pharmacology of the drug is important for establishing the diagnosis of an ADE.

When an ADE is caused by an allergic mechanism or another mechanism unrelated to dose of the drug, ie, a â€œtype Bâ€• ADE, evidence of drug excess usually does not contribute to the diagnosis. In this setting, other factors such as allergy history or pharmacogenetic background are weighed more heavily to support the diagnosis of an ADE.

The next issue to address in considering possible causality is whether there are other more likely etiologies that could be responsible for the observed effects. Although it is important to be appropriately vigilant for possible ADEs, it is equally important not to miss an alternative cause for the patient's condition. There are certain clinical settings in which establishing an ADE becomes a diagnosis by exclusion. For example, in the case of persistent fever, the assignment of the diagnosis â€œdrug feverâ€• should not be made until a complete search for infectious causes has excluded this etiology.

Another factor to consider in contemplating a diagnosis of ADE is â€œWhat is the patient's response to cessation of a suspect drug (dechallenge)?â€• In this case, the pharmacokinetics of the drug and the timing of resolution of the specific condition must be carefully considered. In some instances, the resolution of a â€œtype Aâ€• ADE closely follows the pharmacokinetics of the suspect drug. For example, in the case of acute ethanol intoxication, central nervous system effects resolve in association with decreasing plasma concentrations of ethanol. However, confounding this approach is the case of a penicillin rash, which may develop within 1 or 2 days of starting the medication but may take several days to weeks to completely resolve. In this case of a â€œtype Bâ€• ADE, the resolution of the condition (rash) occurs over a much longer time period than would be predicted by the pharmacokinetics of the drug. When a suspected ADE resolves after discontinuation of exposure to the offending drug, along a predictable time course, then the

result of this â€œdechallengeâ€• would support the diagnosis of ADE.

Last, the clinician may have the opportunity or need to rechallenge the patient with the suspect agent. If the rechallenge results in the identical response or effect, then this would be considered strong evidence to support a causal relationship for the suspect agent and the adverse event. In the setting of a serious or life-threatening adverse event, it is too dangerous to perform a rechallenge with the suspect drug, in which case the response to rechallenge will not be known. In this setting, the weight of evidence previously discussed will then be the only factors available to assign the probability of causality.

Examples of FDA Regulatory Action Because of Safety Concerns for Drugs on the United States Market

When new information about a marketed drug raises concern for the safety associated with its use, the FDA has several options to exercise to either attempt to improve the safety of the drug or terminate the availability of the drug on the market. A frequently employed option is fo the FDA to modify the label of the drug. These modifications can include restrictions on who should receive the drug, what doses should be given for which indications, what type of monitoring should be performed durin therapy and how long should treatment be administered. When potentiall life-threatening safety information comes to light, and if the FDA believes that the risk-benefit relationship still favors availability of the drug, the FDA can require that a â€œblack boxâ€• warning be carried in the label. A â€œblack boxâ€• warning is the most serious warning placed in the label of a prescription medication. Additionally, once a drug's label contains a black box warning, advertisements that serve to remind healthcare professionals of a product's availability are not permitted for that specific product at any time. Additionally, the manufacturer is required in most cases to send a â€œDear Doctorâ€• letter to potential prescribers informing them of the black box warning. Dear Doctor letters

are sent to prescribers to notify them about a significant change in the drug label and not just the addition of a â€œblack boxâ€• warning. An example of current medications with recently added black box warnings include the antidepressant medications which now must warn about the increased risk of suicidality in children and adolescents who receive these agents. Another example is the recent inclusion of a black box warning on the label of COX-2 inhibitors and other nonsteroidal antiinflammatory drugs (NSAIDs) that addresses the increased risk of serious cardiovascular events such as heart attack or stroke. A third example is the 2001 black box addition to the droperidol label intended to increase the prescriber's awareness of and assessment for the potential for cardia dysrhythmias during drug administration, and to encourage that consideration be given to the use of alternative medications for patients at risk for cardiac dysrhythmias.

Another option sometimes employed by FDA is to permit continued availability of a drug for marketing but with specified restrictions. For example, use of the drug isotretinoin (Accutane) requires compliance with a multiple component risk management program including informed consent, prescriber and dispensing pharmacy registration, serial pregnancy testing if applicable, documentation of patient education, and completion of risk management programs by patients who will receive the medication.[8]

When the FDA believes that a drug can no longer be safely used despite implementation of labeling changes, that is, the regulatory threshold is reached when an acceptable riskâ€“benefit relationship for continued availability of a drug product is not possible, the FDA begins a defined process to remove the drug from the market. Table 117-2 in the Seventh edition of *Goldfrank's Toxicologic Emergencies* contains a compilation of products that were withdrawn or removed from the market in the United States for reasons of safety or efficacy. Some recent additions to that list of drugs include valdecoxib (marketed as Bextra) and rofecoxib (marketed as Vioxx), withdrawn because of recognition of elevated cardiovascular risk associated with their use.[13] In the case of the COX-2 inhibitor withdrawals the precipitating factor for withdrawal was the

findings of a strong safety signal for excess cardiovascular mortality and morbidity during the conduct of efficacy studies for other potential therapeutic indications for these agents. The postmarketing surveillance system did not serve as the initial, precipitating data set for regulatory action in this instance.[4,18,24,25] The manufacturers voluntarily withdrew these COX-2 inhibitors and the majority of the drugs listed in Table 117-2 of the Seventh edition of *Goldfrank's Toxicologic Emergencie* from the United States market. In many cases, the manufacturer removes the drug from the market after notification by the FDA that regulatory action is being initiated to remove their drug from the market. Only very rarely has the FDA itself actually removed a drug from the market. One example where the FDA did implement removal is the drug phenformin, which was removed by the FDA after due process was completed. In the case of ephedra containing dietary supplements, the FDA removed these products from the market based on their analysis of safety data obtained from the medical literature and from analysis of cases reported to the MedWatch system. In some cases, the pharmaceutical manufacturers file suit against the FDA to fight or delay the planned regulatory action against the product.

The manufacturer's legal action generally prolongs the time the product remains on the market because the drug usually continues to be sold while the legal proceedings and appeals proceed through the courts.

In addition to the recent COX-2 withdrawals, where an elevated risk of cardiovascular ADEs was cited, the past several years have seen drug withdrawals from the US market because of postmarketing recognition of ADEs in 3 general areas:

- Prolongation of the QTc interval
- Significant drug-drug interactions
- Hepatotoxicity

Prolongation of the QTc Interval

Three significant drug withdrawals in the mid- to-late 1990s exemplified a serious drug safety issue with an agent found to prolong the QTc interval when administered alone or as the result of increasing plasma concentrations of the drug as a result of inhibition of its metabolism by other medications. The three examples in this category are terfenadine (Seldane), astemizole (Hismanal), and cisapride (Propulsid). Numerous deaths were reported to the MedWatch system for patients taking these medications. The FDA funded small prospective clinical studies to confirm a previously unrecognized ability of terfenadine to dramatically alter cardiac repolarization, which can lead to torsades de pointes. The drug was marketed in 1985, cardiac toxicity detected in clinical use in 1990,[22] the FDA funded clinical cardiac safety research performed in 1991[16] and ultimately the drug was withdrawn from the market in 1998. Astemizole (Hismanal), another antihistamine, with similar propensity to alter cardia repolarization was first marketed in 1988. In the early 1990s, the FDA SRS pointed to signals of altered cardiac conduction and prolongation of the QT interval similar to those associated with terfenadine. These reports lead to a â€œblack boxâ€• warning for the potential to prolong the QT interval that could produce torsades de pointes and sudden death In June 1999, the FDA announced that the sponsor was voluntarily withdrawing astemizole from the market.[5] There are substantial parallels between terfenadine and astemizole. Both drugs are nonsedating antihistamines that are metabolized by cytochrome P450 (CYP3A); both parent compounds alter cardiac repolarization to produce prolongation of the QT interval, leading to cardiac dysrhythmias and its complications, and inhibition of CYP3A4 by erythromycin raised serum concentrations of the parent compound leading to dysrhythmia.

Another similar example involves the GI motility drug cisapride (Propulsid). By December 31, 1999, cisapride was associated with 341 reports of cardiac dysrhythmias including 80 fatalities. The mechanism fo the prodysrhythmic effect was similar to astemizole and terfenadine, (potassium channel inhibition), and inhibition of cisapride metabolism

increased the risk for dysrhythmia and death. Administration of cisapride with inhibitors of CYP3A such as clarithromycin results in prolongation of the QTc (QT interval corrected for heart rate) interval on the surface electrocardiogram.[28] Despite several modifications in the drug label to enhance the warnings for the product, reports of significant cardiotoxicity continued. In March 2000, the manufacturer agreed to stop marketing this agent as of July 2000.[6] Unlike the voluntary withdrawals of astemizole and terfenadine, the sponsor was able to retain the ability to make cisapride available to patients who meet specific clinical eligibility criteria for a limited-access protocol. It is unclear at this point whether or not this drug will eventually be completely withdrawn from the US market.

In addition to the drug-drug interactions that lead to accumulation of toxic cardiac parent drugs as in the case of terfenadine, astemizole and cisapride, drugs shown to inhibit multiple metabolic pathways, especially of drugs with narrow therapeutic indices, have been removed from the market.

Significant Drug-Drug Interactions

The case example of mibefradil (Posicor) presented at the beginning of this chapter is a prime example of drug withdrawn from the US market because of postmarketing discovery of a plethora of drug-drug interactions. Mibefradil, a pharmacologically unique calcium channel blocker was approved by the FDA for the treatment of patients with hypertension and chronic stable angina. The FDA approved mibefradil for marketing in 1997 and at that time information regarding its inhibition of hepatic CYP isozymes were known and printed on the drug label. The initial labeling for mibefradil specifically listed three drug-drug interactions: astemizole, cisapride, and terfenadine. During the one year that mibefradil was marketed, information accumulated regarding drug-drug interactions with many other drugs as well. As the in vitro and in vivo drug interaction data continued to accumulate for mibefradil, the FDA made labeling changes and issued a public warning for these

potential drug interactions within 5 months of its initial approval. Additionally, the sponsor distributed a letter to healthcare professionals warning of drug-drug interactions. In the face of a growing and significan list of drug-drug interactions, and a 3-year international study demonstrating no clinical benefit of mibefradil over placebo for congestiv heart failure, the FDA initiated regulatory action. In an unprecedented step for a drug with numerous drug interactions, the FDA requested approximately 1 year after it was approved that it be withdrawn from the market. The FDA felt that the diversity of drug-drug interactions could no be addressed by standard drug label instructions and additional public warnings.[7]

Drug-Induced Hepatotoxicity

Another category of ADE of recent concern is those drugs that cause hepatotoxicity. In June 1998, the manufacturer of the NSAID bromfenac sodium (Duract) withdrew this agent from the US market. The NDA was submitted for review to the FDA in 1994 and after 28 months of review was approved. The drug was withdrawn approximately 11 months later after postmarketing discovery of significant hepatotoxicity. Although no cases of serious liver injury were reported during premarketing clinical trials, after introduction to the market a higher incidence of liver enzyme elevation was found in patients who were being treated with the drug. Post approval exposure of patients to bromfenac generally resulted in longer periods of treatment than that of the subjects in the clinical trials. Because of a pre approval concern by the FDA that long-term exposure to bromfenac could cause hepatotoxicity, bromfenac labeling specified that the product was to be used for 10 days or less. This dosing limitation appeared to be in conflict and inconsistent logically, with the initial approved drug indication for treatment of a chronic condition (eg, osteoarthritis). Information concerning elevated hepatic enzymes was actually included in the original product labeling. The postmarketing surveillance of this product identified rare cases of hepatitis and liver failure, including some patients who required liver transplantation, among those using the drug for more than the 10 days specified on the

label. In February 1998, approximately 6 months after approval for marketing, the FDA amended the drug label for bromfenac sodium with a special â€œblack boxâ€• warning indicating that the drug should not be taken for more than 10 days and emphasizing the risk of severe hepatitis and liver failure. The label change was done in conjunction with a required â€œDear Doctorâ€• letter to prescribers informing them of this labeling change. Nonetheless, severe injury and death from long-term us of bromfenac sodium continued to be reported, and ultimately, the sponsor agreed to voluntarily withdraw bromfenac sodium from the market. The withdrawal of bromfenac sodium raised several important questions concerning interpretation of â€œsafety laboratories,â€• such as liver enzymes during the drug development program, and also raised questions concerning the effectiveness of drug labeling.

Another example of a drug withdrawn for safety concerns related to hepatotoxicity is the oral antidiabetic agent troglitazone (Rezulin). It was approved in the mid-1990s and severe liver toxicity was detected by postmarketing surveillance in 1997. Increasingly serious labeling changes and warnings to prescribers recommending close monitoring of liver function tests in patients taking troglitazone were issued over the next 2 years. In March 1999, an FDA advisory committee reviewed the status of troglitazone and its risk of liver toxicity and recommended continued marketing of this drug in patients with type II diabetes who were not wel controlled by other drugs. When two newer agents for type II diabetes, rosiglitazone and pioglitazone, became available, the FDA concluded that the risk profile for troglitazone was significantly worse than these newer agents and asked the manufacturer to remove troglitazone from the market.[15] Analogous to the example with mibefradil, this FDA-initiated drug withdrawal was based on a change in the risk-benefit profile for the specific agent in light of new safety information discovered during the post approval phase for the drug.

A recent example of post marketing discovery of hepatotoxicity occurred with interferon Î²-1b (marketed as Betaseron), a drug used to treat multiple sclerosis. The manufacturer recently sent a â€œDear Doctorâ€•

letter to prescribers to remind them of the need to check hepatic enzymes periodically while administering this agent. If reminders such as these are ineffective in limiting the reported rate of hepatic ADEs, the usual next step is a â€œblack boxâ€• warning and if the problem persists, the potential for drug removal from the market becomes increasingly more likely.[15]

Other Examples of Postmarketing Safety Problems Leading to Drug Withdrawal

One voluntary withdrawal of 2 separate drugs used in combination serves as an example of the discovery and publicizing of an unusual adverse event occurring years after individual drug approval but after a significan increase in the prescription use of the combination product. The drug fenfluramine was approved in 1973 after an FDA review period of 75 months. Clinical investigation of a similar agent, dexfenfluramine, began in 1991 in the United States with approval of its IND. The new drug application for this product was filed in 1993, and after 35 months of review the drug was approved for marketing in 1996. A significant increase in prescription use of a combination product of fenfluramine with phentermine (referred to as â€œfen-phenâ€•) began to occur in the 1990s when clinical data suggested that this drug combination was effective in a weight loss program.[30,31,32] Dexfenfluramine was approved for weight loss as a single agent for up to 1 year of use. Use of the fen-phen drug combination, however, was never fully approved by the FDA and was therefore considered an â€œoff-label usageâ€• of the product. The number of prescriptions for the drug combination soared in the mid-1990s. In July 1997, research from the Mayo Clinic reported 24 cases[2] of an unusual form of cardiac valvular disease causing aortic and mitral regurgitation in patients using the fen-phen combination. The publicity surrounding the potential linkage of this drug combination to an unusual adverse event led to a significant increase in reports of possible adverse events associated with this drug combination. The FDA issued a public health advisory and initiated further epidemiologic studies to

ascertain its prevalence. The FDA also encouraged echocardiographic studies of valvular diseases in patients taking fenfluramine or dexfenfluramine either alone or in combination with phentermine. Although at the onset neither the FDA, the product manufacturers, nor the medical community expected valvular lesions to be associated with either fenfluramine or dexfenfluramine, the epidemiologic evidence suggested a possible association, leading the FDA to conclude that these agents should be removed from the US market. The potential association of valvular heart disease with these agents is an example of the use of a case-control study to explore a possible causal relationship between drug exposure and an ADE. In this case, it is unclear what the strength of the MedWatch signal was for the possible association of cardiac valvular disease with exposure to the fen-phen combination. If the association between cardiac valvular lesions and exposure to the drug combination o components of the combination is ultimately proven to be true, however, this would serve as an example of elucidation of a rare, unexpected ADE as the result of a dramatic increase in the number of exposed patients using a product.

The Role of the Toxicologist in the Detection and Prevention of Adverse Drug Events

Toxicologists can have significant beneficial impact in ADE diagnosis and prevention. These areas include patient care, education, and administrative functions. In patient care, it is common for the medical toxicologist to be the first medical specialist to be consulted for a patient with a potential ADE. As a result, medical toxicology occupies an important position as sentinel for drug-induced disease. Maintenance of clinical skills and appropriate continuing education is essential, especially in the area of newly approved therapeutic agents or newly recognized ADEs caused by older approved therapeutic agents. Maintenance of a current knowledge base in the area of therapeutics enhances the ability of the medical toxicologist to diagnose drug-induced disease. Perhaps

more than any other medical specialty, medical toxicologists are likely to include a thorough medication history that also includes nonprescription products and dietary supplements. As stated previously, obtaining a history for drug exposure is an essential component in attributing an observed adverse medical event to a specific drug product. The medical toxicologist's active involvement in the clinical arena, especially in settings in which the initial diagnosis of ADEs can be made, serves to provide an important role model: the medical toxicologist is an educator in the specialty to promote the detection and prevention of ADEs.

Medical toxicologists occupy many different roles in clinical practice in the United States. An obvious role for the medical

toxicologist is as educator in the academic setting of a medical school and affiliated teaching hospitals. Here, the academic toxicologist can champion the inclusion of education in therapeutics in the curriculum for medical students and house officers and take an active role in the implementation of the instruction. Assuring that the curriculum in therapeutics includes recognition and prevention of ADEs and medical errors that lead to ADEs could have a significant beneficial impact on the ultimate outcome of the education process toward reduction of preventable ADEs. In addition to making sure that quality information is presented in the curriculum for trainees, the medical toxicologist can often create a special teaching opportunity for this type of education by establishing an elective or, in some cases, required experience in the curriculum for training in therapeutics. Participation in a quality learning experience can significantly impact on the graduates' knowledge of and attitudes toward therapeutics and risk reduction in the practice of medicine. Although a recent Institute of Medicine report on medical errors[19] did not focus on education initiatives in its main recommendations for reduction of medical errors in United States, it seems logical that education be considered a useful tool to improve medication use and prevent ADEs and medical errors with therapeutic agents.

In the private practice setting, the medical toxicologist sometimes has an

opportunity to educate fellows in training in the medical specialty and peers who call on them for consultations. In these settings, a consistent approach to the patient that includes the listing of drug-induced disease, drug excess, or potential drug-drug interactions in the differential diagnosis to explain an unexpected drug response can provide an exampl for medical colleagues.

The administrative functions that the toxicologist can perform could also beneficially impact on enhancing detection and prevention of ADEs. The main administrative functions that fall into this category include the reporting of ADEs and serving on hospital or health organization committees that oversee therapeutics (eg, the pharmacy and therapeutics committee).

ADEs are known to be significantly underreported in the United States.[14] [23] , [26] Reporting ADEs at the local (hospital) and national level (MedWatch) has been a priority and has been made less difficult administratively. Despite efforts to encourage filing of ADE reports, the overall reporting rates do not appear to have changed significantly. A well-documented, complete report to MedWatch made by a healthcare professional is given priority review by the FDA. The MedWatch system encourages reporting of serious adverse events by all practitioners. The toxicologist is likely to encounter a significant number of drug-induced disease cases from a diagnostic and management standpoint, therefore practitioners of the specialty can make a significant impact on ADE reporting. Toxicologists and their trainees should always submit an adverse event report locally for appropriate cases they encounter. Hospitals generally do not mandate or request that the reported event be â€œseriousâ€• as a requirement. The FDA's MedWatch system asks that reported events be serious in nature or not previously associated with the medication involved. Manual review of reports and database checks are performed by FDA, and duplicative reporting is accounted for when noted In addition to reporting of the ADE, the toxicologist should promote publication of case reports of all new adverse events or adverse events occurring with newly approved products. Such publication often stimulates appropriate reporting of ADEs from other practitioners.

Service on hospital or healthcare organization committees is another important opportunity for toxicologists to impact on the drug-induced disease problem. Whenever possible, toxicologists should participate in the local hospital pharmacy and therapeutics committee. Often these committees have ADE-monitoring or medication safety committees where the expertise of the medical toxicologist in diagnosing drug-induced disease could prove beneficial to the organization. These committees systematically analyze trends in ADEs and occasionally recommend various interventions for the medical, pharmacy, or nursing staff to reduce the potential risk for ADEs. These interventions include a targeted educational program, system modifications to reduce error risk, or limitation of a specific drug usage by certain components of the organization. Another committee where the toxicologist can have an impact on ADEs and medical error prevention is the quality assurance committee of the hospital or healthcare organization. Careful analysis of medical errors or ADE reports brought to the quality assurance committee can often reveal significant trends that are sometimes amenable to educational initiatives or systematic improvements in process. The medical toxicologist is ideally suited to play an important role on the committee as a practitioner of clinical medicine with specialized expertise in the potentially harmful effects of drugs.

Summary

Drug-induced disease is common in both inpatient and outpatient settings in the practice of medicine. Despite significant advances in medical science applied to drug development and regulation, ADEs continue to occur. These ADEs have a significant impact on patient mortality and morbidity in addition to producing a significant burden on the healthcare system. ADEs caused by newly approved drugs and ADEs resulting from a previously unrecognized association with therapeutic agents with a long marketing history continue to be a significant cause of mortality and morbidity. The specialty of medical toxicology is well-positioned to have a beneficial impact toward recognition and prevention of ADEs. Early

recognition of drug-induced disease by the medical toxicologist can benefit the individual patient in many cases and may lead to prevention of further patient harm by prompt ADE reporting to local authorities and, if appropriate, to the FDA. The rapidly expanding number of approved therapeutic agents requires that the medical toxicologist and other practitioners have a strong continuing education commitment to reduce the risk for ADEs in medical practice. Local and national-level involvemen by the specialty of medical toxicology to design and implement programs and activities aimed at decreasing the occurrence of preventable ADEs should benefit patients and, by extension, society.

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Chapter 134
Medications, Errors, and Patient Saf

Pat Croskerry

In the summer of 2004, a group of Americans and Canadians that include minister, and students, set out to climb Mount Kilimanjaro in Tanzania. Th more challenging ascent routes that would take about 10 days. Since leav had incurred a variety of mishaps, but by day 7 had arrived reasonably s injury at the Lava Tower camp, a small plateau below the Western Breach about 15,500 feet and the temperature is below freezing. There remained steep wall of the breach, to the final crater camp. Everyone was suffering altitude sickness that had started at about 12,000 feet. Some had very r one of the students, a 19-year-old, had an oxygen saturation measured b low sixty percents. Other symptoms included headache, fatigue, nausea, palpitations, and mild confusion. Each of the three physicians had brough medications for the climb. These included antibiotics, antiemetics, aceta and benzodiazepines.

Some had taken medications for altitude sickness, others had not. The m completing the ascent without medication, had begun to show significant sickness. One of the physicians, an internist, became concerned and advis complete the climb if he didn't relieve his symptoms with medication, sp

dexamethasone. Being so close to the summit, he reluctantly agreed. He and began the ascent with the group. About 20 minutes later, the internist mg tablet of dexamethasone and realized, to his horror, that the one he smaller and must have been the 10-mg diazepam tablet. He immediately and gave him 4-mg dexamethasone.

The breach climb is steep but not technically difficult. It is mostly up pat slopes, with occasional rock-climbing sections. About an hour after taking minister became increasingly light-headed, disoriented, and unsteady. The could not be reversed and they could not stay exposed on the breach unt retrace their path back down would have been more hazardous than cont not appear to be any option but to continue. They did so by boxing in the climbers to assist him and prevent his falling, and slowly made their way done, and the minister successfully climbed the breach. He went on to su Kilimanjaro (19,340 ft) the next day.

In the summer of the previous year, a 65-year-old man presented to the department (ED) of a teaching hospital where one of the Kilimanjaro phys major complaint was left-sided weakness, which started about 2 hours ea of mild holocranial headache and nausea, both of which started at the sar He had no other neurological symptoms and had never had similar sympto history included lung cancer for which he was currently undergoing chem mellitus, and hypertension. He had no allergies. Medications included de metoprolol, and ranitidine.

Vital signs at triage were: blood pressure 170/96 mm Hg; pulse 130 bea breaths/min; and O_2 saturation of 95% on room air. His bedside rapid re mg/dL. His speech was normal and he had no cranial nerve abnormalities abdomen were unremarkable. Marked weakness and increased reflexes we side. Sensory examination was normal. A noncontrast CT scan was compl A neurologist was consulted, describing the stable condition of the patient nonhemorrhagic cerebrovascular accident. The physician then gave a verb â€œ10mg Maxeran IVâ€• for nausea and headache.

The physician was called to his bedside 10 minutes later as the patient h with a respiratory rate of 8. A discussion followed with his family, in whicl apparently deteriorating condition was discussed. A decision was made to

CT scan, and reassess him at that time. However, a second nurse noticed medication vial attached to his IV bag was not Maxeran (metoclopramide) immediately given the benzodiazepine antagonist, flumazenil IV, following appeared to recover to his baseline condition.[24]

Both these incidents involve medication errors. Although both medications the therapeutic range, and without apparent interaction with other medic that might have led to a catastrophic outcome. This is an important distin medications and patient safety. The first issue is whether or not a medica second concerns the conditions under which a safe medication is adminis review both issues, with a focus mostly on factors that compromise the s

Although both errors occurred in markedly different settings, they share 134-1). In the Kilimanjaro incident, the tablets were green, the route of the dose-range was similar, both medication names begin with the same stored together in a backpack. In the emergency department (ED) incide in brown glass vials, both had a white label with black print, there was ar midazolam vial and a lighter orange marking on the Maxeran vial, both v the dose range was similar, both began with the same letter, and they w other in the same drawer.

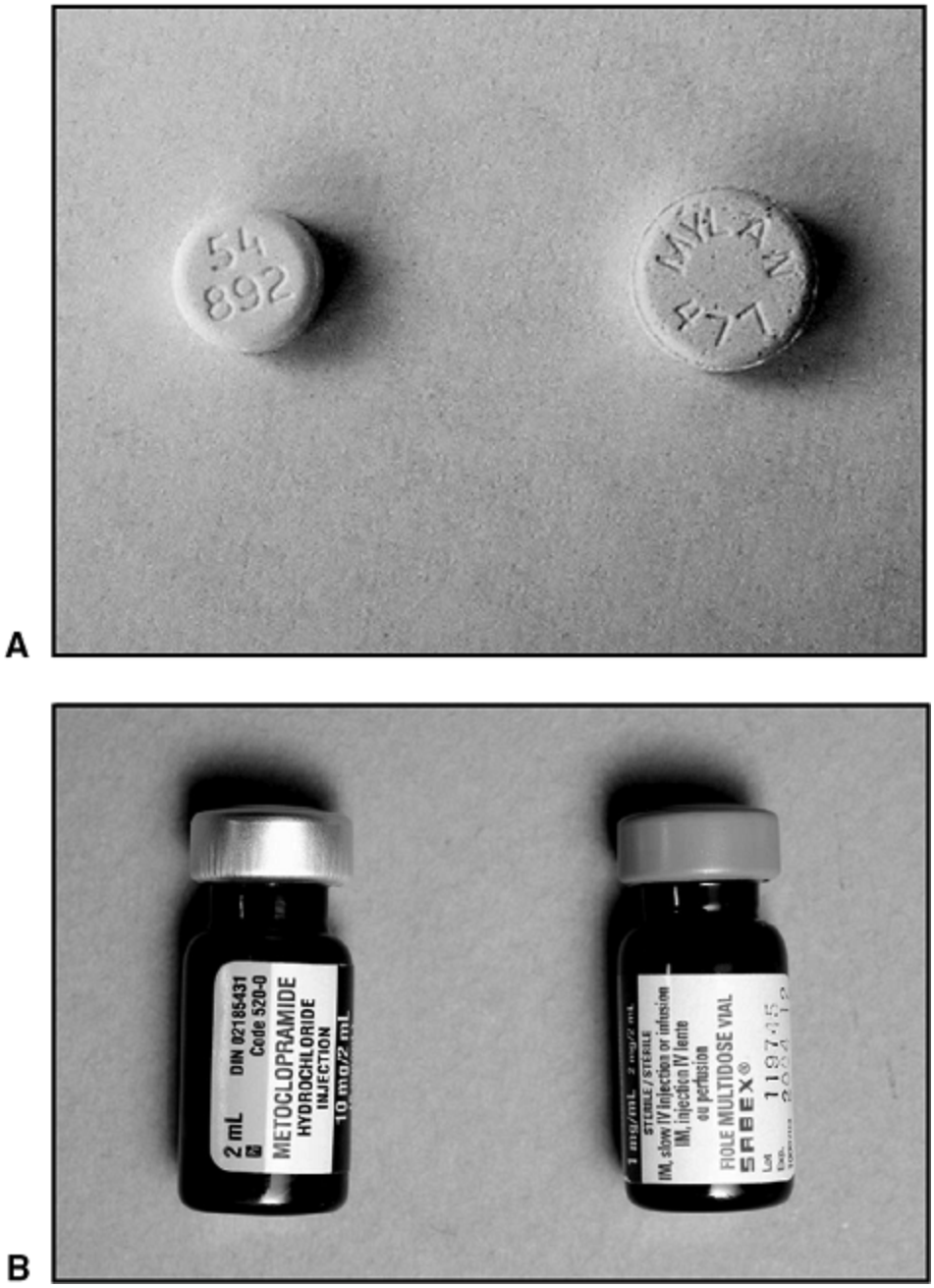

Figure 134-1. Examples of look-alike medicationsâ€”side-by-side photos two examples in the text. A: Dexamethasone (4 mg) and Diazepam (10 r and Midazolam.

It is estimated that 25% of medication errors reported to national report confusion with look-alike and sound-alike drug names.[48] Lists of such dru

potential harm to patients have been developed by the Joint Council on Organizations (JCAHO) for specific healthcare settings, together with rec preventing medication errors. Also, individual health organizations have d supplementing these recommendations.[64] Medication name suffixes are al confusion.[16] The suffixes of one medication alone, diltiazem, include CD, I suffixes used are ER, ES, S, XL, and CR. A number of errors have arisen Additionally, a variety of problems associated with color-coding of medica described.[49]

There are other common factors that predispose to adverse drug events described above. Firstly, in neither case was the medication dispensed by are the only professional group to be formally trained in dispensing medi surprisingly, their presence is associated with a lower medication-dispens and other restraints, pharmacists cannot be assigned to every area in wh or even those in which tightly coupled dangerous medication use is high su Tight coupling[78] refers to the administration of time-dependent, potent m rapid and significant onset of action, and may not be easily reversed; ex and those used in rapid sequence intubation.[24] In one ICU study, the pre pharmacist's input at rounds was estimated to save $270,000 annually in because of ADEs.[63]

Secondly, in both incidents, ambient conditions were less than favorable performance. The internist was probably distracted by the cold, fatigue, a altitude sickness, prominent among which is insomnia. The ED nurses we busy and hurried conditions in a workplace that has been described as pr Additionally, they worked 12-hour high-acuity shifts and were scheduled and nights, which compromise performance through their effects on sleep In a study of intern's performance following a traditional schedule with ex hours or more) serious medication errors occurred 17% more frequently in which the maximum number of consecutive hours worked was limited t of serious medical errors was with medications at nearly 1 for every 5 pa other error-producing conditions and violation-producing factors have bee with human performance.[82, 27, 103] Table 134-1 lists some of the more errors often manifest as a simple slip of action, or execution failure, arisi attentional capture by something other than the task at hand.[81] Vigilance individuals who are well-rested and working without interruption or distra

environment. It was recognized more than a decade ago that fewer medi optimally designed environments.[62]

Fatigue
Sleep deprivation/debt
Transitions of care
Interruptions
Distractions
Attentional capture
Motivation/morale
Work acuity/cognitive load
Workplace ergonomics
Resource availability (RACQITO)
Inexperience

RACQITO refers to Resource Availability Continuous Quality Improvement For further details on contributing factors to medication errors see Santell Cousins DD: Medication errors: Experience of the United States Pharmac reporting system. J Clin Pharm 2003;43:760â€“767.

TABLE 134-1. Common Factors That May Affect Human Performan

The Production of Safe Medications

There is probably a widely held view among the general public that medi approval through the Food and Drug Administration (FDA) are generally sa maintains close ongoing surveillance of drugs that are approved. The first the second unrealistic. Prior to 1900 in the United States, there was no l manufacturers to establish the safety of their products through testing, ar restrictions on the therapeutic benefit claims that could be made. The firs came with the Food and Drugs Act (1906) under which medications were for strength and purity. Throughout its first century of existence the FDA stringent requirements for the safe introduction of new drugs.

There are a number of factors that influence the development of a new d

consideration is that pharmaceutical manufacturers are commercial concerr effectively compete in the market place and satisfy their shareholders. F is often the prime motivator in deciding whether to target research and d medication to a particular therapeutic area. Once these initial decisions ha research phase will develop potential candidate medications to undergo p purity, carcinogenicity, toxicology, and other properties of the medication testing on animals. The safety of selection of first-time dose in humans ca variety of approaches, eg, using interspecies scaling of clearance of the subsequently files an investigational new drug application (IND) with the testing the medication on humans. If it is approved, the clinical testing o proceeds in 4 phases, successively approximating it to its intended clinical

The Medicating Process

Five stages in the sequence of ordering a medication to its delivery are transcription â†' dispensing â†' administration â†' monitoring.[4] In a stud errors, 39% were found to occur at the prescribing stage, 12% at transc and 38% at administration.[62] Despite medication errors being the most co patients, only a relatively small proportion actually cause patient harm wit injury or ADE. Nevertheless, the incidence of ADEs in hospitalized patients from a little over 2â€“20% or higher,[14] and about 7000 deaths are attrib annually in the U.S.[57] The rate of medication errors will depend on the in methods of surveillance. In a study using a comprehensive method, the ra medication orders in general medical units, including an ICU, over a 51-da errors resulted in an ADE, and all were considered preventable. Thus, the written was 0.05%. The greatest number of errors resulting in preventable prescribing stage.[5] In a study of prescribing errors in 17,808 inpatient an only 342 (0.5%) were found to be clinically significant.[11] Although no dire made between studies, it appears that prescribing errors may have more errors at later stages of the process.

The more steps there are in any process, the greater the likelihood of err correctly 99.5% of the time, there will be a 5% probability of failure in a probability proportionately increasing with an increased number of steps in there are 25 steps, excluding fatigue and other factors that affect perfor

error will have reached 12%.[46] Although the medicating process has only multiple steps within each stage and so the potential for error is high. An been added to describe errors that may arise in follow-up after medicati Figure 134-2 describes typical errors that occur at each stage in the proc strategies.

Communication issues are very important at all stages in this process. All in writing, printed, speech, or by other means, must be transmitted in a timely fashion. Physician's handwriting is still an important issue. In its 2 Goals, JCAHO developed a minimum list of 5 sets of dangerous abbreviat symbols that should not be used, and proposed preferred terms.[52] The In Practices (ISMP) has also published a comprehensive list.[50] Communicatior important between physicians and patients. In a study of 661 patients in practices, patient reports of medication side effects to their physicians led 76% of cases. A failure to identify medication-related symptoms resulted 2% preventable ADEs. Ameliorable ADEs were defined as those in which could have been reduced substantially had different actions been taken.â the point that the first error of a preventable ADE is compounded by the identify it.

Monitoring is another very important stage in the process and has receiv The sixth stage was added to emphasize the final part of the medication drawing attention to considerations that should be made for patients afte hospital, ED, or physician's office.[24 , 33] Monitoring needs to be seen as a begins at the time the patient receives the medication, wherever they ma system, and continues for as long as they are on the medication. In the such as in the hospital or ED, the process is especially important and rec between the pharmacy, laboratory, and physician,[88] but it continues thro system. In the primary care setting, 17 separate tasks were identified fro order a laboratory test through to getting the result to the patient.[44] In undertaken by 40 Massachusetts hospitals, 9 safe practice recommendatic improve communication of critical test results.[41]

Adverse Drug Events, Adverse Drug Reactio Related Morbidity

Thus far, most of the emphasis in improving medication safety has been preventability of ADEs, which (in contrast to adverse drug reactions [ADR errors. The National Coordinating Council for Medication Error Reporting a defines a medication error as â€œâ€¦ any preventable event that may ca medication use or patient harm while the medication is in the control of t professional, patient, or consumer. Such events may be

related to professional practice, health care products, procedures, and s prescribing; order communication; product labeling, packaging, and nom dispensing; distribution; administration; education, monitoring and use.â morbidities (MRMs) is a more encompassing term that describes the failur achieve its intended therapeutic outcome, but also may include biosocial related problems such as noncompliance, undertreatment, and others.[42]

Stage	*Error Producing Conditions*	*Medication Error Reducing Strategies*
Prescribing	Incomplete knowledge of medication	Readily available medication reference systems
	Incomplete knowledge of patient	Increased pharmacist availability
		Take a thorough medication/medical/allergy history
		Physician order entry
		Computerized decision support
		Pediatric patients:
		Determine accurate weight in kilograms
		Be alert for calculation/decimal point errors
		Caution with 'off-label' prescribing
		Geriatric patients:
		Consider co-morbidities and drug-drug interactions in particular
		Consider possibility of falls with new medications
		Consider renal, hepatic and thyroid function
		Follow Beers criteria[8,9]
		Potentially pregnant patients:
		Rule out pregnancy
		Careful evaluation of risk:benefit
Transcribing	Verbal orders	Avoid verbal orders except in emergencies
	Poor penmanship	Write legibly; print if necessary
	Abbreviations, symbols	Avoid acronyms or prohibited abbreviations
		Electronic order transcription
		Team communication errors
		Indicate decimal point clearly
		No trailing zeros
		Avoid apothecary terms
		Include physician phone number/pager

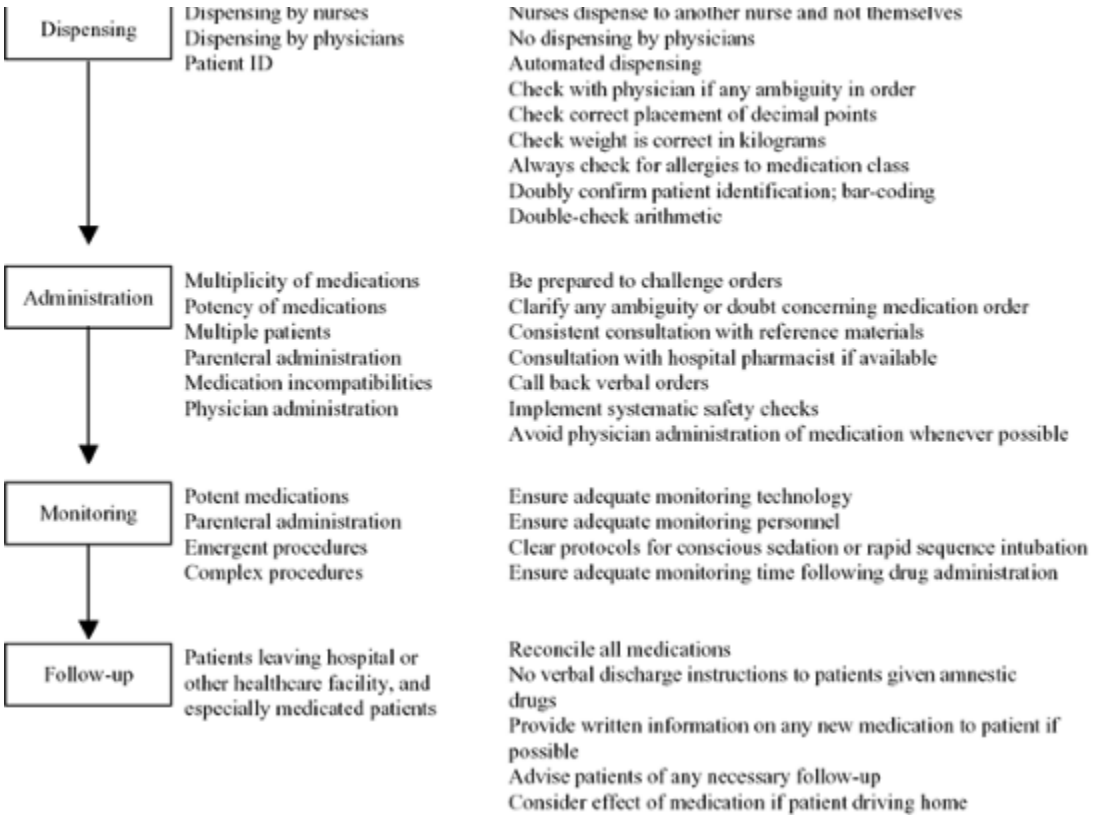

Figure 134-2. Stages in the ordering and delivery of a medication, and with each stage.

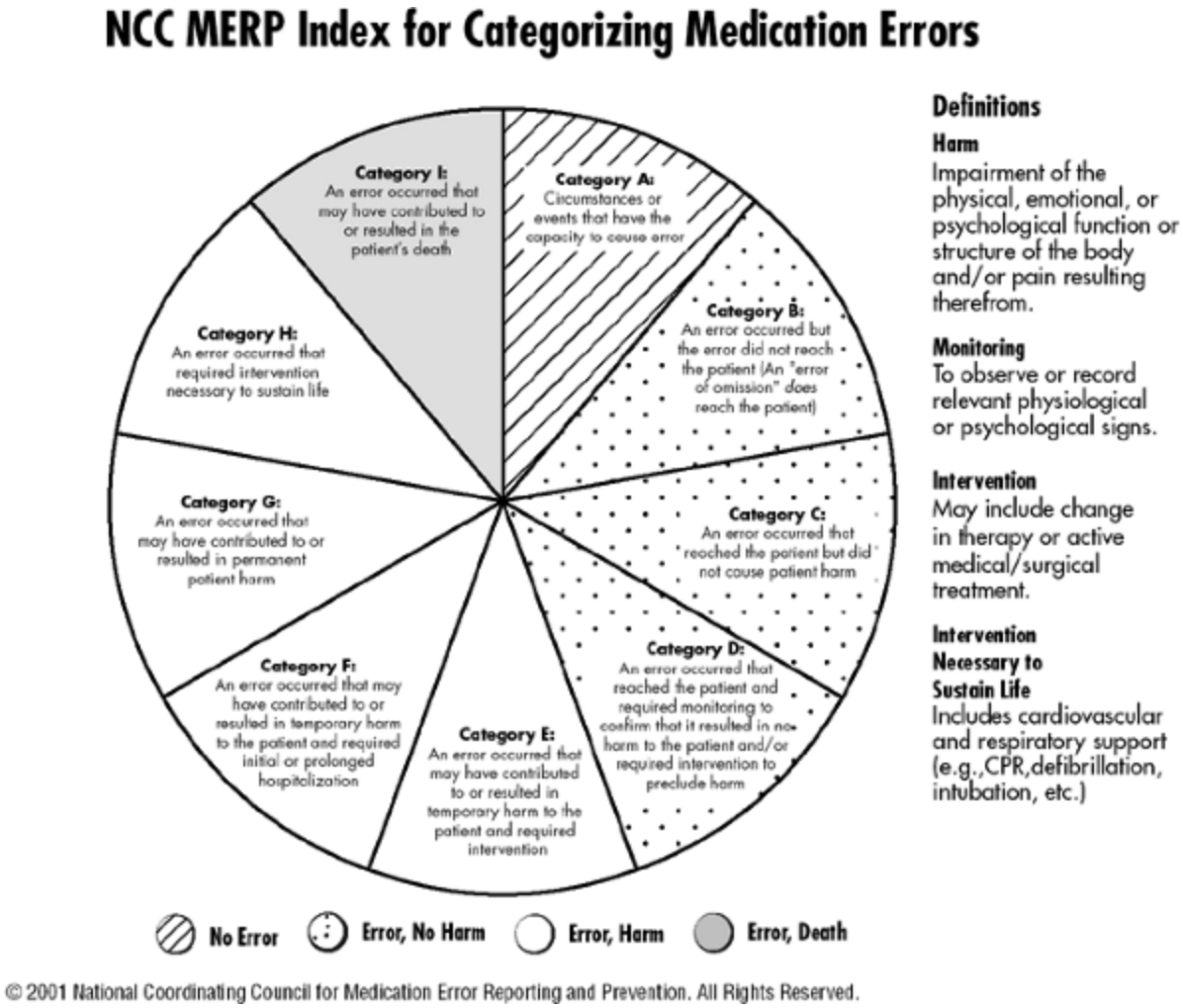

Figure 134-3. Pie diagram showing NCC MERP categories of medication to errors with no impact on patient care.

An ADR is not a medication error. For example, if a patient with no known medication and subsequently develops a reaction to it, an ADR has occurr foreseeable or preventable with the information available. The World Hea generally defines an ADR as any noxious, unintended, and undesired effec occurs at doses used in humans for prophylaxis, diagnosis, or therapy, e failures, intentional and unintentional poisoning, and medication abuse, a events because of medication administration errors, or noncompliance.[104] hospitalized patients from 1966â€“1996 estimated the overall incidence of and fatal ADRs at 0.32%. In 1994, 106,000 deaths were attributed to AD

A useful medication error taxonomy developed by the NCC MERP, classifi according to severity (Figure 134-3).[73] Importantly, the categories of lea describe circumstances or events in which the potential to cause error ex but does not reach the patient. These â€œnear missesâ€• or â€œnear hi critical source of information and learning about medication error, but ar and underappreciated. MEDMARX, a national database for medication erro United States Pharmacopeia (USP) in 1998. It is an Internet-accessible r program, using multiple reporting methodologies, that is confidential, de (importantly) anonymous. The results of a 3-year review (1999â€“2001) submitted to MEDMARX from hospitals and health systems found the majo total), followed by B (32%), A (10%), D (13%), E (2%), F (0.4%), H (0.(There were 19 errors in category I, contributing to or resulting in patient The top 4 types of error were

omission (30%), improper dose/quantity (21%), unauthorized medication prescribing (12%).[87]

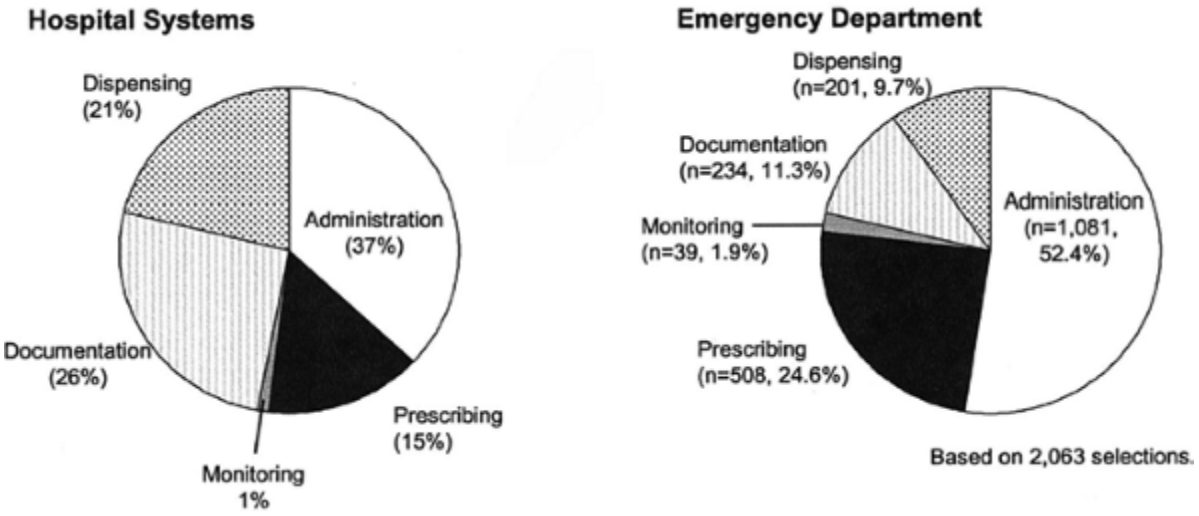

Figure 134-4. Pie diagrams showing MEDMARX data for (A) hospital syst one settingâ€”the ED. Adapted from United States Pharmacopeial Conve

The origin of errors was identified in Categories Bâ€“I (Figure 134-4A), the most frequently reported at 37%. The monitoring category at 1% is underreported because of its lower visibility. The pattern of errors will var

healthcare delivery. In contrast to these data for hospital systems overal specific data for a particular site, the ED. The differences reflect the ope ED[24 , 79] that lead to fewer dispensing and documenting errors, but more administering errors.

The most frequently reported cause of error in each of the 3 years of stu at 43%â€”more than double the next most frequent cause *procedure/proto* performance deficit means that the individual making the error had the avoid the error but failed to do so. As noted above, there are numerous contribute to performance deficit, including many ergonomic issues such resource limitations, staff shortages, and others. *Documentation* was thir *knowledge deficit* was fourth at 10%.

In 2001, the most frequently cited medications associated with harmful e morphine (3%), heparin (3%), potassium chloride (3%), warfarin (2%), the 2003 data, the same products remained in the top five.[45]

These data are subject to various forms of reporting bias. There are a va documentation and reporting of medication errors may be discouraged, ar underreported. Nevertheless, they do provide an overall picture of chara errors that is helpful.

There are significant costs associated with an ADE. In 1997, excluding the or malpractice costs, the cost of one ADE was estimated at $2000â€“2500 almost double that.[6 , 15] Nearly 10 years ago, other studies estimated the medication-related morbidity and mortality to be over $77 billion in the $2 billion in hospitals,[6 , 15] and $4 billion in nursing home settings.[13] The cost was estimated to have more than doubled to $177 billion by the yea not take account of legal or psychological cost to the patient, and to thei

The Impact of Age

There are important medication safety issues for children and older adults underrepresented or excluded from clinical trials. It is estimated, for exam the medications used to treat children have been adequately tested in th concerns apply to medications used in older adults.[47] It is important to n studies on medication error has been on preventability. Errors associated

inappropriate prescribing of antibiotics) or underuse (eg, failure to prescr such as a cholesterol-lowering agent) are typically not captured and rem

Children

Adverse exposure to medications may occur during pregnancy and lactat may occur in all settings: the home, in ambulatory care, the ED, hospita care unit (PICU), and neonatal intensive care unit (NICU) (Chap. 31). Er home environment with nonprescription medications, but the true incidenc survey, the inaccuracy of home antipyretic use was estimated at almost 5 typically one of underdosing, this may periodically be beneficial in avoidir antipyretics that lead to liver failure from dosing at levels greater than t dose.[85] In the ambulatory setting, the incidence is again unknown but or â€œnumerousâ€• errors in prescription writing in a pediatric clinic.[99] In rate was estimated at 10% of all charts,[59] and the sources of some of th The incidence for medication errors of hospitalized patients is estimated a written, about 20% of which were classified as potentially

harmful; the majority (74%) occurred at the ordering stage.[34] Generally, care unit appear to be at higher risk for errors, presumably reflecting the disease and the medications used.[56] The most commonly reported produc medication errors in children are intravenous fluids.[28] A number of errors also found in discharge instructions from the hospital.[54]

Children are vulnerable to medication errors for a variety of reasons. Firs communication difficulties. Before language has developed fully, children m articulate their symptoms, cannot report whether or not they have taken or how much they have taken in an overdose situation, and other proble only infer what has happened. The patient does not play an active role in process, and the child is entirely dependent on adults. This dependency i exposure to medications during pregnancy and lactation. Secondly, confu the child's weight. Children may be weighed in either kilograms or pounds information is usually in kilograms, an additional calculation may be requ kilograms. Thirdly, their lower weights make them vulnerable for several adults, weight-based dosing is necessary, which introduces an additional a

process. Also, there is often a requirement for dilution of stock medicatio dose, usually without the input of a pharmacist. Erroneously calculated d make incorrect dosing the most commonly reported error. Fourthly, there vulnerability of critically ill children to injury from medication, especially i systems are immature; children are three times more likely to suffer harm medication error compared with adults. As noted above, the majority of have not been studied sufficiently to provide safe labeling information,[83] literature, there is clear evidence that publication bias has undermined s medication errors and their causes in the pediatric setting, and a compre recommendations is provided in the 2003 policy statement of the America (AAP).[18]

Older Adults

As in the case of children, medication errors in older adults occur in all s ambulatory care, in nursing homes, in the assisted living setting, and in t The incidence of medication error at home with nonprescription medicatio reasons outlined below, would be expected to exceed that of the younger ambulatory care setting, using a variety of methodologies, ADEs were eva period in a multispeciality practice in a cohort of 27,617 Medicare enrolle 30,000 person-years of observation. Extrapolating their findings to all Me or older), estimated to number 38 million, would predict nearly 2 million >25% would be considered preventable. About 180,000 fatal or life-threa predicted.[40]

There are more than 1.5 million nursing home residents in the United St uses six different medications, and 20% use ten or more.[10] Extrapolating study of 18 community-based homes in Massachusetts over a one-year p 350,000 ADEs annually, more than half of which would be preventable.[39] ADEs would represent 20,000 of these predicted events of which 80% wo Approximately one million other seniors live in assisted-living facilities, ar medication errors from a variety of reasons including: inadequate physic trained staff, and staffing shortages.

Addressing these issues is becoming increasingly important as the US Ce increase of 62 million in the number of Americans 65 years or older by th

represents a 78% increase in the number of older adults in 2001. Over th population of 85 or older will increase by 7.4 million, an increase of 68%.

Advancing age brings with it several important considerations from the pc safety:

- There is an increasing morbidity with age, and therefore an increasing medication. In the US, people over age 65 comprise 15% of the total one third of prescribed medications.[94] Comorbidities and disease chro of concurrent medications, and therefore the number of potential int the relative efficacy of medication with increasing age have made sor treat aggressively. The use of thrombolysis in acute coronary syndrom counter-therapeutic after the age of 75 and actually present a disadv have argued that this may constitute underuse of therapy: neither re nor the serious complication rates should negate the therapeutic bene is very good evidence to the contrary less attention should be paid to Given the preponderance of women among older adults, there should, emphasis on female geriatric pharmacotherapy.[93]
- Frailty and cognitive decline in older adults may result in errors in s require the assistance of family members or others for proper medica
- The majority of medications are developed and tested on healthy you adults are underrepresented the slowing of metabolism, renal functior variety of other changes that result in altered pharmacokinetics are considered (Chap. 9). Alterations in medication absorption, metaboli elimination may all affect the efficacy of the medication.

Recognizing the special problems that medications pose for older adults, both the US[8 , 9] and Canada[72] to determine appropriateness of medicatio home residents. The authors identified 48 medications, or classes of med medications to avoid in the presence of 20 diseases/conditions.[32] In a re 750,000 patients 65 years or older over, 21% had filled a prescription fo that should have been avoided, psychotropic medications accounting for a cases.[29] The prevalence of inappropriate medication use in older adults ha be estimated in the range 12â€“40%.[90] Both the medication effect and th

implications should be considered. Older adult patients medicated with b example, have a 4-fold increase in falls. Significant differences within the were found: the risk of injury associated with benzodiazepine use genera

be independent of half-life; there was no increase associated with long-ac was there a dose-effect, whereas there was an associated risk with the u oxazepam. Flurazepam and chlordiazepoxide (both long-acting) were asso increase in risk of injury.[92] An alternate approach has been taken to dev indicators of preventable medication-related morbidity (PMRM) in older ad technique, the four unique elements of a PMRMâ€"that it be recognizabl and controllableâ€"were used to develop an expert consensus on 52 clini follow-up study, the top seven indicators were found to account for almos technique has the potential to prospectively identify patients at risk for a optimize medication use in this age group.

Solutions

Although the importance of medication safety issues has long been recog emergence of a commitment to patient safety has brought them into cons refreshing number of new initiatives have emerged in recent years. The fo US in 1994 was an important step. It is an independent, nonprofit organi funding from the pharmaceutical industry. It provides a number of useful newsletter with individualized editions to acute care, community/ambulato sectors. ISMPs have now been established in Canada and in Spain.

The last decade has seen a significant number of publications on medicat data has been made available from reporting systems. Although reported selective and subject to various biases, those gathered by the USP throug programs provide a useful overview of trends that might guide research s Long-standing issues have been addressed, such as the confusion over a and look-alike and sound-alike medications. Attention has also been direct concern. In some, a useful consensus has evolved resulting in the publica such as that of the AAP on the prevention of medication errors in the pe number of innovative approaches toward prevention have been proposed. their early stages of development and all will continue to undergo furthe

Response to Medication Error

The leading cause of medication errors is human performance deficit. Inva precede the ADE, and this temporal contiguity of action and consequence tendency to blame someone; this will usually be the last person to have h patient. In recent years, however, a consensus has emerged that blaming counterproductive. The number of ADEs that result from truly egregious b more often than not the explanation will be found within the system. Roo term originally used to investigate major industrial events, is a technique structured, process-oriented analysis of sentinel events. Its use was mand accredited hospitals in 1997. It is a time-consuming process requiring m specialized training, and is subject to various biases and methodological judiciously conducted RCA may provide insights into systemic failures und identify areas that require change. An alternative approach that more eff off the individual and onto the system is a clinical incident analysis proto It uses a framework of seven factors to map out the ground to be covere organizations have developed a hybrid combining these two approaches. B incident analysis are conducted retrospectively, and therefore subject to alternative approach is failure mode and effect analysis (FMEA), which pr identify errors that might occur, to implement preventative measures. On 1993,[17] it is now a requirement under the JCAHO Patient Safety Standard ISMP.[51]

Human Factors Approach

That human performance deficit is the primary cause of medication errors in a medical environment that is extremely complex. This environment is enriched by many properties inherited from its historical past. Human fac draws on a variety of disciplines including industrial engineering, industr psychology, information technology, and others. There is much that can b interface between humans and the work environment and to ensure that efficiently. As a general principle, it would be preferable if the dominant medical devices and processes was that they fit human users, and not th

A particularly important goal is the reduction of cognitive load. Many me

from cognitive failings because of interruptions, distractions, inexperience overloadingâ€”referred to as performance deficit. Further effort needs to reduce cognitive failure. The adoption of some very simple strategies bas engineering principles will reduce error, such as simplification of the num reducing reliance on memory, applying cognitive forcing strategies,[23] and particularly useful aid is the color coded Broselow-Luten system, which ca medication dosing.[65] This approach has the potential for further developm of nonprescription medications and other potentially dangerous products us universal standard color-coding drug labeling system has been proposed i between-class medication errors.[1 , 76]

Information Technology Innovations

Information technology (IT) in healthcare has been ponderously slow to c use in other organizations, but it is now gathering momentum and has o patient safety.[7] Although considerable gains may be made, new technolog introduce new types of error. USP announced in 2004 that nearly 20% o reported to MEDMARX involved computerization or automation.[87] One stu computerized physician order entry (CPOE) in one tertiary care hospital fo actually facilitated a wide variety of medication error risks.[43] Another stu types of failures associated with CPOE but suggested that many could be particular by concentrating on organizational factors.[58] This part of the c technology is sometimes referred

to as â€œtransitional instability,â€• when â€œturbulence and chaos often harbingers of new forms of order.â€•[106] Recently, more detailed insights why process-supporting information technology systems fail.[100] Much of t medication area is relatively simple and straightforward, amenable to rap and cross-checking, and it would be expected that, in time, CPOE and oth ultimately prove very effective at reducing medication error rates.

Drug Selection

- Laboratory findings contraindicates drug

â€“ Pregnancy test â€“ ACE inhibitor

â†‘BUN/Cr-metformin
Prevents prescription writing or dispensing

- Laboratory finding suggests indication for drug

â†‘TSH-levothyroxine
â†‘Cholesterol-lipid-lowering treatment
Generates timely reminders, tracking intervention
Dosing

- Laboratory finding affects drug dose

â†‘Creatinine-digoxin, aminoglycosides
Performs dose calculations based on age, sex, value, weight

- Drug requires laboratory measure for titration

Warfarin sodium-PT/INR
Anticonvulsants-drug levels
Statistical process control dosing adjustment charts
Monitoring

- Abnormal laboratory value signals toxicity

Liver enzymes-isoniazid, glitazones
â†“ HCT, WBC-chloramphenicol
Triggers alert, assesses likelihood

- Drug warrants laboratory value monitoring for toxicity

Clozapine-WBC
Amphotericin B â€“ creatinine
Oversees scheduling of both baseline and serial monitoring tests
Laboratory Interpretation

- Drug influences or interferes with laboratory finding

Carbamazepine-free thyroxine
Quinolones-false-positive urine opiates
Warns against/interprets false-positives and false-negatives

- Drug impacts on response to laboratory finding

Insulin-â†“or â†‘glucose
Penicillin â€“RPR
Resets alarm threshold for treated patients
Improvement

- Drug toxicity/effects survelliance

Detects signals of previously undocumented reaction (eg. hepatotoxicity)
Data mining of laboratory and drug data to generate new hypotheses of

- Quality oversight

Treatment delay after abnormal results
(â†‘TSH, â†‘K^+ , +blood culture) and initiation of appropriate treatment.
Monitors time internal between testing and prescription change, adequa
laboratory monitoring
Abbreviations: ACE, angiotensin-converting enzyme; Cr, creatinine; HCT,
international normalized ratio; K^+ , potassium; lab, laboratory; PT, proth
plasma reagin; BUN, blood urea nitrogen; TSH, thyotropin; WBC, white b
* Plus sign indicates positive
From Schiff GD, Klass D, Peterson J, et al: Linking laboratory and pharm
reducing errors and improving care. Arch Intern Med 2003; 163:893â€“9
modified with permission.

Examples of Drugâ€“Laboratory Special
Category Concept Pairs*

TABLE 134-2. Strategies to Improve Care Through Laboratory an

Smart cards have been developed that allow compression of a variety of
With one swipe these â€œhealthcare passportsâ€• allow rapid retrieval o
as medications and doses that a patient is currently receiving, along with
are potentially valuable for patients being admitted to an ED, or other he
patient's transitions of care when discontinuities occur and vulnerability t
transfers within or between facilities. They have been in use in some he
2001.[91] In 2004, the FDA gave approval for medical use of a grain-of-ri
identification (RFID) microchip that is implanted subdermally,[21] a technol
the livestock industry. Bar code technology reduces administration errors
errors. Bedside bar-coding, in particular, has considerable potential for r
medication administration errors by nurses. Computerized medication ad
achieve significant reductions in administration and transcription errors. Fu
by improvements of the interface between the laboratory and the pharma
critical values can be transmitted simultaneously to the attending physici
specific examples. Software applications can also be developed to track th
medications or antidotes that might have been used in the treatment of a
a continuous quality monitoring strategy. Computerized links between the
office, and pharmacies can improve the safety of patients being discharged
healthcare facility (stage 6 in Figure 134-2).

Ward-Based Clinical Pharmacists

Pharmacist participation at the clinical interface reduces medication errors
involvement of a clinical pharmacist in work rounds of an adult ICU reduc
66%,[63] and in the PICU reduced the serious medication error rate to one
rate.[55] However, fiscal restrictions will inevitably mitigate against the exp
professionals and cost-benefit arguments will be applied. An unintended co
clinical pharmacist is present, nurses, residents, and attending physicians
them and spend less time developing and maintaining their own skills for
such help may not be available.

Improving the Workplace

Working long hours, experiencing sleep deprivation, and incurring sleep de
compromise cognitive and psychomotor performance[12] and are, undoubte

medication errors. The reduction of residency work hours to 80 hours

per week (still double the industry standard) has met with concern that p deteriorate as care is being transferred more frequently.[80] This is probabl dissuade us from efforts to reduce the impact of circadian disruption, sle debt. Whereas errors because of hand-overs probably increase in a fairly successive hand-overs, those associated with fatigue and sleep loss prob Thus, the goal should be to find the optimum shift length for safe patient effort in improving the quality of hand-offs. More work needs to be done that optimize both healthcare worker safety and patient safety.[26] Like tru to be regulated for the total number of clinical hours they work each wee

Education

The prevailing emphasis in physician training is on knowledge acquisition. inculcating critical thinking skills and teaching reasoning, the assumption passively acquired during the process of training. Although this is partially opportunities to improve these cognitive faculties by direct intervention.[2] reasoning can be improved and expertise cultivated by specific teaching variety of other strategies have been proposed to reduce predictable cog the beginning of the medicating process improved clinical judgment has t patient safety. For example, errors of omission or undertreating are often commission, but may have equal or greater impact.

Many aspects of the medicating process are not formally taught during u training. There is little explicit medical school training for students in the dosing, weight-based calculations, medication interactions, and so on. Ver in how to achieve medication safety or in how to pursue multidisciplinary these goals. A study of medication dose calculation in emergency medicin this appeared to be a discrete skill, responsive to a relatively brief educa in the short term.[74] Generally, there appears to be a tacit assumption tha acquired during clinical training, but this study suggested that they might independently and that specific training is indicated.

Importantly, communication theory should receive more emphasis in trai skills both within and between disciplines, and especially between practiti

will limit errors. As patients are admitted, transferred within, and discha facilities there is an ongoing imperative to communicate exactly what me doses they are receiving, and ensure that any changes are accurately rec of medication reconciliation and has been adopted by JCAHO in 2005 as c Safety Goals. It is an important communication strategy to ensure safe co other aspects of patient safety, these issues should be formally introduce curriculum. Improving the training of health professionals is two of only there is evidence of efficacy.[84]

Improved Accountability of Medication Ma

There are many ways in which pharmaceutical companies might improve Initiatives are already underway to insure the appropriate naming and pr minimize confusion.

The entire structure of pharmaceutically funded clinical research must be to be a number of changes in the way in which research is conducted. Id to have an independent body, publicly funded, that would evaluate new d efficacy and safety with that which is currently available. The National Ce Technology, established in 1978 was such a body, but expired after only pressure. Other efforts along these lines have met a similar fate. It remai greater proportion of pharmaceutical research independent of industry an sources, but until that balance is redressed clear standards have to be e pharmaceutical companies' research to the accepted rigor and scrutiny of method. A recent agreement among editors of a number of leading journa pharmaceutical companies to register any trial begun after July 1, 2005 in all trials that have been done on a particular drug will be known and pre data.

Throughout the pharmaceutical, nursing, and medical professions, there is awareness regarding the marketing practices of pharmaceutical companie need to be taken. In 1992, the McMaster University Department of Medic that restricted contact of trainees with pharmaceutical company represen in posttraining found they had less contact with these representatives. C from another medical school that had no such restrictions the McMaster pharmaceutical company representatives to be less helpful.[70] Restrictions

companies' activities, and especially restricting contact with medical stude now been adopted by many institutions.

Another pharmaceutical practice that undermines safety and efficacy of m distribution by physicians of drug samples. Despite some obvious immedi benefits of this practice, it has a variety of inherent flaws and violates fu drug safety that have been described.[37] Several recommendations for cha improve safety have been proposed.[66]

Finally, advertising of pharmaceutical products is another area that should two areas of concern. The first is advertising to the medical profession. A the availability of references and sponsorship of original research cited i advertisements in medical journals for the year 1999.[19] Approximately 30 medical claims contained no references. Of those with references, about on file. When the authors tried to access this data from the pharmaceutic unavailable 80% of the timeâ€"in contravention of the WHO policy on eth drug promotion.[104] They also found that 58% of original research cited had authors affiliated with the same pharmaceutical company. The second legalized approach of direct-to-consumer marketing for prescription medic clearly aimed at inducing the public to pressure their physicians for newer expensive drugs. The practice is illegal in many countries. The rationale this is an educational process and is about choice is unacceptable. There educating about disease and raising awareness

without using direct consumer advertising. Because even physicians are n research that have been perpetrated by industry, it seems unlikely that t meaningfully evaluate the claims made by drug advertisers, and choose t themselves.

The variety of ethically questionable behaviors of industry has attracted recent years and will need constant monitoring. The confidence of the sc communities, and the general public has been seriously undermined by r a growing and disquieting awareness that the problems are more wide re believed.

Summary

Medications are the principal commerce of modern medicine, and medicati importance to healthcare systems. With the emergence of the new indust safety, renewed attention and energy has been directed at the problem. safely to patients is a more complex process than originally imagined. It but creates special problems at the extremes of age, in the children and components, the development of safe medications, and their safe use, re and vigilance. The multiplicity of stages in the delivery process results in preventable errors, some of which may be fatal. Many innovations, especia information technology, hold promise for significant improvement.

The process can no longer be perceived as a simple 3-way relationship b physician, and pharmacist. Patient safety requires a collaborative effort p medication manufacturer, but also federal regulation authorities, indepen organizations, error theorists, hospital administrators and managers, inf nurses, cognitive psychologists, human factors ergonomists, geneticists, this new multidisciplinary approach, there is considerable potential for re This appears to be one area in patient safety in which tangible and measu

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Chapter 135

Risk Management and Legal Principles

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The use of emergency services has increased dramatically since the early 1970s, and along with it the number of toxicologic emergencies has increased steadily and continues to rise today. This chapter is concerned primarily with the medical-legal management of patients who present to an emergency department (ED) with an organic impairment, that is, a relatively recent deterioration in the level of cognitive or behavioral function caused by the effects of xenobiotics or alcohol. A secondary component of this chapter addresses the legal dilemmas associated with the social and ethical issues that emergency practitioners routinely face.

Patients who are experiencing toxicologic emergencies require immediate care yet are often unable to give consent because their impaired consciousness prevents them from making decisions. Treating patients who present with an acute organic impairment

manifested by confusion and irrational, or even dangerous, behavior is extremely difficult. Emergency physicians must recognize the medical-legal problems created when the impaired patient refuses treatment or admission to the hospital and insists on leaving against medical advice. No clear guidelines are available to the physician confronted with such a toxicologic emergency. There is no nationally recognized standard of law relating to these issues; instead, the relevant laws vary from state to state. The emergency physician must become familiar with the legal requirements of informed consent and the essential management necessary to avoid liability for negligence and abandonment. Of particular concern are the risk management and liability issues that relate to the patient who attempts to leave the ED while impaired. The legal requirements of informed consent in emergency settings, the duty to treat, medical malpractice, battery, and negligence are examined here, and guidelines based on generally accepted common law principles, and New York State case law and statutes, are suggested for developing appropriate patient care plans and departmental policies.

Informed Consent

Patient 1 An 18-year-old college student was brought by ambulance to the emergency department (ED) after a friend reported seeing her in the bathroom with slit wrists and an empty bottle of acetaminophen by her side. In the ED, the patient was alert and oriented to person, place, and time. Vital signs were: blood pressure 120/65 mm Hg; pulse 95 beats/min; respiratory rate 16 breaths/min; and temperature 99.1Â°F (37.3Â°C). A rapid bedside glucose was 120 mg/dL. She had bandages on her wrists placed by emergency medical services. The patient stated that she ingested the acetaminophen approximately 5 hours earlier. The healthcare team wished to measure acetaminophen levels to determine whether *N*-acetylcysteine should be administered. The patient refused a venipuncture and stated that she would refuse

any medications offered. The physicians informed the patient that she might suffer irreparable damage to her liver and possibly die if not treated immediately.

Deciding to medically treat an individual against their will poses a difficult problem. Even if justified, forcible treatment violates a patient's autonomy, and an individual's right to privacy. Is the physician ever justified in administering medication to an alert and oriented individual who refuses treatment? Does the patient need to be suffering from a mental illness such as depression to treat against their will? If the harm that faces the patient is not immediate, but subacute, or chronic, does the physician have the same authority to treat? For example, compare detoxification programs for substance abusers versus *N*-acetylcysteine after an acetaminophen overdose. The right to die will not be specifically discussed here as it is far too complex for a cursory analysis, however, general principles of patient autonomy and informed consent will be elucidated.

A patient's right to choose their own course of medical treatment was first recognized in the early 19th century in a landmark case decided by the US Supreme Court, *Schloendorff v Society of New York Hospital*.[16] Mary Schloendorff was treated at the hospital with abdominal pain and was subsequently found to have a mass on abdominal examination. Her physicians offered her a more thorough examination under anesthesia and the option for surgery. She consented only for the examination; however, during that examination the mass was removed. Schloendorff experienced a number of postoperative complications and sued the hospital. In its decision, the Court upheld Schloendorff's right to self-determination, and the right to refuse treatment. It stated:

> Every human being of adult years and sound mind has a right to determine what shall be done with his own body and a surgeon who performs

> an operation without his patient's consent commits an assault, for which he is liable in damages, except in cases of emergency in which the patient is unconscious and it is necessary to operate before consent can be obtained.[16]

This decision became the foundation for the â€œDoctrine of Informed Consent.â€• Informed consent serves to protect a patient's autonomy, the concept that each individual has the right to choose the course of medical treatment.[27] This includes the right to refuse care, and

the right to terminate care already in process. In a nonemergent situation, it is the physician's responsibility to obtain approval from the patient or their surrogate before rendering treatment.

Generally accepted components to the informed consent process consist of (1) an explanation of the treatment/procedure, (2) alternative choices to the intervention, and (3) relevant risks, benefits, and uncertainties to each alternative. Furthermore, it is the duty of the physician to assess how well the patient understands the above information. Before a physician may accept a patient's approval the patient must demonstrate adequate understanding of the information discussed.

State courts may apply one of two standards to determine if the information communicated by the physician was sufficient. The reasonable person standard requires that a physician disclose to the patient information that which a reasonable person in the same position as the patient would need to make an informed decision.[5] The alternative is the reasonable physician standard, which requires that a physician reveal information that a reasonable physician in a similar circumstance would disclose.[5] With this standard, the physician must assess what another physician might disclose if placed in a similar circumstance. States

vary on which standard they apply.

Courts recognize that the requirement for informed consent is not absolute, and that there are exceptions in which a physician does not need to obtain permission before rendering treatment. In *Schloendorff v Society of New York Hospital*, the Court recognized that consent is not required in emergency situations. Situations are generally considered emergent if a patient's care would be compromised if there were a delay in treatment. In New York, an emergency is defined as a situation that includes both the immediate endangerment of life or health or the need for the immediate alleviation of pain.[19] Physicians need to determine the specific requirements of informed consent in their states.

Often a physician's well-intended efforts to communicate treatment information to an impaired patient prove ineffectual and present the practitioner with a medical-legal dilemma. The physician is unable to discuss in a meaningful way the implications of the proposed treatment with the patient; nevertheless, there is a duty to treat a patient who presents with a life-threatening condition or the potential for permanent disability. In these situations, consent on the part of the impaired patient is considered to be implied, and emergent treatment should be provided. Support for this view of implied consent is a general tenet of tort law.[14]

Risk Management Consideration and Documentation

Patient 2 6:05 PM. A 28-year-old woman was brought to the ED by the police. The police believed she might be a â€œbodystufferâ€• (an individual who swallows drugs to avoid arrest and prosecution).

6:10 PM. The triage nurse helped the patient onto a stretcher and brought her to the treatment area. The physician was asked to see

the patient. Her vital signs were: blood pressure, 130/70 mm Hg; pulse 78 beats/min; respiratory rate 24 breaths/min; temperature 98Â°F (36.7Â°C).

As the physician initiated the examination, the patient became combative and uncooperative. The physician verbally ordered that the patient be restrained. The patient was given 40% oxygen via face mask, cardiac monitoring was begun, and an intravenous line was started with 0.9% sodium chloride at 125 mL/hr; a bolus of 100 mL of $D_{50}W$ and 100 mg of thiamine were then administered IV. Orogastric lavage was then performed, and 50 g of activated charcoal (AC) were administered.

7:10 PM. The patient's vital signs were: blood pressure 120/70 mmHg; pulse 82 beats/min; and respiratory rate 24 breaths/min. The patient was noted to be stable and transferred to the other observation unit. Oxygen and cardiac monitoring were discontinued. No further orders were written, and the patient remained restrained.

11:15 PM. The vital signs were: blood pressure, 110/60 mm Hg; pulse 92 beats/min; and respiratory rate 18 breaths/min. A nurse's note stated the patient was resting comfortably.

11:50 PM. The initial physician completed his shift and was replaced at midnight by another physician. The first physician informed his replacement that the patient was stable and resting in the holding area.

4:20 AM. The patient was found unresponsive, with agonal respirations. She was hypotensive and had a weakly palpable pulse. She felt very hot to the touch and had a rectal temperature of 108Â°F (42.4Â°C). Resuscitative efforts were initiated but unsuccessful.

4:50 AM. The patient was pronounced dead.

Several important risk management questions frequently arise in

medical malpractice litigation involving the ED. To prove that a case constitutes medical malpractice, a plaintiff's attorney must show clear and convincing evidence of a departure from good practice by the physician. The attorney must further demonstrate that the negligent act or omission by the physician proximately caused the patient's injury. Courts have held that where â€œthere is substantial probability that the [defendant physician's] negligent conduct caused the resulting injury, that sufficient evidence has been developed against [the] physician.â€• [26]

The problems associated with an improperly documented ED record are numerous, but they can be minimized if the practitioner is cognizant of risk management principles. When the attorney for the patient (plaintiff's attorney) introduces evidence to prove the case, the central document in the medical malpractice trial is likely to be the ED record. Thus, every entry in that record is scrutinized with great care by both parties (plaintiff and defendants), and the importance of completing it with knowledge of risk management implications should be a concern for all healthcare providers.

The physician is required to write a medical record that will amply support the basis for the medical judgments exercised. When a physician chooses to write only a summary statement on the record without noting supporting clinical data or patient history, claims alleging failure to diagnose will be extremely difficult, if not impossible, to defend. One of the basic elements of the defense in a medical malpractice case is that the physician's judgment was appropriate, given the clinical facts and the patient's history available at that time. Therefore, physicians who do not record supporting clinical data and history deprive themselves of a strong â€œmedical judgmentâ€• defense.

Inappropriate entries or markings on the medical record can weaken the defense in a liability case. For example, in attempting to correct and error in entering a PO_2 value, if the physician or nurse totally obliterates the number, an attorney representing a

patient may suggest to the jury that the obliteration was done intentionally to conceal clinical data harmful to the position of the defense. If a physician must correct a prior entry made on the record, the preferable method is to draw a single line through the value or word to be changed, insert the correct information directly above and initial

the correction. Dating the correction also precludes potentially difficult questions of timing and responsibility in a courtroom setting. By following these suggestions, the physician avoids any accusations that he or she intentionally concealed an error in judgment (Figure 135-1).

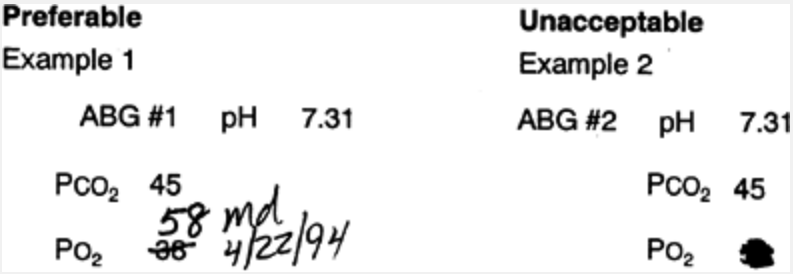

Figure 135-1. Examples of the preferred and an unacceptable procedure for correcting an error in the medical record.

A frequent claim is that the patient was abandoned or improperly monitored. For the above patient, although the chart appears to document repeated vital signs at appropriate intervals, no temperature is included after the first set until the patient is moribund; nor is any mention made again of the continued use of restraints, the patient's continued need for these restraints, or any

adverse effects developing from the use of restraints. Quality assurance reviews of ED records often demonstrate inadequate charting by physicians and nurses monitoring patients who remain in the department for prolonged periods of time. Under any circumstances, a lapse of documentation of the patient's clinical condition for four hours or more after the initial physician and nursing assessment creates a potential risk management problem. In a lawsuit, the plaintiff's attorney would undoubtedly use such a record to develop the theory that no care whatsoever was given to the patient during this time interval, and that the patient was abandoned.

Monitoring notations in the patient's record are considered inadequate when they do not offer insight into the patient's clinical status. Thus, any monitoring note for a patient who must be restrained in the ED for a lengthy period of evaluation, observation, or until an inpatient bed becomes available must include specific clinical data and observations (laboratory results, radiographic findings, hemodynamic changes, and infusion of medications and solutions). All of these deficiencies would undoubtedly be noticed and highlighted at trial by a plaintiff's expert, who frequently is a board-certified physician in the specialty in question.

Any documentation supporting the restraint of an impaired patient against his will must include a clinical description to support such a forcible impediment to the patient's right to liberty and freedom of movement. Such a clinical description should specifically describe any manifestation of agitation and uncooperative behavior. The record should refer to the specific uncooperative acts of the patient and, most importantly, should comment on the difficulties in providing care to the patient because of the patient's actions. If such documentation is present, a theory of negligence against the physician for inappropriate restraints would be virtually impossible to sustain.

Physicians who order restraints for patients must exercise extreme caution in the language used to describe such patients. A judgmental physician's note stating that a patient is â€œa chronic drunk and obnoxiousâ€• could undermine the support for the use of restraints. Poorly written physician's notes can become an issue in a medical malpractice action, with the plaintiff's attorney focusing on the derogatory nature of such a statement and suggesting a less-than-caring attitude by the doctor toward the patient. A plaintiff's appeal criticizing the ethical and social consciousness of the physician could very likely be seized by a jury and result in a punitive verdict against the physician. As a general rule, all healthcare professionals should depict a compassionate and professional manner by describing patient behavior and life styles in objective and concrete terms. An alternative and more appropriate description of a patient comparable to the one above would note that the patient had a â€œhistory of alcohol abuse and was uncooperative and combative.â€• To summarize, a well-documented ED record consistent with the accepted risk management principles set forth is the best course for the physician managing a difficult overdose situation in which legal principles may appear to present problems in providing proper medical management.

Forcible Restraint of the Impaired Patient

Patient 3 A 31-year-old woman was found unresponsive on the street and brought to the ED by emergency medical services. Friends on the scene reported that the patient used methadone. In the ED she was unresponsive and apneic. She was immediately administered oxygen by bag-valve mask and intravenous access was obtained. The patient was then administered naloxone IV, and shortly thereafter regained consciousness. After 20 minutes of care in the ED, the patient stated that she had taken methadone

and demanded to be discharged. On re-evaluation, she was noted to be fully alert and oriented, with no evidence of hypoxia or other clinical signs to suggest impaired judgment.

The right of a hospital to retain and physically restrain a person who has an altered level of consciousness for evaluation and emergency intervention is generally well supported by states and case law.[6] Reasonably clear guidelines for the management of such impaired patients have evolved from legal precedents governing appropriate medical assessment, from risk management considerations, and from the predictability of patient injury in the event of premature discharge.

A staff decision to allow a treated or partially treated patient with a drug overdose who subsequently becomes alert to return to the community must be based on an assessment of several factors. The initial concern is the patient's capacity to comprehend. Before the patient can be permitted to leave the hospital, a determination would have to be made that the patient is capable of understanding the information presented and has neither a medical nor a psychiatric problem preventing such a voluntary decision. The next consideration is that of medical stability. Has the initial process that caused the clinical scenario completed its course? The history of drug use in this patient is cause for concern that the underlying toxic metabolic process is not yet resolved, and alteration in mental status, significant respiratory compromise, or other medical symptoms may recur when the naloxone is metabolized, again placing the patient at risk.

Common ED practice and sound legal principles suggest that both the hospital and its staff have a duty to prevent such a person from leaving if the duration of the effect of the involved xenobiotics is longer than that expected for the antidote. Because the duration of

effect for naloxone is considerably shorter than that of methadone,

the physician can predict with reasonable certainty that coma or apnea will reoccur in the near future. The physician has the duty to inform the individual of the life-threatening nature of the condition, and then to retain, with restraints if necessary, the patient in the hospital until he or she is medically stable.

Liability in this situation is further reduced when the chart substantiates the medical judgment that was the basis for the decision to retain the patient and, if applicable, the use of restraints. Such documentation should specifically note the likely relapse of the patient into a symptomatic state and that this occurrence could place the patient and others in a life-threatening situation. When documented in a clear manner, legal challenges to the decision to restrain the patient have a limited chance at success. Sound risk management principles support treatment and detainment. Conversely, prematurely releasing a patient with a significant overdose exposes both the physician and the hospital to a claim of negligence on the grounds of failure to foresee a likely and harmful event.

Blood Alcohol and Evidence Collection

Patient 4 A 41-year-old man who was the driver involved in a motor vehicle crash was taken to the ED by ambulance. Two motorists in another car were killed. The patient had no physical complaints, but was brought to the hospital for medical clearance. On arrival, he was alert and oriented, responded appropriately to all commands, and demonstrated a normal gait and motor function. Police officers suspected that he was driving while intoxicated but he refused a breath alcohol test at the scene.

The police officers informed the ED staff that he was arrested and might be charged with vehicular homicide. The officers then requested that the emergency physician draw a blood specimen to determine the blood alcohol concentration. The patient stated that he would not allow the ED staff to draw blood for a determination

of an alcohol level.

Traffic crashes are the leading cause of death in person's age 3â€“33 years and the eighth leading cause of death in all age groups.[9] In 2003, alcohol was involved in 40% of traffic fatalities. Of these crashes, 74% of drivers had a blood alcohol concentration (BAC) of 0.08% (80 mg/dL) or higher.[10]

The judicial system has historically been one of the most effective tools to combat drunk driving, and its effectiveness depends on the ability to identify and punish individuals who violate the law. It is essential, however, that the collection of evidence does not violate the rights afforded by the US Constitution. Does forced phlebotomy for patients suspected of driving while intoxicated violate these protected rights? This has long been debated in the courts, and issues specifically brought into question include the Fourth Amendment,[22] the right against unreasonable search and seizure; the Fifth Amendment,[23] the right against self-incrimination; and the Due Process clause of the Fourteenth Amendment.[24] Past decisions on these issues help guide current laws and practices.

Every state, and the District of Columbia, has driver â€œimplied consentâ€• laws. When a person obtains a driver's license, he or she consents at the time of acquisition to a chemical alcohol test if suspected of driving while intoxicated. Under the implied consent laws, when a person suspected of driving while intoxicated refuses to take an alcohol test, he or she is then subject to a penalty. Specific penalties for refusals vary from state to state. At a minimum, the refusal results in suspension or revocation of a driver's license. Some states assign additional fines and penalties for this action. A few states allow the refusal itself to be submitted at the trial in support of the prosecution, making it possible to be convicted of an intoxication charge without chemical evidence.[1] Certain states, for example Texas and Illinois, allow blood tests to be performed on patients as ordered by a law officer, when there

is probable cause of driving while intoxicated resulting in severe injury.[13,21] Other states, such as New York and California, allow forced blood samples with a warrant issued by a judge.[3,11] State laws regarding the approach to this situation vary and it is important that the ED staff be familiar with the specific requirements of the law of that state.

How much force may be used to collect chemical evidence? Is a physician violating human dignity and privacy in obtaining evidence for the state? These issues have been addressed by the United States Supreme Court. In *Rochin v California*,[15] the Court overturned a conviction of drug possession based on violation of the Fourteenth Amendment. In this case, police were informed that Rochin was selling drugs. While entering the defendant's home, the police witnessed the defendant swallow 2 pills that were lying on the nightstand. When the officers failed to recover the pills on the scene, the officers took Rochin to the ED, where they directed the physician to administer an emetic through a nasogastric tube. The capsules were recovered from the vomit, identified as containing morphine, and *Rochin* was convicted by the trial court for possessing morphine.[1,15] The Supreme Court reversed this decision, based on the 14th amendment, â€œnor shall any State deprive any person of life, liberty or property, without due process of lawâ€¦.â€•[25] The term due process is vague, and is defined on a case-by-case basis, but it essentially means that states must use fair legal procedures when depriving an individual of life, liberty, or property. In *Rochin*, the court concluded that forced emesis by a physician was believed to violate Due Process, stating

> This is conduct that shocks the conscience. Illegally breaking into the privacy of the petitioner, the struggle to open his mouth and remove what was there, the forcible extraction of stomach contents-this course of proceeding by

> agents of government to obtain evidence is bound to offend even hardened sensibilities. They are methods too close to the rack and the screw to permit constitutional differentiation.[15]

The Supreme Court revisited the issues presented in *Rochin* four years later in *Breithaupt v Abram*.[2] Breithaupt was the driver of a truck that killed three occupants of another vehicle. In the ED, a police officer requested that a blood alcohol level be drawn. The blood, drawn while the patient was unconscious, was above the legal limit for alcohol and the patient was convicted of involuntary manslaughter. Breithaupt argued that the blood draw, as in forced emesis in *Rochin*, violated Due Process as he did not consent to its collection. Justice Clark disagreed, stating â€œthe distinction rests on the fact that there is nothing â€˜brutalâ€™ or â€˜offensiveâ€™ when done, as in this case, under the protective eye of a physicianâ€• and that the â€œblood test procedure has become routine in our everyday life.â€•[1,2] Phlebotomy while the patient is unconscious and unable to give consent, did not violate the Due Process Clause of the Fourteenth Amendment.

The Supreme Court continued to expand the scope of permissible phlebotomy in *Schmerber v California*.[17] Schmerber was

involved in a motor vehicle crash in which the officer suspected he was intoxicated. Unlike in *Breithaupt*, Schmerber was not unconscious, and a physician drew a blood sample on the officer's request despite the patient's verbal refusal. Schmerber argued that this act violated several constitutional rights. He argued that forced phlebotomy violated the Fourth and Fifth Amendment. Schmerber argued that a forced blood draw without his consent denied him Due Process of law under the Fourteenth Amendment, violated his privilege against self-incrimination, and his right not to be subjected to unreasonable searches and seizures in violation of the Fourth and Fourteenth Amendments.[1,17] The court rejected

all of Schmerber's arguments. The phlebotomy did not violate the Due Process clause because â€œthe extraction was made by a physician in a simple, medically acceptable manner in a hospital environment. â€¦we cannot see that it should make any difference whether one states unequivocally that he objects or resorts to physical violence in protest or is in such condition that he is unable to protest.â€• [17] Furthermore, the forced blood draw did not violate the Fifth Amendment's privilege against self-incrimination because the Fifth Amendment only protects evidence of a â€œtestimonial or communicative nature,â€• such as writings or speech. Finally, there was no violation of the Fourth and Fourteenth Amendments' protecting against unreasonable searches and seizures of property:

> The delay necessary to obtain a warrant, under the circumstances, threatened the destruction of evidenceâ€¦. Similarly, we are satisfied that the test chosen to measure petitioner's blood-alcohol level was a reasonable one. Extraction of blood samples for testing is a highly effective means of determining the degree to which a person is under the influence of alcohol. Such tests are a commonplace in these days of periodic physical examinations and experience with them teaches that the quantity of blood extracted is minimal, and that for most people the procedure involves virtually no risk, trauma, or pain.

To ensure compliance with standards set forth in *Schmerber*, the states have tailored laws and regulations governing the seizure of blood for the purpose of blood alcohol testing. Laws generally require the procedure be (1) done in a reasonable, medically approved manner, (2) be incident to a lawful arrest, and (3) be based on the belief that the arrestee is intoxicated. It should be

remembered that the issues raised by any one case are complex, and the application in real situations is difficult. Laws and regulations governing blood draws for alcohol testing vary from state to state and are the subject of frequent restructuring and amendment. It is therefore recommended that medical staff review with hospital counsel the local laws and regulations that pertain to these issues. It should be remembered, however, that physician and patient safety must always be the priority. The benefits of determining a patient's alcohol level must be weighed against the risks of the procedure. For example, drawing blood in an agitated patient may place the staff at risk of a needle stick.

Confidentiality

Patient 5 A 32-year-old woman was fired from her job as a high school mathematics teacher. The school board called for her termination after learning that she had a history of alcohol dependence and had a previous hospitalization for detoxification at the local community hospital. A parent on the school board was also employed as a nurse at the hospital, where the teacher had received alcohol therapy. The school board member (and nurse) had inadvertently accessed the teacher's medical record while caring for a patient with the same last name.

The Health Insurance Portability and Accountability Act (HIPAA) was created in 1996. Initially, the purpose of HIPAA was to increase the portability of health insurance, and allow employees to maintain insurance when they changed jobs. The Act called for the establishment of several provisions, among them an electronic database designed to facilitate the exchange of information between healthcare providers, insurance companies, and those involved in financial and administrative transactions.[8] However, the idea of developing an electronic database brought to light already growing concerns regarding the maintenance of patient privacy. For the first time, patients' medical records would be

accessible to an unlimited amount of people working in healthcare, from billings processors to pharmacists to clinicians. Would a patient's right to privacy be jeopardized by a system designed to increase efficiency?

Prior to HIPAA, individual hospitals or physician offices designed their own methods for maintaining confidential patient information. Records were maintained on computers in some circumstances and on paper in others. Accessibility to that information was largely regulated by state laws, and supported by some federal regulations and ethical codes of conduct. During the 1990s, however, the weaknesses of the existing system gained attention as multiple high profile breeches of confidentiality surfaced. For example, the medical records of a congresswoman were released to the media during her campaign, making her history of depression and a past suicide attempt public knowledge.[18] There were also several cases of the medical records of hospital employee's being read by staff members not involved in the employees' care, health insurance companies releasing heath care information to employers without permission, and physicians releasing information to pharmaceutical companies that subsequently solicited the patient.[28] These breaches of ethics were each a testament to the fact that a patient's right to privacy needed more stringent regulation. If these examples could occur in the previous system for recording information, then it could be assumed that further increases in access would occur through an electronic database.

The Privacy Rule of HIPAA has become the most well publicized aspect of this Act among healthcare personnel. The Privacy Rule governs the use and disclosure of protected health information in the hands of healthcare providers, health plans, and healthcare clearinghouses.[8] The terminology used in the Privacy Rule is extensively defined. The following is a brief summary of the terms used:

Protected Health Information: This includes any individually identifiable information concerning the past, present, or future health of an individual. This includes medical information pertaining to assessment and treatment in addition to payment and billing information. All forms of information, written, oral, or electronic, are protected by this rule.

Covered Entities: This includes any person or business that provides health-related services or products. All those providing health-related services, for example clinicians, pharmacists, medical equipment providers, and other healthcare providers, are considered covered entities. Companies that provide disability insurance, car insurance, or casualty insurance are not included in the rule.[8,25]

Healthcare Clearinghouses: These are entities that compile healthcare information, such as billing companies or data processing centers.

Institutions are required to provide all individuals with written notice of their privacy policy when they first seek medical care. Patients must be informed of how the institution may use and disclose information. The notice must also describe patients' rights, including the right to access their medical information and their right to file a complaint if they believe their rights are violated. The notice must be written in plain language, and the individual must provide written acknowledgement that they received the information.

The Privacy Rule of HIPAA was not intended to impede healthcare. There are several exceptions to the rule. A covered entity is permitted to use and disclose protected health information for the purposes of evaluation and treatment. Physicians have the freedom to consult with each other, in their own institution and outside, to provide clinical care. Additionally, there are several specific exceptions to the Privacy Rule listed within the document-

situations in which protected health information may and often must be disclosed, and may be done without an individual's permission. For example, activities related to public health, such as reporting communicable diseases, information necessary to report actual or suspected abuse, neglect or domestic violence, or information pertaining to cadaveric organ or tissue donation are specifically exempt from the Privacy Rule.[7]

The HIPAA Privacy Rule specifically addresses consultations with poison centers (PCs). It states: â€œWe consider the counseling and follow-up consultations provided by poison control centers with individual providers regarding patient outcomes to be treatment. Therefore, poison control centers and other healthcare providers can share protected health information about the treatment of an individual without a business associate contract.â€•[7]

Violations of the Privacy Rule are subject to penalties, the severity of which is dependent on the type of infraction. Simple noncompliance violations may be charged financial penalties, however, more significant or intentional disclosures of information may have steeper fines in addition to criminal charges and potential jail time.[28]

Legal Considerations for Poison Centers and Information Specialists

Patient 6 The PC received a call from a concerned mother that her daughter might have ingested one of the grandmother's diabetes medications. The mother stated that the child was acting normally all day at the grandmothers' house, but when the family returned home the child had become drowsy. When contacted, the grandmother had confirmed that 1 pill was missing from her purse although she did not know the name of her medication. The PC advised that the parents give the child juice and closely observe

her for the next 6 hours. Approximately 2 hours later, while sleeping, the child had a seizure. The child continued to seize in the hospital, where medical evaluation revealed hypoglycemia. The patient subsequently suffered permanent neurological damage. The medication was later identified as glyburide. Action was brought against the local PC, alleging inappropriate advice and failure to recommend transport to a hospital.

As a general rule, any physician who decides to treat a patient enters into a physician-patient relationship that creates well-established legal duties. Courts have ruled that the physician-patient encounter need not be a face-to-face interaction to have legal consequences. For example, the absence of physical contact between a physician and patient as in the practice of radiology and pathology does not preclude a patient from asserting that a duty of care exists.[4] More particularly and quite relevant to the practice of a PC, a New York State court ruled that an initial telephone call from a patient to a physician can be sufficient basis to hold that physician responsible for inappropriate advice or a significant error in judgment.[12] Given the legal precedents previously stated, it is eminently clear that contact with a poison information specialist is a sufficient foundation for a subsequent legal action if inappropriate advice was given.

Standards of Care Applicable to Poison Information Specialists

Any discussion of the standard of care to which a poison information specialist should be held would be misleading without mentioning several operational aspects of most PCs. The specialists are required to have a rapid and accurate access to a standard information resource system, that contains both basic information and recommendations to deal with most encountered toxic exposures. Advice that differs significantly from an existing protocol or standard of care could be subject to critical review in a

civil lawsuit. If a patient were to bring an action, the negligence theory against the PC might rely particularly on deviations from the standard recommendations.

It would be inaccurate to suggest, however, that the duty of care owed by a poison information specialist can be measured only by how closely the advice given compares with the standard resources. Frequently, an information specialist may encounter situations that cannot be managed in accordance with an information system alone, and may seek counsel from a clinical pharmacist or a medical toxicologist working with the PC. If this were to occur, any subsequent legal proceeding would also review carefully the content of the information given to the consultant regarding its accuracy and appropriateness regarding the underlying toxicologic problem.

Practices of Regional Poison Centers that can Reduce Potential Liabilities

Clearly there are some inherent risks of potential liability for a PC. To minimize such risk and the risk of civil actions against a PC, quality assurance and risk management programs should be a regular function. Daily audits or monitoring of the advice given by poison information specialists should be done. Such interactions enhance care and ensure patient safety for the individual and establish a higher general standard.

The medical toxicologists and clinical pharmacists responsible for supervising the poison information specialists must be able to adequately assess the competence and capabilities of the staff and to make recommendations, take corrective actions, and provide suggestions for improvement to involved members. This process is facilitated by such actions as audiotaping calls made to the PC and the subsequent advice given, and reviewing written records maintained by the information specialist on each particular case.

Documentation is extremely important, because in the event of a

lawsuit, the most likely area of dispute will be what was actually said to the patient.

Summary

The risk management and legal issues of an active ED have implications for many patients. The ability of providers to function responsibly is dependent on an understanding of these ever-evolving principles. Those patients whose consciousness is abnormal because of a toxin represent an acute complex medicolegal emergency. A well-organized hospital is dependent on a close working relationship among the legal, risk management, and medical personnel. Only in this manner can they learn, cooperate, and meet the needs of the ever-evolving clinical dilemmas they confront.

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Appendices

Normal Vital Signs by Age

Adult
120
80
60â€“100
16â€“24
16 years
120
80
80
16â€“30
12 years
119
76
85
16â€“30
10 years
115
74
90
16â€“30

6 years
107
69
100
20â€“30
4 years
104
65
110
20â€“30
2 years
102
58
120
25â€“30
1 year
100
55
120
25â€“30
6 months
90
55
120
30
4 months
90
50
145
30â€“35
2 months
85
50
145

30â€“35
Newborn
65
50
145
35â€“40
The normal temperature is defined at 95â€“100.4Â°F (35â€“38Â°C) for a ages. For children â‰¤1 year of age these values are the mean values fo 50th percentile. For the older children these values represent the 90th percentile at a specific age for the 50th percentile of weight in that age g

Age	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse (beats/min)	Respiration (breaths/mi

Common Equations

Temperature

$$°C = [°F - 32] \times 5/9$$
$$°F = [°C \times 9/5] + 32$$

Weight

$$lbs = kg \times 2.204$$
$$kg = lbs \times 0.454$$

Anion Gap (mEq/L)

$$Na^+ - [Cl^- + HCO_3^-]$$

Calculated Osmolarity (mosm/L)

$$2Na^+ + \frac{BUN}{2.8} + \frac{Glucose}{18} + \frac{EtOH}{4.6}$$

SI Units from Conventi

$$mmol = mg \div MW$$
$$mEq = mmol \times cha$$

Serum Concentration

$$C_0 = \frac{S \times F \times Dose}{[Vd\ (L/kg) \times Wt\ (kg)]}$$

Half-Life

$$t_{1/2} = \frac{0.693}{k_e}$$

where

$$k_e = \frac{[\ln C_1 - \ln C_2]}{t_1 - t_2}$$

Body Surface Area (m^2)

$$\sqrt{\frac{Ht\ (in) \times Wt\ (lb)}{3131}}$$

or

$$\sqrt{\frac{Ht\ (cm) \times Wt\ (kg)}{3600}}$$

A–a Gradient (on room air)

$$150 - PO_2 - [1.25 \times PCO$$

Creatinine Clearance (mL/mi

$$\frac{(140 - age) \times Ideal\ Body\ Wt \times [0.85\ for\ women]}{72 \times Cr_{serum}}$$

Toxic Syndromes

Anticholinergic agents
-/â†‘
â†‘
Â±
â†‘
Delirium

â†‘
â†“
â†“
Dry mucous membranes, flush, urinary retention
Cholinergic agents
Â±
Â±
-/â†‘
-
Normal to depressed
Â±
â†‘
â†‘
Salivation, lacrimation, urination, diarrhea, bronchorrhea, fasciculations, paralysis
Ethanol or sedative-hypnotics
â†“
â†“
â†“
-/â†“
Depressed
Â±
â†“
-
Hyporeflexia
Opioids
â†“
â†“
â†“
â†“
Depressed
â†“
â†“
-

Hyporeflexia
Sympathomimetic agents
â†‘
â†‘
â†‘
â†‘
Agitated
â†‘
-/â†‘
â†‘
Tremor, seizure
Withdrawal from ethanol or sedative-hypnotics
â†‘
â†‘
â†‘
â†‘
Agitated, confused
â†‘
â†‘
â†‘
Tremor, seizure
Withdrawal from opioids
â†‘
â†‘
-
-
Normal, anxious
â†‘
â†‘
â†‘
Vomiting, rhinorrhea, piloerection, diarrhea, yawning
â†‘ = increase; â†“ = decrease; Â± = variable; - = no change

Vital Signs

Mental Pupil
Group BP P R T Status Size Peristalsis Diaphoresis O

Selected Emergency Antidotes with Common Initial Doses*

N -acetylcysteine
Acetaminophen: *IV* : 150 mg/kg infused IV over 60 min, followed by 50 mg/kg over 4 hours, then 100 mg/kg over 16 hours. Must dilute in D_5 W 140 mg/kg, followed by 70 mg/kg every 4 hours for 17 doses. NOTE : Sp IV dilution required for children.
544
Atropine
Cholinesterase inhibitors: *Adults* : 1â€“5 mg IV, doubled every 3â€“5 until bronchorrhea resolves. *Children* : 50 Âµg/kg (min 0.1 mg; max 0.5 IV, doubled as for adults. NOTE : Use 3â€“5 mg starting dose for adults severe poisoning.
1519
L-Carnitine
Valproic acidâ€“induced hyperammonemia or valproic acidâ€“indu elevated AST/ALT: *Clinically ill:* 100 mg/kg (up to 6 g) infused IV over min, followed by 15 mg/kg infused over 30 min every 4 hours. *Clinically* 100 mg/kg/day oral divided every 6 hours up to 3 grams/day.
746
Cyanide antidotes (Nitrites and sodium thiosulfate)
Cyanide: *Adults:* 1) Sodium nitrite: 300 mg (10 mL of a 3% conc) infuse over 2â€“5 min. 2) Sodium thiosulfate: 12.5 g (50 mL of a 25% conc) in IV over 10â€“30 min or as a bolus. *Children* : 1) Sodium nitrite: 6â€“8 m (0.2 mL/kg of a 3% conc) (max 300 mg) infused IV over 2â€“5 min. 2) S thiosulfate: 7 g/m^2 (0.5 g/kg) (max 12.5 g) infused over 10â€“30 min or bolus. NOTE: In both adults and children, avoid sodium nitrite when

carboxyhemoglobin is expected to be elevated.
1725 , 1728
Deferoxamine
Iron: Begin continuous IV infusion at 5 mg/kg/h, titrate to 15 mg/kg/h a tolerated with a total dose of 6â€“8 g/day.
638
Dimercaprol (BAL)
Lead encephalopathy: 75 mg/m^2 deep IM every 4 hours. First dose to precede edetate calcium disodium ($CaNa_2$ EDTA) by 4 hours. Contraindica peanut allergy.
1265
Digoxin-specific antibody fragments (Fab)
Cardioactive steroids: Known level : # of vials = [wt (kg) Ã— level (ng/mL)/100] rounded up to nearest vial. Empiric dosing : Acute: 10-20 Chronic: *Adults* : 3â€“6 vials; *Children* : 1â€“2 vials. Usually given as IV infusion over 30 min. An IV bolus is acceptable for asystole. NOTE : Non-digoxin cardioactive steroids, use empiric dose.
983
Edetate calcium disodium ($CaNa_2$ EDTA)
Lead encephalopathy: 1500 mg/m^2 /day as a continuous IV infusion. N Dimercaprol (BAL) should be administered 4 hours prior to starting this c
1331
Folinic acid (leucovorin)
Methotrexate: 100 mg/m^2 infused IV over 15â€“30 min every 3â€“6 hou several days or until methotrexate serum conc < 1 Ã— 10^{-8} M in the abs of bone marrow toxicity.
826
Fomepizole
Methanol or ethylene glycol: 15 mg/kg infused IV over 30 min; next 4 at 10 mg/kg every 12 hours; additional doses at 15 mg/kg every 12 hour needed.
1460
Glucagon
Î²-Adrenergic antagonists: IV infusion over 1â€“2 minutes. *Adults:* 50

Âµg/kg. *Children* : 50 mcg/kg. Dose may be increased up to 10 mg in an as needed.

942

Methylene blue

Methemoglobinemia: 1â€“2 mg/kg IV over 5 min followed by a 30 mL f flush.

1746

Naloxone

Opioid-induced respiratory depression: 50 Âµg IV titrated upward to reversal, while avoiding opioid withdrawal.

614

Octreotide

Sulfonylurea-induced hypoglycemia: *Adults* : 50 Âµg SQ every 6 h. *Children* : 1.25 Âµg/kg (max 50 Âµg) SQ every 6 hours.

770

Physostigmine

Anticholinergic syndrome: IV infusion over 5 min. *Adults* : 1â€“2 mg. *Children* : 20 Âµg/kg (max 0.5 mg).

794

Pralidoxime

Cholinesterase inhibitors: *Adults* : 1â€“2 g infused IV over 30 min and up to 500 mg/h by infusion for sickest patients. *Children* : 20â€“50 mg/k (max 1â€“2 g) infused IV over 30â€“60 min and then 10â€“20 mg/kg/h (500 mg/h).

1513

Pyridoxine

Isoniazid: 1 g for each gram of isoniazid up to 70 mg/kg (max 5 g) infus at 0.5 g/min until seizures stop, with the remainder infused IV over 4â€“ hours.

872

Succimer

Lead poisoning: *Adults:* 10 mg/kg orally every 8 hours for five days fol by every 12 hours for 14 days. *Children:* 350 mg/m^2 orally as for adults.

1325

Footnote

*Consult pages listed for complete information regarding dose, route, du of therapy, adverse effects, safety issues, contraindications, and other considerations. For up-to-date information, contact your regional poison at 800-222-1222.

Common Toxicology Laboratory Valu

Acetaminophen
10â€“30 Âµg/mL
66â€“199 Âµmol/L
Arsenic
<5 Âµg/L
<0.665 Âµmol/L
Arsenic (urine)
<50 Âµg/day
<6.65 Âµmol/day
Caffeine
1â€“10 Âµg/mL
5.2â€–51 Âµmol/L
Carbamazepine
4â€–12 mg/L
17â€–51 Âµmol/L
Carboxyhemoglobin
< 2 %
< 2 %
Cyanide
<1 Âµg/mL
<38.5 Âµmol/L

Digoxin
0.8â€“2 ng/mL
1.1â€“2.6 nmol/L
Ethanol
100 mg/dL
22 mmol/L
Ethlyene glycol*
<25 mg/dL
<4 mmol/L
Iron
80â€“180 Âµg/dL
14â€“32 Âµmol/L
Lead
<10 Âµg/dL
<0.48 Âµmol/L
Lidocaine
1.5â€“5 Âµg/mL
6.4â€“21.4 Âµmol/L
Lithium
0.6â€“1.2 mEq/L
0.6â€“1.2 mmol/L
Mercury
<10 Âµg/L
<50 nmol/L
Mercury (urine)
<20 Âµg/L
<100 nmol/L
Methanol*
<25 mg/dL
<7.8 mmol/L
Methemoglobin
< 1 %
< 1 %
Phenobarbital

15â€“40 mg/L
65â€“172 Âµmol/L
Phenytoin
10â€“20 mg/L
40â€“79 Âµmol/L
Salicylates
15â€“30 mg/dL
1.1â€–2.2 mmol/L
Thallium
<2.0 Âµg/L
<9.78 nmol/L
Thallium (urine)
<5.0 Âµg/L
<24.5 nmol/L
Theophylline
5â€“15 Âµg/mL
27.8â€–83 Âµmol/L
Thiocyanate
<30 Âµg/mL
<100 Âµmol/L
Valproic acid
50â€–120 mg/L
347â€–833 Âµmol/L
Therapeutic or generally acceptable levels are listed. Please see the appropriate chapter for details regarding specific situations. Normal rang may vary by laboratory. * = Level must be interpreted based on the pati serum pH and clinical status

Conventional SI

Common Standard Laboratory Values

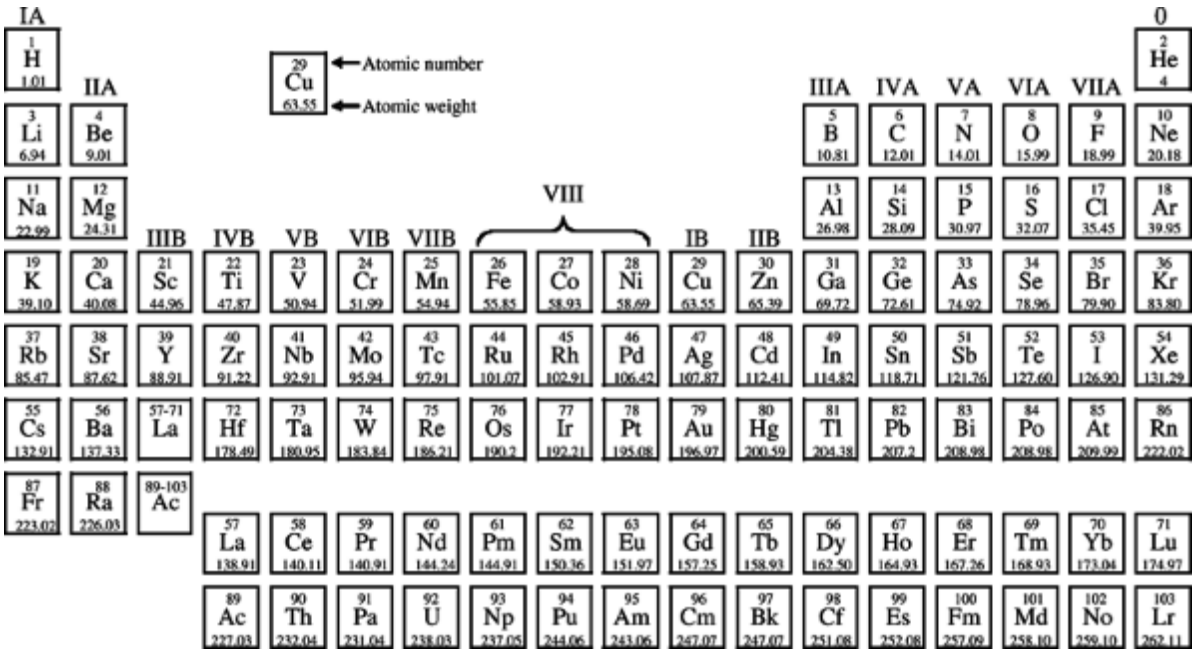
Ammonia
10â€“80 Âµg/dL

6â€“47 Âµmol/L
Bicarbonate
18â€“24 mEq/L
18â€“24 mmol/L
BUN
7â€“18 mg/dL
2.5â€“6.4 mmol/L
Calcium
8.4â€“10.2 mg/dL
2.10â€“2.55 mmol/L
Chloride
98â€“106 mEq/L
98â€“106 mmol/L
Creatinine
0.6â€“1.2 mg/dL
0.053â€“0.106 mmol/L
Glucose
60â€“110 mg/dL
3.3â€“6.1 mmol/L
Lactate
18 mg/dL
<2 mmol/L
Magnesium
1.3â€“2.1 mEq/L
0.65â€“1.05 mmol/L
PCO_2 (art)
35â€“45 mm Hg
4.7â€“6 kPa
PCO_2 (ven)
45â€“55 mm Hg
6.0â€“7.33 kPa
pH (art)
7.35â€“7.45
7.35â€“7.45

pH (ven)
7.33â€“7.4
7.33â€“7.4
PO_2 (art)
90â€“100 mm Hg
12â€“13.3 kPa
PO_2 (ven)
30â€“50 mm Hg
4.0â€“6.67 kPa
Phosphorus
3â€–4.5 mg/L
1â€–1.4 mmol/L
Potassium
3.5â€–5.0 mEq/L
3.5â€–5 mmol/L
Sodium
135â€–145 mEq/L
135â€–145 mmol/L
art = arterial; ven = venous

Conventional SI

Periodic Table of the Elements



Clinical and/or Laboratory Findings Poisoning

Agitation

Anticholinergics[a] , hypoglycemia, phencyclidine, sympathomimetics[b] , et and sedative-hypnotic withdrawal

Alopecia

Alkylating agents, radiation, selenium, thallium

Ataxia

Benzodiazepines, carbamazepine, carbon monoxide, ethanol, hypoglycem lithium, mercury, phenytoin, nitrous oxide

Blindness or decreased visual acuity

Caustics (direct), cocaine, cisplatin, mercury, methanol, quinine, thallium

Blue skin

Amiodarone, FD&C #1 dye, methemoglobin, silver

Constipation

Anticholinergics[a] , botulism, lead, opioids, thallium (severe)

Tinnitus, deafness

Aminoglycosides, cisplatin, heavy metals, loop diuretics, quinine, salicyla

Diaphoresis

Amphetamines, cholinergics[c] , ethanol and sedative-hypnotic withdrawal, hypoglycemia, opioid withdrawal, salicylates, serotonin syndrome, sympathomimetics[b]

Diarrhea

Arsenic and other metals/metalloids, boric acid (blue-green), botanical irritants, cathartics, cholinergics[c] , colchicine, iron, lithium, opioid withdr radiation

Dysesthesias, paresthesias

Acrylamide, arsenic, ciguatera, cocaine, colchicine, thallium

Gum discoloration

Arsenic, bismuth, hypervitaminosis A, lead, mercury paresthesias

Hallucinations

Anticholinergics[a] , dopamine agonists, ergot alkaloids, ethanol, ethanol a sedative-hypnotic withdrawal, LSD, phencyclidine, sympathomimetics[b] , tryptamines (e.g., AMT)

Headache

Carbon monoxide, hypoglycemia, monoamine oxidase inhibitor/food inter (hypertensive crisis), serotonin syndrome

Metabolic acidosis (elevated anion gap) [MUDPILES]

Methanol, uremia, ketoacidosis (diabetic, starvation, alcoholic), paraldeh phenformin, metformin, iron, isoniazid, lactic acidosis, cyanide, protease inhibitors, ethylene glycol, salicylates, toluene

Miosis

Cholinergics[c] , clonidine, opioids, phencyclidine, phenothiazines

Mydriasis

Anticholinergics[a] , botulism, opioid withdrawal, sympathomimetics[b]

Nystagmus

Barbiturates, carbamazepine, carbon monoxide, ethanol, lithium, monoar oxidase inhibitors, phencyclidine, phenytoin, quinine

Purpura

Anticoagulant rodenticides, clopidogrel, corticosteroids, heparin, pit viper

venom, quinine, salicylates, warfarin

Radiopaque ingestions

Arsenic, chloral hydrate, enteric coated tablets, halogenated hydrocarbor metals (e.g., iron, lead)

Red skin

Anticholinergics[a] , boric acid, disulfiram, scombroid, vancomycin

Rhabdomyolysis

Carbon monoxide, doxylamine, HMG CoA reductase inhibitors, sympathomimetics[b] , *Tricholoma* mushrooms

Salivation

Arsenic, caustics, cholinergics[c] , ketamine, mercury, phencyclidine, stryc

Seizures

Bupropion, carbon monoxide, cyclic antidepressants, ethanol and sedative hypnotic withdrawal, *Gyromitra* mushrooms, hypoglycemia, isoniazid, theophylline

Tremor

Antipsychotics, arsenic, carbon monoxide, cholinergics[c] , ethanol, lithium mercury, methyl bromide, sympathomimetics[b] , thyroid replacement

Weakness

Botulism, diuretics, magnesium, paralytic shellfish, steroids, toluene

Yellow skin

Acetaminophen (late), pyrrolizidine alkaloids, Î²-carotene, *Amanita* mushrooms, dinitrophenol

[a] Anticholinergics: e.g., antihistamines, atropine, cyclic antidepressants, scopolamine

[b] Sympathomimetics: e.g., amphetamines, Î²-adrenergic agonists, cocain ephedrine

[c] Cholinergics: e.g., muscarinic mushrooms, organic phosphorus compou and carbamates, including Alzheimer's drugs and physostigmine, pilocarp and other direct acting drugs